

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE  
(65th Meeting)

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Friday,  
October 16, 1998

Kennedy Grand Ballroom  
Holiday Inn  
8777 Georgia Avenue  
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Call to Order

William Craig, M.D., Chairman

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Division of Anti-Infective Drug Products, FDA

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 Rhode Island Hospital

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Division of Special Pathogen and  
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1                                    P R O C E E D I N G S                                    (8:08 a.m.)

2                                    DR. CRAIG: Good morning. I'd like to call  
3 this meeting to order, and we're going to go right along as  
4 the schedule said, and we'll have our discussion starting  
5 at 9:10. The first talk this morning is on the regulatory  
6 perspective from Gary Chikami.

7                                    DR. CHIKAMI: Good morning and welcome back to  
8 our meeting. Thank you, Dr. Craig.

9                                    This is actually the second part of the session  
10 to discuss some issues in clinical trial design, and also,  
11 as we got into a discussion yesterday afternoon toward the  
12 end of the session, we'll also be discussing issues  
13 relevant to how much information do we need to collect in  
14 the setting of clinical trials to support determining if  
15 products are effective for the treatment of resistant  
16 organisms. I just wanted to make some general statements  
17 and give a little regulatory perspective on the  
18 requirements for defining substantial evidence as a  
19 background for the talks this morning and for the  
20 discussion of the questions.

21                                    For a new drug to be commercially marketed in  
22 the U.S., it has to be the subject of a review of a New  
23 Drug Application, and that application must contain  
24 acceptable scientific data, including the results of tests  
25 to evaluate safety and to provide substantial evidence of

1 effectiveness for the conditions for which the drug is  
2 being offered. The operative phrase here is "substantial  
3 evidence." This is the basis for not only the approval of  
4 a new drug on the market, but also a new use for an already  
5 approved drug.

6 Next slide.

7 Substantial evidence is defined in the statute  
8 as "evidence consisting of adequate and well-controlled  
9 investigations, including investigations by experts  
10 qualified by scientific training and experience to evaluate  
11 the effectiveness of the drug involved, on the basis of  
12 which it could be fairly and reasonably concluded by such  
13 experts that the drug will have the effect it purports or  
14 is represented to have."

15 Next slide.

16 This was added to the Food, Drug, and Cosmetic  
17 Act by an amendment in 1962. It not only describes sort of  
18 the quality of the evidence, but the agency has over the  
19 years interpreted the amount of evidence that should be  
20 submitted, and based on the language in the statute and  
21 also the legislative history, the agency has interpreted  
22 this as being at least two adequate and well-controlled  
23 studies.

24 Next slide.

25 Now, the scientific basis for this is

1 essentially the need for independent substantiation to try  
2 and account for or address the possibilities of chance  
3 observations; spontaneous changes in the course of the  
4 disease or a placebo effect; biased observations, such as  
5 center-dependent effects; or, in rare cases, fraud. So  
6 again, the need for adequate and well-controlled studies  
7 and the interpretation really comes from this sort of  
8 scientific basis.

9 Next slide.

10 Now, over the years the FDA has been flexible  
11 in the interpretation of this statutory requirement. New  
12 uses may be supported by studies of other uses, so that in  
13 that case a single study of a new use, if there is  
14 corroborative evidence, may be sufficient. A single robust  
15 study which demonstrated an effect on survival or other  
16 important clinical benefit may also be considered to form  
17 substantial evidence for either a new use or a new drug.  
18 Many of these concepts were recently codified in the FDA  
19 Modernization Act, where data from adequate and well-  
20 controlled investigations and confirmatory evidence may  
21 constitute substantial evidence.

22 This has also been detailed in a recent  
23 guidance document entitled "Providing Clinical Evidence of  
24 Effectiveness for Human Drug and Biologic Products," and it  
25 speaks of several situations where a single well-done study

1 may provide substantial evidence with additional  
2 information. These include situations where extrapolation  
3 or support from existing studies may provide corroborative  
4 information, there may be information from related adequate  
5 and well-controlled studies in related diseases or  
6 conditions, and it also speaks to, in certain situations,  
7 as I've already alluded to, where the results of a robust  
8 single study which is well done and demonstrates a  
9 significant effect on a clinically important endpoint, such  
10 as mortality, in an area of particular need may provide  
11 substantial evidence.

12 Next slide.

13 Now, all of these should be interpreted or  
14 evaluated in the context of the usual development for an  
15 anti-infective development program. Whenever we're in the  
16 situation where we have a single clinical trial, there is  
17 always other information, and it's important to think about  
18 how much this other information provides to our ultimate  
19 understanding of how effective an anti-infective product  
20 may be. This information may include in vitro and animal  
21 model activities, PK/PD information, Phase I and Phase II  
22 clinical development information, including safety, PK/PD  
23 information and early clinical activity, and finally the  
24 context of the Phase III clinical development is also  
25 important. Many anti-infective products undergo broad

1 clinical development, including many different types of  
2 infections, different dosing regimens, routes of  
3 administration, and are studied in many different  
4 populations.

5           So in that context, the amount of information  
6 required to support determining efficacy in a new use may  
7 be quite different from a product which undergoes a more  
8 focused development program, in which there may be study of  
9 fewer indications and it may directed toward a specific  
10 pathogen. For example, a resistant pathogen.

11           Next slide.

12           In the setting, for example, of sort of a  
13 broader based development program, clinical efficacy for a  
14 specific pathogen may accrue, for example, in the setting  
15 of a randomized well-controlled trial for a specific  
16 clinical indication, such as pneumonia, due to many  
17 different organisms, and as was alluded to yesterday, in  
18 the setting of such a trial, we don't expect all of these  
19 subsets of the specific pathogens to be large enough to  
20 draw statistical conclusions. Rather, we look at those  
21 subsets in the context of the overall effect to determine  
22 if in fact effectiveness has been demonstrated for each of  
23 those specific pathogens.

24           The points to consider document, which was  
25 written in 1992, speaks to this point, where it talks

1 about, in the setting of certain indications, the number of  
2 pathogens isolated within the context of the controlled  
3 clinical trials that would provide evidence to support  
4 labeling for those specific pathogens. One example that's  
5 given is that the number of pathogens should either be 10  
6 percent of the total number of pathogens isolated or at  
7 least 10 organisms, whichever is larger.

8           The other specific situations which are cited  
9 in the points to consider document are for otitis media and  
10 acute sinusitis, where there are three principal pathogens  
11 which have been identified -- namely, strep pneumo,  
12 Haemophilus influenzae, and Moraxella -- and the document  
13 actually gives specific numbers for each of those in terms  
14 of the minimum number of isolates.

15           I think with that context we will now move into  
16 the rest of the program, which will speak to some of these  
17 issues, and I think our plan is to sort of return to the  
18 discussion of the prior Questions 1 and 2 for this session,  
19 just to finish up those discussions, and then we'll move on  
20 to Questions 3 and 4.

21           Thank you.

22           DR. CRAIG: Thank you, Gary.

23           Our next speaker will start two talks on the  
24 industry perspective, and the first will be by Dr. Rex  
25 Williams from RW Johnson.

1 DR. REX WILLIAMS: Thank you, Mr. Chairman.

2 Could I have the first slide, please?

3 We have been asked to address our experience  
4 and describe it in the treatment of community-acquired  
5 pneumonia with levofloxacin due to penicillin-resistant  
6 *Streptococcus pneumoniae*.

7 By way of background, we know that Levaquin was  
8 approved for treatment of mild, moderate, or severe  
9 community-acquired pneumonia due to *Streptococcus*  
10 *pneumoniae*, along with other pathogens, in December of  
11 1996, and has been marketed in the United States since  
12 January of '97. We have compiled extensive in vitro data  
13 which supports the efficacy of levofloxacin in the  
14 treatment of infection due to pen-susceptible,  
15 intermediate, or resistant strains, but that's not going to  
16 be the focus of my brief presentation. Rather, we would  
17 like to show you the data that we've accumulated to date in  
18 treatment of CAP against penicillin-resistant strep pneumo  
19 between our company and our operating company, Ortho-McNeil  
20 Pharmaceutical.

21 This is a busy slide and I want to spend a  
22 little bit of time with you to give you an appreciation of  
23 the extent of the efforts that we've made. We have done  
24 eight clinical trials, some of which are ongoing, between  
25 1992 and 1998. I've divided the trials into three

1 sections. The first is the NDA trials, which were done in  
2 support of the New Drug Application and were done between  
3 1992 and 1994. A single European trial done by our  
4 development partners, mostly in Europe, but also in centers  
5 in South Africa and Latin America, was done between 1994  
6 and 1996. Then we've done four postmarketing trials  
7 between 1996 and 1998, mostly in the U.S., but also  
8 involving some Canadian centers. Three of those trials are  
9 ongoing. Four of the trials were comparative and four were  
10 noncomparative.

11 For the NDA trials, we enrolled 951 subjects  
12 with community-acquired pneumonia, and 656 of those were  
13 treated with levofloxacin. We had culture-positive either  
14 blood or sputum cultures, primarily, in 116 of those for  
15 strep pneumo, and of those four have proved to be  
16 penicillin-resistant.

17 In the single European trial, there were 518  
18 patients with mild to moderate pneumonia enrolled by HMR,  
19 and 172 were dosed at levofloxacin 500 milligrams I.V., but  
20 actually it was orally in that particular trial. Forty-  
21 four of those proved to have culture-positive strep pneumo,  
22 and of those one had penicillin-resistant strep pneumo.

23 The four U.S.-Canadian postmarketing studies  
24 done by either Ortho-McNeil or by our company enrolled in  
25 excess of 1,000 patients, and 954 of those were treated

1 with levofloxacin, and 231 have been culture-positive for  
2 strep pneumo and eight of those have been penicillin-  
3 resistant.

4 So in total we've enrolled over 2,500 patients,  
5 and 1,762 of those have been treated with levofloxacin, 391  
6 are culture-positive for strep pneumo, and in total we have  
7 13 cases of fully pen-resistant strep pneumo.

8 This is the distribution of MICs for  
9 levofloxacin versus the 300-odd pathogens that we have MIC  
10 data for. Virtually all of them, with the exception of one  
11 isolate, reside below the break point of 2 and are fully  
12 susceptible to levofloxacin. The single isolate with an  
13 MIC of 16 was isolated in the United States, and of  
14 interest is the fact that it's fully susceptible to  
15 penicillin.

16 Next slide, please.

17 This is the distribution of MICs we see for  
18 penicillin versus the strep pneumoniae isolates. Many are  
19 fully susceptible to penicillin. We have a fair number of  
20 intermediate strains, many of which have an MIC of 1, and  
21 then these are the 13 MICs we have for the 13 resistant  
22 isolates. Virtually all but one have an MIC of 2.

23 Of interest, and not highly germane to the  
24 conversation, is the MIC data we have for erythromycin. I  
25 think this is very interesting in the fact that we have

1 actually more isolates that are erythromycin-resistant than  
2 fully pen-resistant, and actually the numbers are probably  
3 going to be much higher, because these are only data from  
4 PRI trials, not the entire database from which we have  
5 culled the pen-resistant data for the -- this comes from  
6 really two-thirds of the data that I showed you before.  
7 Some of the trials have not tested erythromycin, but from  
8 the ones that did we can see that we have a substantial  
9 number of isolates with high-level erythromycin resistance.

10 We looked at the 13 isolates that are fully  
11 pen-resistant and have tested them. Not all of them,  
12 because we didn't have the abilities or had trouble  
13 retesting the isolates, because some of them had been  
14 frozen for a long period of time and we could not restore  
15 them.

16 But of the ones that were tested versus the  
17 three macrolides, we see that 40 to 50 percent of those are  
18 also resistant to those three macrolides. Four out of six  
19 are susceptible to pyrimethamine sulfur. Not shown on the  
20 data is the susceptibility to doxycycline. We only tested  
21 five of those, and all five, interestingly, are susceptible  
22 to doxycycline. For levofloxacin, we tested all of them  
23 and they were all susceptible in vitro.

24 This is the subject data from the 13 subjects  
25 that had penicillin-resistant isolates. The mean age was

1 47.7 years, with a range of 24 to 74 years. Five were  
2 male, eight were female, 11 were Caucasian, and two were  
3 black. For comorbidities taken from the case record form  
4 by the past medical history section, we find that eight of  
5 the 13 had chronic obstructive lung disease or asthma, two  
6 had hypertension, and two had coronary artery disease.  
7 Nine were initially hospitalized for treatment by their  
8 investigator and four were treated entirely as outpatients.  
9 Five were bacteremic and six meet our criteria for defining  
10 a severe infection. The outcome assigned by the  
11 investigator was success, either cured or improved, in all  
12 13 cases.

13 We went back and looked through our experience,  
14 and tried to figure out why we did not see more penicillin-  
15 resistant cases. We took this from an article that was in  
16 CID that was published earlier this year, which identified  
17 a number of pertinent risk factors for penicillin-resistant  
18 strep pneumo, and then compared our exclusion criteria,  
19 seeing if there was a way that we may have biased our  
20 investigation to exclude these patients.

21 The risk factors that we did not exclude  
22 included institutionalized subjects, nursing home subjects,  
23 patients with a coexisting illness or an underlying  
24 disease, such as a malignancy or chronic obstructive lung  
25 disease, for example. We obviously didn't exclude family

1 members, the adults of children attending a daycare center,  
2 for example, although I can't go back and look at that  
3 data, because we didn't collect it. We didn't exclude  
4 immunodeficient patients, other than those with  
5 neutropenia, which we define as 500 white cells per cubic  
6 millimeter or less. Although we didn't put any of our  
7 studies in military institutions, we didn't exclude those,  
8 and we certainly didn't exclude elderly patients. We had  
9 in the PRI trials, which were about two-thirds of the  
10 total, actually about 30 percent of our database is in  
11 patients greater than or equal to age 65.

12 We did exclude patients who had received recent  
13 antimicrobial therapy, unless they were not improving on  
14 that particular therapy. We allowed those patients in,  
15 provided they called the medical monitor at PRI and  
16 discussed those cases with him, and we made exceptions for  
17 compelling cases of either deterioration or failure to  
18 improve.

19 We did not exclude HIV-infected patients,  
20 unless their CD4 count was less than 200. We did allow  
21 them in if their CD4 count was higher.

22 We didn't allow any children in our trials  
23 because of the potential of chondrotoxicity.

24 Lastly, we did not allow patients in with  
25 nosocomial pneumonia. These are community-acquired

1 pneumonia trials, and we did not capture data in patients  
2 who were recently hospitalized, but we certainly did not  
3 exclude those.

4 Concluding from the small number of penicillin-  
5 resistant subjects, we realized that surveillance data for  
6 penicillin resistance which are published or presented at  
7 recent meetings are not predictive of accrual in  
8 prospective clinical trials, and one of the reasons for the  
9 disparity may be that in the publications in which I am  
10 aware, those are published from lower respiratory tract  
11 isolates, but we don't know how many of those had chronic  
12 obstructive lung disease, how many had nosocomial  
13 pneumonia, or how many had community-acquired pneumonia.  
14 That may account for some of the issue. We don't really  
15 know what the incidence of pen-resistant infection is in  
16 community-acquired pneumonia.

17 We've shown that resistance of strep pneumo to  
18 levofloxacin is rare. Resistance of strep pneumo to  
19 penicillin is not associated with resistance to  
20 levofloxacin, unlike macrolides or pyrimethamine sulfur.  
21 Lastly, we can conclude that levofloxacin is efficacious in  
22 the treatment of CAP due to strep pneumo regardless of  
23 penicillin susceptibility.

24 In summary, between 1992 and 1998, to repeat  
25 what I told you at the beginning, we've done eight clinical

1 trials in community-acquired pneumonia, primarily in the  
2 U.S and Canada, enrolling over 2,500 patients with the  
3 disease, and 1,762 of those were treated with levo, 391  
4 were culture-positive due to strep pneumo, and only 13 of  
5 these were infected with penicillin-resistant strains.

6 So that leads us to our last slide, which I  
7 think is one of the questions you've been asked to address.  
8 How much clinical data are needed to support a PRSP claim  
9 for an antibiotic?

10 We feel that a minimal threshold should be  
11 necessary for any drug with a low prevalence of resistance  
12 to strep pneumo, no cross-resistance to other antibiotics  
13 that are commonly used to treat the condition, and  
14 operating by a different mechanism of action. A well-  
15 established safety profile for the drug should be present,  
16 there should be established efficacy against penicillin-  
17 susceptible isolates, and in vitro microbiologic data,  
18 animal studies, pharmacokinetic and pharmacodynamic data  
19 predictive of efficacy in penicillin-resistant strep  
20 pneumo.

21 Thank you for your attention.

22 (Applause.)

23 DR. CRAIG: Thank you, Rex.

24 The next presentation will by Vincent Ahonkhai  
25 from SmithKline Beecham.

1 DR. AHONKHAI: First, I'd like to thank you,  
2 Mr. Chairman, and indeed I want to also thank the FDA in  
3 particular and Dr. Meyerhoff for extending an invitation to  
4 me as a contributor to the pharmaceutical industry response  
5 in this discussion.

6 The pharmaceutical industry has been  
7 particularly successful in meeting the needs of the health  
8 of all peoples in the past several years, and that has  
9 engendered a number of responsibilities in the process of  
10 doing that, some of which are summarized in this overhead.  
11 The responsibilities include anticipating and responding to  
12 unmet medical needs; innovation, and using that to enhance  
13 existing products or indeed to develop new products; to  
14 deliver drugs efficiently by working with government and  
15 academia and policymakers and address the needs of all  
16 stakeholders, including patients, caregivers, prescribers,  
17 payers, and providers. The purpose and the focus of my  
18 discussion will really be on this piece here, which is  
19 enhancing the utility of existing drug products.

20 Next slide, please.

21 With respect to choosing an organism or  
22 identifying an organism, we spent a fair part of yesterday  
23 reaching agreement that *Streptococcus pneumoniae* meets the  
24 number of definition points that were rendered by several  
25 groups for a resistant organism based on the criteria of

1 MIC increasing, untoward clinical consequences resulting  
2 from this infection, with clear clinical syndromes  
3 available -- pneumonia, meningitis, otitis media. The  
4 public health concerns have been made with regard to the  
5 distribution of the morbidity and mortality from this  
6 disease or from this organism, and there is broad  
7 geographic distribution. We heard not only from this  
8 country, but indeed from WHO.

9 Treatment is currently limited for infections  
10 caused by these organisms. Therefore, what I'm saying,  
11 ladies and gentlemen, is that the stage is set for a  
12 solution to be provided for this particular problem, and  
13 I'm here to propose some.

14 Next slide, please.

15 What I'm saying is that we need to create a  
16 development scenario for this prototypic case. This case  
17 is a drug-resistant *Streptococcus pneumoniae*. The clinical  
18 syndrome that I'm proposing is acute otitis media. A  
19 target drug, prototypic drug, is a marketed beta-lactam  
20 antibiotic, and clinical trial design and regulatory issues  
21 regarding the approval of such a drug will use existing  
22 regulatory provisions, and that will address issues  
23 relating to claimed indication, labeling, and promotion.

24 So let me just go back to this organism. It  
25 represents very differently from all of the issues we

1 discussed yesterday with VRE and other isolates, an  
2 organism that clearly shows in vitro resistance with high  
3 MICs. There is no other mechanism that's involved there.  
4 Now, the drug in question may be able to demonstrate that  
5 high MICs can be abrogated by the use of high doses of the  
6 antibiotic.

7           Why do I choose otitis media? There was ample  
8 evidence from yesterday's presentation. CDC indicated that  
9 over 350,000 cases under two years of age may have otitis  
10 media due to this organism. The frequency of resistance  
11 has been mentioned to be probably as low as 5 percent or as  
12 high as 30 percent.

13           Otitis media is a nice, neat diagnosis to study  
14 because it represents a unimodal population in several  
15 regards. The patients are clean, relatively speaking.  
16 They do not have the comorbidities that were talked about  
17 yesterday. They do not, therefore, have the confounding  
18 variables that will impact pharmacokinetic or  
19 pharmacodynamic parameters.

20           With regard to the targeted drug, a marketed  
21 beta-lactam antibiotic, I am advocating something that  
22 already has a robust database for safety and efficacy, that  
23 has in vitro and in vivo criteria that have been met  
24 previously.

25           Next slide, please.

1           So how do we then further develop this  
2 prototypic beta-lactam agent currently marketed? There are  
3 still going to be the known clinical data that should be  
4 developed for the purpose of establishing that the proposed  
5 higher dose will overcome the in vitro resistance that has  
6 been described. The same proposed higher dose and  
7 formulation should be able to meet in relevant animal PK/PD  
8 models and models for infection a confirmation that, just  
9 as in the penicillin-sensitive arena, this new drug dose  
10 will be effective against these resistant organisms, and in  
11 human models, in the human situation, it is necessary also  
12 to conduct the relevant PK/PD models to again demonstrate  
13 that this drug with the new dose meets the expectation for  
14 a requirement of therapeutic efficacy, as have been very  
15 well described by George Drusano, Mike Dudley, and Mr.  
16 Chairman yesterday, and other contributors.

17           So having done these nonclinical studies, our  
18 proposal is that there should be really a need to conduct a  
19 clinical trial. That clinical trial should essentially be  
20 sized for safety, the safety of the new formulation  
21 compared to the previous existing formulation. There may  
22 be a reason to have some efficacy variables, but it cannot  
23 meet all the efficacy parameters. Then finally, there  
24 should be conservation to conduct bacteriologic efficacy  
25 studies, but I don't believe that that should be completed

1 before an approval is given.

2 Next slide, please.

3 Having met those earlier conditions, with the  
4 exception of the efficacy trial, the prototypic drug should  
5 receive FDA approval under provisions that currently exist,  
6 Subpart H, which is currently reserved for serious and  
7 life-threatening illnesses. I believe, Mr. Chairman, that  
8 the resistance issue should be included under this  
9 category. So the drug will have met all the requirements  
10 according to this proposal or according to this provision  
11 for surrogate endpoints, and there will be a commitment to  
12 do a specific clinical efficacy study.

13 Of course, there are withdrawal procedures and  
14 advertising and promotion steps that insure that the FDA  
15 will have the ability to limit the distribution and use of  
16 this new formulation or new drug.

17 Next slide, please.

18 Now, the labeling will include statements on  
19 nonclinical data, including the PK/PD resistance. There  
20 should be clear indication of the safety of the new drug  
21 compared with the existing safety profile that has been  
22 seen previously, essentially confirmatory, and subsections  
23 that address additional clinical data that may not yet meet  
24 the total burden of adequate and well-controlled studies.

25 Next slide, please.

1           Now, that bacteriologic efficacy study is going  
2 to be ultimately very, very difficult to conduct. We've  
3 heard that even this morning again from Rex Williams, and  
4 yesterday from several people. Sheldon Kaplan ran down  
5 what it would take, the sample size it would take, to  
6 demonstrate a superiority study, but I want to make sure  
7 that everybody understands that superiority studies in this  
8 indication are probably not going to be feasible, and it's  
9 probably out of the question that equivalent studies which  
10 require higher sample size will be available.

11           So wide well-controlled clinical trials will be  
12 the gold standard. We're in an era where that cannot be  
13 the only option, and I've mentioned a couple of other  
14 options here. In particular, the comparator should include  
15 medically appropriate agents if we use a comparator, and  
16 the previous formulation of the drug in question certainly  
17 should be considered as a comparator.

18           Next slide, please.

19           The patients who should be included in this  
20 study are not only those who have the pathogen of interest,  
21 the resistant pathogen of interest, but a population of  
22 children who are very likely to have the organism of  
23 interest.

24           As for the number of evaluable patients or  
25 pathogens, Dr. Chikami advised us earlier today about the

1 number of 10 or higher, and I'm suggesting that while it is  
2 difficult to advocate any specific numbers, when I do the  
3 math to arrive at five evaluable patients with the given  
4 organism, the resistant organism, in a comparative trial,  
5 we're talking about a minimum of several hundreds, if not  
6 between 1,000 and 2,000 patients. Consideration should be  
7 given to pooling organisms from different infection sites.

8 Next slide, please.

9 Also, enrichment studies or enrichment methods  
10 in terms of going to areas where the organism is prevalent  
11 should be considered. In this particular arena, a preentry  
12 tympanocentesis should be performed, and a confirmatory one  
13 for the strict purpose of documenting bacteriologic  
14 eradication should be conducted when the organism in  
15 question is isolated from the pretreatment sample.

16 Next slide, please.

17 So having done all of that, we meet what Dr.  
18 Chikami earlier addressed as substantial evidence of safety  
19 and efficacy, and full labeling and full promotion.  
20 However, it is very difficult and we all agree that this is  
21 not accomplishable in the short term.

22 Let's go to the last slide, please.

23 So what I have attempted to do here is to  
24 indicate to you that the development of antibiotics for  
25 resistant pathogens should be made as pragmatic as the

1 current environment dictates. We can certainly use  
2 existing regulatory provisions which are practiced in other  
3 therapeutic areas into anti-infective drug products.

4 Currently marketed antibiotics are appropriate  
5 for suitable modifications for short-term solutions to the  
6 question of antibiotic resistance. Longer term, new drugs,  
7 and perhaps vaccines, specifically for this infection are  
8 the target, but the lead time for that is measured in a  
9 question of five to 10 years, whereas this is  
10 accomplishable within a reasonably short time.

11 Thank you.

12 (Applause.)

13 DR. CRAIG: Thank you, Vince.

14 The next presentation will be by Andrea  
15 Meyerhoff, medical officer for the FDA, on "Resistant  
16 Pathogens: Where Are They?"

17 DR. CHIKAMI: Dr. Craig?

18 DR. CRAIG: Yes?

19 DR. CHIKAMI: Can I just make a point of  
20 clarification? I think the statement about the number of  
21 organisms, I think what the points to consider document  
22 states is that within the context of a controlled clinical  
23 trial, such as for pneumonia, when analyzing the subset of  
24 specific pathogens, that the guidance is either 10 percent  
25 of the total number of isolates or 10 organisms, whichever

1 is greater. So in fact in the setting of a trial, if you  
2 have 600 patients, all of whom have microbiologic isolates,  
3 then the number would be 60, not 10. So just to clarify  
4 that point.

5 DR. MEYERHOFF: Good morning. In 1998, I think  
6 that we can say that resistant pathogens have emerged, and  
7 indeed many are among us in force. As we've heard this  
8 morning and as we've heard previously, particularly at our  
9 meeting in July of this year, many sponsors developing  
10 agents to treat these infections report considerable  
11 difficulty in finding enough isolates to provide adequate  
12 clinical trial data to support drug efficacy. Today, I'd  
13 firstly like to characterize this problem and then discuss  
14 some proposed solutions.

15 Data from the SENTRY surveillance study provide  
16 us with a recent snapshot of the epidemiology of resistance  
17 among certain important gram-positive pathogens. This  
18 subject was reviewed comprehensively by a couple of our  
19 speakers yesterday, and what I'd like to do now is focus  
20 particularly on the first entry on this slide, and that is  
21 resistant strep pneumoniae.

22 In the SENTRY database, nationwide somewhere  
23 between 30 and 40 percent of pneumococcal isolates were  
24 deemed nonsusceptible to penicillin. A little more than  
25 half of these fell into the MIC range that is traditionally

1 regarded as intermediate susceptibility and a little less  
2 than half truly resistant. That is, with an MIC value of  
3 greater than 2 micrograms per mL.

4 Next slide, please.

5 For several of these resistant pathogens,  
6 resistance is outpacing drug development. This was well  
7 illustrated by Alexander Tomasz in a 1994 editorial to the  
8 New England Journal, where he pointed out that the  
9 pneumococcus is accelerating in its ability to outstrip the  
10 effectiveness of the available agents we have to treat it.  
11 He particularly pointed out that cefotaxime resistance was  
12 acquired even more rapidly by the pneumococcus than was  
13 penicillin resistance, and that the situation with some  
14 pneumococcal infections was approaching that of the  
15 situation presented by multidrug-resistant staph aureus.

16 Next slide, please.

17 This slide depicts graphically the rate of  
18 resistance in the early part of the 1990s to cefotaxime  
19 among pneumococcal isolates and how that compares to  
20 penicillin. What I'd like to call your attention to is in  
21 1991 the rate of cefotaxime resistance was somewhere around  
22 1 percent of pneumococcal isolates, and progressed to about  
23 10 percent at the end of that interval 1996. That's a 10-  
24 fold increase in resistance, where for penicillin  
25 resistance went from about 5 percent to 20 percent, or a

1 four-fold increase in the same time period.

2 Next slide.

3 The problem of scarcity of resistant isolates  
4 in clinical trials was articulated repeatedly in the  
5 meeting between representatives of industry and FDA in July  
6 of this year. I heard more than one account of trials  
7 attempting to enroll 1,000 or more patients, only to come  
8 up with perhaps 10 patients with the resistant clinical  
9 isolate of interest. I think in the best case scenario we  
10 could estimate approximately 1 percent of study patients  
11 had a resistant pathogen that could be studied.

12 Next slide, please.

13 Three questions arise when we try and address  
14 this problem. If clinical isolates are hard to find, are  
15 clinical trial data always needed? If they are needed, how  
16 might trial design be improved to study the populations of  
17 interest? How might drugs for resistant pathogens be  
18 developed when clinical trial data are needed and are  
19 scarce? I'd like to explore the implications of each of  
20 these questions individually.

21 When we consider the necessity of clinical  
22 trial data, I'd like to think about a special case. The  
23 pneumococcus has elaborated a resistance mechanism to a  
24 clinically important class of drugs, the beta-lactams, by  
25 alterations in penicillin-binding proteins. In vitro data

1 on the mechanism of action of quinolones tells us that this  
2 class of drugs acts by binding to one or more bacterial  
3 topoisomerases, and suggests that changes in penicillin-  
4 binding proteins will not affect the activity of  
5 fluoroquinolones.

6           There are several quinolones currently marketed  
7 for which clinical trial data support drug efficacy against  
8 penicillin-susceptible strains of pneumococcus. In vitro  
9 data exist demonstrating that the drug mechanism of action  
10 is unaffected by the pathogen mechanism of resistance.  
11 Could in vitro testing of resistant clinical isolates from  
12 some number of patients be substituted for efficacy data  
13 from prospective clinical trials?

14           Next slide, please.

15           As we think about the need for clinical trial  
16 data in this special case of a drug with a mechanism of  
17 action that is unaffected by the organism's mechanism of  
18 resistance, I'd like to raise a few points for your  
19 consideration.

20           The epidemiology of resistance may suggest a  
21 special patient population. We've seen this illustrated  
22 with the vancomycin-resistant enterococcus, more likely to  
23 be found and studied in the intensive care unit than are  
24 vancomycin-susceptible enterococcal isolates. The patient  
25 population likely to yield VRE for study is perhaps sicker

1 than the patient population infected with VSE.

2           There may be more than one mechanism of  
3 resistance. While fluoroquinolones appear not to be  
4 affected by alterations in penicillin-binding proteins,  
5 there are data that suggest certain gram-positive organisms  
6 elaborate resistance to quinolones by the presence of an  
7 efflux pump, a more generic resistance mechanism which may  
8 affect more than one class of antibiotics.

9           As we consider the necessity for clinical trial  
10 data for any combination of bug and drug, we need to ask  
11 ourselves is there any link between resistance and  
12 virulence?

13           If in vitro testing of clinical isolates were  
14 an adequate substitute for prospective clinical trial data,  
15 how many isolates are enough?

16           Next slide, please.

17           If clinical trial data are needed, I think two  
18 questions can be raised. How might the trial design be  
19 improved to study the populations of interest? That is,  
20 those patients infected with the resistant pathogen of  
21 interest. How might drugs for resistant pathogens be  
22 developed when clinical trial data are scarce?

23           Next slide, please.

24           To address the first of these questions, I'd  
25 like to focus on two epidemiologic surveys from the 1990s

1 that look at pneumococcal resistance in the U.S. One of  
2 these was undertaken by the CDC, the other supported by  
3 industry.

4 The first of these is summarized on this slide.  
5 It is a study undertaken by the CDC for 10 months of the  
6 calendar year 1994, studying invasive clinical isolates  
7 from hospital laboratories in the Greater Atlanta area.  
8 The break points for intermediate and truly resistant  
9 pneumococcal isolates are as you see on this slide. Four-  
10 hundred and thirty-one isolates were available for study.  
11 Twenty-five percent of them were determined to be not  
12 susceptible to penicillin, 18 percent fit the definition of  
13 intermediate susceptibility, and 7 percent truly resisted.  
14 That is, an MIC value of greater than 2. Of all of these  
15 invasive isolates, 96 percent came from the blood.

16 One demographic group was identified as being  
17 particularly high risk for infection with resistant  
18 pneumococcal isolates, and that is white children under the  
19 age of six. Suburban residence was also identified as a  
20 risk factor.

21 Next slide, please.

22 A second survey, published by Thornsberry and  
23 coworkers, encompassed 45 states and the District of  
24 Columbia from the end of 1996 through early 1997. Clinical  
25 isolates from a wide variety of hospital microbiology labs

1 were studied. Rather than randomly selected, each  
2 laboratory was asked to work up 50 current isolates  
3 associated with respiratory disease. The break points were  
4 similar to, although not identical to, those used in the  
5 CDC study, and over 9,000 pneumococcal isolates were  
6 identified. About a third of them were not susceptible to  
7 penicillin, a little more than half met the criteria for  
8 intermediate susceptibility, and a little less than half,  
9 approximately 14 percent, high-grade resistance. The  
10 highest risk was found in the larger institutions, those  
11 with 600 to 1,000 beds. Of clinical isolates associated  
12 with respiratory disease, 59 percent came from sputum and  
13 21 percent from blood.

14           These epidemiologic studies are showing us very  
15 different numbers from those cited by drug developers who  
16 seek to study disease caused by resistant pathogens. The  
17 two epidemiologic surveys are showing 25 and 33 percent  
18 penicillin nonsusceptibility, with 7 and 14 percent high-  
19 grade resistance. Our colleagues in the pharmaceutical  
20 industry, despite what appear to be herculean efforts to  
21 study patients with resistant pathogens, are perhaps able  
22 to identify them in 1 percent of patients enrolled.

23           As we consider this disparity, I think we need  
24 to recognize that there are very different denominators in  
25 these populations. Patients who meet the entry criteria

1 for clinical trials are often defined by a clinical  
2 syndrome, such as community-acquired pneumonia. Of that  
3 population, some proportion have a bacterial infection. A  
4 smaller proportion are infected with a pathogen of a  
5 particular species of interest, and an even smaller number  
6 are infected with resistant strains of that species. The  
7 clinical study population that is defined only by a  
8 clinical syndrome can be viewed as quite dilute with  
9 respect to resistant pathogens.

10 Next slide, please.

11 To further illustrate the variability of the  
12 rates of pneumococcal resistance, I'd just like to show  
13 this slide from the CDC's nine surveillance sites from the  
14 1995-96 surveillance period. You can see that rates of  
15 pneumococcal resistance range from a low of 8 percent in  
16 the Greater Toronto area to as much as a third of clinical  
17 isolates in the Southeastern United States.

18 Next slide, please.

19 Depending on how one defines one's search for  
20 resistant pneumococcal isolates, different sites of the  
21 body will have higher yield. This pie chart represents the  
22 body sites contributing pneumococcal isolates from the CDC  
23 survey I've been describing. The yellow portion of the pie  
24 shows you that an overwhelming majority come from the  
25 blood.

1                   Next slide, please.

2                   Similarly, the Thornsberry database studying  
3 respiratory isolates is showing us that certainly a  
4 significant number come from the blood, as well as from the  
5 sputum.

6                   Next slide, please.

7                   So how might trial design be improved to study  
8 these patients with resistant pathogens? Some of the  
9 epidemiologic data I've presented suggests that study  
10 populations might be enriched by certain strategies. We've  
11 seen that certain geographic locations are more likely to  
12 yield resistant pneumococcal pathogens. This includes  
13 particular parts of the U.S., as well as making the  
14 distinction between urban and suburban communities.  
15 Certain age groups may also be more likely to be infected  
16 with resistant isolates. The contribution of blood culture  
17 isolates in both of the surveys I've described suggests  
18 that inpatients, rather than outpatients, may be more  
19 likely sources of these organisms. Certain body sites, as  
20 we've seen, are particularly high yield.

21                   We can consider this idea of differences in  
22 denominators when we think about possibly enriching this  
23 clinically defined study population, perhaps with rapid  
24 diagnostic techniques that tell us early on which patients  
25 could be infected with the resistant organism of interest,

1 or perhaps even the species of interest.

2 Next slide, please.

3 There are other observations from the medical  
4 literature that suggest other patient populations who may  
5 be more likely to yield resistant isolates, such as those  
6 who have failed prior treatment, those with a history of  
7 daycare exposure, or multiple courses of antibiotics.

8 The idea of pooling organisms has been  
9 suggested repeatedly. Pooling means that very few isolates  
10 can be culled from any one site. Is it possible to get  
11 enough isolates for clinical study by prospectively  
12 designing a trial where it is planned to study patients  
13 with infections at several body sites, cull a small number  
14 from each of those, and make an overall evaluation of drug  
15 efficacy by the sum of isolates under study?

16 Next slide, please.

17 As we consider the prospect of pooling, I'd  
18 like to raise a few questions. Might it be more  
19 appropriate to pool across sites that are all normally  
20 sterile? Might it be more appropriate to pool across sites  
21 all in the same body system, such as the respiratory tract?  
22 Might it be preferable to pool across sites none of which  
23 are closed spaces? Might it be appropriate to pool across  
24 studies, some of which may have very different design? Can  
25 more serious indications, such as community-acquired

1 pneumonia, be used to support less severe disease, such as  
2 acute bacterial exacerbation of chronic bronchitis?

3 Next slide, please.

4 There may be settings where pooled efficacy  
5 data support an efficacy claim. A corollary of this  
6 concept is the organism-driven indication. Drug X is  
7 effective in the treatment of Organism Y in community-  
8 acquired pneumonia, sinusitis, otitis.

9 As such a strategy is considered, it's  
10 important to bear in mind that the relationship between the  
11 host, the pathogen, and the drug can differ in different  
12 tissues. Some examples, pneumococcal isolates from the  
13 respiratory tract are more resistant, on the whole have  
14 higher MICs, than those from the blood; staph aureus  
15 replicates faster in extracellular, than in intracellular,  
16 environments; the pathophysiologic significance of  
17 enterococcus in the bloodstream differs from that in a  
18 polymicrobial intraabdominal infection. It's also  
19 important to recognize that data resulting from a study  
20 with an organism-driven design will have very different  
21 implications for labeling.

22 Next slide, please.

23 How might drugs for resistant pathogens be  
24 developed when clinical trial data are scarce? There are  
25 two concepts I'd like to look at when N is small. One is

1 the statistical power of small numbers. The other is the  
2 concept of a hierarchy of types of evidence.

3 Next slide, please.

4 A question that is repeatedly asked of the  
5 review divisions when clinical isolates are scarce is how  
6 many isolates are enough? Many factors suggest that this  
7 number may differ for different bug and drug  
8 combinations, but if we assume for a moment that all other  
9 factors are equal, we can look at the conclusions that can  
10 be drawn from point estimates of efficacy in a few small  
11 study populations.

12 The left-most column on this table shows  
13 samples sizes of 10, 15, and 20 patients. The next column  
14 over shows us some success rates we might like to see, and  
15 point estimates of efficacy that can be drawn from those  
16 populations. I think if we look at sample sizes of 10 and  
17 the lower and upper bounds of the 95 percent confidence  
18 interval that a point estimate of 90 percent provides, we  
19 see that there is not a lot of precision in that point  
20 estimate.

21 When we look at sample sizes of 15, the width  
22 of the confidence interval is somewhat improved, but we  
23 also see that there is considerable risk in a small N.  
24 That is, that one less successful outcome can markedly  
25 affect the confidence interval around the point estimate,

1 and therefore our assessments of the drug efficacy.

2 Next slide, please.

3 During our meeting in July and again during our  
4 discussions yesterday, the concept of a hierarchy of types  
5 of evidence was raised. In the absence of prospective  
6 clinical trial data, can we consider a small number of  
7 cases infected with the organism of interest supported by  
8 pharmacokinetic and pharmacodynamic data, as well as  
9 microbiology data, that are consistently affirming drug  
10 efficacy?

11 Next slide, please.

12 I'll turn one more time to the case of the  
13 fluoroquinolones in community-acquired pneumonia due to  
14 penicillin-nonsusceptible pneumococcus. A, B, and C on  
15 this slide refer to three types of data. Choice A is some  
16 of the pharmacodynamics that we've heard about, such as the  
17 AUC over MIC value or the Cmax over MIC value, that can  
18 attest to drug efficacy or good clinical outcome. Choice  
19 B, clinical response in some number of patients infected  
20 with the resistant organism of interest. Choice C,  
21 documented clinical efficacy in penicillin-susceptible  
22 strains of pneumococcus.

23 Some of these combinations may be appropriate  
24 to support drug efficacy. For some, none. What would be  
25 enough data?

1                   Next slide, please.

2                   If we want to accept pharmacodynamic data, such  
3 as the AUC over MIC value or the Cmax over MIC value, what  
4 is an acceptable level? If clinical data from a small  
5 number of patients infected with the pathogen of interest  
6 can support efficacy, what is that number? If there is  
7 only a small number available, what body sites might be  
8 pooled to strengthen that study population?

9                   Next slide, please.

10                  Two questions arise from the presentations  
11 occupying the second half of this module. I'm going to  
12 state those two questions, though I understand we're going  
13 to return to some of the earlier questions this morning  
14 first.

15                  Question 1. What trial design strategies might  
16 enhance enrollment of patients with resistant organisms?  
17 Please consider pooling across body sites, targeted or  
18 enriched study populations, the use of rapid diagnostic  
19 tools, and any other enhancement strategies that have not  
20 been suggested.

21                  Question 2. Under what circumstances, if any,  
22 can we accept less clinical data for the evaluation of  
23 drugs to treat resistant pathogens?

24                  Thank you.

25                  (Applause.)

1 DR. CRAIG: Let's get back to the questions.

2 Yes, Dr. Bell?

3 DR. BELL: I'd like to follow up on the  
4 excellent summary by Dr. Meyerhoff and offer the comment  
5 that some simple demographic considerations might help to  
6 explain the difficulty in accruing patients as spoken about  
7 by Dr. Williams.

8 First, I want to reiterate that the CDC  
9 pneumococcal surveillance system, which is active  
10 population-based surveillance in nine regions, is really a  
11 Cadillac system in the world of surveillance. Every  
12 clinical laboratory in these regions is repeatedly queried  
13 actively regarding whether they have isolated a  
14 pneumococcus, and then that pneumococcus is tested for  
15 susceptibility using standardized methods. This system  
16 replaced an earlier sentinel system of one laboratory here,  
17 one laboratory there, because it was found that that early  
18 system gave misleadingly low results regarding the  
19 prevalence of resistance.

20 Now, the data from these population-based sites  
21 has indicated several things. One is, as has been  
22 mentioned, the prevalence on nonsusceptibility, as distinct  
23 from resistance, is in the range of 20 to 30 percent  
24 nationally and resistance at a lower rate than that. I  
25 don't have my numbers with me, but it's in the teens.

1           Several things have come to note. One is that  
2 the nonsusceptibility and resistance has been rising in the  
3 1990s and is notably higher now than it was in the early  
4 '90s. So, for example, when I look at the slide presented  
5 by Dr. Williams and find that about a third of the patients  
6 were enrolled in 1992 to 1994, it's quite possible to me  
7 that there might not have been as much resistance in that  
8 era.

9           We have also noted that for reasons that we do  
10 not understand the prevalence of resistance is much lower  
11 in Canada than it is here, so when Dr. Williams presented a  
12 row on his slide of U.S.-Canadian trials, I don't know what  
13 percent of the patients came from Canada, but it would have  
14 been expected to be a lower resistance.

15           The second row is European data from 1994 to  
16 1996, and that again is in the sort of middle, as opposed  
17 to late, '90s. I don't know the European data, but it's  
18 possible that there might have been just fewer resistant  
19 patients during that time period in those countries.

20           But the final comment that I think is the most  
21 telling is that we have found in our analysis of the U.S.  
22 data that there are notable differences between the inner  
23 city and the suburbs, with resistance being notably higher  
24 in the suburbs than in the inner cities. We have actually  
25 done zip code analyses of drug use data, antibiotic use

1 data, and pneumococcal resistance data, and there are  
2 donuts around all of the major cities with correspondence  
3 of higher antibiotic use in the suburbs, for a variety of  
4 reasons we could get into later, and also higher resistance  
5 in the suburbs. In addition, there are other factors, like  
6 nonwhite race, which is really probably a reflection of  
7 inner city, although not entirely, and then there is the  
8 fact that resistance is higher in children.

9 So Dr. Williams, I wonder what was the source  
10 of accrual of your patients? Because if it was the sort of  
11 study that was done using university investigators and  
12 inner city clinic populations, for example, then you might  
13 really have missed some opportunities to find these  
14 pathogens.

15 DR. REX WILLIAMS: Okay, and there are a number  
16 of issues that you raise. One, in 1992 to 1994, we were  
17 interested in supporting a general claim of community-  
18 acquired pneumonia, and the resistance issue was not  
19 something we had foremost in our minds in terms of finding  
20 resistant isolates. Those trials were more of an issue in  
21 1995 at the first FDA discussion of this issue, and then in  
22 the '96 through '98 trials, we did our trial, the big  
23 trial, the PRI-sponsored trial, with the idea of finding  
24 these isolates in mind. So in the '96 through '98 efforts,  
25 we went to centers where we had found either a high number

1 of intermediate or resistant isolates, and went back to  
2 those sites to place the '96 through '98 study.

3 Our experience for the 12 cases that we  
4 identified from the United States was that most of those  
5 cases came from what you would call suburban areas in South  
6 Carolina, as well as Kentucky and New Orleans. That's  
7 where the most number of sites were, and that kind of  
8 supports what we know about the distribution, at least in  
9 terms of the southeastern quadrant of the U.S. being more  
10 involved, for whatever reason.

11 The second criteria, really, in terms of  
12 selecting sites is really the motivation of the  
13 investigator and their capability. You can have the  
14 hottest spot in the world, but if you don't have a good  
15 investigator there, you're not going to accrue anything.  
16 So those were the two criteria in which we placed sites for  
17 the '96 through '98 trial.

18 In answer to an earlier comment you made about  
19 Canada, yes, you're right. We went to Canada and we found  
20 nothing. So I would encourage other companies not to go  
21 there.

22 (Laughter.)

23 DR. REX WILLIAMS: The Canadian sites enrolled  
24 about 100 patients, plus or minus 20. I don't remember the  
25 exact number. In the PRI trial, about 20 percent of the

1 patients came from Canada, and we found very little even  
2 intermediate resistance there, and maybe none, as far as I  
3 can remember.

4 Does that answer most of your comments or  
5 questions?

6 DR. BELL: It addresses some of them, sure.  
7 Thanks.

8 DR. CRAIG: Joan?

9 DR. CHESNEY: As a Canadian, I'd just like to  
10 say there are other things in Canada.

11 (Laughter.)

12 DR. CHESNEY: But I also wanted to confirm what  
13 Dr. Bell said. We did a similar study in Memphis, and you  
14 may have noticed that the highest percent in the country  
15 are in Memphis, and the highest percent in Memphis are in  
16 white suburban children. It's very, very striking, very  
17 similar to what you found in Atlanta.

18 DR. CRAIG: I think we want to get on to the  
19 questions, instead of necessarily identifying -- we can get  
20 to that when we get to the enhancement questions. So  
21 anybody that has something on that, when we get to that,  
22 let's do it.

23 But one of our consultants needs to leave, and  
24 so we need to get those topics covered. So again, on  
25 Question 1, which was talking about an adequate dose-

1 response trial, what I was hearing yesterday is that what  
2 one needed for an adequate dose-response trial was one that  
3 clearly resulted in variation in the dose-exposure  
4 response, and I think that there were suggestions of taking  
5 the PK/PD data, doing some simulations, so that if one was  
6 going to do this kind of trial design, one could insure  
7 that the doses that one was picking would actually have a  
8 good chance of varying the exposure, so that one would  
9 stand a chance of getting some meaningful data out of it.

10 But again, since the numbers would be  
11 relatively low with a relatively rare resistance mechanism,  
12 I think there were still suggestions that pharmacokinetics  
13 should still even be employed in those dose-response  
14 studies to try and again get additional PK/PD data that  
15 would support efficacy. At least, that's what I think I  
16 heard yesterday.

17 Barbara?

18 DR. MURRAY: Yes, I don't think I even  
19 commented on that yesterday. I must say, I listened to all  
20 the arguments yesterday and I heard it all, and it sounds  
21 to me like it's still just a guise for a placebo-control  
22 trial in a way, and if you're kind of using your PK to  
23 predict what's likely to show you your dose-response, I  
24 just get this feeling like you're asking to put a certain  
25 number of patients on a subtherapeutic dose.

1                   For it to have a comparison -- I can see a head  
2 shaking down there. I'm just telling you my reaction to  
3 this in terms of how it strikes me, and I have the concern  
4 that if you don't choose the dose right, then you're left  
5 with no answer. I don't have a solution to that.

6                   DR. CRAIG: Yes. I mean, it's the kind of  
7 thing I don't think you're going to do in bacteremia. The  
8 kind of infections that you would try and do this in, if  
9 you could, would be those in which mortality is essentially  
10 zero, so that if you did have a subtherapeutic response,  
11 it's not going to be terribly harmful to the patient.

12                   George, on this particular issue?

13                   DR. DRUSANO: Yes, just very briefly.

14                   I understand where you're coming from, Barbara,  
15 but at the end of the day, I think we have to be a little  
16 humble. No matter what we do with the dose and the  
17 exposure, we don't control the MIC of the organism that the  
18 patient is infected with, and since it is some hybrid of  
19 exposure relative to MIC, no matter what dose we choose we  
20 can never guarantee a greater than 98 percent, or whatever  
21 the number is, response rate. So any drug dose that we  
22 choose for such trials will be subtherapeutic in some  
23 patients owing to MIC.

24                   We have to, I think, have a responsibility to  
25 do exactly what Chairman Craig said, which is not choose

1 doses and not choose scenarios that are at excess risk, but  
2 to be able to choose doses and schedules that are likely to  
3 give us the information that we require.

4 DR. CRAIG: Dr. Murphy?

5 DR. MURPHY: I think I'd just like to also put  
6 a -- again, I think this brought up yesterday a slightly  
7 different perspective on it, in that often in the desire to  
8 make sure that they had effective dose, we actually get  
9 doses that are higher than we really do need, and so I  
10 think that there is a definite need or ability to look at  
11 various doses, and you just have to be careful and  
12 thoughtful in picking that you are into a level of toxicity  
13 at one end or a level that you really can anticipate will  
14 be subtherapeutic.

15 But I would say that actually one of the common  
16 concerns we have is that too high a dose has been picked,  
17 just because of the need to make sure that there is  
18 definite efficacy. In other words, you get toxicities you  
19 don't need. You could obtain efficacies without as much  
20 toxicity sometimes.

21 DR. CRAIG: Tom, did you have some additions  
22 here for this?

23 DR. FLEMING: Yes, I do, but I had a number of  
24 additions, so if there was a -- was there a single comment?  
25 Go ahead.

1 DR. RELER: Actually, it's a question that I  
2 wanted you to address, Tom. Intuitively, it would seem to  
3 me that with a graded dose-response design, that one would  
4 need larger numbers to get an answer, rather than smaller  
5 numbers, because you're subdividing the -- and all we've  
6 heard yesterday and today is the problem is small numbers  
7 of these resistant organisms, so I would like for you to  
8 address what seems to me to be a fundamental mismatch there  
9 in looking to that as an answer, as opposed to other plans.

10 DR. FLEMING: A good insight. That could  
11 definitely be true. The numbers that we need are driven by  
12 the magnitude of the effect that we're trying to detect,  
13 and if we were to do a placebo-control or standard of care-  
14 control against the addition of an intervention and you  
15 were anticipating a larger magnitude of difference than  
16 would be plausible than would be between two active, but  
17 differentially active, doses of the same agent, then the  
18 sample size would be much larger in that dose-response  
19 trial to the extent that you're having to detect smaller  
20 differences.

21 DR. RELER: Thanks.

22 DR. CRAIG: Go ahead.

23 DR. FLEMING: Time is short and the issues are  
24 many. What I'd like to try to do is provide some brief  
25 comments on, since we actually have four questions --

1 yesterday's questions were Questions 1 and 2, and the data  
2 safety monitoring board issue is one issue we haven't  
3 discussed as yet. We have discussed dose-response. If we  
4 could flash to Question 2 from yesterday's discussion,  
5 there are also these issues that pertain to active control  
6 or equivalence trial design, using standard of care-control  
7 designs, and in a standard of care setting, using single  
8 versus multiple standard of care. So I count that as five  
9 issues just in Questions 1 and 2, and what I'd like to do  
10 is take a few minutes and try to touch on each of these.

11 I'd begin by pointing out that in my view there  
12 are in fact several very relevant and informative designs  
13 that we can use in randomized comparative studies. We've  
14 talked at length now about this multiple dose scheme, and  
15 talked about some advantages that it provides and some  
16 disadvantages that it provides.

17 Touching quickly on the active control design,  
18 I think the active control design also certainly has a  
19 role. In particular, it's relevant when we're looking at  
20 an experimental intervention to be used, let's say, instead  
21 of a standard antimicrobial treatment, and it has a very  
22 practical, relevant aspect in that it allows us to compare  
23 head-to-head standard against the particular regimen that  
24 we're interested in if in fact we're thinking of replacing  
25 the standard with this agent.

1           There are some considerations, though. In  
2 order to be able to interpret an active control trial,  
3 there are some basic considerations that are key. The  
4 first is the active control needs to have a high level of  
5 efficacy, and secondly, a level of efficacy that is  
6 precisely defined, and particularly in the context in which  
7 this comparative trial is going to be done. So those are  
8 three major restrictions that are important in order to be  
9 able to interpret the results of an active control trial.

10           One other quick issue is I believe also we have  
11 to be careful to define a rigorous set of equivalence  
12 criteria. If, for example, the standard antimicrobial can  
13 deliver resolution of symptoms in 50 percent of patients,  
14 an equivalence trial is technically positive when you have  
15 ruled out all clinically meaningful differences, when you  
16 can say in fact I'm at least equivalent, that I have  
17 efficacy that is comparable or better. We do that by  
18 defining the smallest difference of clinical relevance and  
19 ruling that out.

20           Often we're inclined to say, well, if it's 50  
21 on standard of care, I only have to rule out that I'm 30  
22 percent or less. Well, is in fact 30 versus 50 truly  
23 clinically relevant? I think often we're too lenient on  
24 these differences, and probably in reality it's more toward  
25 ruling out that you're only 10 percent worse. Certainly,

1     though, as you get more rigorous about those differences,  
2     active control study designs can become very large studies.

3             A third approach is against a standard of care;  
4     i.e., where we have standard of care versus standard of  
5     care plus your experimental regimen, and in a context where  
6     that is a clinically relevant question -- i.e., where I  
7     would be thinking of using my new or experimental  
8     antimicrobial in addition to standard of care -- this  
9     design certainly is particularly relevant.

10            In many cases, we say, but we don't have a  
11     standard of care. We don't have a single standard of care.  
12     We may have several, as this issue up here is addressed.

13            From my perspective, that doesn't preclude  
14     doing a standard of care design. I think it is appropriate  
15     to allow some flexibility in what the standard of care is.  
16     In my view, a clinical trial should be designed in a way to  
17     address questions that are clinically relevant, and carried  
18     out in a way that addresses these questions to give answers  
19     that are relevant in the real world context. If in the  
20     real world context standard of care does differ somewhat  
21     from center to center, having some flexibility in allowing  
22     that difference to occur is, from my perspective,  
23     acceptable, and the rigors of the clinical trial are  
24     maintained if you're randomizing to site-specific standard  
25     of care versus the addition of the antimicrobial.

1           In a recent study in Oncology, by allowing that  
2 flexibility there was a major advance, in that we were able  
3 to see that the benefit of treatment was profound with a  
4 certain standard of care and it hadn't been with another.  
5 This kind of generalizability is certainly very helpful as  
6 well.

7           I might quickly point out that it would in fact  
8 not be ethical to randomize to a placebo or to no treatment  
9 if in fact standard of care has been shown to be  
10 beneficial. A single or combination of antimicrobial  
11 treatments, if it's been shown to be effective in a given  
12 setting, should in fact be the control regimen against  
13 which we would add the experimental intervention.

14           To the extent that that's true, it points out  
15 the weakness of doing an uncontrolled study; i.e., an  
16 observational study where you simply look at the addition  
17 of the new experimental regimen to an existing standard of  
18 care. It's difficult to interpret to what extent any  
19 beneficial effects seen are due to the experimental therapy  
20 versus the other existing standard of care regimens.

21           The fourth issue that I wanted to touch on  
22 relates to data safety monitoring boards, and certainly  
23 such boards can be extremely helpful in maintaining  
24 integrity and credibility of trials, and first and foremost  
25 in protecting the interests of participating patients.

1           What I'd like to do is to quickly give two  
2 examples to illustrate how these data safety monitoring  
3 boards have been influential in studies, and through these  
4 two examples bring out a couple of other issues, and that  
5 is is it possible to accrue in settings that we thought we  
6 couldn't, particularly in pediatric settings, and are  
7 placebo-controls not possible to be done, and what are the  
8 benefits of clinical efficacy versus surrogate endpoints?

9           So the two quick examples that I want to give  
10 are both from examples of anti-infectives in pediatric  
11 trials. The first study that I had a chance to serve on a  
12 data safety monitoring board for was a study in children  
13 with chronic granulomatous disease, and the interest was  
14 whether gammainterferon would be effective in that setting.  
15 It was anticipated that in the U.S. and Europe there may  
16 only be 500 to 1,000 cases, so a very rare setting, as we  
17 have been discussing in the meeting throughout the last two  
18 days. It was anticipated that a controlled trial would  
19 need 250 children in order to provide power adequate to  
20 detect effects on the clinical endpoint of reducing the  
21 risk of serious infections in these kids.

22           There was a data safety monitoring board that  
23 monitored the data and halfway through the study it found  
24 compelling evidence of benefit, the study was terminated  
25 early after only 125 children, and the study showed that

1 there was a three-fold reduction in the risk of serious  
2 infections to these children.

3           Interestingly, the study had originally been  
4 proposed to be much shorter, much smaller, and in some  
5 settings people said uncontrolled, because the argument was  
6 we can't give placebos to children and we can't accrue  
7 enough children when there are only 500 to 1,000 cases  
8 known in the U.S. and in Europe. In addition to that, we  
9 wanted to use a measure of biologic activity. The  
10 intention was to use bacterial killing and superoxide  
11 production based on the anticipated mechanism of  
12 gammainterferon.

13           Well, interestingly, the placebo-control trial  
14 could be done, the accrual was successfully completed in  
15 six to 12 months, and the results that actually showed a  
16 profound clinical effect when you stepped back and looked  
17 at biologic activity, there was no detectable effect of  
18 gammainterferon on bacterial killing or superoxide  
19 production.

20           So if the study had been done as a shorter  
21 trial using a biologic activity measure, an effective  
22 intervention in children would have been missed.  
23 Ultimately, later on there's a sense that the mechanism of  
24 action was other than what had originally been anticipated.

25           The second quick example is a study that I'm

1 currently serving on a data safety monitoring board for for  
2 treatment of meningococemia, another rare disease in  
3 children, with obviously a profound clinical consequence,  
4 20 percent mortality. The sponsor had done small  
5 historical control experiences and had shown some  
6 considerable difference in historical controls for the  
7 treated versus the untreated, and again the argument here  
8 was it would take years to accrue 25 to 50 children to a  
9 placebo-control trial with a mortality endpoint.

10 With persistence from the FDA and others, it  
11 was decided to conduct this trial. It's ongoing, I'm  
12 monitoring it, and I can't convey the results at this  
13 point, but what I can convey is that in 18 months we have  
14 now successfully accrued 350 when we were told that it  
15 would not be possible to accrue 25 to 50 children to a  
16 placebo-control trial.

17 Both this meningococemia trial and the chronic  
18 granulomatous disease studies have pointed out the  
19 invaluable role that DSMBs can play, the fact that you can  
20 in some instances and should in some instances consider  
21 placebo controls, even in the setting of infants. You can  
22 accrue to studies when, at least at first pass, it's stated  
23 that you're not going to be able to accrue. We found that  
24 in many cases you can, and ultimately also having clinical  
25 efficacy endpoints is critical.

1           In tying up my comments, I'd like to just close  
2 on this point, and that is I would like to reinforce some  
3 comments that have been made that it is critical whenever  
4 possible to establish effects on clinical endpoint  
5 measures, on mortality, on clearance of symptoms,  
6 hospitalization. Biologic activity measures, such as  
7 clearance of bacteria, are certainly important measures of  
8 biologic plausibility, but ultimately we should whenever  
9 possible be addressing the actual effects on clinical  
10 efficacy.

11           The final comment is when we do such a study  
12 that does look at clinical efficacy endpoints, we need to  
13 measure the endpoint in all people. It's not adequate to  
14 measure the endpoint only in those people that have  
15 sufficient treatment duration with no adverse events that  
16 haven't received prohibitive concomitant medications and  
17 who die early. By the time you've excluded all of those  
18 people, you've lost the integrity of randomization, so it's  
19 important to design studies that will adequately address  
20 what the actual efficacy is on clinical efficacy endpoints  
21 following all of the people to those endpoints.

22           Thank you.

23           DR. CRAIG: Any other comments from any of the  
24 members? I think one of things that I think we would have  
25 difficulty with, or at least I would see problems with

1 antimicrobials, is in the way that you were doing the  
2 standard of care design, where you were adding on the drug.  
3 The other standard of care is also probably an  
4 antimicrobial agent, and oftentimes what they're trying to  
5 do is to get the drug approved for susceptible organisms as  
6 well as for resistant organisms.

7 I can think, for example, in meningitis  
8 probably the standard of care would be a third-generation  
9 cephalosporin plus vancomycin in areas where resistance is  
10 common. That has a very high degree of potential success,  
11 at least microbiologic success, and I think in that  
12 situation it would probably be what the companies would  
13 want to do was compare their agent with that, and if you've  
14 got such high efficacy, I think probably what you're really  
15 looking for in that situation would be equivalence.

16 I think, just looking at some of the questions  
17 that were asked here about equivalence versus superiority  
18 in Question 2, I think obviously if the success of your  
19 standard of care is very high, exceedingly high, it's going  
20 to be very difficult to try to get superiority.

21 On the other hand, if your standard of care,  
22 outcomes, are relatively on the low end, then, sure,  
23 superiority we would like to be. However, it may be  
24 superiority not necessarily in efficacy, but it might be  
25 some superiority in toxicity, that the standard of care

1 doesn't work very well, but it is quite toxic, while  
2 something new might come along that works about the same,  
3 but is clearly less toxic.

4 DR. FLEMING: That's a key point. In fact, the  
5 distinguishing characteristics to me, as I think of whether  
6 I would advocate an equivalence trial versus a superiority  
7 trial, relate to what it is that I'm trying to achieve. If  
8 I believe standard of care can be improved on and should be  
9 improved on, and I would be intending to do so by the  
10 addition of my agent to standard of care, then the  
11 superiority trial is the obvious approach.

12 On the other hand, as you say, Dr. Craig, if  
13 the goal is to say, all right, standard of care, the active  
14 control agent is out there, it's either highly effective or  
15 moderately effective, but I believe I can obtain a better  
16 overall risk/benefit profile by having the equivalent level  
17 of efficacy using my agent instead of the standard, and in  
18 particular motivated either by the anticipation that we  
19 will be less toxic, we will be easier to administer, or we  
20 will be more cost-effective, any of those kinds of features  
21 put on top of equivalent efficacy against the active  
22 control would give you a favorable profile, and that's the  
23 kind of setting that would typically motivate the  
24 equivalence or active control design.

25 DR. CRAIG: Janice?

1 DR. SORETH: I think that whether we're talking  
2 about a dose-response or a dose-ranging trial, or one in  
3 which we would employ a standard of care, that although  
4 beating the standard of care, or one dose beating another  
5 of a test drug, is a clear win, the converse is not true.  
6 That lack of showing superiority or showing equivalence is  
7 not a clear loss, that these other factors that we have  
8 spoken of -- toxicity issues, and perhaps looking at  
9 endpoints beyond the traditional endpoints of bacteriologic  
10 eradication, and clinical cure versus failure, time to  
11 resolution of symptoms, and things like that -- have to be  
12 taken into account.

13 But what we are trying to do is I think steer  
14 away from what has been put forth as the only thing we can  
15 do is an uncontrolled trial, because then I think we can't  
16 even deal with some of these other less traditional  
17 endpoints. We won't have anything to compare it to.

18 I think certainly with a standard of care in  
19 which the test drug is not shown to be superior to the  
20 standard of care, we have to then look at the body of  
21 evidence that motivates one and enables one to use that  
22 standard of care as a control regimen, that gives you the  
23 basis to say, "I believe that this drug or combination of  
24 drugs has efficacy and acceptable toxicity, though it is  
25 not FDA-approved," and that's the kind of thinking that

1 goes into choosing a standard of care or standards of care.

2 DR. CRAIG: Any other comments from anyone  
3 around the table on Questions 1 and 2?

4 (No response.)

5 DR. CRAIG: Any other questions or comments  
6 about 1 and 2 from people in the audience? Is this about 1  
7 and 2?

8 PARTICIPANT: Yes.

9 DR. CRAIG: Okay. Quick, go ahead.

10 PARTICIPANT: I would like just to challenge  
11 the concept of standard of care as we discussed. I think  
12 it's obvious that the standard of care definition will be  
13 very difficult to establish, and so far there is no  
14 privileged material, I think, nationwide regarding what  
15 could be the standard of care regarding, for instance, VRE  
16 infections, and these standards of care may also vary from  
17 one patient to another patient. It's not only from one  
18 institution to another institution. Therefore, I guess it  
19 will be very difficult, again, to in a very valid way  
20 compare the efficacy of our drug to what the so-called  
21 standard of care means.

22 The second point is about also how to cover the  
23 safety profile of your drug when you will have so many  
24 different regimens out there.

25 The third point is about in terms of logistics.

1 The standard of care for many patients will be also the  
2 best therapeutic options, and for some patients right now  
3 regarding VRE, it's for these patients to go to some  
4 emergency use protocol, like Synercid programs, which have  
5 their own criteria for enrollment, and therefore what's  
6 important for the patients and for the site to be enrolled  
7 in a kind of dose comparative trial of this kind. So in  
8 our mind, I think the Chinese milieu, unless it's  
9 glutamate-free, will be rather indigest regarding what we  
10 are proposing right now.

11 DR. CRAIG: Tom?

12 DR. FLEMING: What is the goal here? And if  
13 the goal is to determine whether or not the addition of  
14 your experimental agent to what is current standard of care  
15 practice yields a clinical benefit, then the design should  
16 be specified in a manner to address that question, and it's  
17 cleanest and preferable if there is a consensus on what  
18 that standard of care is.

19 On the other hand, in many real world  
20 situations, there isn't, and to the extent that we can at  
21 least somewhat focus the issue -- i.e., we don't have to  
22 come up in my view with a single standard of care, but to  
23 the extent that we can focus it somewhat to a certain well-  
24 defined number of regimens that would be used, in my view  
25 the insight that we would gain from such a design, even

1       though it wouldn't be as simple as against a single  
2       standard of care, would still be very important and in a  
3       certain sense is more generalizable, because you're looking  
4       at the comparison against a real world spectrum of what  
5       standard regimens would be.

6                A slightly larger sample size is necessary to  
7       address that variability that exists, but the integrity of  
8       that design is valid. There is in fact an unbiased and  
9       valid assessment that you would make if you would show  
10      superiority in such a design, and if we had time, there are  
11      certainly other illustrations where this has been done  
12      successfully.

13               DR. CRAIG: Dr. Reller?

14               DR. RELLER: Tom, in following that up, it  
15      seems to me when there is controversy over standard of  
16      care, there are basically two reasons. One is there's real  
17      doubt that any of them work, and secondly, that with expert  
18      guidance that one could boil it down to two or three things  
19      that are not perceived to be appreciably different, but  
20      probably have some efficacy that would lead to several, but  
21      not innumerable, standards of care that could be employed  
22      in a trial.

23               If it's the former and there is real doubt that  
24      any of them are any good, isn't this the time that one  
25      would ideally employ a data safety monitoring board

1 approach?

2 DR. FLEMING: I would argue that a data safety  
3 monitoring board would be imperative in all of these  
4 designs that we've talked about. It may well be, as you're  
5 pointing out, that the standard of care that we might use  
6 if there are disagreements and a myriad of them, some of  
7 them may be more or less effective and some of them  
8 relatively ineffective.

9 The key issue here is in this design, where  
10 we're looking at standard of care versus standard of care  
11 plus your agent and you're showing superiority, the  
12 conclusion of efficacy does not require your specific  
13 knowledge that all of those specific standards of care that  
14 you're using in your control are effective. In fact, in a  
15 worst case scenario, where they're all ineffective, it's  
16 the same as a placebo against placebo plus active  
17 intervention. The key is here you're showing superiority.

18 Where I have concerns about the point that  
19 you're making is in an active control design. If I'm  
20 looking at one or a selection of standards of care against  
21 which I'm going to compare my experimental agent, and I'm  
22 trying to show equivalence, I worry if I'm showing  
23 equivalence to something that's ineffective. That's why I  
24 was arguing in the beginning there are some critically  
25 important conditions that must be met in doing an

1 equivalence trial. Your active control comparator must be  
2 very efficacious with a precisely known level of efficacy  
3 in the specific setting in which you're doing the trial.

4 So your concern about potentially diverse  
5 standards of care, some of which would be potentially  
6 ineffective, is a major concern in an active control  
7 design, but I don't view it to be a problem in a  
8 superiority design.

9 DR. CRAIG: Dr. Gerding?

10 DR. GERDING: Just to use an example, I'm still  
11 having a problem with this design here of a standard of  
12 care and an add-on agent. Let's say for VRE that your  
13 standard of care is high-dose ampicillin or high-dose  
14 amcillbactam, and you were to add on an agent here to your  
15 standard of care like lamayzalide or Synercid, and you were  
16 now looking for superiority in that study.

17 I guess if you did show superiority I wouldn't  
18 be sure whether the combination of the standard of care  
19 plus the new agent was the new superior regimen or whether  
20 the new agent was the new superior regimen, and I don't  
21 know how you would interpret that study in light of the new  
22 agent. In other words, every time a new agent is used, do  
23 you now have to use the previous standard of care with it  
24 in order to show efficacy? How do you address that kind of  
25 a question?

1 DR. FLEMING: A valid point. If you choose  
2 some specific antimicrobial as your standard of care in VRE  
3 and you add the new agent to it, what you have proven is  
4 that the new agent provides added benefit to that base or  
5 to that specific standard of care. So the combination has  
6 been proven to be efficacious and more efficacious than the  
7 single-agent antimicrobial, and to the extent that I'm  
8 comfortable that that single agent wasn't harmful, I have  
9 the conclusion that the combination is efficacious, but in  
10 fact, you're right. That's really the essence of what I  
11 have proven.

12 DR. GERDING: And then to carry it one step  
13 further, if you were doing an active drug comparator, you  
14 would have the problem of is the high-dose, say, ampicillin  
15 or amcillbactam actually a very efficacious treatment --  
16 something that I think we're still debating somewhat -- and  
17 if you showed superiority to that, would you really have  
18 shown clear superiority? Is that a rational kind of  
19 comparator that might get you useful information and  
20 actually impress the FDA that this is a better product?

21 It seems to me you have another issue there,  
22 that you might do that and you might show superiority, but  
23 then somebody might come along and say, well, your standard  
24 comparison drug here really wasn't very good to begin with  
25 or something like that.

1 DR. CRAIG: Mark?

2 DR. GOLDBERGER: I'll make a couple of comments  
3 in response to what you said. The first issue you raised,  
4 if you used the two products together, I think we would  
5 anticipate that unless you had other data that in fact the  
6 product labeling would say to be used in combination with.  
7 It would describe basically what the clinical data were.

8 As for the second point, presuming you were  
9 superior to, say, the ampicillin amcillbactam by itself,  
10 unless one believed that that regimen was beyond being  
11 ineffective -- that is, that it actually had reduced  
12 effectiveness over, perhaps, nothing -- then one would I  
13 think believe that superiority to it was still useful.

14 Unfortunately, at times that issue of what a  
15 regimen could do is unclear. Normally, as part of the  
16 development plan, we like to see information, and obviously  
17 in some of the areas it's not as good as we would always  
18 like to justify what's being used, for instance, as the  
19 control. Obviously, it's not going to be perfect  
20 information, but at least that there is some basis for  
21 selecting this as a control, so we don't get into that  
22 problem after the clinical trial is done.

23 DR. CRAIG: I think we need to move on to  
24 Questions 3 and 4, which are 1 and 2 for today, in order to  
25 make sure that we get those covered, and specifically

1 discuss trial designs that might enhance enrollment of  
2 patients with resistant organisms. Rapid diagnostics is  
3 the first one. Anyone want to take that on? Yes? Go  
4 ahead, then, Gordon.

5 DR. ARCHER: No. Yes.

6 DR. CRAIG: No one wants to take it on.

7 DR. ARCHER: Yes, it's good.

8 (Laughter.)

9 DR. CRAIG: Well, I mean, where is it going to  
10 be applicable to? I guess right now the potential would be  
11 for MRSA in terms of using gene probes to enhance the  
12 identification of methicillin-resistant staph, so that you  
13 might possibly then be able to, if you wanted to just get  
14 that indication, do that, but I would think most people  
15 would be going after both.

16 The one advantage that maybe gene probes would  
17 have where there is some question about the  
18 pharmacodynamics, at least if you are able to identify the  
19 organism relatively early, then you could include some  
20 pharmacokinetics into the trial design, so that you could  
21 get more data specifically in terms of PK/PD in  
22 relationship to those potential organisms, and not need to  
23 get PK/PD on essentially everybody that's being entered in  
24 the trial to enhance that. So I can see that being  
25 somewhat useful.

1 Mark?

2 DR. GOLDBERGER: Yes. One other issue perhaps  
3 someone would want to address is if you had in fact a very  
4 selective spectrum product under development and felt that  
5 in many clinical situations you needed to combine it with  
6 another product, because you were not sure of the etiologic  
7 agent, one question that came up is could rapid diagnostics  
8 be useful in being able to quickly eliminate the companion  
9 agent so you could study the one of interest? And I guess  
10 one question is where we are in terms of development of  
11 those products and how much weight you might want to put on  
12 such data.

13 DR. CRAIG: Since most of the products are  
14 designed for gram-positives, being able to eliminate the  
15 gram-negatives, I'm not aware of anything that we really  
16 have that would be quite useful to let you know that you  
17 didn't have to worry about those, at least right now, at  
18 least as far as I know.

19 Anybody else have any comments on that? Barth,  
20 anything that you're aware of? No? Okay.

21 The next question, though, the B one, I think  
22 is an important one. It's pooling across body sites and is  
23 this a way that one can enhance enrollment? For example,  
24 if you have cases of sinusitis, cases of otitis media,  
25 cases from pneumonia, those would essentially in a way --

1 you could say respiratory tract -- would it be appropriate  
2 to pool the results on resistant organisms from those  
3 various sites or does one need to get whatever the number  
4 is going to be at each one of those various sites?

5 Go ahead.

6 DR. RELLER: Before getting into the A, B, C, D  
7 part of this, I'd like to raise a question that deals just  
8 with the basic one first off. Throughout these  
9 discussions, maybe it's because I'm just slow, but I am  
10 bothered by the numbers that we see from the surveillance  
11 with how many patients there are with, specifically,  
12 resistant *Streptococcus pneumoniae*, and the other numbers  
13 that we've heard of the difficulty of finding these  
14 patients or ending up with them in the clinical trials that  
15 have been done.

16 In considering these approaches to enhancement,  
17 all of the proposed solutions or most of them, it seems to  
18 me, are not based on evidence that failure to do so in the  
19 previous enrollments were responsible for the differences  
20 observed between what one would expect and what one ended  
21 up with in terms of resistant cases.

22 Now, Dr. Bell got us on that track in part in  
23 terms of "targeted populations" and the fascination of the  
24 donut concept in terms of where these patients are, and it  
25 seems to me fundamental, or at least it would be very

1 helpful, if there could be a more detailed examination of  
2 plausible explanations of why this discrepancy, and then  
3 they might provide more focused attempts to enhance the  
4 resistant strains, and then there are some other issues  
5 having to do with diagnoses that I'll come to, or maybe  
6 I'll just mention now.

7           When one starts out, just to follow through on  
8 a possible enrichment of resistant patients -- yesterday we  
9 had reviewed with us that, for example, with pneumonia,  
10 admittedly that accompanied by bacteremia, so that one was  
11 certain of the diagnosis, that the outcome with bacteremic  
12 pneumococcal pneumonia, regardless of susceptibility, that  
13 antimicrobials do not affect outcome in the first five  
14 days, that the effectiveness of any antimicrobial was  
15 observed later. Now, this is looking at mortality.

16           Well, unless other criteria were assessed to be  
17 crucially different for the patient, if one fuses that with  
18 Keith Klugman's presentation that in fact penicillin for  
19 pneumonia or things that work like penicillin, other beta-  
20 lactams that are efficacious against pneumococci, even the  
21 ones that are intermediate or at the lower levels of  
22 resistance 2 and 4, that there was no clinical difference,  
23 and a good bit of data were presented on that issue, could  
24 one not design a trial that put the emphasis on those  
25 persons with confirmed diagnosis?

1           And we're not talking about two or three days.  
2           With today's blood culture systems, for example, many  
3           pneumococci come up if one employed them correctly in terms  
4           of not sending them off someplace or a distant site where  
5           the machines are only looked at, even though they're  
6           monitoring every 10 minutes, once a day. Most of our blood  
7           cultures with pneumococci, and we're a 24-hour a day  
8           operation, including setting up susceptibility testing, but  
9           most pneumococci, if they grow out of blood, and it's a  
10          substantial number -- we're talking about pooling body  
11          sites, but for invasive disease, Dr. Meyerhoff showed that  
12          90-plus percent of the invasive isolates are actually from  
13          blood cultures, and there no one argues about etiology in  
14          those cases.

15                 So most blood cultures in the United States  
16          today with instrumented systems are positive in the order  
17          of six to 12 hours, and we see them in two to four hours,  
18          and almost all of them within 24 hours. It is a rare  
19          pneumococcus if it's ever grown out of blood that's not  
20          there within 24 hours.

21                 The gram stain, I realize that there are many  
22          places that don't have access to this anymore, but if one  
23          had a gram stain of someone producing sputum and it shows  
24          pneumococci in a specimen devoid of squamous epithelial  
25          cells in someone who has a radiograph that shows an

1 infiltrate and they have pneumonia -- in other words, some  
2 of these patients who are enrolled in these studies, it's  
3 really questionable whether they have pneumonia in the  
4 first place, but if one starts out with a clinical  
5 definition of pneumonia and a reasonable sputum specimen  
6 accompanied by blood cultures, I mean, one knows the answer  
7 within 24 hours or should be able to know using tools that  
8 are readily available.

9           Now, if the outcome in terms of mortality is  
10 decided at five days or more, you know -- and penicillin  
11 might be a superb comparator. In fact, one might argue  
12 that based on some of the surrogate data that one is  
13 considering that one might even be able to go after an  
14 indication for the treatment of *Streptococcus pneumoniae*  
15 caused by resistant pneumococci, to add that to the package  
16 insert for penicillin, just to be provocative. I mean, if  
17 one used some of the criteria we're talking about.

18           Certainly, with some of the elegant trial  
19 designs that Dr. Fleming has put forward, it seems to me  
20 that on this particular agent, and I realize this paradigm  
21 can't be extrapolated to all of the resistant issues that  
22 have been discussed, but with this particular one it seems  
23 to me that there is plenty of room to get resistant  
24 patients with a trial design that would satisfy the  
25 scientific rigor that has been the standard to which we

1 should be aspiring.

2 I know that's long, but I've tried to weave in  
3 some of these issues about let's concentrate on why the  
4 discrepancy, some possible answers to it, and there are  
5 rapid techniques available that, with all the importance of  
6 probes and molecular techniques that are available, if  
7 employed on this particular pathogen that could or should  
8 be possible to enhance the enrollment of what we're really  
9 going after and maintain standards. Okay? For discussion.

10 DR. CRAIG: I guess in my mind, and maybe Clyde  
11 can put some evidence on this, at least I know in South  
12 Africa if you look at adults compared to children, the  
13 incidence of resistant pneumococci markedly drops in the  
14 adult population, unless they're HIV-infected, where then  
15 it comes back up again, but if you were just doing your  
16 experiment in adults in South Africa, which is supposed to  
17 have a relatively high incidence, your percentage would be  
18 much lower, more like around 5 percent, than the  
19 percentages that are seen here.

20 I don't know if Clyde has that kind of data  
21 here in the United States.

22 DR. THORNSBERRY: You just took half my  
23 statement, because we find exactly that. It's very much  
24 age-related and if you look at the amount of resistance you  
25 see in patients less than two years of age, it's twice as

1 much at least as you see if you look at patients who are 60  
2 to 70. So if you're looking at doing a study with a  
3 fluoroquinolone, the very patients who have all the  
4 resistance are the ones that you can't use.

5 Now, there's also a second issue here. If you  
6 look at strains from blood cultures as compared to those  
7 from sputum, for example, there is much more resistance in  
8 the sputum. Well, maybe I shouldn't say much more, but  
9 there clearly is a significant increase in resistance in  
10 the sputum isolates as compared to the blood isolates.

11 So when you begin to put all these things  
12 together, the reason that they have more resistance in and  
13 around Atlanta is because those are the people who can  
14 afford to send their children to daycare centers, and  
15 daycare centers are loaded with these things.

16 There's one other thing I wanted to say, if I  
17 might be permitted to stick this in. I think it's very  
18 dangerous for us to assume that third-generation  
19 cephalosporin resistance in strep pneumo is rising faster  
20 than penicillin. The cefotaxime-resistant strain devoid of  
21 penicillin resistance is a very, very rare animal, and the  
22 vast majority of third-generation resistance kicks in when  
23 the penicillin MIC gets about 2. Very little happens below  
24 that, and so what you're measuring is not overall the  
25 penicillin when you compare those, but the rise in high-

1 level resistance, and if you compare that to cefotaxime,  
2 it's pretty close.

3 DR. CRAIG: Thanks, Clyde.

4 Dr. Bertino?

5 DR. BERTINO: One other comment about enhancing  
6 recruitment in target populations. I think it's important  
7 for us to remember that we can know that Memphis, Tennessee  
8 has lots of PRSP, but if you can't enroll the patients for  
9 whatever reason there, that's not going to help at all.  
10 With the ICH guidelines, it's becoming more and more  
11 rigorous to conduct studies, and so I think that's just a  
12 practical point to keep in mind.

13 DR. CRAIG: Yes, Barbara?

14 DR. MURRAY: Yes. It's more of a question.  
15 I've heard this come up sometimes. If a new agent is being  
16 compared to an older one in a randomized trial, and the  
17 patient is found to be infected with an organism resistant  
18 to the older drug -- say, penicillin or ampicillin -- and  
19 they're on ampicillin, so the patient, I presume, needs to  
20 come off of ampicillin at that time, if they're determined  
21 to be resistant.

22 Is this an accrual problem? If they're on the  
23 active drug, but now you've broken the blind, is that  
24 patient lost from accrual of data for the resistant  
25 organism? How can that be handled? If that makes sense.

1 DR. CHIKAMI: Well, I think it's been handled  
2 in a number of different ways. In the setting of a  
3 randomized double-blind study, where you don't want to  
4 break the blind at that point, then in fact the patient  
5 would be dropped from the study on the basis of those  
6 results. The issue of differentially keeping patients on  
7 study drug is more problematic, because then at that point  
8 you would be breaking the blind. So I think it does pose  
9 some design issues in terms of how to deal with that  
10 problem.

11 Again, in the past, in blinded trials patients  
12 were dropped on result of that, and in fact you do raise a  
13 good point. That has led to in fact patients being  
14 excluded from the analysis of trials for that reason.

15 DR. CRAIG: Would it possible to use a  
16 temporary different break point for the comparative agent  
17 for that particular trial if there was clinical data like I  
18 think there is that was talked about for beta-lactams  
19 against penicillin-resistant pneumococci?

20 DR. CHIKAMI: That could certainly be designed  
21 in the trial. You would then, of course, have to design  
22 into the trial appropriate monitoring, so that if a patient  
23 had a clinical failure, they would then be taken off study  
24 drug -- again, in a blinded fashion -- and treated  
25 appropriately.

1 DR. MURRAY: Yes, but my concern really was  
2 that if they're on the investigational drug and the  
3 resistance is to the other agent, but because they're  
4 randomized you don't know that, that doesn't that add an  
5 additional burden on the sponsor to accrue more cases,  
6 because they've just lost a patient that otherwise would  
7 have been evaluation of a resistant organism?

8 DR. CRAIG: Well, the way the break points are  
9 established, based on meningitis levels, virtually all your  
10 resistant organisms --

11 DR. MURRAY: It doesn't even have to be  
12 pneumococci. I'm talking about a general problem. Is  
13 there a way to incorporate into a design that that  
14 information doesn't get lost?

15 DR. CHIKAMI: And part of it relates to the  
16 intent of the study. If your intention is to demonstrate a  
17 similar activity to an approved agent overall for a  
18 syndrome, including multiple different potential pathogens,  
19 most of which are susceptible to both the control agent and  
20 the test agent, that leads to one design. If your specific  
21 intent of the trial is to target resistant pathogens, then  
22 of course, in an active control setting you would  
23 necessarily pick a control agent to which the resistant  
24 organisms were susceptible, and would deal with that issue.

25 So again, it depends on how you want to collect

1 the data. If you want to collect efficacy data on a  
2 resistant pathogen as sort of in addition to establishing  
3 overall efficacy, it makes the trial design a bit more  
4 difficult.

5 DR. CRAIG: We have a couple of things here --  
6 go ahead. Quick, Gordon.

7 DR. ARCHER: It's not quick.

8 DR. CRAIG: We're behind on our time and we've  
9 clearly got to answer these questions, so I'd like to try  
10 and get through those. Does this deal with back up on the  
11 standard of care?

12 DR. ARCHER: No, it's Number 2 under Session  
13 II.

14 DR. CRAIG: Okay. Could we just finish the  
15 other three real quick, just a little bit more on  
16 enhancement? Specifically, I want to get the feeling of  
17 the committee on pooling across body sites, whether that is  
18 something that's appropriate or does it need to be looked  
19 at in each infection site?

20 DR. ARCHER: Could I ask a question about that  
21 with our PK/PD people maybe?

22 DR. CRAIG: Yes.

23 DR. ARCHER: When you pool across body sites,  
24 doesn't it determine to a great extent how much of the  
25 agent gets into the body site, and therefore may there not

1 be a different MIC cutoff at each site? And therefore  
2 establishing a single level of resistance for all sites may  
3 be very difficult. I mean, obviously, urine and sputum  
4 would be two good examples, but the sputum in sinus or  
5 sputum in middle ear might even be different.

6 DR. CRAIG: I would say, at least from the  
7 animal data that's out there, looking at different sites of  
8 infection, one does not find a difference in the PK/PD  
9 parameter for different sites. That's looking at  
10 peritonitis, pneumonia, skin and soft tissue infections,  
11 and again, the data from those kinds of models tend to  
12 follow along with otitis, and from the limited data that is  
13 available on sinusitis with beta-lactams, it also seems to  
14 fit.

15 And what we do, at least in my mind, is we give  
16 one break point. We don't have a break point for the ear,  
17 a different break point for the lung. There's one  
18 susceptibility break point, so that as long as it's a site  
19 where serum concentrations are sort of the one that are the  
20 primary determinant of the level that you're going to see  
21 there, I think it's perfectly fine. I don't think that you  
22 could necessarily do meningitis with something else or, as  
23 you say, doing the urinary tract with something else, but  
24 other tissue sites, in my mind, I think it is appropriate  
25 to pool.

1 DR. MURRAY: Yes, I conceptually agree with the  
2 idea of pooling for organisms that are very scarce with  
3 caveats like you can't apply pneumonia to meningitis, but  
4 the reverse you probably can.

5 DR. CRAIG: Any other comments on that? Does  
6 it sound okay with you, too, Dale?

7 Okay. Let's go on then on targeted  
8 populations. I think the one we know about in kids is  
9 clearly those that have failed therapy. I think there's  
10 good data out there to show that that significantly  
11 increases the number of penicillin-resistant organisms in  
12 ear fluid. So clearly, that would be one of the targeted  
13 populations.

14 I think we've heard about going down to Atlanta  
15 and places, the southeastern part, and again, HIV patients  
16 are another group which appear, if you're looking at  
17 adults, to tend to have a higher incidence of having the  
18 organism around, but again, as I say, in children it may be  
19 easier than looking at adults.

20 Yes?

21 DR. SORETH: I just wanted to make a brief  
22 comment about the finding that, at least in children,  
23 penicillin-resistant pneumococci seem to be concentrated in  
24 suburbs, and when you think about the kinds of  
25 investigators enrolled in trials who can do

1 tympanocentesis, I would submit to that that probably most  
2 of those physicians are not practicing in the suburbs.  
3 There are exceptions, and I can think of one locally, but I  
4 think maybe we need to reexamine who we train in doing  
5 tympanocentesis and where they practice, because I think  
6 they're not often in the suburbs.

7 DR. CRAIG: Very true.

8 Anybody have any other enhancement strategies?

9 DR. MURPHY: I guess the only thing I would add  
10 to that is that we're going to have to get them paid. I  
11 think one of the issues, too, is if you're going to go to  
12 the suburbs, you're going to have to look at the time  
13 commitment in designing these trials for these physicians.

14 DR. CRAIG: Let's move on then to Number 2, and  
15 go ahead, Gordon.

16 DR. ARCHER: I wanted to comment on Dr.  
17 Ahonkhai's and Dr. Williams' comments, if I could. I think  
18 there are two issues here, the efficacy of treatment versus  
19 what I'd like to call out of class resistance, which would  
20 be quinolones versus resistant pneumococci, and in-class  
21 resistance. I think they're two entirely different issues  
22 and should be approached differently.

23 In-class resistance, an example would be using  
24 higher doses of a beta-lactam, for instance, to treat a  
25 penicillin-resistant pneumococci, but other examples might

1 be neuroquinolones, which have more activity, possibly, but  
2 have some cross-resistance, to treat quinolone-resistant  
3 pneumococci, or new macrolides that may have more activity  
4 to treat macrolide-resistant pneumococci.

5 I think these are very difficult issues for two  
6 reasons. Number one, resistance is obviously a moving  
7 target, and we know it's moving, with penicillin  
8 resistance, as it gets higher and higher. So the more  
9 beta-lactams that are used, the higher doses that are used,  
10 the average MICs of resistant organisms are going to rise.  
11 So it seems to me very difficult to say you can use  
12 amoxicillin to treat ear infections when we don't know six  
13 months from now what the MIC is going to be. If we set the  
14 MIC at 2 for amoxicillin-susceptible, but the average MIC  
15 is 4 six months from now, then some of those may fail. We  
16 don't really know what level mediates failure. The target  
17 is going to move, as opposed to out of class resistance.

18 Secondly, there are sites of infections, like  
19 otitis, and the point was made that most people don't do  
20 tympanocentesis, so we're not sampling the target organism  
21 from this site on a regular basis. So if we use in-class  
22 resistance and the MICs begin to rise at that site six  
23 months or a year down the road, infections may increasingly  
24 fail, even though there's a labeling indication saying you  
25 can treat otitis media with higher doses of beta-lactams if

1 the MIC's not above X, Y, or Z, but in fact that MIC might  
2 get higher and higher. So I would think you've got to be  
3 very careful about licensing for in-class resistance.

4           Secondly, on a different note, but something I  
5 think that was brought up right at the beginning when we  
6 first started that I'd like to really comment on, and that  
7 is the issue of concentrating on penicillin resistance of  
8 pneumococci, when resistance to other classes is just as  
9 important. I would like to maintain that macrolide  
10 resistance of pneumococci is a huge issue, and somebody who  
11 said that macrolide resistance use is less common than  
12 penicillin use for treating otitis probably hadn't been out  
13 treating patients recently. The use of macrolides is huge  
14 and rising, and the treatment of choice in many cases and  
15 the physician's treatment is often macrolides, and not  
16 beta-lactams.

17           So concentrating on penicillin resistance and  
18 not macrolide resistance, or possibly in the future  
19 quinolone resistance, among pneumococci I think is a blind  
20 man and the elephant kind of strategy, and I don't know why  
21 penicillin resistance is being commented on. I think we  
22 need to think about multiresistant pneumococci and each of  
23 the agents in turn.

24           Okay. Off of my soapbox.

25           DR. CRAIG: I think the problem comes up when

1 you're looking at beta-lactams or looking at in-class. The  
2 question is what are the alternatives that you have, since  
3 the quinolones are not there and, as you say, many of these  
4 organisms are resistant to other drugs. You frequently do  
5 have to, in order to try and find a solution, sometimes  
6 stay within the same family of drugs and use higher doses.

7 I also, however, have a tendency to agree with  
8 you that I think I would want to see a little bit more  
9 clinical documentation, and I think what I saw from what  
10 SmithKline Beecham proposed was actually looking at  
11 bacteriologic efficacy and double-puncture studies in  
12 tympanocentesis, which I think is probably the most  
13 sensitive way of trying to see whether really a drug has  
14 activity. The evidence from the trials is that if you  
15 eliminate it there, you're going to have 98 or 99 percent  
16 clinical efficacy. If you don't, then about a third of  
17 them will fail. So I think it's a good design, and I would  
18 want to see it, and I would want to see it in a significant  
19 number of patients, and what that is we may need to decide.

20 But go ahead, Barbara.

21 DR. MURRAY: Yes, I was just going to comment  
22 that if we try to do the crystal ball, we probably  
23 shouldn't approve any fluoroquinolone for a lot of  
24 infections, because I would predict, as somebody who's  
25 worked with resistance in 20 years, that in five years it

1 may be a dead game. So I think that's not quite fair,  
2 because we don't really know what's going to happen, but I  
3 think to hold somebody to the standard of the future is  
4 asking a bit too much.

5           The other point is, and I wasn't sure you were  
6 getting at this with the in-class, but there certainly is a  
7 lot of effort, as you know, looking at potential in-class  
8 problems with both the streptogramins and macrolides and  
9 the ketolides and macrolides. So when it gets to the stage  
10 of looking at those, if we were to try to compare efficacy  
11 with resistant versus susceptible organisms, and if we held  
12 to the standard of it has to not show any difference in in  
13 vitro or animal model tests, those will probably have been  
14 explored, because everyone's looking at induction with  
15 macrolides, mutational rates to ketolides, and all these  
16 different manipulations to push on those in-class sort of  
17 observations. So there'll be some data to direct I think  
18 when we get those.

19           DR. ARCHER: I guess my response to that is  
20 just in-class the target moves very quickly, and  
21 particularly at sites where you can't monitor resistance, I  
22 think it's dangerous if you're using, for instance, a  
23 quinolone with a one log lower MIC but falls below the  
24 break point, we know that one-step resistance occurs very  
25 quickly, and if you're not monitoring susceptibility --

1 now, Dr. Ahonkhai may be monitoring it for the purpose of  
2 getting to show that a beta-lactam will work in otitis,  
3 which is fine. Six months or a year from now, you're not  
4 doing tympanocentesis, and there's not going to be any  
5 monitoring to see if otitis is now failing because the MIC  
6 is changing, and if it's in-class I predict that it will  
7 fail very quickly, and the MIC will rise. We've seen that  
8 in one year at ICAAC the penicillin resistance, the level  
9 of MIC, if somebody calculated it, has gone up two to  
10 three-fold, and it'll continue to go up.

11 DR. CRAIG: I'll say there's some debate on  
12 that of how high it may eventually go, but the point that I  
13 think is that those things would be taken care of in the  
14 label. They'd be taken care of with the break point. So  
15 that what you would essentially be having would be that  
16 you'd be activity against organisms below a certain MIC.

17 DR. ARCHER: No. You'd have to have sampling  
18 in the ear.

19 DR. CRAIG: What?

20 DR. ARCHER: You know what's going on inside  
21 the middle ear.

22 DR. MURRAY: Yes, but you've got 5,000  
23 respiratory pneumococci which are sort of the base of the  
24 iceberg and not the tip.

25 DR. CRAIG: But I don't want to get into that.

1     What I want to get into are what are the circumstances when  
2     you would be willing to accept less clinical data for  
3     evaluation of drug safety. I guess that's a separate  
4     issue, but I want to emphasize primarily right now efficacy  
5     when targeting resistant pathogens. We can take safety  
6     second.

7                     DR. MURPHY: Well, I would also ask that in  
8     addressing this question the committee, just so we have a  
9     real focus here, take which model they're addressing, the  
10    VREF model or the sort of pneumococcal model, where you  
11    have totally different sets of issues.

12                    DR. CRAIG: So what was the first one you said?

13                    DR. MURPHY: The vancomycin-resistant type,  
14    where you have no other options, you have very sick  
15    patients, life-threatening disease, versus the other  
16    scenario. So please, when you're addressing, make it very  
17    clear which model you're talking about.

18                    DR. CRAIG: Okay. Who wants to start off?

19                    (No response.)

20                    DR. CRAIG: Nobody wants to start off? Always  
21    leave it up to me.

22                    Well, to me, when I would be willing to accept  
23    less clinical data I think is when I've got a population of  
24    organisms, I have a drug that, say, has a unimodal  
25    susceptibility -- it's a new mechanism of action, for

1 example -- and all the previous PK/PD data essentially  
2 suggest that the organism behaves just as, let's say, a  
3 penicillin-susceptible strain does.

4 I would want to see a lot of MIC data. I'd  
5 want to see some animal. I think we need in vivo data. So  
6 I would want to see a good bit of in vivo data with a  
7 variety of strains that were clearly convincing me that  
8 there was a difference between susceptible and resistant  
9 strains.

10 Then I'd want to see a small number of patients  
11 from the clinical trials that suggested that in the small  
12 number of patients -- and again, what that number is, I  
13 personally think 10 is reasonable for me. Especially with  
14 the pneumococcus, I mean, if we look at that 13 that the  
15 levofloxacin people had, I think five of them were  
16 bacteremic cases, and so that if you can get bacteremic  
17 cases in there, where we know that the natural history of  
18 poorly treated bacteremia has essentially up to around an  
19 80 percent mortality, that is to me very good evidence to  
20 make me believe that the drug is going to be active against  
21 those kind of organisms. So those would be the situations  
22 where I would be willing to accept less.

23 Now, if you're talking about a new drug, and  
24 I'll still stay with the pneumococcus, or an old drug that  
25 has increased activity, against a mechanism that is

1 actually the same mechanism that produces resistance, so  
2 let's say a new beta-lactam or something like that, then  
3 again I'd want to see a lot of good PK/PD data, but since  
4 there might be from the Phase I studies, if there is  
5 significant variation in the pharmacokinetics and  
6 pharmacodynamics, and if simulations started to say that  
7 you might be at the borderline or it might be at the cusp,  
8 depending on what the MIC might be, then that's the kind of  
9 situation where I would think I would want more clinical  
10 data.

11 Specifically, I'd like to try and get more  
12 bacteriologic data, because I think it's a little bit more  
13 sensitive. Sure, you've got to get both, but I would like  
14 to, in the trial design, see if I could collect  
15 bacteriologic data, so that if they were going after otitis  
16 or if they were going after sinusitis, I would try, at  
17 least for any organism, since they frequently puncture at  
18 the beginning of therapy, and if you knew then that you had  
19 a resistant organism, those would be the ones then that I  
20 would try and get subsequent punctures on, so that one  
21 could get better bacteriologic data that the organism is  
22 really being killed.

23 Yes?

24 DR. GOLDBERGER: Dr. Craig, from a regulatory  
25 point of view, it'd be helpful if you would, when talking

1 about the amount of clinical data, distinguish between data  
2 that might be submitted at the time a marketing application  
3 is submitted versus a commitment to submit clinical data  
4 that might come in sometime after an approval. I got the  
5 sense from your comments you were thinking about the  
6 former, but it'd be helpful if you could sort of confirm  
7 that.

8 DR. CRAIG: Well, I mean, I don't know when you  
9 need to obtain the data. I think it's nice if you can  
10 obtain it in the initial clinical trial, where the number  
11 is relatively a subset of the population, but it may be  
12 that, at least in the numbers that we saw, you're not going  
13 to be able to get it that way, and if that's the case, I  
14 would sort of apply what you do with your additional  
15 applications that come in to add organisms to the --

16 DR. GOLDBERGER: No, what I meant was in the  
17 initial application or in a subsequent application to add  
18 the organism, would you want to see the clinical data in  
19 order to make the decision versus having a commitment to  
20 have the clinical data come in sometime after the decision?

21 DR. CRAIG: You mean you're willing to give  
22 them the indication without?

23 DR. GOLDBERGER: That's up to you. I didn't  
24 say that.

25 DR. CRAIG: Well, I'm saying that if it's such

1 a problem that we're having horrible results, we don't have  
2 effective therapy, and you really need to get something out  
3 there, yes, if I had the earlier data, the pharmacokinetic  
4 data, the pharmacodynamic data, suggesting that it would  
5 work and we needed to get something out there because there  
6 was a lot of morbidity and, let's say, even mortality in  
7 the absence of something, sure, I would support it with a  
8 commitment to getting additional data.

9 On the other hand, if there are plenty of  
10 alternatives available, then I wouldn't feel pushed to do  
11 it and I would want to see the data before the approval  
12 would be given.

13 Yes, Dr. Archer?

14 DR. ARCHER: It's kind of getting back to the  
15 problem about moving resistance. What if you give  
16 licensing, for instance, indications for the pneumococcus  
17 for higher doses of a beta-lactam at a cutoff point MIC  
18 which you think is reasonable in most body fluids, and in a  
19 year MRL says that 60 percent of respiratory isolates now  
20 have an MIC of 4? Would you then compel additional  
21 studies, knowing that there's a higher MIC cutoff now, to  
22 reassess that indication? Would there be ongoing  
23 monitoring techniques after the licensing if there's a  
24 change in resistance?

25 DR. MURPHY: I would say that, first of all, it

1 would depend on how it was written in the label, okay?

2 That's one thing. If it was written for a certain level of  
3 resistance, then in a way that is the direction a physician  
4 should take.

5           However -- and this is one of the issues if we  
6 can try to decide which approach we're taking -- there is a  
7 regular approach of trials which are not under accelerated  
8 approval, where you may have alternative designs or we're  
9 trying to look at how to enrich studies. We're trying to  
10 address the issue of scarce numbers. That's one set of  
11 questions here.

12           Then the other set of questions is in the  
13 situation where you have no other options, it's serious and  
14 life-threatening disease, we do have some regulatory  
15 options here, and what is the bar, as we mentioned  
16 yesterday, that we have for the first part of approval?  
17 Because all of that approval is always linked to continuing  
18 data being required, ongoing studies.

19           So I'm trying to separate, if we can, because  
20 one is simply looking at some of the enhancement issues,  
21 and the other is looking at a different type of approach  
22 and less data early, assuming more data is coming in.

23           DR. MURRAY: Well, I think you keep hearing  
24 everybody trying to stick with the pneumococcus because  
25 it's a lot easier to talk about, and you have drugs that

1 are being looked at that have a large safety profile for  
2 susceptible organisms and so we're comfortable there, and  
3 you're talking about doing trials with comparators, so it's  
4 just something that is more familiar.

5           Every time we start trying to get into the VRE,  
6 I think we sort of naturally back away, just as you  
7 probably do, because we're on much less familiar ground and  
8 it's just as unfamiliar for us as it is for anyone else,  
9 and I think that's one of the problems.

10           But I think it's clear that as the acuity gets  
11 higher, the standards drop, and we would accept that, but  
12 it's very difficult, at least for me, to say how acute and  
13 how much of a drop. If you have a drug, in my mind, that  
14 has been looked at and has a good safety profile and is  
15 being looked at for other organisms, so then you're  
16 applying it to the VRE also, again, I'm probably going to  
17 have a lower threshold for wanting that to be applied to  
18 the VRE.

19           Then you get into the situation where it's an  
20 entirely new compound and it's not being looked at for  
21 other indications. We're talking at the far end, of the  
22 small company, the biotech firm that's going to come  
23 forward with perhaps a true orphan product for VISA. I'll  
24 keep going back to that one, where there are five isolates  
25 in the world that we know about, and there may be a few

1 more, but there may be a compound that's not targeted to  
2 any other organism and we're not going to have a lot of  
3 background safety information to feel comfortable that what  
4 we're doing is not causing harm. On the other hand, we'll  
5 probably be willing to let you do whatever you can  
6 regulatory-wise to let it be used in those patients that  
7 need it.

8           So we're talking on a scale like this, and  
9 we've focused down at this end, and I know you're trying to  
10 get us up to here at least, and we're probably not going to  
11 worry about here for awhile, and I guess again it sort of  
12 would depend if there's a good profile and if it's working  
13 for other organisms and it looks reasonably safe, and what  
14 are the data that you need to say that it works against  
15 VRE. If you had a few really good cases, I'd be very happy  
16 with that. You give me a couple of meningitis or  
17 endocarditis that are cured, which, of course, at one far  
18 extreme of the clinical spectrum -- and then you back it up  
19 with animals, pharmacokinetics, safety in general, and  
20 applicability for other organisms, I'll probably go with it  
21 then and there.

22           DR. MURPHY: And when you say go with it then  
23 and there, you're saying I'll go with the less data under a  
24 Subpart A, serious and life-threatening disease, where  
25 we'll give it approval, but we're still requiring ongoing

1 information and data to be accumulated over time. I just  
2 want to make sure that that's what you're saying.

3 DR. MURRAY: Well, but you're asking me to put  
4 a regulatory phraseology to it that I don't -- I'm not -- I  
5 can't --

6 DR. MURPHY: Okay. We're just saying that's  
7 what it would mean to us, that if we did it --

8 DR. MURRAY: I think that's what I'm saying,  
9 yes.

10 DR. CRAIG: Sure.

11 (Laughter.)

12 DR. CRAIG: I mean, you're not just going to  
13 stop there and not have some additional data be collected  
14 as more information is --

15 DR. MURRAY: Sure.

16 DR. GOLDBERGER: Let me ask you, Dr. Murray,  
17 though, then a specific question about VREF. How useful  
18 for a new compound would, for instance, a companion trial  
19 be against either ampicillin-resistant or susceptible  
20 enterococci using either ampicillin or vancomycin as the  
21 comparator and studying the new drug to get an idea how it  
22 worked on susceptible enterococci, since presumably it  
23 ought to work in those if it works in resistant? Is that  
24 something that you think would be useful?

25 DR. MURRAY: It depends, because there are

1 certain species differences, as you know, between E.  
2 fecalis and E. fecium, and the drug in question, Synercid,  
3 is not active against E. fecalis, which would be the more  
4 likely -- that's the one you could probably reliably study,  
5 because it's ampicillin-susceptible most of the time.

6 But to do a study of ampicillin against E.  
7 fecium could be problematic, depending on how resistant  
8 they are, so it may or may not be doable to get the data  
9 against a susceptible organism, and we don't really know if  
10 biologically fecium and fecalis have the same pathogenesis.  
11 I mean, it might be like comparing S. typhy and S.  
12 typhameriam, in which sometimes they cross-react in the  
13 disease syndrome and sometimes they don't. They're  
14 different species in the same genera.

15 It's difficult to answer that question, but say  
16 if they had the same susceptibility profiles to Compound Y,  
17 and you were collecting data that it worked in fecalis, I  
18 suppose that would give me --

19 DR. CRAIG: And you had some in vivo animal  
20 data, so that it wasn't just test tube stuff.

21 DR. MURRAY: And some in vivo animal data, yes.  
22 That would probably help make the decision easier. It  
23 doesn't help a compound that doesn't have activity, good  
24 activity, against fecalis.

25 DR. CRAIG: I think most of us would be very

1 ill at ease to just base it on MIC data. I think there  
2 needs to be some in vivo evaluation, and whether that  
3 initially is in animals and specifically looking at that,  
4 and then a small number of humans to make sure that the  
5 predictions fit, but just to base everything on MIC values  
6 alone, at least the feeling I've been getting, is the  
7 committee would be concerned about that. Am I right?

8 DR. MURRAY: Particularly if there is some  
9 class potential, streptogramins with macrolides, perhaps  
10 glycolipopeptides with glycopeptides. I mean, if there are  
11 underlying questions that come into our minds, we'd  
12 probably want to further push on some of the standard other  
13 resistant organisms that might have a cross-reaction in the  
14 laboratory.

15 DR. CRAIG: Any other comments on this last  
16 question?

17 DR. RELER: There's been much discussion about  
18 innovative ways to deal with design or numbers to get at  
19 the efficacy issue, but the safety can only come from  
20 people, and even for the VREF, a proportion -- at most,  
21 over half -- even where there's high levels of vancomycin-  
22 resistance are susceptible to vancomycin.

23 Isn't there some way that one could get the  
24 putative new drug, different class, et cetera, which should  
25 work in the susceptible ones, to garner the safety data

1 from treating the vancomycin or ampicillin-susceptible  
2 strains, even if it were a design that one took everyone in  
3 before susceptibility testing?

4 Dr. Danner was discussing this approach with me  
5 yesterday afternoon, of taking all of them in when it has  
6 susceptibility, then, even though it would break the code,  
7 with some monitoring device putting people over to the new  
8 agent that was by PK/PD in vitro active, of getting the  
9 patients who in fact had a resistant strain to vancomycin,  
10 but you would that way get the numbers on the susceptible  
11 one to enhance the resistant ones with objective criteria  
12 for endpoints.

13 DR. MURRAY: Well, I doubt that there are  
14 enough vancomycin-susceptible enterococcus fecium  
15 infections out there to get good numbers, because remember,  
16 prior to vancomycin resistance, fecium only accounted for  
17 about 10 percent of enterococcal isolates, and the increase  
18 in the number of fecium-causing infections is a direct  
19 reflection of vancomycin resistance. So it might be  
20 difficult to get fecium infections to get your baseline.

21 But again, in a drug that has had good safety,  
22 because it's being studied for other indications, that's  
23 going to be easier, to me personally, from a safety point  
24 of view. It's when you get further away into a real  
25 specialty drug that's not even being looked at for another

1 case.

2 But then I think if you have a patient with  
3 endocarditis with VISA who's going to die without therapy,  
4 then of course your threshold for using anything is pretty  
5 low. We poison patients all the time with amphotericin and  
6 we could poison them with something else for a life-  
7 threatening disease, but there's a lot in between.

8 DR. CRAIG: And clearly there are  
9 postmarketing, or at least postapproval, ways of collecting  
10 toxicity. In fact, some of the very rare toxicities you're  
11 just not going to pick up with your initial patient load  
12 anyway, so that you're going to need to incorporate that,  
13 and in a situation where there's nothing else out there and  
14 it falls under the criteria that you mentioned for life-  
15 threatening infection, I think you frequently may need to  
16 put it out without getting all the toxicity data that you  
17 would, with the understanding that additional data would be  
18 collected.

19 DR. MURRAY: Of course, I could play the  
20 devil's advocate and go the other way. If it gets out  
21 there for other indications, it'll be used by the  
22 physicians for VRE even if it doesn't have the approval,  
23 but that won't help you when you get to the stage that the  
24 VRE is the only organism that's being looked for with a new  
25 drug.

1 DR. CHIKAMI: And as Dr. Murray pointed out,  
2 safety data can come from a number of different sources  
3 within a clinical development program. It can come from  
4 randomized controlled trials and other situations. It can  
5 come from Phase I and Phase II studies.

6 If you're doing a targeted Phase III  
7 development program for a resistant organism in a  
8 particular patient population, there could also, for  
9 example, be a treatment use of the product under a  
10 treatment IND, which could also provide helpful safety  
11 information, and that's the model that has been used early  
12 on in some of the AIDS drugs, where there are relatively  
13 smaller numbers of patients enrolled into randomized  
14 controlled trials, but there were large expanded access  
15 programs, which did provide some safety information which  
16 was useful, and some of it even was dose-comparative.

17 DR. CRAIG: Unless anybody has any other  
18 comments, I think we'll take our break now. We're clearly  
19 behind. We'll catch this up another time, but I think  
20 before we break Dr. Chikami has a little announcement that  
21 he needs to make.

22 DR. CHIKAMI: I have two brief announcements.  
23 One of them deals with the fact three of our committee  
24 members are actually rotating off this year. Dr. Banks-  
25 Bright and Dr. Henry are not here, and we'll be sending

1       them a certificate of our appreciation.

2                   The third member, Dr. Don Parker, has served  
3       the committee very well over the years. We've appreciated  
4       his input, particularly in the area of statistical issues,  
5       and I just want to present him with this plaque.

6                   (Applause.)

7                   DR. CHIKAMI: The other person I want to  
8       acknowledge is Ermona McGoodwin, who is our executive  
9       secretary. Ermona will be retiring in January, and we  
10      appreciate her long service to this committee. I've worked  
11      with her as well on the Antiviral Committee, and always  
12      found her to be very professional and really instrumental  
13      in making these meetings work. So we appreciate her long  
14      service to the FDA and to this committee.

15                   (Applause.)

16                   DR. MURPHY: For the committee, there's a cake  
17      for Ermona. The committee's welcome to have some during  
18      their break.

19                   DR. CRAIG: We will meet right at -- well,  
20      we'll make it 11 o'clock.

21                   (Recess.)

22                   DR. CRAIG: We're going to move on now with  
23      bacteremia as an indication. What we will plan to do is go  
24      through all of the talks, so that means lunch will probably  
25      be about 20 or 25 minutes later, and we'll pick up some of

1 that time later in the afternoon, so I still plan to  
2 adjourn by the same time that's listed on the schedule.

3 So the first person to speak will be David  
4 Ross, one of the medical officers at the FDA, who will be  
5 giving the introduction on bacteremia as an indication.

6 David?

7 DR. ROSS: Thank you, Dr. Craig.

8 What I'd like to do, in terms of opening this  
9 module, is give a historical perspective on bacteremia as  
10 an indication. Some of the historical material,  
11 transcripts from advisory committee meetings in 1993  
12 dealing with this issue, are in the briefing package, along  
13 with a presentation by an FDA medical officer, Dr. Linda  
14 Sherman, that was presented at that time.

15 Can I have the next slide, please?

16 Prior to 1992, the indications of bacteremia  
17 and septicemia were granted for various anti-infective  
18 products, and these were defined in a clinical context as  
19 being bacteremia representing one positive blood culture  
20 and septicemia representing two positive blood cultures.

21 Now, things that I think are important to keep  
22 in mind are that the clinical context for different drugs  
23 for different applications in different studies either  
24 varied or was not specified in the study protocols. These  
25 entities included both bacteremia associated with focal

1 infections and bacteremia of unknown origin. Finally, it  
2 was frequently the case that these entities were not  
3 necessarily studied on their own. Data for approval were  
4 garnered from patients with bacteremia or septicemia from  
5 data that was pooled from trials of drugs for other  
6 indications, such as pneumonia or urinary tract infection.

7 Next slide.

8 This situation was unsatisfactory to both  
9 sponsors and the agency because of the lack of consistency  
10 in definitions. So in 1992, the entity of bacteremic  
11 sepsis was proposed as an addition to the points to  
12 consider as an indication, and the criteria for this would  
13 have been a systemic inflammatory response syndrome  
14 characterized by two or more of the following features, and  
15 two positive blood cultures. The proposed definition  
16 implied, but did not explicitly state, that patients with  
17 this entity would have an identifiable focus of infection.  
18 The primary endpoint would be clinical cure, with  
19 bacteriologic response a secondary endpoint.

20 Next slide, please.

21 I just want to say, before talking about this  
22 slide, that I want to thank Dr. Linda Sherman, from whose  
23 presentation this slide is taken.

24 The question confronting the Division of Anti-  
25 Infective Drug Products at that time was, given that

1 there's a continuum of infection, all the way from absence  
2 of illness through localized infection through localized  
3 infection plus bacteremia through SIRS to septic shock and  
4 death, could we make a clinically meaningful distinction  
5 among patients with localized infection and SIRS between  
6 those without bacteremia and those with bacteremia? Did  
7 these patients require different therapy to such an extent  
8 that they should be classified differently for regulatory  
9 purposes, with bacteremic patients constituting a separate  
10 indication?

11 Next slide.

12 This question was presented to the advisory  
13 committee five years ago, and the formal question presented  
14 was as follows. Are infected patients with evidence of  
15 SIRS and concurrent bacteremia, but without organ  
16 dysfunction, hypoperfusion, or hypotension, a clinically  
17 different group of patients than other similarly infected  
18 patients without concurrent bacteremia?

19 Next slide.

20 The discussion by the advisory committee  
21 touched on a number of issues, and I'm going to just  
22 highlight the major points here. Dr. Sherman presented  
23 data suggesting that bacteremic and nonbacteremic SIRS  
24 patients had similar outcomes in a large data set. There  
25 was a consensus that, except for entities such as

1 endocarditis, bacteremia is due to infection at a primary  
2 site. There has to be a portal of entry, in other words.  
3 Bacteremic SIRS patients were felt to comprise a  
4 heterogeneous population, and finally, the committee felt  
5 that the data were insufficient to determine if bacteremic  
6 SIRS patients are really sicker than nonbacteremic SIRS  
7 patients.

8 Next slide.

9 The committee's conclusions and recommendations  
10 to the agency were as follows. That bacteremia is less  
11 important than site of infection in terms of classifying  
12 infections for regulatory purposes. The study of  
13 bacteremic sepsis as a separate indication was felt not to  
14 be feasible, given the heterogeneity of the patient  
15 population. The committee did feel that in order to guide  
16 prescribing physicians labeling should include bacteremia  
17 in the context of site-specific infections using  
18 phraseology, for example, such as pneumonia with associated  
19 bacteremia.

20 Next slide.

21 So since that time, there have been no further  
22 approvals given for the indication of bacteremia. In terms  
23 of reasons for reconsideration, I guess the question that  
24 comes up is, as Yogi Berra would say, is this deja vu all  
25 over again? Well, there has been an increase in the

1 incidence of bacteremia with resistant pathogens,  
2 particularly gram-positive pathogens for which selective  
3 spectrum agents are being developed, an increase in  
4 incidence of bacteremias without an identifiable source,  
5 and finally increased incidence in using positive blood  
6 cultures to enrich clinical trials for patients infected  
7 with a pathogen of interest.

8 In addition, we need to address the relevance  
9 of these issues of patient heterogeneity and the  
10 significance of bacteremia versus site of infection in  
11 bacteremic patients without considering SIRS.

12 So let me stop there and I will turn things  
13 over to Dr. Mermel, who will speak about definition of  
14 bacteremia.

15 DR. CRAIG: Yes, our next speaker is Leonard  
16 Mermel from Rhode Island hospital, who will talk on the  
17 definition of bacteremia.

18 DR. MERMEL: I'm honored to be here. Dr. Ross  
19 called me a few weeks ago and asked me if I could do  
20 something for my country by coming here today. As a first-  
21 generation American, it's not as though I'm a concentration  
22 camp survivor, but I'm honored to be here. What he didn't  
23 tell me was that I had a choice of defining bacteremia or  
24 solving Fermi's last theorem.

25 (Laughter.)

1 DR. MERMEL: I decided to attempt the  
2 bacteremia.

3 I first wanted to talk a little bit about the  
4 magnitude of the problem of bloodstream infection. I think  
5 it's a little more clearly defined with nosocomial  
6 bloodstream infection. There are about 250,000 cases each  
7 year in the United States of nosocomial hospital-acquired  
8 bloodstream infection, with an attributable median  
9 mortality of 27 percent and a range of 14 to 38 percent, so  
10 it's a formidable problem.

11 With regards to cost, there is quite an array  
12 of some data available looking at attributable cost. Some  
13 of the more recent data from the University of Iowa  
14 suggests that the attributable excess cost of hospital-  
15 acquired bloodstream infection from a series of patients  
16 for the surgical intensive care unit was as high as \$40,000  
17 per survivor, so this is a formidable problem of high  
18 incidence, high mortality, and high cost.

19 I want to spend a little bit talking about  
20 mortality, because I think this is an endpoint for clinical  
21 trials that always comes up, and if you'll look at a large  
22 study published last year, in looking at crude mortality  
23 and independent risk factors associated with crude  
24 mortality in patients with bloodstream infections, what was  
25 found was that patients with a pulmonary source of their

1 bloodstream infection, a GI source, or an unknown source  
2 were independent risk factors for crude mortality;  
3 inappropriate antibiotics given at two different times  
4 during the treatment course; hypotension; a bloodstream  
5 infection due to fungi or gram-negative bacteria other than  
6 E. coli; the absence of fever; malignancies, AIDS, or renal  
7 failure; and the elderly.

8           However, there are some problems using crude  
9 mortality and suboptimal control for confounding variables.  
10 Some studies have found the source of a bloodstream  
11 infection and the etiologic agent have a dramatic impact on  
12 crude mortality, such as a study by Roberts published two  
13 years ago. Other studies, adjusting for confounding, in  
14 measuring attributable mortality have not found this to be  
15 the case, and what I'd like to show you is an important  
16 study in this regard.

17           Bates and colleagues in Boston carried out an  
18 important study that was published in JAMA a few years ago  
19 looking at mortality and using some rigorous statistical  
20 analyses. What they showed, firstly, was that most of the  
21 additional risk of death from bloodstream infection  
22 occurred within 30 days. Relative risk of attributable  
23 mortality within 30 days of a bacteremic episode was 2.6  
24 compared to 1.3 after 30 days, suggesting that if we were  
25 going to study mortality for FDA-approved indication we

1 should look at mortality within 30 days.

2 In their study, the only independent predictors  
3 of attributable mortality within 30 days was severity of  
4 underlying disease and shock, not the type of pathogen, not  
5 the type of antibiotic, not even if the antibiotic was  
6 appropriate. The only independent predictors within 30  
7 days were severity of underlying illness and shock.

8 This was a few of their conclusions I wanted to  
9 share with you. "We found that patients with bacteremia  
10 had a high mortality, but that mortality was much more  
11 strongly correlated with underlying severity of disease  
12 than with the presence of bacteremia." They also in their  
13 conclusion stated that "a high percentage of patients with  
14 bacteremia will do well regardless of therapy," regardless  
15 of the antibiotics they were given, and a very large group  
16 of those patients who do poorly have another rapidly fatal  
17 disease.

18 So does bloodstream infection source impact on  
19 mortality? I believe after controlling for confounders  
20 some studies have demonstrated that the source of infection  
21 was not an independent predictor of attributable mortality.

22 However, withdrawal of a removable focus of  
23 infection should improve outcome, and if we think about it,  
24 you have a festering thorn in your foot and you remove it,  
25 that should affect outcome, and I think the same should go

1 for, say, a festering or infected intravascular device.  
2 These studies may not have enrolled enough patients whose  
3 catheters were the source of infection, and who did and did  
4 not have a catheter withdrawal to show that infection from  
5 a removable focus reduces mortality.

6 So although in some rigorous studies they could  
7 not prove that, for example, a catheter-related infection  
8 was different than a noncatheter-related bloodstream  
9 infection or removing a focus affected mortality, I don't  
10 believe that the studies have enough power to rule that  
11 out, and common sense would dictate that that would have an  
12 effect.

13 A few points if you're, again, thinking about  
14 clinical trials of bloodstream infections, particularly  
15 those related to catheters. I think it's important to know  
16 what happens with regard to adjunctive therapy -- again,  
17 such as removing a catheter -- and I wanted to point out  
18 three important observations.

19 Dr. Raad and colleagues have shown that there  
20 was a three-fold higher risk of recurrent coagulase-  
21 negative staphylococcal bacteremia if patients with a  
22 colonized catheter did not have the catheter removed. So  
23 these were patients who by quantitative blood cultures had  
24 a colonized central venous catheter, the bloodstream  
25 infection was eradicated with initiation of antibiotics,

1 but when they followed those patients throughout their  
2 hospitalization, there was a dramatically increased, three-  
3 fold higher risk of recurrent bacteremia. If you were  
4 going to look at an antibiotic efficacy trial and you did  
5 not keep track of whether or not the catheters were  
6 removed, you would have lost out on that important and  
7 confounding variable.

8 In another study, published recently in the  
9 Archives of Internal Medicine, there was a four-fold higher  
10 risk of death from staph aureus from catheter-related  
11 bloodstream infection if the catheter was left in situ for  
12 more than 48 hours after the onset of bacteremia. Again,  
13 removal of the catheter impacting on the ultimate endpoint  
14 of mortality.

15 Then Dr. Maki and colleagues looked at patients  
16 with candidemia and found that those patients whose  
17 candidemia was transient had a catheter in place for a day  
18 or less after the candidemia was detected. However, when  
19 they looked at the patients with septic thrombophlebitis  
20 due to candida, so septic thrombophlebitis of the great  
21 central veins, the medium duration of catheterization after  
22 the first blood culture was positive was six days, again  
23 suggesting that leaving the catheter in place led to a bad  
24 outcome, despite initiation of antimicrobial therapy.

25 Independent risk factors for crude mortality

1 from catheter versus noncatheter-related bloodstream  
2 infection. Mortality from staph aureus-related bacteremia  
3 was 17-fold higher if due to pneumonia, and 12-fold higher  
4 if the source was unknown, compared to an intravascular  
5 catheter as a source of bloodstream infection. This is  
6 from a publication within the last couple of months, again  
7 suggesting that looking at crude mortality, and staph  
8 aureus in this case, the source of the bloodstream  
9 infection had a dramatic impact on mortality.

10 In a study that Dr. Maki and I and another  
11 physician, Dr. Felesak, carried out a few years ago, we  
12 also show that mortality from a catheter-related  
13 bloodstream infection was 12-fold lower if you compared  
14 that to other sources of bloodstream infection, again  
15 suggesting that catheter-related bloodstream infections  
16 have a lower associated mortality, and I believe that's  
17 because you have identified a source and it's a source that  
18 can be removed, unlike, for example, bloodstream infection  
19 from pneumonia, you can't remove the lung. If it's unknown  
20 source, you don't know if there's an abscess to drain. So,  
21 again, another important confounder.

22 I left out a slide, but put this blank here to  
23 remind me also of a study by Arno that was published in CID  
24 in 1993, where they looked at complicated catheter-related  
25 bloodstream infections and what they found was that 83

1 percent of those cases were due to staph aureus or candida,  
2 and the highest attributable cost of these infections, by  
3 far and away, were associated with staph aureus compared to  
4 other pathogens. So I think the pathogens do play a role,  
5 looking at some potential endpoints with regards to cost  
6 and mortality.

7 Well, why are we talking about this today? As  
8 Dr. Ross pointed out, the incidence of bloodstream  
9 infection is increasing. There are a number of studies  
10 that have shown that. This is the CDC data published in  
11 the American Journal of Medicine in 1991 looking at primary  
12 bloodstream infection in the U.S. at hospitals of various  
13 sizes. For example, these are large teaching hospitals,  
14 these are numbers of bloodstream infections per 1,000  
15 discharges, and you can see the rate during the 1980s  
16 nearly doubled for large teaching hospitals and increased  
17 also for other smaller teaching and non-teaching hospitals.  
18 So the incidence of bloodstream infection per 1,000  
19 discharges is clearly going up.

20 Now, why is it going up? This is again from  
21 the CDC data. If you'll look, there's one striking  
22 increase here compared to -- these are different pathogens.  
23 Again, number of bloodstream infections per 1,000  
24 discharges, these are years, and you can see this dramatic  
25 rise here and this is coag-negative staph. So coag-

1 negative staph accounts for a large part for this increase  
2 in bloodstream infection in U.S. hospitals today.

3 This was from a publication this month in our  
4 Infection Control Journal, where it was a meta-analysis of  
5 coag-negative staph bacteremia. This was the incidence of  
6 coag-negative staph nosocomial bacteremia per 1,000  
7 admissions at university hospitals throughout the United  
8 States. This starts here at 1970 and this ends up here.  
9 Actually, I think the last data point was 1993.

10 You can see here the striking increase. This  
11 is coag-negative staph bacteremia episodes, again per 1,000  
12 admissions. So a striking increase of coag-negative staph  
13 bacteremias per numbers of admissions in U.S. hospitals  
14 today.

15 Why is this the case? I think, in large part,  
16 this is due to an increased placement, an increased number  
17 of patients in hospitals today with intravascular devices.  
18 So what is the role of intravascular devices in defining  
19 this increased incidence of bloodstream infection in the  
20 U.S.?

21 Again, these are the studies by Weinstein,  
22 Reller, and colleagues where they looked at a thousand  
23 bloodstream infections in two multicenter studies. If you  
24 look at what was the role of the intravascular catheter as  
25 the source of these bloodstream infections from the first

1 study in the 1970s, 3 percent of the bloodstream infections  
2 had an intravascular catheter as the defined source  
3 compared to the study in the early 1990s, 19 percent.

4 So the number of bloodstream infections are  
5 increasing, the incidence of coag-negative staph as a cause  
6 of those bloodstream infections is increasing and is in  
7 large part responsible for the increase, and that may also  
8 reflect the increased placement and use of intravascular  
9 catheters today.

10 Positive blood cultures. Just kind of setting  
11 a foundation here, most common isolates in order of  
12 incidence in the Weinstein study, and this should actually  
13 be 1997 and not 1998, coag-negative staph was number one;  
14 staph aureus, number two; E. coli, number three;  
15 enterococcus, four; and then miscellaneous gram-negatives.

16 It's important to know that isolation in the  
17 blood of coag-negative staph often, more than 80 percent of  
18 the time, represent contamination or clinically  
19 insignificant isolation. Isolation of corynebacteria,  
20 bacillus, or P. acnes nearly always, more than 90 percent  
21 of the time, represents contamination. In this large  
22 study, nearly half of the strep viridans in the blood  
23 culture were contaminants or of no clinical significance.  
24 However, candida, acid fast organisms, gram-negatives, and  
25 staph aureus were essentially considered true pathogens in

1 nearly 100 percent of the cases.

2           So coag-negative staph, while it is the most  
3 common blood culture isolate and cause of true bloodstream  
4 infection, it's also the most common contaminant, and  
5 therein lies one of the quagmires that we're trying to  
6 define today.

7           Just so we're all on the same footing, primary  
8 bloodstream infection as something used in the literature,  
9 it's in part a surveillance term, and that is to define  
10 bloodstream infections where there is no clear source based  
11 on physical exam or available cultures, and many of these  
12 cases are I.V./catheter-related.

13           The other thing I wanted to point out before I  
14 forget is I've tried to use the term "bloodstream  
15 infection." I've seen in the literature people writing  
16 about there were 10 candida bacteremias, and so I would  
17 like to suggest that we use the term "bloodstream  
18 infection" rather than bacteremia for defining anything  
19 that can grow in a blood culture.

20           A secondary bloodstream infection is defined as  
21 where the source is identified based on exam or available  
22 cultures, such as from a urinary source or otherwise. It's  
23 also important to realize, again, with clinical studies  
24 that bloodstream infections may be transient, and most of  
25 them are, and these may follow something as simple as

1 manipulation of a nonsterile mucous membrane or may be  
2 associated with an acute infection, and they may be  
3 intermittent, as can occur with an undrained abdominal  
4 abscess, or continuous with endocarditis, suppurative  
5 thrombophlebitis, and a few other infections.

6           How about detecting the bloodstream infection?  
7 Blood culture volume is the single most important  
8 determinant of yield. It's very important to realize that  
9 the concentration of bacteria in the blood of adult  
10 patients who are bacteremic can be pretty low. In one in  
11 five adults with bloodstream infection with a bacteria,  
12 there is less than 0.1 colony forming unit per mL. So if  
13 you draw less than 10 mLs, you're going to miss one in five  
14 bloodstream infections. So it's very important for any  
15 studies that the investigators collect at least 20 or 30 mL  
16 of blood in adults from two separate sites. Never collect  
17 a single blood culture set in an adult patient. I'll come  
18 back to drawing blood cultures through catheters in a few  
19 moments.

20           Back to the Bates and Lee study, the few  
21 studies that were published JAMA, they looked at what were  
22 the independent predictors of true positive and false-  
23 positive bloodstream infection, and I just wanted to share  
24 their results with you, as I think they are important to  
25 think about in clinical trials.

1                   Growth of pathogens in the blood within 24  
2 hours was a marker of true infection. When the same  
3 microbe was cultured from another source -- say, a catheter  
4 tip in a blood culture -- this was an independent marker of  
5 a true positive blood culture. When there were at least  
6 two positive blood cultures that eventually turned positive  
7 in the same patient, that was an independent predictor.

8                   Then predictors for false-positive blood  
9 cultures were when the blood culture was drawn through a  
10 catheter and when the patient was uncooperative. The  
11 uncooperative patient is something that I think had  
12 previously been underappreciated. Recognize that a patient  
13 is moving around and you send your third-year medical  
14 student down the hall to draw the blood culture, and the  
15 patient is thrashing around in the bed, this is obviously  
16 going to be a greater risk of contamination and is  
17 something to keep mindful of.

18                   Now, should we define bloodstream infection  
19 using clinical criteria or microbiological criteria such as  
20 clearance? One of the problems that I have is, for  
21 example, with terms like "catheter sepsis." Dr. Ross  
22 talked about the definitions of sepsis, but if you look at  
23 studies of coag-negative staph bacteremias, their symptoms  
24 may be more subtle than with some other pathogens.

25                   For example, I looked at four relatively recent

1 prospective studies of coagulase-negative staphylococcal  
2 bloodstream infections, and if you look at the percent of  
3 patients that had a temperature greater than 38 degrees  
4 centigrade, it varied in the studies from 71 percent to 100  
5 percent. Leukocytosis varied 55 percent to 71 percent. So  
6 many of the patients with coagulase-negative staphylococcal  
7 bloodstream infection may not meet some of the criteria,  
8 for example, for sepsis, despite the fact they're known to  
9 have an ongoing bacteremia.

10 The other question that comes up with coag-  
11 negative staph, and I wanted to spend a few moments on this  
12 because, again, I think this is going to be an isolate any  
13 study on bloodstream infection would have to contend with,  
14 is how should we define whether or not it's a true isolate  
15 or a contaminant?

16 Lorraine Herwaldt a few years ago published  
17 this study in CID. They actually came to a conclusion, I  
18 think, suggesting that one positive blood culture with  
19 coag-negative staph with the appropriate clinical symptoms  
20 could cause true infection, and I would agree with that.  
21 However, I think in doing clinical studies to get a drug on  
22 the market, I would suggest requiring for coagulase-  
23 negative staph two or more blood cultures.

24 If you look at her data broken down with one  
25 positive blood culture versus two or more nonsimultaneously

1 drawn cultures, and if you look at how many of these  
2 patients had clinical infection using CDC criteria, 63  
3 percent of the patients with two or more positive blood  
4 cultures compared to 11 percent with one positive blood  
5 culture for coag-negative staph.

6 So can you have bacteremia true bloodstream  
7 infection with coag-negative staph defined by a single  
8 positive blood culture and have clinical symptoms? Sure,  
9 you can, but I think to do clinical trials approving a new  
10 antimicrobial I would suggest that we would have greater  
11 power using two or more positive blood cultures.

12 How many of these patients had a left-shift in  
13 their CBC? Forty percent with two or more positive blood  
14 cultures, 6 percent with one positive. How many had growth  
15 of staph epidermitis which was an independent marker of  
16 true bloodstream infection? Ninety-five percent with two  
17 or more positives, 76 percent with one positive. Also, in  
18 her study the most predictive independent variable of  
19 clinical infection was two positive simultaneously drawn  
20 blood cultures with an odds ratio of 6.

21 So it suggests to me that, yes, patients with  
22 one positive blood culture for coag-negative staph can have  
23 true infection, but my humble opinion is we should require  
24 two or more positive blood cultures.

25 Well, then the issue comes up there are various

1 different strains of coag-negative staph. I wanted to  
2 share with you this relatively shocking study that came out  
3 of one of the Boston groups that was presented a couple of  
4 weeks ago at ICAAC. What these investigators did is they  
5 looked at coagulase-negative staphylococci growing out of  
6 blood cultures, presumably coagulase-negative staphylococci  
7 bloodstream infection, and they looked at using pulse field  
8 gel electrophoresis when patients had two or more positive  
9 blood cultures within 14 days, although with 88 percent of  
10 these patients the blood cultures were positive within five  
11 days.

12           How often were these different blood cultures  
13 representing a single clone versus a polyclonal bloodstream  
14 infection? We would like to believe that most of these  
15 episodes, or the predominance of them, are due to a single  
16 clone, but interestingly, in a relatively small number of  
17 patients, when they looked at how many met CDC criteria for  
18 bacteremia, there really was no dramatic difference when  
19 they looked at whether or not this was a single clone or  
20 multiple clones of coag-negative staph. When they looked  
21 at whether or not the physicians treated the patients,  
22 there were somewhat fewer that were treated when they were  
23 polyclonal, but no marked differences.

24           So should we use something like genomic  
25 analysis to determine whether or not someone has a true

1 coagulase-negative staphylococcal bloodstream infection?  
2 Now, I would like to see this data. I think we should, and  
3 I'll come back to that in a moment.

4           If you look at the study again, these were  
5 blood cultures collected within 14 days, most of them  
6 within five days. I would venture to guess, although I  
7 don't have proof, that if this study was replicated with  
8 blood cultures collected over 48 hours, at most, or 24  
9 hours, that most of those repeated positive blood cultures  
10 would represent a single clone.

11           Some support of that was a study in the Journal  
12 of Clinical Microbiology a few years ago of suspected coag-  
13 negative staph catheter sepsis. The study criteria were  
14 two or more positive blood cultures growing coag-negative  
15 staph for each of 11 episodes with positive catheter-drawn  
16 and percutaneously-drawn blood cultures obtained within  
17 seven days, but the median was actually 17 hours. So here  
18 were two sets of blood cultures drawn percutaneously and  
19 through a catheter, most of them drawn within hours of each  
20 other, they both grew coag-negative staph, and the isolates  
21 were all clonal in all of these 11 cases by pulse field gel  
22 electrophoresis.

23           Also interestingly, with regards to drawing  
24 blood cultures through catheters, they had eight instances  
25 in which all the blood cultures were drawn through the

1 catheter and in which two or more of the blood cultures  
2 were positive, and these were actually drawn within minutes  
3 of each other, but through different catheter lumens and,  
4 interestingly, half of these were polyclonal, I think  
5 making the picture somewhat murky.

6           So I think, based on some of this data, that if  
7 blood cultures are drawn within a relatively short period  
8 of time between sets and from two different sites and they  
9 grow coag-negative staph, then most of these are going to  
10 be one clone by pulse field gel electrophoresis.

11           Then how should we define bloodstream  
12 infection? Well, it is the presence of microbes in the  
13 bloodstream as measured by blood cultures, antigens, and I  
14 think starting now and into the future, by oligonucleotides  
15 using PCR or possibly other technology that is usually, but  
16 not necessarily, accompanied by an inflammatory response.  
17 The symptoms may vary. Microbial invasion of the  
18 bloodstream is often transient, which is going to make it  
19 difficult to study -- if the bloodstream infection is going  
20 to be cleared even without antibiotics in some cases, how  
21 are you going to measure endpoints? -- but may be  
22 continuous, and symptomology seems to be somewhat pathogen  
23 and host-dependent.

24           There is no unique set of symptoms to define  
25 bloodstream infection. I'm going to skip the rest of this

1 slide, but I think that's something very important, is  
2 basically there's no unique set of symptoms that I know of  
3 to define bloodstream infection and separate it by symptoms  
4 and signs from other sorts of infection.

5 For the purposes of clinical investigation at  
6 the present time, bloodstream infection should be  
7 determined by the presence of microbes from at least one  
8 percutaneously-drawn blood culture. Although a single  
9 blood culture with growth of bacteria that are potential  
10 skin contaminants, such as coag-negative staph, may reflect  
11 a true infection, growth of the same microbe -- and there's  
12 a typo on this slide, I apologize -- growth of the same  
13 microbe from greater than or equal to two -- not one, but  
14 two -- blood cultures, at least one percutaneously drawn,  
15 so two blood cultures, at least one percutaneously drawn,  
16 should be required for potential skin contaminants.

17 How about defining intravascular catheter-  
18 related bloodstream infection? Well, concordant microbial  
19 growth between one of the following: a catheter segment,  
20 hub, infusate, or exit site, or tunnel exudate, and a  
21 percutaneously drawn blood culture. If quantitative blood  
22 cultures are used, I think this can also be defined then as  
23 concordant microbial growth between a quantitative  
24 catheter-drawn and percutaneously-drawn blood culture, in  
25 which case the colony forming units of the catheter-drawn

1 blood culture is at least four-fold higher than with  
2 percutaneously-drawn blood cultures. So this would be to  
3 define catheter-related infection, say, in those instances  
4 when the catheter is not going to be removed.

5           How should we define concordance of isolates,  
6 such as with coag-negative staph? When evaluating an  
7 intervention in a clinical trial with bloodstream infection  
8 as an endpoint, I think this requires rigorous and  
9 reproducible criteria. If blood cultures in a catheter  
10 segment or hub infusate or exit site exudate grow a  
11 potential skin contaminant, concordance should be defined  
12 as genetically related by genomic DNA by molecular  
13 fingerprinting, such as using pulse field gel  
14 electrophoresis with three or less band differences among  
15 the isolates.

16           What are some of the essential variables that  
17 should be studied? I think, clearly, that if and when  
18 these studies are carried out for FDA approval, the  
19 pathogen obviously needs to be noted. I talked a bit about  
20 the importance of underlying comorbidities, as the Bates  
21 study suggested, that this has a profound impact on  
22 mortality, obviously, and this potential confounder needs  
23 to be clearly controlled for, as well as immunosuppressive  
24 medications. Whether or not this source is a primary  
25 bloodstream infection, which basically is an unknown

1 source, or a secondary, a known source, as that also may  
2 affect mortality, adjunctive therapy is extremely  
3 important, and it's of utmost importance to know if looking  
4 at, say, a new antimicrobial that is used for catheter-  
5 related infections whether or not the device or foreign  
6 body, or any other foreign body, for that matter, is  
7 removed or abscesses are drained or whatever other  
8 adjunctive therapy is taking place in the patient  
9 population.

10 Duration of bacteremia, fungemia, fever, and  
11 duration of leukocytosis after initiation of treatment with  
12 the agent under study also needs to be measured and could  
13 potentially be used as your endpoints.

14 I think it's also important to determine in  
15 these patients whether or not they have a complicated or an  
16 uncomplicated bloodstream infection. This is a term  
17 seemingly simple, but Sam Raad I think elucidated this in a  
18 study of staph aureus bloodstream infections a few years  
19 ago, and what he found was that for those patients that had  
20 three or more days of positive blood cultures and/or fever  
21 after initiating appropriate therapy, all had much more  
22 complicated hospital courses. They had endocarditis,  
23 meningitis, septic embolyte of the lung, abscesses of solid  
24 organs, et cetera.

25 So I think this needs to be separated out with

1 new intervention studies whether or not these patients have  
2 complicated or uncomplicated bloodstream infection, and for  
3 complicated cases, I think it's very important that studies  
4 systematically do the appropriate workup to rule out things  
5 such as endocarditis, septic thrombophlebitis, and  
6 metastatic infections.

7           Looking at mortality, based on the Bates study  
8 and others, I think mortality needs to be measured within  
9 14 to 30 days, as mortality after that is much more likely  
10 to be due to the underlying illness. It's important also  
11 to then look at attributable cost.

12           Some of the unanswered questions. There are  
13 many. We're here today discussing something that in the  
14 minds of a clinician every day they have to grapple with.  
15 The average physician or the better than average physician  
16 still doesn't know the answer to some of the most important  
17 questions with regards to bloodstream infection.

18           How do we differentiate blood cultures  
19 contaminated with skin flora from skin flora causing true  
20 bloodstream infection? What parameters should be used to  
21 separate a clinically significant from a clinically  
22 nonsignificant bloodstream infection? How should we  
23 interpret catheter-drawn versus percutaneously-drawn blood  
24 cultures and what is the clinical significance of each? Do  
25 we need to treat these patients with I.V. antibiotics or

1 oral antibiotics? How long do we treat these patients?  
2 These are very important, pressing questions that are posed  
3 to clinicians every day, and that I think clearly need to  
4 be answered.

5 So I'll stop there with a quote. "Now that I  
6 know I'm no wiser than anyone else, does this new wisdom  
7 make me wiser?"

8 I appreciate your time and your attention.  
9 (Applause.)

10 DR. CRAIG: Thank you, Leonard.

11 The next presentation will be an industry  
12 perspective by Mike Zeckel from Eli Lilly and Company.

13 DR. ZECKEL: First of all, I'd like to thank  
14 the committee for allowing me to address you today and also  
15 to the FDA for giving me an opportunity to discuss our  
16 concerns about bacteremia as a potential indication for  
17 approval.

18 First of all, I'd like to show you why some  
19 companies such as ours are interested in looking at  
20 bacteremia or bloodstream infection as an indication. In  
21 the early 1990s we noticed this trend, and this is  
22 essentially NNIS data where I combined gram-positives  
23 together and gram-negatives together to show the difference  
24 in the epidemiology of bloodstream infections between 1980  
25 and 1990.

1           As you can see also looking at the percent of  
2 those pathogens that are resistant, one also sees a pretty  
3 definite trend among gram-positives. Looking at the  
4 proportion of coagulase-negative staph that are now  
5 resistant to beta-lactams, it's up to around 80 percent,  
6 and you can see for MRSA, PRSP, and now VRE, and soon GISA,  
7 or glycopeptide resistant staph aureus, there seems to be a  
8 trend that would suggest there is a need for agents active  
9 against resistant gram-positive infections, which, of  
10 course, is why we and other companies are interested.

11           Our problem was that when we looked at what are  
12 allowable indications within the United States and how can  
13 we develop a drug against these resistant pathogens, we had  
14 a problem. When you look here, we could look at meningitis  
15 where we can define the pathogen, but many of the  
16 indications are actually syndromes that are defined by  
17 symptoms, and one often does not know the results of  
18 culture prior to beginning treatment, and actually waiting  
19 for the results of culture prior to starting treatment  
20 actually changes the natural course of the disease.

21           We didn't see anything that made us comfortable  
22 except perhaps osteomyelitis, septic arthritis, and  
23 endocarditis as indications, and perhaps skin. But we  
24 didn't want to jump to those more severe infections until  
25 we had an idea whether the drug might work for less serious

1 infections, and one that we thought about was bacteremia,  
2 for several reasons.

3 We think that bacteremia is the justifiable  
4 indication for consideration for approval for several  
5 reasons. First, we think, as Dr. Mermel stated so nicely  
6 before, that it is an important cause of morbidity and  
7 mortality. Actually, in all countries that have at least  
8 intensive care units, it seems to be a well-recognized  
9 clinical entity, although different individuals differ on  
10 how they define it.

11 Bloodstream infections are similar to currently  
12 approvable indications, given that there is patient  
13 heterogeneity, there are questions about the significance  
14 of positive cultures, and there are diversity among the  
15 clinical and microbiological outcomes depending on the  
16 primary site of infection, but we maintain that these  
17 differences, these heterogeneities, are not unique to  
18 bacteremia and they actually occur in other infections.  
19 For instance, intraabdominal infection, is that truly one  
20 disease or is it really a conglomeration of similar  
21 diseases?

22 Then lastly, we're concerned that the absence  
23 of a bacteremia indication actually leaves clinicians  
24 without clear guidance as to what drugs might work and what  
25 drugs clearly don't work in bacteremia.

1 I think I'll skip this slide except to show  
2 that the data agrees very much with Dr. Mermel's slide that  
3 this is an important cause of morbidity and mortality.

4 Looking at attributable mortality, there have  
5 been several case-control studies that have looked at how  
6 much mortality might be attributable to the finding of  
7 bacteremia. Now, all of these are case-control studies and  
8 they all have potential flaws, but they seem to show a  
9 similar story. That is, that there is some evidence that  
10 one can attribute some mortality to the occurrence of  
11 bacteremia after matching for other factors that may affect  
12 mortality.

13 This is just one very large meta-analysis that  
14 appeared in JAMA that reviewed 122 papers on pneumonia  
15 looking at prognostic factors for death. You can see that  
16 in this meta-analysis involving over 30,000 patients that  
17 there appears to be an association, whether or not there's  
18 a true risk factor or not, at least an association between  
19 the occurrence of bacteremia in patients with community-  
20 acquired pneumonia and death.

21 Similarly for ICU patients, at least if you use  
22 a technique of multiple logistic regression, you can see  
23 that there is evidence that for patients admitted to the  
24 ICU there appears to be at least an association between  
25 bacteremia and mortality in ICU patients.

1           This is a study that tried to match patients  
2 admitted to the ICU. Looking at all the patients admitted  
3 to this ICU, 384 patients, matched controls -- that is,  
4 controls to patients with bloodstream infection -- there  
5 were only 34 in this study, and they matched them based on  
6 their Apache scores, and then asked does bacteremia add  
7 extra mortality over and above what one might expect based  
8 on Apache scores upon ICU admission?

9           This is not Apache score at the time of sepsis,  
10 and you can see that there is equal predicted mortality  
11 based on Apache, but the actual mortality in patients with  
12 bloodstream infection in this study suggested that there's  
13 incremental mortality just by having bacteria in the blood  
14 in this setting.

15           There's also worldwide differing opinions about  
16 what could be a definition for bacteremia, but at least  
17 there are people that have spent a considerable amount of  
18 time trying to standardize definitions. Of course, these  
19 are definitions mostly for surveillance, but they could  
20 serve as a basis for standard definitions for clinical  
21 trials for intervention.

22           One of the complaints about bacteremia as an  
23 indication is that the blood culture has a lot of false-  
24 positives and false-negatives. I just took this data from  
25 Weinstein's large study looking at positive predictive

1 value of a positive blood culture. Of course, you see for  
2 coagulase-negative staph, CNS up there, that the predictive  
3 value of at least a single positive blood culture is not  
4 very good, but for staph aureus it's around 85 to 90  
5 percent, for enterococcus and for strep pneumonia it's very  
6 good, and of course for gram-negatives it's excellent. So  
7 as a diagnostic test, except for coag-negative staph and  
8 maybe viridans streptococci, the test is really pretty  
9 good.

10 With regard to coagulase-negative staph, from  
11 this same study, if you look at the number of positive  
12 cultures for coag-negative staph divided by the number that  
13 were actually drawn, it appears that you don't start  
14 getting a high true positive rate until you get at least  
15 two positive blood cultures. But after that, it appears to  
16 be very good. That is, between 60 and 100 percent positive  
17 predictive value.

18 The other problem that people are concerned  
19 about is the heterogeneity of patient populations. The  
20 first thing I'd like to show on this slide, this is just  
21 four different studies looking at the different sources for  
22 bacteremia, and you can see that there are a wide number of  
23 different sources. For awhile we thought that maybe we  
24 could try to develop a study for intravenous line-  
25 associated bacteremia, but when we looked at data such as

1 these, we became concerned that we would then exclude about  
2 80 percent of such cases if we required that they all have  
3 lines, and besides, there's evidence that since lines are  
4 removable, maybe we would actually develop misleading  
5 information if we only studied line-related disease.

6 Of course, the other possibility is looking at  
7 primary infections and then their bacteremia component,  
8 such as nosocomial pneumonia with bacteremia. The trouble  
9 with the selective spectrum agent is how does one define  
10 gram-positive pneumonia in the ICU setting?

11 We already know that MRSA colonizes a large  
12 number of patients. We know if we have 100 patients with  
13 pulmonary infiltrate and positive blood cultures that we  
14 can't necessarily assume that the organism in the blood is  
15 the same organism as in the lung. So there are a lot of  
16 problems with identifying a specific site of infection,  
17 and, furthermore, about one in four patients with  
18 bacteremia have an unknown source for their primary  
19 infection. Those people probably should be studied and, of  
20 course, treated with approvable agents also.

21 This is looking at, well, what if we tried to  
22 identify primary sites of infections in patients with  
23 bacteremia? This is a study by Myers that was published  
24 now 15 years ago and it was looking at MRSA. You can see  
25 the percent of these different sites that turned out to be

1 culture-positive in patients with bloodstream infection.

2           If you total up the percentages, they are more  
3 than 100 percent, suggesting that actually a majority of  
4 patients have multiple positive sites for culture, making  
5 it even more difficult to attribute the infection to a  
6 primary site. About 27 percent of patients with staph  
7 aureus bacteremia have at least one metastatic site, about  
8 27 percent, but half of those have more than one metastatic  
9 site. So, again, finding the primary site and then saying  
10 we're going to study patients with a primary infection  
11 complicated by bacteremia is much easier said than done.

12           There's also been some concern that there are  
13 great differences among the different pathogens with regard  
14 to how serious an infection they can cause. That may well  
15 be true as you look at these data. The light blue is  
16 sepsis, the red is severe sepsis, and the yellow is septic  
17 shock, accounting for 100 percent. In this study, the  
18 patients had sepsis, which is not a high threshold to meet  
19 anyway, SIRS, prior to getting the blood culture.

20           So this was a naturalistic study and it shows  
21 that patients with coagulase-negative staph may have less  
22 severe sepsis than patients with staph aureus, but it  
23 doesn't appear to be a great difference in kind. That is,  
24 it may be a difference in quantity, but not a difference  
25 any greater than one would expect looking even at otitis

1 media and the difference between strep pneumonia and H. flu  
2 in terms of the seriousness of disease or even spontaneous  
3 resolution.

4 I'm going to skip this slide. This just shows  
5 the mortality for different pathogens. They do differ  
6 among pathogens.

7 What I would like to show, though, is that  
8 although there may be differences in outcome, a lot of  
9 heterogeneity based on the primary source of infection,  
10 there is also a lot of heterogeneity related to other  
11 factors, such as the severity of illness, Apache score,  
12 whether or not there is shock, whether or not the patient  
13 received adequate therapy, as well as whether or not the  
14 patient had or did not have meningitis.

15 What I'm saying is that even though there is a  
16 lot of heterogeneity among patients with bacteremia,  
17 depending on the primary site of infection, that  
18 heterogeneity is no greater than the heterogeneity related  
19 to differences in patients -- elderly patients versus  
20 healthy adults -- and that that heterogeneity could be  
21 taken care of in large part by the randomization process  
22 and not by overstratification.

23 In conclusion, I'd like to support the idea  
24 that bacteremia is an important cause of morbidity and  
25 attributable mortality; that bacteremia can be recognized

1 and clinically defined, and although the definition can  
2 never capture all patients or be totally satisfactory,  
3 that's not unique to bacteremia; that bacteremia is similar  
4 to currently approvable indications in that there is a test  
5 with a reasonable positive predictive value; that there is  
6 heterogeneity among patients and outcomes, but that that  
7 heterogeneity is not significantly greater than that we  
8 accept for currently available indications; and that there  
9 is a need to account for adjuvant therapy in bacteremia  
10 that can be designed within trials, so even though we say  
11 we need to account for whether a line is pulled or  
12 retained, that can be designed in the trial prospectively.

13 A bacteremia indication should not be  
14 restricted to line-related disease, we believe, because it  
15 then excludes 80 percent of patients with bacteremia and  
16 could give people a false idea of the efficacy of the drug,  
17 and people might extrapolate that to people with more  
18 serious bacteremic disease. We think all bacteremia should  
19 be studied.

20 Then lastly, that the absence of a bacteremia  
21 indication is not a neutral stance. Essentially, it takes  
22 away from clinicians the potential for having some  
23 guidance. That is, should one use a macrolide to treat  
24 staph aureus bacteremia or not, and in the absence of an  
25 indication that says for this drug it is reasonable to use

1 it, for this type of indication it is not, the absence of  
2 that kind of distinction also puts clinicians at a  
3 disadvantage.

4           Lastly, we'd just like to propose, if I can  
5 have one last slide, please, that if one believes that  
6 bacteremia could become an indication, that there are  
7 several points that one might start from. We would like to  
8 request that the committee at least consider the  
9 possibility of a bacteremia indication and that we look at  
10 some potential design components that could be thrashed out  
11 over time in a way that would give clinicians clear  
12 guidance as to what drugs may work in the treatment of this  
13 disease.

14           I'd like to thank you.

15           (Applause.)

16           DR. CRAIG: Thank you, Mike.

17           The next speaker is my colleague, Dennis Maki,  
18 from the University of Wisconsin Medical School, who will  
19 provide an argument for bacteremia as an indication based  
20 on clinical data.

21           DR. MAKI: First of all, I'd like to just  
22 reaffirm what some of the others have said. Namely, that  
23 the evidence is very clear that the incidence of  
24 bloodstream infection has increased very substantially in  
25 the last 25 years. These are federal Medicare data and

1 they look at both community and hospital-acquired  
2 bloodstream infections, and there was a doubling between  
3 1979 and 1987.

4           If we look at bloodstream infections acquired  
5 in hospitals, these are the NNIS data from the CDC over the  
6 decade of the 1980s, and the increase was more than 60  
7 percent. I would particularly point out that the greatest  
8 increase was in primary bacteremias, which are defined as  
9 bacteremias originating from an intravascular device or for  
10 which a primary source is not identified by the clinicians  
11 in the hospital.

12           In terms of vascular devices, there are 200  
13 million intravascular devices used in this country every  
14 year. Dr. Mermel gave us a little bit of an inkling of the  
15 magnitude of this problem. There's probably over 100,000,  
16 perhaps 200,000, bloodstream infections originating from  
17 intravascular devices alone.

18           Moreover, as you've heard for the last two  
19 days, the incidence of infections with antibiotic-resistant  
20 organisms is skyrocketing, whether we're talking about  
21 MRSA, vancomycin-resistant enterococcus, gram-negative  
22 bacilli resistant to extended spectrum beta-lactams and now  
23 quinolones, or even candida. These NNIS data show that the  
24 incidence of candida infections of the bloodstream in U.S.  
25 hospitals has increased more than six-fold in the last 15

1 years. Coagulase-negative staph has increased six-fold.

2 Now, I'd like to present some data from a large  
3 teaching hospital that I think lends support to the  
4 argument that bloodstream infection ought to be accorded a  
5 clinical indication by the Food and Drug Administration.

6 First of all, as you've seen and Dr. Zeckel  
7 pointed out, only a relative fraction of nosocomial  
8 bloodstream infections are currently linked to an  
9 intravascular device. In most centers, less than a  
10 quarter. There's a large proportion of bloodstream  
11 infections in most centers that the source is never  
12 identified. We call these cryptogenic bacteremias or  
13 bloodstream infections.

14 This is an analysis of about 1,100 nosocomial  
15 bloodstream infections identified in my hospital over a  
16 five-year period. I'm going to try and convince you that  
17 probably most of these are device-related. I also want to  
18 point out to you that the morbidity/mortality of all of  
19 these infections is substantial, and that these infections  
20 deserve to be included in FDA-approved indications for new  
21 anti-infectives.

22 First of all, in our hospital, in our  
23 surveillance program we use the CDC definitions for primary  
24 bacteremias and for secondary bacteremias. Basically,  
25 primary bacteremias are true bloodstream infections without

1 a documented source or in which the source is a device, and  
2 that usually is based on a semi-quantitative culture  
3 showing large numbers of the same organism from the device  
4 and we have not been able to identify clearly another  
5 source for the patient's bloodstream infection. Secondary  
6 bloodstream infections clearly originate from a local  
7 nosocomial infection.

8 My hospital I think is a pretty typical  
9 university hospital. We have a large population of high-  
10 risk patients, do a lot of trauma care, a tremendous amount  
11 of cancer care, and we're the second largest surgical  
12 transplant center in the world. We analyzed about a  
13 thousand of these bloodstream infections over this five-  
14 year period of time, and we particularly want to contrast  
15 the profile of clearly line-related versus primary  
16 bloodstream infections not linked to a line or cryptogenic  
17 or secondary bloodstream infections. We collected quite a  
18 bit of data on each one of these cases, including  
19 mortality.

20 Over the five-year period of time, we have  
21 1,100 bacteremias of which only 24 percent were line-  
22 related. I'd point out that the largest portion of  
23 bloodstream infections in our hospital are primary  
24 bloodstream infections and the source is never identified.

25 If we look at the demographic features of these

1 patients, it's very interesting. They are very similar in  
2 terms of age, sex, service, and if we look in an intensive  
3 care unit we're much more likely to have line-related or  
4 cryptogenic without a source, because so many devices are  
5 used for access in ICUs. We also see many more cryptogenic  
6 bacteremias in neutropenic patients and these are very  
7 commonly line-related. If we look at mortality, it is 15  
8 to 19 percent, but does not differ significantly between  
9 these three groups. These are deaths during  
10 hospitalization.

11 Now, if we look microbiologically, only 3  
12 percent of the secondary bloodstream infections were caused  
13 by coagulase-negative staph, whereas 20 to 35 percent of  
14 the primary bacteremias, and cryptogenic was very similar  
15 to I.V.-related. In terms of candida, the largest  
16 proportion of candida bloodstream infections were caused by  
17 lines, but a substantial number were cryptogenic. We find  
18 that gram-negative rod bacteremias or anaerobic bacteremias  
19 were primarily secondary bacteremias and the vast majority  
20 of these were surgical site infections. Strep viridans  
21 were almost exclusively cryptogenic and these were in  
22 profoundly neutropenic patients, who commonly probably have  
23 invasion by severe mucositis in association of  
24 chemotherapy.

25 So to summarize microbiologically, coagulase-

1 negative staph was mainly primary, secondary or primary  
2 gram-negative rods or anaerobes, staph aureus was primarily  
3 I.V.-related, and strep viridans, cryptogenic primary.

4 At the present time, the largest portion of  
5 nosocomial bloodstream infections in our center, more than  
6 half, are cryptogenic. The cryptogenic have a very similar  
7 profile to I.V.-related and are substantially different  
8 from the secondary. We think that probably a very large  
9 proportion of the cryptogenic indeed derive from  
10 intravascular devices, but this was not confirmed by  
11 removing and culturing a device or using paired  
12 quantitative blood cultures or other technologies for  
13 clearly identifying a device as the source of bloodstream  
14 infection.

15 More consistent efforts to diagnose line-  
16 related infections would result in many fewer cryptogenic  
17 bloodstream infections, but this large proportion of  
18 cryptogenic points up starkly the enormous role that  
19 vascular access probably plays in all nosocomial  
20 bloodstream infections and the need for greater efforts to  
21 prevent line sepsis. The morbidity and mortality of  
22 cryptogenic I.V.-related and secondary are comparable.

23 Let me just talk about treatment of bloodstream  
24 infections. This famous paper from Austrian points out  
25 very dramatically it makes a big difference as to whether

1 or not you treat a bacteremia or not. The mortality of  
2 untreated bacteremic pneumococcal pneumonia in the pre-  
3 antibiotic era was close to 90 percent.

4 We also know in terms of multiple studies have  
5 shown that appropriateness versus inappropriateness of  
6 therapies have profound impact on survival of a bloodstream  
7 infection. The most recent data from the paper by Dr.  
8 Weinstein and Dr. Reller have certainly reaffirmed that.

9 If we look at studies in gram-negative  
10 bacteremia, the same thing has been found. Appropriate  
11 therapy as opposed to inappropriate therapy has a profound  
12 impact on survival. In the early antibiotic era, it did  
13 not have much impact on rapidly fatal disease because we  
14 didn't have very good drugs, but if you look at more recent  
15 studies, the more recent studies suggest that even in  
16 patients who have leukemia and have very severe underlying  
17 disease, the best therapy significantly improves outcome.

18 In terms of line-related infections, which is  
19 probably a very large population of bloodstream infections  
20 that need to be treated in hospitals, we can clearly study  
21 bacteremias. I'm going to show you four studies that have  
22 looked at strategies for prevention of line-related  
23 bacteremia. Bacteremia is the endpoint, not colonized  
24 catheters -- bacteremia.

25 Here's a study of a cuff that can be attached

1 to a central catheter at the time of insertion. This  
2 multicenter trial in our hospital and two Stanford  
3 affiliates showed a substantial reduction in bacteremias.

4 Two studies published in the Annals of Internal  
5 Medicine last year looked at the strategy of coating  
6 catheters with anti-infective compounds. This study looked  
7 at chlorhexidine and silver sulfadiazine and showed an 80  
8 percent reduction in line-related bloodstream infections.  
9 This is a blinded trial.

10 A similar study in the same issue from the M.D.  
11 Anderson Center looked at coating catheters with two  
12 antibiotics that have a very broad spectrum of activity and  
13 similarly showed a very substantial reduction in line-  
14 related bacteremias.

15 This final study is a European study looking at  
16 a novel antiseptic hub and was able to demonstrate a very  
17 substantial effect in line-related bacteremia. This is a  
18 very high rate of infection in the control group.  
19 Nonetheless, it's a comparative trial and showed benefit.

20 Now, I would reaffirm that I think bloodstream  
21 infections of all types deserve to be included. I would  
22 particularly point out that the incidence of bacteremia is  
23 increasing and it will probably continue to increase, and  
24 bacteremias cause substantial morbidity and mortality.

25 Secondly, we can define bloodstream infection

1 accurately for the purposes of research.

2 Thirdly, a very large proportion of bloodstream  
3 infections that need to be treated in hospitals are  
4 cryptogenic or they're line-related. We need good data on  
5 how best to treat these infections and we're not going to  
6 get those data without good studies and particularly  
7 studies that provide the justification for recommended  
8 regimens.

9 Fourthly, I think we have to reassess our  
10 endpoints. I think mortality is a crude endpoint. With  
11 bloodstream infection, the rapidity of clearing the  
12 bloodstream, the length of hospital stay, the cost of  
13 hospitalization, and, not least of all, the side effects  
14 associated with the therapy. Many patients treated get  
15 antibiotic-associated diarrhea or colitis, or  
16 superinfection by candida.

17 My last point is that it's astounding to me  
18 that 40 years into the antibiotic era, with the great  
19 importance of bloodstream infection as a life-threatening  
20 infection, that we have so little data that has examined  
21 the relative utility of different classes of drugs for  
22 treating the same infection.

23 For instance, perhaps using a quinolone for  
24 treating gram-negative bacteremia would have a  
25 substantially different outcome than if we used an

1 aminoglycoside or a beta-lactam, because we know that these  
2 drugs have greatly different effects on endotoxin release  
3 and on cytokine production in vitro and in animal models  
4 and probably clinically, and it's not implausible that  
5 different classes of drugs may be associated with not only  
6 different outcomes in terms of efficacy, but substantially  
7 different side effects in terms of antibiotic-associated  
8 diarrhea, colitis, candida, superinfection, and the like.

9 Thank you.

10 (Applause.)

11 DR. CRAIG: Thank you, Dennis.

12 The last presentation, which I understand will  
13 be a little more brief, is David Ross again on the  
14 regulatory perspective.

15 DR. ROSS: I'm going to spend a few minutes  
16 talking about regulatory aspects of bacteremia as an  
17 indication. The central theme that I would ask the  
18 committee to think about is how we define what an  
19 indication is. I'm going to start by presenting the  
20 regulatory framework for this issue, talk about how we've  
21 defined anti-infective indications, talk about some issues  
22 with bacteremia as an indication within this framework, and  
23 then finally finish with questions for the committee.

24 I think a question I'd like to start with is  
25 what is a drug intended for? Well, it can be intended for

1 a lot of things, but under the Food, Drug, and Cosmetic  
2 Act, a drug is defined as something that's intended for use  
3 in the diagnosis, cure, mitigation, treatment, or  
4 prevention of disease. In other words, it has to be  
5 something that is clinically relevant. The act goes on to  
6 provide that approval of marketing for intended use has to  
7 be based on demonstration of effectiveness for the intended  
8 use in adequate and well-controlled investigations.

9 In terms of implementing this in the  
10 regulations, the question of what is a drug indicated for  
11 is answered as follows. A drug can be labeled as being  
12 indicated for treatment, prevention, or diagnosis of a  
13 recognized disease or condition, an important manifestation  
14 of a disease or condition, for relief of symptoms  
15 associated with a disease or syndrome, or as an adjunct to  
16 a primary mode of therapy.

17 So in terms of implementing this with respect  
18 to anti-infectives, at the current time an anti-infective  
19 indication is defined as infection at a specified body site  
20 due to a specified susceptible microorganism, and that's a  
21 definition found in the points to consider document from  
22 1992.

23 I think it's important to note that this  
24 definition allows us to account for differences in drug  
25 efficacy for infections at different sites, which is a

1 point I'll talk about a little more in a minute, and it  
2 allows demonstration of effectiveness from adequate and  
3 well-controlled investigations by letting us study an  
4 identifiable patient group with infection at a specified  
5 body site due to a specified susceptible microorganism.

6 So to summarize sort of what the essentials of  
7 an anti-infective indication are, it has to be a recognized  
8 disease or condition or an important manifestation of a  
9 disease, and it has to be defined in terms of clinical  
10 manifestations, diagnostic criteria, and therapeutic  
11 requirements that allow us to study a specified patient  
12 group, so that effectiveness of a drug for an indication  
13 can be demonstrated by adequate and well-controlled trials  
14 using clinically relevant endpoints.

15 In terms of what is an indication, and an anti-  
16 infective indication, and what is not an indication, we  
17 have some well-recognized anti-infective indications and  
18 non-indications. Again, I want to emphasize these are  
19 anti-infective indications. Osteomyelitis, for example, is  
20 a well-recognized indication. An elevated erythrocyte  
21 sedimentation rate is not, even though it may be clinically  
22 relevant and may play an important role in deciding how to  
23 treat a patient.

24 So let me move on to talk about some issues  
25 from a regulatory perspective with bacteremia as an

1 indication. I think it's important to recognize that the  
2 set of bacteremic patients is composed of a lot of  
3 different subsets, some of which overlap with the  
4 population of bacteremic patients and some of which don't  
5 and, obviously, within any of these subgroups there can be  
6 a fair degree of heterogeneity.

7 But I think one reason for using the current  
8 definition of an indication is that it allows us to  
9 determine drug efficacy within a particular set of  
10 patients, whereas it's maybe difficult to extrapolate from  
11 one indication to another. For example, a drug that is  
12 effective in treating urinary tract infection, for example,  
13 due to E. coli with associated bacteremia, may not be  
14 effective when treating E. coli meningitis with associated  
15 bacteremia.

16 Furthermore, I think it's important to remember  
17 that if you're enrolling patients in a trial on the basis  
18 of bacteremia, so bacteremia is basically driving  
19 enrollment, then it's important to insure that each of  
20 these groups -- and I've only shown, obviously, a portion  
21 of the number of infections that are associated with  
22 bacteremia -- are balanced across treatment groups. While  
23 it is true that randomization will accomplish this, it is  
24 important to remember that as you do subgroup analysis and  
25 divide things into smaller and smaller groups, the chances

1 that you will have an imbalance may increase.

2 Now, I've got an area in this large circle that  
3 doesn't have any overlap, and that would correspond to  
4 bacteremia of unknown origin or, as Dr. Maki pointed out,  
5 cryptogenic bacteremia. There's also a circle that I don't  
6 have on here, which are catheter-related infections. So  
7 let me just speak to those briefly.

8 I think it's important to recognize with  
9 bacteremia of unknown origin that this, unlike other  
10 conditions, is defined by what it is not. It is a  
11 diagnosis of exclusion.

12 This represents a heterogeneous patient  
13 population in terms of possible sources of infection data  
14 from Leibovici's group in Israel, suggesting that, in  
15 addition to line-related infections, these patients may  
16 also have infections resulting in bacteremia arising from  
17 endogenous sources such as tumor, as well as the urinary  
18 tract. In addition, there's different mortality risk among  
19 patients with bacteremia of unknown origin depending on  
20 factors such as appropriateness of antibiotic therapy and  
21 place of acquisition of bacteremia. Finally, in some way,  
22 in order to study this as an indication, it would need to  
23 be defined as a clinical syndrome.

24 Finally, in terms of issues with catheter-  
25 related bacteremia, again, it will be important to define

1 this if one were to study it as an indication in terms of  
2 clinical manifestations, diagnostic criteria, including the  
3 number of positive cultures needed for diagnosis, which  
4 sites should be cultured, and how other infections should  
5 be excluded.

6 In addition, it will be important to address  
7 what therapeutic requirements there were for patients, such  
8 as duration of antimicrobial therapy and whether lines  
9 needed to be removed, including the issue of whether  
10 infections could be treated simply by line removal and  
11 whether antibiotic therapy was necessary or could be  
12 considered an adjunct to line removal.

13 So let me finish with these questions for the  
14 committee. What combination, if any, of clinical  
15 manifestations, diagnostic criteria, therapeutic  
16 requirements, and clinically relevant endpoints would serve  
17 to define bacteremia as a unique indication? And secondly,  
18 what combination, if any, of the same factors would serve  
19 to define catheter-related bacteremia as a unique  
20 indication?

21 I just want to thank my colleagues from the FDA  
22 for working on this issue. I also would like to thank Drs.  
23 Mermel, Zeckel, and Maki for their willingness to come and  
24 speak to the committee on this issue.

25 Thank you.

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(Applause.)

DR. CRAIG: Thank you, David.

We will meet back here in one hour after lunch  
for the committee questions and discussion.

(Whereupon, at 12:20 p.m., the meeting was  
recessed for lunch, to reconvene at 1:20 p.m.)

AFTERNOON SESSION

(1:30 p.m.)

1  
2 DR. CRAIG: Well, this is the time where we  
3 have to come up with an answer. I think these are a couple  
4 of things that I think are specific enough that we could  
5 even end up voting on the indications at the end, so I will  
6 plan to obtain a vote from the members that are here.

7 There are two questions, and one is talking  
8 about bacteremia, and the other one is talking about  
9 catheter-associated bacteremia. Then I think if we look at  
10 the old decision that was being made, it was really back  
11 then, at least from my interpretation of it, it was talking  
12 primarily about secondary bacteremia or bacteremia in which  
13 there was a known focus, and I think when Dr. Maki sort of  
14 put his data together and organized for it, he organized it  
15 as three, essentially being secondary bacteremia or  
16 bloodstream infection, cryptogenic, and then catheter-  
17 associated.

18 Maybe the way to get started on those is,  
19 first, to see if people feel that those are different  
20 entities or are they things that actually should be grouped  
21 more together and looked at as one entity?

22 Barth, you were involved in the earlier ones,  
23 the earlier discussion, at least I saw your name there.  
24 Why don't you start off?

25 Okay.

1 (Laughter.)

2 DR. CRAIG: Dr. Bell?

3 DR. BELL: I have a general question I'd like  
4 to raise. These are very specific questions, and I call it  
5 a question rather than a concern, because I'm not 100  
6 percent sure it rises to that level.

7 But my question is, if certain antibiotics are  
8 given an indication for bacteremia, to what extent would  
9 that alter the pattern of antibiotic use in a hospital,  
10 and, particularly, to what extent would it alter the  
11 pattern away from older, narrower spectrum, cheaper drugs,  
12 like, say, nafcillin, toward newer, more expensive, broader  
13 spectrum drugs? I'm not sure how many companies would seek  
14 indications for generic drugs for bacteremia, and I wonder  
15 if the spectrum of resistance might be impacted.

16 For example, the common situation in an ICU is  
17 we have a patient who crashes and sepsis is a worry, the  
18 patient is started on broad spectrum antibiotics, and after  
19 three days a blood culture may come back showing an  
20 organism with a particular sensitivity, and what we strive  
21 to encourage is that the antibiotic spectrum will be  
22 narrowed to a drug that is appropriate for the particular  
23 pathogen but not much broader than that.

24 We have trouble doing that because clinicians  
25 sometimes tend to reason, well, you know, we had a sick

1 patient getting better and why not just keep going with the  
2 tried and true, even if it's a much broader spectrum than  
3 the I.V. folks say is needed, and if we add to that that  
4 the new drug that the person is on has this cachet of an  
5 indication for bacteremia, they might say, well, you know,  
6 this is helpful, we know this is going to work.

7           Might that be one more additional point of  
8 reluctance towards narrowing the spectrum to a drug like  
9 nafcillin? I don't have an answer to this question, but I  
10 just wanted to raise it in case anybody has any thoughts.

11           DR. CRAIG: Well, I guess, at least from my  
12 clinical experience, one of the big problems we have is  
13 that when we get back those blood cultures they're  
14 oftentimes related to resistant organisms for which the  
15 choices that we have are relatively limited. I mean, you  
16 put up an MRSE as one of your emergency organisms in terms  
17 of things for which it seemed like new drugs were needed.

18           I don't know of another infection, outside of I  
19 guess so-called primary bacteremia or catheter-related,  
20 where one's going to get data on effectiveness of new  
21 drugs. They don't cause pneumonia, nobody believes them  
22 very much with skin and soft tissue infections, and so  
23 trying to obtain that kind of data, so that maybe we'd get  
24 off of what we've tended to focus on with just primarily  
25 one drug now with questionable efficacy, that we might do

1 better for those more resistant. So looking at the  
2 clinician that has the problem, I think, at least in my  
3 mind, looking at some of these entities makes sense.

4 I might as well come out right in the -- for other  
5 situations, where it's a secondary bacteremia or it's a  
6 bacteremia with pneumonia and things like that, I do not  
7 believe that that should be a separate indication. That's  
8 my feeling and I think some of the previous data would go  
9 along with that. So that if it was pneumonia, it should  
10 be, as they've done before, pneumonia with bacteremia, and  
11 the same thing for urinary tract infections with associated  
12 bacteremia.

13 But to me, the thing that's different now is we  
14 are seeing primary bacteremias and, again, a lot of these  
15 are associated with I.V. catheters and they do result in a  
16 lot of use of drug and many of those organisms are  
17 resistant organisms, so that we don't really have good  
18 therapy right now.

19 DR. BELL: I don't have any argument with  
20 anything you said. We desperately need drugs for these  
21 resistant infections and I think we also could benefit from  
22 more study about the optimal treatment of bacteremia.

23 It's just that if we're dealing with an  
24 infection that's not resistant, for example, that would be  
25 treated by a cheap generic drug like nafcillin, what would

1 happen if we changed the patterns of antibiotic use in the  
2 hospital? It's just a question, that's all.

3 DR. CRAIG: My own feeling is that what you'd  
4 probably see is that it would change oftentimes out in the  
5 community where maybe the marketing efforts are more  
6 successful. I would think in academia you'd still have  
7 many of the people still switching to nafcillin if it was  
8 susceptible and using it appropriately.

9 Dr. Maki, then Barbara.

10 DR. MAKI: I think, first of all, that's a very  
11 valid concern, but I would simply make the observation that  
12 right now drugs are being used for bacteremia sort of based  
13 on the studies that were done in the indications for  
14 nonbacteremic infections. Third-generation cephalosporins  
15 are not approved for bacteremia, but they're being used  
16 very, very widely for bacteremia because we know they are  
17 pretty effective for treating lower respiratory infections,  
18 soft tissue infections, urosepsis, and the like.

19 I think that what could possibly counter that  
20 would be comparative trials. The comparative drugs that  
21 are chosen should be older agents, older established  
22 regimens, that are considered the drugs of choice, and if  
23 you show equivalence, then in that circumstance I think  
24 that the FDA would be well advised to grant approval to the  
25 older comparative agent. It's a way of sort of

1 grandfathering in older regimens, like nafcillin for staph  
2 aureus bacteremia, if the older comparative regimens are  
3 shown to be effective.

4           The other comment that Bill made, I agree  
5 completely, in terms of I think secondary bacteremic  
6 infections, bacteremia is an extension of severity of  
7 illness. Where we really need an indication is for this  
8 very substantial population of cryptogenic bacteremias of  
9 which many are line-related, many of them the source is not  
10 found, but they have substantial morbidity and mortality.  
11 There has to be a way to study them and find better  
12 information how to treat them.

13           DR. CRAIG: Barbara?

14           DR. MURRAY: He made the point.

15           DR. CRAIG: Okay, you're on, Barth.

16           DR. RELLER: Barbara didn't --

17           DR. CRAIG: No, she just said that he made the  
18 point.

19           DR. MURRAY: Dennis made the point about the  
20 older, comparative drugs would be used, like nafcillin.

21           DR. RELLER: I'm feeling a little lonely.

22           (Laughter.)

23           DR. RELLER: No one in the world knows more  
24 about access or catheter-related infections than Dr. Maki,  
25 who has labored more than 30 years since serving as an

1 epidemic intelligence service officer in the then new  
2 hospital infections program at CDC, and labored to prevent,  
3 diagnose, and treat catheter-related infections. So it's  
4 with both admiration, Dennis, and a great deal of  
5 trepidation that I'll present a different perspective.

6 I think it would be a mistake to lump all  
7 bacteremias, all bloodstream infections, to encompass the  
8 fungemias as a single approvable indication for an anti-  
9 infective by the FDA, fundamentally because it flies in the  
10 face of pathophysiology, or at least what we know about it,  
11 and I'm talking about BSI as an indication itself.

12 The current dichotomous categorization of  
13 primary and secondary I believe is fundamentally flawed in  
14 that most I would hope would agree that the secondary, as  
15 Bill has already said, should not be lumped with the  
16 primaries. And the primaries, as best as I understand the  
17 literature, and actually encompassing the wonderful data  
18 that was presented this morning, falls into, to me, three  
19 broad categories.

20 One is device-related bloodstream infection  
21 that may, with accompanying SIRS, be considered device-  
22 related sepsis. The commonest device of which that's  
23 associated with are access devices that are clearly  
24 increasing in their numbers. I hope someday to do a paper  
25 called "Lines, Lumens, and Lunacy."

1 (Laughter.)

2 DR. RELLER: But it's not going to go away, so  
3 that the purest approach, for example, in negating any  
4 blood culture drawn through a catheter is just  
5 fundamentally flying in the face of reality. You know that  
6 Dr. Bell has been there from the comments that he makes,  
7 and anyone who would steadfastly maintain that never under  
8 any circumstances would blood drawn through a catheter be  
9 acceptable for culture has not been there or is not  
10 currently there.

11 So that these three components of primary that  
12 might serve reality, scientific integrity, and the  
13 development of new agents well would be to think about them  
14 in terms of device-related. Most specifically, catheter-  
15 related is the biggest one, not that there aren't other  
16 devices associated with coagulase-negative staphylococcal  
17 bacteremia. One might say in the absence of a device or  
18 catheter, it is a vanishingly infrequent real organism in  
19 the blood. There are a few endocarditities that are caused  
20 by coagulation or native valves that are caused, but there  
21 are few.

22 The second is the patients with neutropenia who  
23 have bacteremia. That has been a subject of much  
24 discussion, I think really good discussion, and a revision  
25 in approach by the agency in accordance with current

1 reality. There are indications for empirical use of drugs  
2 and approved drugs now and criteria for new drugs that  
3 would become available for bloodstream infection that  
4 occurs in the setting of neutropenia which in our studies  
5 was apart from devices.

6 In fact, the commonest place in which one sees  
7 organisms for which there is not an identifiable source for  
8 the infection, and that encompasses nowadays most of the  
9 viridans streptococcal bacteremias that are real that are  
10 not endocarditis, and there are a few meningitides and so  
11 on, but for the most part we're talking about endocarditis  
12 or viridans bacteremia in association with neutropenia. So  
13 there may be new drugs associated with febrile neutropenia  
14 as this becomes an increasing player that might be  
15 considered in that indication that's already delineated by  
16 the agency.

17 The third one that I hope that we can avoid,  
18 and one of my reasons for this position, is inadequate  
19 diagnostic efforts. The clinician who has a staphylococcal  
20 bacteremia that is not associated with a catheter or not  
21 associated with a recognized, who ignores it as not being  
22 important and does not seek or watch the patient carefully  
23 or get them back and follow them to find, if not where it  
24 started, at least where it's lodged, is going to be fraught  
25 with a morbidity and mortality that is unacceptable.

1           There's going to be a lot of data coming out on  
2 this. Some of it is in press. Some of it is coming out  
3 not only from our place, but others.

4           So inadequate diagnostic efforts to delineate a  
5 source, now, that's a clinical statement, but for the  
6 purposes of trials, putting that category of people in as a  
7 solitary indication for bacteremia is a very important  
8 issue that opens a lot of difficulties.

9           So, to lump, for example, the bacteremias owing  
10 to coagulase-negative staphylococci, most of which when  
11 they are real are associated with intravenous catheters,  
12 that the removal is not absolutely necessary but often the  
13 more important component of the therapy -- in fact, in data  
14 that Weinstein as a fellow and later as a full professor 15  
15 years later repeating the study that encompassed our own  
16 center's, whether it was 3 percent in the mid-1970s or 15  
17 percent in the 1990s of real catheter-related, when one had  
18 catheter-related infection with coagulase-negative  
19 staphylococci, the mortality especially, but even without,  
20 but especially with catheter removal was really no  
21 different than having no adverse.

22           In other words, it was as good as having no  
23 underlying illness whatsoever. That is an outcome reality  
24 that is vastly different in my mind from, for example,  
25 pneumococcal bacteremia associated with pneumonia where

1 things have not changed in terms of mortality from Austrian  
2 and Gold's magnificent review in the 1960s to the present,  
3 regardless of whether the agents have changed in their  
4 susceptibility or not, and we're talking about 19 or 20  
5 percent mortality with bacteremic pneumococcal pneumonia.

6           So that lumping all bacteremia as an indication  
7 I think is a mistake. To separate out device-related and  
8 to get the kind of specificity and the criteria for  
9 denoting what experts would accept as device-related  
10 bacteremia, and especially with that most common organism  
11 that is associated there, which happens to be one  
12 associated with the highest resistance to oxacillin, would  
13 be a great service, because I think one could argue in the  
14 context of these two days of discussion that one of the  
15 largest factors, perhaps the largest factor, driving the  
16 emergence of vancomycin-resistant enterococci is the  
17 profligate use of vancomycin for the treatment of  
18 contaminants in blood cultures.

19           So my concern is that to have an indication  
20 that is not very precise and denotes the need for  
21 concomitant therapy, like removal, would lump things  
22 together in a way that would be adverse for patient care,  
23 would not serve precision in clinical trials, and would not  
24 enable scientifically valid conclusions about efficacy of  
25 new agents for these situations in which previously puny

1 organisms in the right setting can, indeed, cause  
2 difficulty and are quite resistant sometimes to currently  
3 available therapies and may become more so in the future.

4 So that's the way I look at this, is BSI as an  
5 indication is a mistake. Delineation of primary  
6 infections, even scrapping that concept and getting at  
7 device-related, the neutropenic patients, and establishing  
8 where it went to if you can't establish where it came from  
9 is a more important issue.

10 DR. CRAIG: I guess I'd ask a question, and  
11 then Dr. Maki. At least from my knowledge, and maybe  
12 Barbara can add on this, on VRE, I've thought it has been  
13 associated with oral vanco, metronidazole, third-generation  
14 cephalosporins, not so much with I.V. vancomycin use in  
15 terms of VRE.

16 DR. MURRAY: Well, yes. Len might be able to,  
17 from an epidemiological point, respond, but certainly any  
18 vancomycin use has been related in a number of studies, as  
19 have third-generation cephalosporins, for actually showing  
20 an effect on fecal flora, direct effect, there haven't been  
21 any studies that I'm aware of done with parenteral  
22 vancomycin. Those studies have been with oral vancomycin,  
23 but as an epidemiological associated risk factor, yes, I.V.  
24 as well as oral.

25 DR. MAKI: I would agree. Vancomycin is a risk

1 factor, but it's not nearly as strong as third-generation  
2 cephalosporins, I think, or anaerobic drugs. There's a  
3 beautiful case-control study at ICAAC this year where they  
4 very, very carefully dissected the effect of antimicrobial  
5 pressure, and parenteral vanco came out relatively weak as  
6 a risk factor, but it is a risk factor.

7 One thing I would point out, as I was telling  
8 Barbara beforehand, we've seen three infections with  
9 vancomycin-dependent enterococci. The organism needs  
10 vancomycin to grow. We're talking about these were three  
11 infections, two of them were serious infections, and all  
12 three patients died. What they had in common, they had  
13 very prolonged vancomycin therapy. So I think there has to  
14 be a powerful incentive to be able to control all  
15 antibiotic use, not just vancomycin.

16 I'd like to just respond to Barth's very  
17 eloquent comments. I'm a little intrigued that here, as  
18 probably one of the quintessential authorities in the world  
19 on diagnostic microbiology, you are sort of able to accept  
20 marginal diagnostic efforts in catheter-drawn blood  
21 cultures, but you're very critical about they're too sloppy  
22 in their therapy and not looking enough at the source. I  
23 think we have to have it consistent both ways.

24 I think it is possible to have rigorous  
25 criteria for device-related infection. I think it is

1 clearly possible. I think it is possible to have rigorous  
2 criteria for bacteremia. If we talk about the reality of  
3 the world, you say, well, you're not there. I agree with  
4 you. You do have to draw catheter-drawn blood cultures.  
5 You have patients in the ICU who have no sites for access  
6 and you have no option and you're not going to get a blood  
7 culture, and we have to accept that, but we have to  
8 interpret the data accordingly.

9           The reality of life is that you can look very  
10 hard on many patients and you cannot find a source of a  
11 bacteremia. That may be a limitation of our technology,  
12 and it's not just the profoundly neutropenic patient. I  
13 agree with you completely about the strep viridans. We  
14 pointed that out in our data. Strep viridans probably is a  
15 direct mucosal invasion, but there are plenty of patients  
16 that get a gram-negative bacteremia, get another type of a  
17 bacteremia, and the reality of life in a modern day  
18 hospital is that they don't find the source.

19           If you look at all the series that have been  
20 published from excellent centers across the country, 25  
21 percent of the nosocomial bacteremias in most of those  
22 centers they don't find the source and yet they are  
23 considered to be legitimate bacteremias. In your center,  
24 where I think there probably is even a greater intense  
25 effort to try and find the source, you may have a small

1 proportion that are cryptogenic, but the reality is in most  
2 centers with the best doctors and doing their best job, a  
3 substantial number they don't find a source.

4 I would come back again to the fundamental  
5 issue. We need good data on what are the best drugs to  
6 treat device-related bacteremia, certainly that's very  
7 important, but also it's important to know there are  
8 cryptogenic bacteremias. People get primary bacteremias  
9 with respiratory pathogens who may be immunologically  
10 compromised. There are children. There are pediatric  
11 patients. That's the only way you prove they have a  
12 serious infection, they have a bacteremic infection. You  
13 never prove they have a pneumonia or another source, and  
14 it's such a substantial proportion of the serious  
15 infections that cause morbidity and mortality that I think  
16 that it deserves to be studied well and to be accorded an  
17 indication if studies show relative efficacy.

18 DR. CRAIG: I think if you sort of eliminated  
19 them, and I'll let you, if you sort of eliminated the  
20 neutropenics which already there's something there, so that  
21 if neutropenia was not an indication because they fall  
22 under the fever and neutropenia criteria, if you eliminated  
23 secondary bacteremias, you're probably going to come down  
24 to primarily staphylococci, both coagulase-positive and  
25 coagulase-negative, and maybe enough gram-negatives. But,

1 again, I don't think you would --

2 DR. MAKI: And enterococci.

3 DR. CRAIG: And enterococci, yes. That's the  
4 other one.

5 DR. MAKI: And lumped in a lot of candida.  
6 Candida is probably a very substantial portion of endpoint  
7 infection as well.

8 PARTICIPANT: Microphone.

9 DR. CRAIG: Yes. His comment was that candida  
10 is another one in which one would find a lot of cases.

11 DR. RELLER: On that last point, to me, this is  
12 an argument of not having -- Dennis, fungemia that's  
13 something else. I don't think there are any agents out  
14 there that are efficacious for enterococci, staphylococci,  
15 and candida concomitantly.

16 We have a terrible problem with candidemias,  
17 not necessarily knowing where they're coming from in our  
18 innumerable transplant patients. Presumably, those are in  
19 concert with Kraus' classic experiment of swallowing, the  
20 massive numbers of candida where these people are colonized  
21 owing to their many organisms and, in effect, are getting  
22 it from their gut, though it's not clearly delineated as  
23 coming from a -- I mean, there are more in the category of  
24 the overwhelming colonization patients like the neutropenic  
25 patients, but are profoundly immunocompromised because of

1 what has been done to save their organ with  
2 transplantation, which has now become actually the  
3 commonest setting in which we see candidemias without a  
4 focus, is in the transplant patient.

5 But to have those thrown in as an indication  
6 along with the others, it's just not consonant with the  
7 pathophysiology as we know it.

8 DR. MAKI: First of all, candida bloodstream  
9 infections cause a great deal of morbidity and mortality.  
10 They have a very high mortality. A substantial number are  
11 from lines. Many are probably mucosal infection.

12 I don't think that's as relevant as the fact  
13 that many candida bloodstream infections, the only  
14 identifiable infection you get is positive blood cultures  
15 and they're septic. The thing is that we need to know how  
16 best to treat them and we need to have indications for  
17 drugs.

18 I would finally conclude, I didn't interpret  
19 the recommendation on an indication for bacteremia that  
20 we're looking for one super anti-infective that's going to  
21 cover the whole spectrum of organisms. If anything, we're  
22 looking for more narrow therapy, and we'd like to know what  
23 will treat staphylococcal cryptogenic bacteremia, whether  
24 it's device-related or not, or what will treat a  
25 cryptogenic gram-negative rod, or an enterococcus, or

1 candida.

2 DR. CHIKAMI: Yes, I think as a point of  
3 clarification, in fact, we wouldn't consider including  
4 fungemia in with bacteremia as an indication if we were  
5 going to consider that, given the wide differences in the  
6 therapeutic agents that would be used.

7 DR. MURRAY: Well, then, if I can follow up,  
8 you didn't quite answer what I was going to ask, as I  
9 thought you were. So if bacteremia were given a  
10 possibility of an indication, would it not still be  
11 bacteremia due to X that was studied and Y that was  
12 studied?

13 DR. CHIKAMI: Right, due to the listing of the  
14 susceptible organisms.

15 DR. CRAIG: And that's why I was trying to  
16 think of which ones you would primarily get if you  
17 eliminated the secondary ones and you eliminated the  
18 patients with neutropenia. I think enterococci, staph  
19 aureus, and staph coagulase-negative would be the major  
20 organisms, and then you'd probably get some mixtures of  
21 some gram-negatives. Whether you would have enough of one  
22 species to get an indication, that might not happen.

23 Yes?

24 DR. OVERTURF: I feel a little compelled to  
25 point out that I don't think any of these discussions will

1 answer the problem for many of the pediatric patients,  
2 because I would find it difficult to find the adequate  
3 diagnostic method for making the diagnosis in very small  
4 infants. Obviously, the 20 to 30 mL blood culture done  
5 twice is about the weight of some of our patients.

6 (Laughter.)

7 DR. OVERTURF: So we deal all the time with a  
8 huge sampling error, and if this were an indication, the  
9 problem I have is that if you establish criteria which are  
10 based on adults, you might exclude large numbers of  
11 pediatric patients from getting the same information, which  
12 would then lead to an indication for treatment of  
13 bacteremia in pediatric patients, particularly neonates.  
14 Neonates are a substantial portion of the nosocomial  
15 bacteremias.

16 DR. RELLER: Bill?

17 DR. CRAIG: Yes?

18 DR. RELLER: Actually, Dr. Overturf reminded me  
19 of something that I left out in the primary bacteremias  
20 without a recognized focus as being possible to categorize.  
21 I left out, and it was an omission that I didn't intend to  
22 make, about pediatrics. My understanding is, coming from  
23 the community at least in most centers, that pneumococcal  
24 bacteremia is actually the number one organism from the  
25 community, and most of the time, I think, most of the time

1 there isn't a recognized.

2 But that's a special category of occult  
3 pneumococcal bacteremia in children, which might under the  
4 right specific definitions be something that would be  
5 considered as a clinical entity of a special nature for  
6 treatment, but what I was talking about before was  
7 applicable for the adult patients.

8 DR. CRAIG: Dr. Mermel?

9 DR. MERMEL: I apologize if on my slides I  
10 didn't specifically say adults. Obviously, I wouldn't  
11 recommend drawing large volumes for children. I apologize  
12 if I didn't have adults in there.

13 I think that's an area that's not been well  
14 enough studied. The best data I've seen with regards to  
15 pediatrics is actually weight-based volume draws based on  
16 the weight of the child, which I think is something very  
17 underutilized. I think the problem with pediatrics and  
18 line infections is they don't draw for continuous cultures  
19 in many of the hospitals I've trained in and they draw  
20 minuscule volumes, because a child at premature three  
21 pounds gets the same minute volume as a 50-pound child, and  
22 so I think it needs to be probably weight-based.

23 But I think with regards to how a drug is  
24 approved, if one is approved, for catheter infection, I  
25 think it is important to separate out, rather than

1     indicating a drug for catheter infections, I think it's  
2     going to be very important to know in those populations if  
3     the catheter was withdrawn, because antimicrobials do have  
4     different effects on biofilm-producing organisms, as we  
5     know now from a number of elegant animal studies done in  
6     Switzerland. There are some that can sterilize foreign  
7     bodies, some that can't, some that maybe you can eradicate  
8     without removing a foreign body, some that you cannot. So  
9     I think it's going to be exceedingly important if there is  
10    an indication for a bacteremia, if it's device-related, to  
11    absolutely try to discern whether or not the device is  
12    withdrawn.

13                   DR. CRAIG: Other comments about whether people  
14    feel this is an indication? I have my little notes  
15    somewhere from Dr. Archer, who had to leave, who is in  
16    favor of bacteremia as an indicator simply primarily  
17    because, as he says, the unknown site for 20 to 30 percent  
18    of staph aureus, he feels it's a very clean indicator for  
19    infection, and most people really accept eradication of  
20    bacteremia and absence of relapse with stopping therapy as  
21    a very tough and rigorous test of efficacy.

22                   Dr. Danner?

23                   DR. DANNER: I think that catheter-related  
24    infections have a defined pathophysiology and there's  
25    methodology available that allows you to reasonably make

1 that diagnosis. So as a category of bacteremia, that  
2 certainly seems to be not inconsistent with other  
3 indications for using medicines, and in fact in practice we  
4 use antibiotics to treat that infection and we diagnose  
5 that infection as a specific type of nosocomial infection  
6 that is becoming, as has already been said, very common.

7 In terms of other primary types of bacteremias  
8 and using that as an indication, I guess it remains to be  
9 seen how much of an impact giving that indication, if you  
10 made that an indication, how much impact that would have on  
11 the use of antibiotics and the way they're used in  
12 hospitals. I actually don't think it would have a large  
13 impact on the way antibiotics are used and I don't think it  
14 would have a deleterious impact.

15 The advantage of doing it I think is that it  
16 would probably lead pharmaceutical companies to do certain  
17 kinds of trials that ask certain kinds of questions about a  
18 product they're developing, and it's data that we're  
19 currently not getting from some of these trials, because  
20 the question is not being asked because it's not an  
21 indication. So I see it as an advantage to have this  
22 specific indication because new questions will be answered.

23 You could answer a question similar, I guess,  
24 to something Dr. Maki had said, like if you have someone  
25 being admitted to an intensive care unit with septic shock

1 in a population that you feel has a high likelihood of  
2 bacteremia and you randomize people to a standard regimen  
3 versus a new therapy, you could look at outcome and see, in  
4 fact, if antibiotic class, mechanism of action, rate of  
5 killing, things like that correlated with how fast someone  
6 came out of shock, how fast they cleared bacteremia,  
7 ultimate outcome.

8 Questions like that are generally not being  
9 asked of antibiotics, so having this as an indication I  
10 think would perhaps drive some studies to try to answer  
11 questions that haven't been approached up to this time.

12 DR. CRAIG: Barbara?

13 DR. MURRAY: I guess I'm pretty comfortable  
14 with the concept of looking at catheter-associated  
15 bacteremias and the secondaries have already been removed.  
16 Probably where I'm most insecure is with the primaries in  
17 the non-neutropenic sense. I do think some of those are  
18 really secondaries. We just didn't figure out what it was,  
19 and so it's more of a mixed bag. For that reason, I'm  
20 probably a little less comfortable considering that than  
21 the catheter-associated, but maybe there are not so many,  
22 either.

23 DR. CRAIG: Well, I think from your data,  
24 Dennis, that was a relatively large group.

25 DR. MAKI: Yes, it is. It was the largest

1 group.

2 DR. MURRAY: Yes, I was actually curious about  
3 that. So there were some that were definite catheter, and  
4 then there were others that were cryptogenic, but you  
5 thought were probably catheter.

6 DR. MAKI: Basically, 25 percent were  
7 secondary, nondevice-related, 25 percent were clearly  
8 device-related, and about 50 percent were cryptogenic.

9 DR. MURRAY: But they all had catheters in or  
10 reason --

11 DR. MAKI: And what we found in the cryptogenic  
12 is that 95 percent of them had a central line in, and more  
13 than 95 percent of the line-related had a central line in,  
14 and only 55 percent of the secondary had central line in.  
15 So for a variety of ways of looking at the data, we think  
16 that a substantial proportion of the cryptogenic are  
17 probably line-related and somebody didn't pull the Hickman  
18 or they didn't do quantitative blood cultures of the  
19 Hickman, so that we couldn't conclusively link the  
20 bacteremia with the device.

21 I would only make the argument that I agree  
22 with you, device-related can be made very clean, very  
23 precise, and you can study that very well, but if one looks  
24 at the series, all of the series have a substantial number  
25 of cryptogenic bacteremias that need to be treated which

1 have substantial morbidity and mortality. Although it's a  
2 mixed bag, that's okay. Pneumonia is a mixed bag, too, and  
3 so are many other focal infections a mixed bag. Urinary  
4 tract infection is a mixed bag microbiologically, and to  
5 some degree pathophysiologically. All of them are when we  
6 stratify from underlying diseases.

7 So that I think that beyond device-related  
8 bloodstream infections, I think you can make an argument  
9 that if you think it's worthwhile considering device-  
10 related bloodstream infections as an indication, why not go  
11 for the whole ball of wax? Literally, why not go for this  
12 substantial number of cryptogenic? I think it is possible  
13 to stratify and get information.

14 DR. MURRAY: Because a lot of those are in the  
15 catheter-associated --

16 DR. MAKI: A lot of them are going to be  
17 catheter-associated. You're absolutely right.

18 DR. TALBOT: If I were to try to synthesize  
19 what I've heard, I think both the regulatory --

20 DR. CRAIG: That's my job.

21 (Laughter.)

22 DR. CRAIG: So you can give your comment to add  
23 to it.

24 DR. TALBOT: May I continue, Mr. Chairman?

25 DR. CRAIG: Yes.

1 DR. TALBOT: Okay. If I understood the  
2 comments from our regulatory colleagues and also from  
3 others, we have a situation where labeling already allows  
4 for recognition of site-specific indications accompanied by  
5 bacteremia, if I understood that correctly. So there's  
6 already the regulatory paradigm to deal with urinary tract  
7 infection, CAP, what have you, with bacteremia. That  
8 perhaps could be amplified or the clinical data could be  
9 amplified in a clinical study section, which could give the  
10 clinician more information about what was actually studied  
11 in the studies undertaken for that compound.

12 Now, a next logical step would be to think  
13 about catheter-related infections, and I would submit that  
14 you could easily take the next logical step, being to say  
15 that you would add catheter-related infections or vascular  
16 device-related infections as a category, like CAP or NP or  
17 what have you, and then also reflect in labeling whether or  
18 not bacteremia was present, how often it was present, and  
19 what the outcomes were. I think that would be logically  
20 consistent.

21 That then leaves you with the third group,  
22 which Dr. Maki has spoken about so clearly, which is this  
23 cryptogenic group. I would admit that, clearly, some of  
24 those patients have not had their etiology adequately  
25 defined. Whether they ever will is another question, but

1 what is clear is that this is a group that is very  
2 clinically relevant, it hasn't, as Dr. Maki said, been very  
3 well studied, and we don't know about old drugs, not to  
4 mention new drugs, in this very large group of patients.

5 Therefore, I would suggest that if there were  
6 going to be any new category, entirely new, it would be  
7 this group. It would have to be initiated with the  
8 recognition that there would be limitations to what one  
9 could take, but in the context of RCTs and careful analysis  
10 and perhaps protocol-driven attempts to define etiology, I  
11 think you could really learn a lot about this group, and I  
12 think that's a need that's been expressed by many of the  
13 speakers.

14 So I think the existing scientific and  
15 regulatory apparatus, if I could be so bold, allows for a  
16 logical step here, and then the added category that Dr.  
17 Maki has proposed which would benefit everybody --  
18 clinicians; scientists; hopefully, regulatory agencies; and  
19 industry.

20 I hope that's been helpful to you, Mr.  
21 Chairman.

22 DR. CRAIG: Any more comments? Yes, Joan?

23 DR. CHESNEY: Bill, I like the idea of central  
24 line-associated bacteremia. Dennis said of the cryptogenic  
25 95 percent had a line in place. So if the indication was

1 for central line-associated or bacteremia associated with a  
2 central line, it seems to me like that would narrow it  
3 down.

4 I like this idea also of the right questions  
5 needing to be asked. I think you made that point that if  
6 there is a specific indication, a different set of  
7 questions will be asked.

8 DR. CRAIG: How about the community-acquired  
9 cases of staphylococcal bacteremia, 30 or 40 percent which  
10 don't have a focus, which I don't think you were picking  
11 up. You were looking at nosocomial.

12 DR. MAKI: No, I didn't talk about community.  
13 I think if one looks at community-acquired bacteremias, I  
14 think it equally well supports having an indication because  
15 a substantial number of community-associated bacteremia,  
16 particularly staph aureus, may not have a primary source.  
17 A substantial number of them will be endocarditis, but not  
18 all of them, certainly, and there are primary pneumococcal  
19 bacteremias. The bottom line is that they're serious  
20 infections and we need to have information on them.

21 Just in terms of Joan's comment on central  
22 line-associated, I think every effort should be made in  
23 trials to say, if possible, if central line-related. I  
24 think one of the things we would see is that if there was  
25 an impetus to companies to undertake studies of bacteremia

1 to get an indication, we would see investigators making a  
2 much more vigorous effort to diagnose line sepsis. We  
3 would see the use of things like quantitative dual-blood  
4 cultures being done in patients with implanted catheters,  
5 we'd have a greater willingness to remove a catheter and  
6 culture tip and to look more vigorously for all sources,  
7 and I think that this category of cryptogenic would shrink  
8 in a research database, but the realities in the clinical  
9 world, I'm not sure it will shrink that much, at least with  
10 our existent technology and constraints on time and cost of  
11 diagnostic tests and the like.

12 DR. CRAIG: Dr. Reller?

13 DR. RELER: It's for the very reasons that  
14 Dennis just pointed out that I think it is a mistake to  
15 lump these, because those cryptogenics, if one has a  
16 coagulase-negative staphylococcal bacteremia that is  
17 reasonable criteria for its reality are satisfied, and a  
18 catheter is -- I mean, where else is it coming from?  
19 Native valve endocarditities are very rare. Unless there's  
20 a prosthetic joint or some other prostheses and there's a  
21 catheter in place, the emphasis should be on requiring  
22 rigorous criteria for documenting those infections if there  
23 is to be an indication for an intravascular focus of  
24 infection secondary to a catheter line, a Port-a-Cath, all  
25 of the various access devices that are used, owing to, and

1 then the organism, coagulase-negative staphylococci or  
2 staph aureus, or VRE, or whatever it is when there are  
3 enough numbers, with proper exclusions for other potential  
4 compounding factors on outcome with the appropriate  
5 emphasis on separating them out for those that are removed  
6 and not removed. It plays a potentially important part of  
7 therapy in all, more essential in some than others,  
8 depending on what the organism is.

9 But I'd like to see the definitions driving for  
10 specificity and knowing exactly what we're dealing with and  
11 what the concomitants of successful therapy are, including  
12 removal.

13 DR. MAKI: I don't think we disagree at all,  
14 Barth. I think we agree absolutely. Every effort should  
15 be made to identify a source of a bacteremia and source  
16 control is where we should always strive to start our  
17 therapeutic efforts. Sometimes source control is not  
18 feasible. You're just not going routinely pull a Hickman  
19 catheter out with every staph-happy bacteremia where  
20 there's not a tunnel infection. Many of them can be cured  
21 without removing the catheter.

22 But the reality is we should make an accurate  
23 diagnosis as much as possible. We agree completely on  
24 that, but I think we're still going to be left with a  
25 substantial stratum of patients who we don't find the

1 source, they have a bacteremia, it needs to be treated, and  
2 we need to deal with it.

3 I think the only place we disagree is that, and  
4 I don't think we should lump things. I think we should  
5 stratify our analyses and compare the same organisms when  
6 we're looking at different agents. The bottom line,  
7 though, where we probably differ, is I think that for all  
8 the things we've talked about, I think that bacteremia  
9 deserves an indication in terms of new agents.

10 DR. CRAIG: Dr. Davis?

11 DR. DAVIS: I'd like to echo those comments,  
12 but perhaps from a different perspective. I think it is  
13 important that we have a very detailed look at bacteremia,  
14 but I think the perspective is also from a public health  
15 perspective. These nosocomial infections are very  
16 important for the whole patient population in the hospital,  
17 as well as spillover to the community. I think it's  
18 important that we have a very good handle on the source of  
19 these infections. This falls in line with epidemiology,  
20 but, of course, the downside is this is going to add to the  
21 cost of studies, clinical trials, and more regulatory  
22 actions.

23 DR. CRAIG: What I'd sort of like to do right  
24 now is just take a vote from the members of how many feel  
25 that we should consider as a unique indication bacteremia

1 and where we would lump everything together.

2 DR. MURRAY: So you're going to give us various  
3 voting options?

4 DR. CRAIG: Well, the answer is going to be yes  
5 or no for lumping all the bacteremias together.

6 DR. MURRAY: But this will be the only vote  
7 we'll be taking?

8 DR. CHESNEY: We'll have other possibilities.

9 DR. CRAIG: There will be other possibilities  
10 coming down.

11 (Laughter.)

12 DR. CRAIG: That's the first question there,  
13 define bacteremia as a unique indication. So what I'm  
14 doing is lumping everything together here. We still have  
15 to go back and decide what kind of clinical manifestations,  
16 if we decide on that.

17 But right now, if people don't think that  
18 that's a thing to do, then we'll see if we can break it  
19 down farther and see if there's a subset that somebody  
20 feels is worthwhile looking at. Okay?

21 DR. MURPHY: You might want to review the  
22 voting members.

23 DR. CRAIG: I have eight.

24 DR. MERMEL: Would it not make more sense to  
25 start --

1 PARTICIPANT: Start with the simplest.

2 DR. MERMEL: Just start with the --

3 DR. CRAIG: No, I want to start with it this  
4 way.

5 (Laughter.)

6 DR. CRAIG: So, how many would be for lumping  
7 them all together for an indication? Raise your hand.

8 (No response.)

9 DR. CRAIG: Okay. How about for, which was our  
10 second question, catheter-associated bacteremia as a unique  
11 indication? How many would be in favor of us looking at  
12 that?

13 (Show of hands.)

14 DR. CRAIG: No, you're down? You're up, yes or  
15 no?

16 DR. PARKER: Yes.

17 DR. CRAIG: Okay, so you're yes. So that was  
18 unanimous, eight.

19 Again, then, one of them that's not here. That  
20 is subtracting the catheter from the others. Also, getting  
21 rid of all the secondary bacteremias which would be part of  
22 other indications, and so again looking at primary  
23 bacteremia that is not catheter-associated.

24 DR. MURRAY: Not catheter-associated or not  
25 documented to be --

1 DR. CRAIG: Can't be proven to be and would  
2 also include in there, obviously, would include those with  
3 primary staphylococcal bacteremia.

4 DR. CHESNEY: But some of these would have a  
5 catheter in?

6 DR. CRAIG: I think that's what you get to  
7 trying to make your diagnosis or trying to look at the  
8 group. The question is --

9 DR. MURRAY: When you say not catheter-  
10 associated, that could automatically mean you're excluding  
11 anyone with a catheter. I think what we want to make sure  
12 is we're not --

13 DR. CRAIG: No, I'm saying that we've already  
14 agreed to do that. So if we're looking at the catheter --

15 DR. MURRAY: No, I'm sorry, I'm not sure we  
16 did. That's what I'm trying to -- this is only for  
17 clarity. The first group was catheter-associated or  
18 catheter-infection. So you have pus coming out of here,  
19 you have bacteremia. I thought that's kind of what we  
20 voted on. Then there's this 95 percent that he talks  
21 about, the 50 percent of cryptogenic, 95 percent of whom  
22 have catheters.

23 DR. CRAIG: I don't think we --

24 DR. MAKI: I think you voted on, if I  
25 understood correctly, I think you voted on catheter-related

1 where you had some definite agreed upon criteria that  
2 they're catheter-related bloodstream infections. I think  
3 that's what you all agreed on almost unanimously.

4 DR. MURRAY: But that's the problem. He's  
5 saying associated, and to me associated just means you've  
6 got bacteremia plus a catheter.

7 DR. CRAIG: Well, then I think catheter-  
8 related.

9 DR. MAKI: Right. The other category you're  
10 now asking about is cryptogenic where you exclude the  
11 catheter-related.

12 DR. CRAIG: Yes.

13 DR. MAKI: A person can still have a catheter  
14 in. A lot of people have a --

15 DR. CRAIG: But I also want to exclude those  
16 that are secondary bacteremias and that are also those --

17 DR. MAKI: Right. Cryptogenic primary  
18 bacteremias where --

19 DR. CRAIG: Under the fever and neutropenia for  
20 which --

21 DR. MAKI: Where a serious effort has been made  
22 to exclude catheter-related infection.

23 DR. BERTINO: Could I ask Dr. Maki for a  
24 clarification? If somebody has got a catheter in place and  
25 you find a bacteremia, what's the difference between

1 catheter-related and not related to the catheter?

2 DR. MAKI: Well, first of all, all kinds of  
3 people, you're going to find 40 to 50 percent of people in  
4 a hospital have a line of some kind in. In the ICUs,  
5 everybody -- a lot of them have central lines in. A lot of  
6 those patients get bacteremia that aren't from the line.  
7 They get surgical site infections, they get bacteremic  
8 pneumonias. Not every bacteremia is from a line. A  
9 substantial number are. So I frankly don't like the term  
10 "central line-associated" bacteremia because it's not  
11 totally clear to me what we're talking about. Is it  
12 etiologic or does it just happen to be a passive bystander  
13 watching what's going on?

14 DR. BERTINO: Okay. I guess I must have  
15 misunderstood. I thought you meant that you have people  
16 with bacteremias that have catheters in place and you can't  
17 find out any other reason for them to have a bacteremia.

18 DR. MAKI: That's absolutely correct, but the  
19 technology is good enough that if you're willing to use the  
20 existent technology, you're willing to either use paired  
21 quantitative blood cultures before you start anti-infective  
22 therapy or, alternatively, you're willing to pull out the  
23 catheter and to culture the segments and do a rigorous  
24 workup, you can exclude line sepsis with a pretty high  
25 degree of reliability, and that should be a goal of

1 investigators who are going to be doing these studies.  
2 You're still going to be left with a substantial proportion  
3 of patients who have bacteremia, but it's not from the  
4 line.

5 DR. CRAIG: So does everybody know what we're  
6 voting on now?

7 (Laughter.)

8 DR. MURRAY: Cryptogenic.

9 DR. CRAIG: Cryptogenic.

10 DR. MURRAY: But they may have a CVP.

11 DR. CRAIG: But with no secondary, not in those  
12 that have some other established infection. So it's not  
13 secondary bacteremia and it's also excluding patients that  
14 are neutropenic.

15 DR. MURRAY: But they're not excluding patients  
16 who just have an I.V. or a central venous catheter in.

17 DR. CRAIG: Right. We make the criteria later  
18 for that, as Dennis says, of making sure that the line is  
19 not infected.

20 But how many would be in favor of that as an  
21 indication?

22 (Show of hands.)

23 DR. CRAIG: So it's six to two. Those against  
24 I assume are you two.

25 PARTICIPANT: Dr. Craig?

1 DR. CRAIG: Yes?

2 PARTICIPANT: Just a point of clarification.  
3 On Question Number 2 about catheter-related, if I heard  
4 correctly, that's not specifically for central catheters,  
5 correct? This is any kind of intravascular device,  
6 including peripheral lines?

7 DR. CRAIG: At least I didn't make that  
8 distinction when I was doing it.

9 PARTICIPANT: So the question is, is it --

10 DR. CRAIG: I mean, there's a whole variety of  
11 different kind of lines that people use that get infected.

12 DR. MAKI: I think the bottom -- no pun  
13 intended -- the bottom line here is if a patient is being  
14 evaluated for a trial, you know they have a bacteremia or  
15 you strongly suspect it for a variety of reasons, that if  
16 they have lines in, you make every effort to identify it's  
17 from one of those lines. That should be the goal of an  
18 investigator and it should be possible to rule that out if  
19 you're willing to do it thoroughly.

20 If you've done that, and everything comes back  
21 they've got a bacteremia, a true bloodstream infection, but  
22 the line is not implicated, then it's that large  
23 cryptogenic category. It doesn't matter whether we're  
24 talking about a central line, or arterial line, or  
25 peripheral line. It's all the same.

1 DR. CRAIG: Well, could we go back then to the  
2 catheter-associated, or catheter-related, I guess, is the  
3 term that the group feels is more reflective of what we're  
4 talking about. Since that was sort of unanimous in terms  
5 of people feeling that this could be a unique indication,  
6 we need then to look a little bit at what kind of clinical  
7 manifestations because, as was mentioned by Dr. Ross, we  
8 need something that can describe these patients so that one  
9 can look at it in terms of a clinical response. We had  
10 some examples I think from what the Europeans have done in  
11 terms of their criteria.

12 DR. MAKI: I'd be willing to offer a  
13 suggestion.

14 DR. CRAIG: We're always interested in  
15 assistance.

16 DR. MAKI: Despite the fact that I come to talk  
17 about these issues from the perspective of an infectious  
18 disease specialist and also as an intensivist, I'm a little  
19 less enamored of getting caught up in rigorous criteria for  
20 SIRS and all these kinds of things. I think it's far more  
21 useful to stratify people based on some of the established  
22 scoring systems. I think they work, they're much more  
23 objective, they're easier. The SIRS criteria are very  
24 arbitrary. They were chosen arbitrarily, and I don't want  
25 to get into that.

1 I think if you sort of look at it, why do  
2 people get blood cultures on somebody? They get blood  
3 cultures on somebody because there has been a physiologic  
4 change in the patient, almost invariably. They've either  
5 spiked a fever, they've had unexplained hypotension, they  
6 may have had subtle changes that an intensivist would see,  
7 they start to show dysoxygenation, they may show lactemia,  
8 they may show other soft signs of sepsis, but the point is  
9 that there's an impetus to obtain blood cultures. There's  
10 a suspicion they have a systemic infection.

11 Frankly, that's good enough for me. To  
12 arbitrarily state that you've got to have a temperature of  
13 38.5, a lot of people that are septic don't have 38.5 and  
14 they're not necessarily hypothermic either, and some will  
15 have leukocytosis, some will not. My belief is that if you  
16 take people that you discern have true bacteremia, you've  
17 got stringent criteria for bacteremia, you're going to have  
18 plenty of very sick people, you're going to be able to  
19 stratify your patients if you want by severity of illness,  
20 and I think a far greater challenge is exactly what  
21 constitutes true bacteremia or true bloodstream infection,  
22 how many blood cultures, what constitutes device-related  
23 bacteremia, and what needs to be done to exclude device-  
24 related bacteremia. That I think is far more important and  
25 will make the data much cleaner in the long run.

1 DR. CRAIG: What you sometimes would like to  
2 do, though, and we've done this before with many  
3 indications, we know that not everybody may have all the  
4 signs/symptoms you look for, but you frequently at least  
5 try and limit the people that are going to be in a study,  
6 so that you have a group of patients that tend to be a  
7 little bit more homogeneous in terms of the sign and  
8 symptoms that you're looking at.

9 What we frequently as a committee tended to  
10 feel when we've looked at some of these things is at least  
11 trying to find some clinical indicators that would go along  
12 with infection to sort of make sure that we feel more  
13 comfortable that these are clearly people that are having  
14 bacteremia, but are also having some significant  
15 physiologic response or change. Fever is one that if one  
16 does use it, and is one of the ones that was recommended I  
17 think in the guidelines that were used before, sure isn't  
18 going to reach everybody, but at least it's a parameter  
19 that tends to make sure that you're at least dealing with a  
20 significant infection.

21 DR. MAKI: The thing that troubled me about the  
22 SIRS criteria in the studies of adjunctive therapies for  
23 septic shock, of which we participated in a number, they  
24 are very arbitrary, and you would watch a patient who was  
25 critically ill and yet didn't quite fulfill the criteria,

1 so you couldn't even enter them in the trial, and we ended  
2 up excluding large numbers of patients who were ill, may  
3 have had bacteremia, had other serious infections, and it  
4 made me wonder how applicable are our data to the real  
5 world.

6           There's nothing wrong with choosing some  
7 criteria. If you want to say a minimum amount of fever, or  
8 if they don't have fever, do they have hypothermia, do they  
9 have hypotension? My only observation is as you start to  
10 have those kinds of things, you're going to exclude people  
11 who have got significant bacteremias that will even prove  
12 fatal. That's the only problem with that.

13           DR. CRAIG: Yes, Dr. Reller?

14           DR. RELER: Goethe, many years ago, made a  
15 statement in one of his novels that blood is a special  
16 juice. And blood cultures are an interesting diagnostic  
17 tool. We think in terms of sensitivity and specificity of  
18 a diagnostic test, and like many things in life, it's not  
19 possible to have it both ways. But this is one of those  
20 situations I think where sensitivity and specificity,  
21 they're two sides of it, but it's complicated because it  
22 depends on the organism. Let me give a specific example:  
23 specificity, the capacity to rule something in;  
24 sensitivity, its utility in not ruling something out.

25           With pneumonia and many of the others where we

1 are seeing secondary bacteremias, urinary tract infection,  
2 to have a positive blood culture in someone with pneumonia  
3 that is clearly by clinical and radiographical criteria  
4 present, but yet there may be ambiguous results having to  
5 do with the sputum that grows a pulmonary pathogen, gives  
6 great specificity to the diagnosis, and it has been used in  
7 this committee.

8           When I think the first fluoroquinolone was  
9 approved for therapy, the first one that came along that  
10 had substantive gram-positive activity was approved for  
11 pneumococcal pneumonia, the critical issue in that  
12 presentation -- there were many, many patients, some of  
13 whom had documented pneumonia and some didn't, but it  
14 happened to be, my recollection was a figure of 100  
15 patients with bacteremic pneumococcal pneumonia  
16 successfully treated, all of them with this  
17 fluoroquinolone, and the issue was decided right there.  
18 Those 100 patients were more important than the other 3,000  
19 patients.

20           When it comes to coagulase-negative  
21 staphylococci and a positive blood culture, we have great  
22 sensitivity but lacking specificity without other criteria,  
23 some of which have been alluded to by Drs. Mermel and Maki.  
24 And therein, to me, lies the dilemma, when one separates  
25 out the catheter-associated, of what is left and lumping

1 that together as an indication.

2 Now, if the reason for getting blood cultures  
3 or, let's say, the practice of obtaining blood cultures  
4 were on criteria that Dennis outlined, it's difficult to  
5 define exactly what that is, but an experienced clinician  
6 knows it. But, in fact, when we have reviewed our blood  
7 cultures coming in, many don't even come close to being  
8 obtained on that basis. Such things as monitoring response  
9 to therapy -- where are the data that that's important? It  
10 may be, but where are the data? When you have an organism  
11 that susceptibility is established by NCCLS and you drain  
12 remove, whatever it is that is appropriate to do, when is  
13 it necessary?

14 Surveillance cultures. There are some units  
15 that are getting cultures twice a week, every Tuesday.

16 DR. MAKI: Why do you allow it?

17 DR. RELLER: Why do we allow it? They don't  
18 put on there, "I'm getting it because of this reason."  
19 That's why. You don't know. I could turn it around and  
20 say -- and it was a great paper that Dr. Mermel wrote about  
21 use of pediatric blood cultures for adults at the  
22 University of Wisconsin. But I could say why do you allow  
23 blood cultures that are inadequate in terms of volume of  
24 blood?

25 DR. MAKI: We stopped it when we found it.

1 DR. RELLER: Well, you tried to educate, and we  
2 do as well. Our record of 140 blood cultures from one  
3 patient in one month because of some of these reasons --  
4 when this was looked at, it was stopped. I mean, it was  
5 curtailed greatly. Yes, it can be. But one has to, by  
6 clearly looking at these things, delineate them.

7 But the point is that when one casts the net so  
8 broadly with organisms that do not denote specificity, then  
9 one has a grouping that makes it exceedingly difficult to  
10 study. And before the day is up, Bill, I think -- not that  
11 it's going to be decided in one day, but if this committee  
12 and if the FDA follows through, I think it will take more  
13 than fifteen minutes to get agreed-upon criteria for even  
14 the catheter-associated, catheter-related or intravascular  
15 device-related infections.

16 For example, we found in a study of 1,000  
17 catheters that were sent down, doing the Maki technique,  
18 that more than half of those people never had a blood  
19 culture submitted in the previous week. And of those that  
20 had a positive catheter, many of them didn't have a  
21 positive blood culture. And on and on and on. And when  
22 you come down at the end of the day, the ones that had  
23 coagulase-negative staphylococci could clearly be  
24 associated with catheter-related. But to ascribe a  
25 pseudomonas or a staph aureus to the catheter was fraught

1 with grave consequences.

2           So one could flip this around, as I said  
3 earlier. If it's real, and it's coag-negative, it is, for  
4 practical purposes, catheter-related. To have some other  
5 organism in association with a catheter because the  
6 catheter is merely there, to ascribe it to the catheter and  
7 have some sort of, you might say, limited or focused  
8 antimicrobial or a response that doesn't have that vigorous  
9 search for what complication, the catheter can both be the  
10 source for the bacteremia but it also can be the victim of  
11 the bloodstream infection. So it's not that these things  
12 aren't important, but do they constitute an entity that is  
13 amenable to assessment?

14           That's all.

15           DR. CRAIG: Dr. Danner.

16           DR. DANNER: Like Dr. Maki, though having come  
17 after him, I'm also trained in critical care and infectious  
18 diseases and have followed the work on new therapies for  
19 sepsis, particularly immune modifying therapies. I guess  
20 like many intensivists, we are as a group quite skeptical  
21 and unsatisfied with the SIRS criteria and the semantics of  
22 the term itself. You can get quite an argument going just  
23 bringing up that concept.

24           In addition to, I guess, the problem that Dr.  
25 Maki referred to -- i.e., the problem that you exclude

1 people who a reasonable clinician suspects has bacteremia,  
2 so you lose patients -- it also has the problem of  
3 potentially including patients that a reasonable clinician  
4 would consider not to have bacteremia. I think at one time  
5 or another in the course of their illness, almost everyone  
6 with influenza meets SIRS criteria but clearly do not have  
7 bacteremia. So the problem with it is both sensitivity and  
8 specificity.

9 On the other hand, the advantage of that  
10 criteria, and not to call it SIRS, but the basic criteria  
11 and the modifications of that criteria that exists is that  
12 there are a huge number of trials of immune modifying  
13 sepsis therapies that have been done with that criteria or  
14 modifications of it. That body of data constitutes now  
15 over 10,000 patients that have been studied, and for a lot  
16 of that data the actual rates of bacteremia, the mortality  
17 rates in control groups and a variety of other information  
18 is known.

19 So I guess I would say that in terms of  
20 developing criteria for a new study, that that data  
21 represents a very, very important resource that might allow  
22 us to possibly, with modifications, give you an idea when  
23 you're establishing your criteria what kinds of power  
24 analyses you need. It would help with power analyses and  
25 give you an idea of what level of bacteremia you might

1 expect in a certain population like that.

2 So I think that it represents a tremendous  
3 resource. Even though there are problems with the SIRS  
4 definition, per se, there is a lot of data out there based  
5 on it and based on modifications of it that would be very  
6 useful in designing these types of trials with antibiotics.

7 DR. CRAIG: Dr. Mermel?

8 DR. MERMEL: I think, again, coag-negative  
9 staph is the biggest problem. I think as clinicians we  
10 depend on the blood cultures to make, in large part,  
11 decisions in terms of treating or in terms of validity. I  
12 think that for studies, we need to have rigorous  
13 microbiological definitions. Certainly, we can get  
14 catheter-drawn blood cultures maybe that truly have high  
15 specificity for true bacteremia, and maybe those are  
16 freshly drawn catheters. But I think for the purposes of  
17 getting a drug on the market, we need to use the most  
18 stringent microbiological criteria. For one patient or a  
19 patient with one positive blood culture for coag-negative  
20 staph, well, maybe it's true, but maybe it's a contaminant.  
21 So I think we need rigorous microbiological definitions.

22 Within that, there are many quagmires that Dr.  
23 Reller alluded to. For example, Dr. Scheretz did a recent  
24 study doing three different culture methodologies to  
25 culture catheters in a study of catheter-related

1 bloodstream infection and found out that any one technique  
2 only had a 58 percent sensitivity for finding colonized  
3 catheters in this group of patients with suspected  
4 catheter-related infections. So, do you need to use two  
5 techniques? I think there are things that need to be  
6 ratcheted down if the committee decides to do that.

7 I think we need rigorous microbiological  
8 definitions and maybe looser clinical definitions or  
9 criteria. I think you're both right. I think Dr. Maki's  
10 point with regard to you're going to miss a lot of patients  
11 if we have the bar too high or have a bar at all possibly,  
12 if we don't have a bar, then I think it's going to be such  
13 a hodgepodge and we may not have meaningful data. I think  
14 if we have relatively loose requirements with regard to  
15 fever or white blood cell count but more rigorous  
16 microbiological criteria, particularly for potential skin  
17 contaminants, we'll make the most headway.

18 DR. CRAIG: Clearly, with fever and  
19 neutropenia, we've at least required fever. So I think we  
20 need something that clearly tosses it in. It's almost to  
21 me like maybe fever and an elevated white count instead of  
22 a low white count, at least something that would go along  
23 that there's an inflammation that's associated with the  
24 bacteremia.

25 DR. MERMEL: Yes, I just wouldn't have the bar

1 too high.

2           The other point I think with pediatrics is,  
3 I've read some of the studies with pediatric catheter-  
4 related infections, and some of the kids don't have the  
5 same symptoms with regard to temperature elevations and  
6 white blood cell responses. So there may need to be  
7 different clinical criteria to allow a study in pediatric  
8 line-related infections.

9           DR. CRAIG: Dr. Chikami?

10           DR. CHIKAMI: Yes, just a brief comment on  
11 that. I think having decided that catheter-related  
12 bacteremia is an indication that we should consider, and  
13 cryptogenic bacteremia is also an indication we should  
14 consider, one of the issues I think as the discussion has  
15 been evolving is what are those diagnostic criteria? What  
16 would the entry criteria be? It may involve both the  
17 strict and very critical microbiologic criteria, because  
18 you need to understand what the patients have at the  
19 beginning and then what you're going to follow in terms of  
20 the microbiologic response.

21           Similarly, as I think you were alluding to, we  
22 would like to have at least, a priori, defined some  
23 clinical criteria that we could follow as a response  
24 variable as well. So that there are both clinical entry  
25 criteria and clinical response criteria, whatever those

1 might be, depending on the patient population, and  
2 rigorously defined microbiologic entry criteria and  
3 response criteria.

4 If we don't have some sort of definition of the  
5 clinical criteria both at entry and for response, then  
6 we're left with making the decisions solely on  
7 microbiologic response, which, I think, as you alluded to  
8 -- we want to see some clinical response as well.

9 DR. MAKI: I would suggest, I think, a simple  
10 compromise would be something you've already considered,  
11 and that is you can take the SIRS criteria and then require  
12 probably two or more, a fever or two of the other criteria.  
13 For patients who are suspected of having sepsis who may not  
14 have fever, they usually have tachycardia, or hypotension,  
15 or tachypnea, or you could add to that local inflammation  
16 at the vascular access insertion site, which is sometimes  
17 seen. Those would be simple. I don't think they would be  
18 exclusive, but you are having some objective inflammatory  
19 criteria.

20 DR. CRAIG: Dr. Reller.

21 DR. RELLER: In the previous FDA IDSA  
22 guidelines for clinical studies, urinary tract, et cetera,  
23 it was clear in those discussions and in the documents that  
24 for some indications the clinical side is relatively more  
25 important, in some the laboratory side is relatively more

1 important.

2 A great deal of effort to be very explicit for  
3 the purpose of clinical trials in these catheter-related  
4 infections, it seems to me, both makes it a good reason to  
5 have that indication and would be a real service, because  
6 there's a lot of ambiguity, uncertainty, and imprecision  
7 there now. For example, in the studies, in part -- they've  
8 been already referred to -- of Dr. Zydee in neonates, they  
9 have won, over time, acceptance.

10 There's more that needs to be done on this.  
11 But, for example, whether or not one has a quantitative  
12 method from the catheter or the catheter at removal, I  
13 think most people would accept that no matter what you do  
14 with the catheter or from the catheter for the purposes of  
15 study, without there being at least one peripherally  
16 obtained culture, that one is in difficulty. Secondly,  
17 that regardless of where it's from, one needs at least two  
18 isolates. One may be peripheral, one from the cath, or two  
19 peripheral, but that you need two.

20 One might even argue that it has to be, as we  
21 do -- we don't do susceptibility testing, for example, on  
22 isolates from blood. Sometimes we don't know whether it's  
23 catheter or peripheral because it's not always accurate in  
24 the delineation. All we get is a bottle with blood in it  
25 at that point. And as I've said in the talks to the house

1 staff, only you know in the middle of the night what you  
2 actually did and where it came from. So one would need two  
3 isolates.

4 We don't do susceptibility unless they are  
5 within an isolate either on the same day from different  
6 places or the next day, but they are basically 1 to 48  
7 hours apart, because beyond that there is a very poor  
8 correlation by pulse field gel electrophoresis. Since it's  
9 so easy and relatively inexpensive, one might even require  
10 the criteria, to really do a first-class study, of having,  
11 for those two sites and isolates, of having pulse field gel  
12 electrophoresis to really pin it down. To delineate these  
13 things, including the pulse for the purposes of clinical  
14 study -- not that everybody is going to do this -- would be  
15 a tremendous service.

16 Because in reality, as Dr. Bell alluded to, and  
17 in most studies in major centers, particularly when the  
18 newer instrumented blood culture systems, which is what  
19 most people use, often with resins and charcoal -- I mean,  
20 their capacity to isolate a gasping staphylococcus out of  
21 blood is great. So they are very sensitive, maybe too  
22 sensitive.

23 So for most hospitals, coagulase-negative  
24 staphylococci out of blood are more common than all other  
25 organisms put together. So as a consequence, since those

1 that are real are largely -- not exclusively, but largely  
2 related to this issue, to really get the scientific grip  
3 around this thing would be a tremendous service.

4 DR. MAKI: I think you're absolutely right,  
5 Barth. Dr. Mermel and I have been studying device-related  
6 infections for about a decade together and we believe very  
7 strongly that the standard in looking at the efficacy of  
8 preventive measures ought to be molecular subtyping that  
9 confirms the infection of the peripheral blood culture,  
10 that shows concordance with an isolate that's come from the  
11 device, beyond excluding other potential sources. Whether  
12 you want to go that far, that would be the ideal.

13 But I think if we look at the real world and  
14 what clinicians are making judgments on, I think 95  
15 clinicians out of 100, and, in fact, I'll bet 95 infectious  
16 disease specialists out of 100, if they have two peripheral  
17 blood cultures positive for coagulase-negative staph,  
18 they're going to say that's a true bacteremia. Now, we  
19 know that there's polyclonality, and does that mean that  
20 both of them are contaminants, or one's a contaminant and  
21 one's a true positive?

22 I would say that if you have one positive  
23 peripherally that's concordant with a catheter, that's a  
24 catheter-related bacteremia. But if you have two positive  
25 blood cultures for coagulase-negative staph and you've got

1 it on the catheter, the same species, if you're not going  
2 to require DNA subtyping, and I'm not sure you have to in a  
3 large multi-center trial, it may not be feasible, then in  
4 that circumstance I think that would be acceptable. Two  
5 peripheral positives with positive from the device, the  
6 same species. Ideally, DNA subtyping would be the best  
7 standard.

8 DR. CRAIG: Dennis, could I ask you a question?  
9 Do we know what happens with coagulase-negative staph if  
10 you just remove the catheter and you treat with a drug that  
11 has no activity, whether a percentage of those will clear?

12 DR. MAKI: I'm not sure that the data exist  
13 that I'm aware of, because the study that needs to be done  
14 that would be comparable to that would be that somebody  
15 needs to do a study in healthy immunocompetent people who  
16 get coagulase-negative staph bacteremia, and plenty of them  
17 do who are immunocompetent, they have a line put in for  
18 access, and just pulling the line out and not treating them  
19 at all. I'm not sure how many people would be comfortable  
20 with that study.

21 The problem is that enough people get  
22 coagulase-negative staph bacteremia and may have other  
23 vascular implants, they may have prosthetic heart valves,  
24 they may have joints, they may have other reasons, they may  
25 be very immunocompromised. And so I don't think there's

1 good enough data to answer that question, other than  
2 anecdotal.

3 DR. CRAIG: Because there's clearly reports  
4 with enterococci, especially vancomycin-resistant  
5 enterococci, that removing catheters has sometimes resulted  
6 in the organism disappearing. If I remember right, I think  
7 when the FDA specifically looked at the bacteremia with  
8 Synercid, one of the things they were looking at was  
9 primarily concentrating on those cases where there was  
10 bacteremia present after the catheter was removed.

11 And so the question comes, how do we know with  
12 a central line -- I mean, if it's a peripheral line, you  
13 can see that there's inflammation at the site and you get  
14 the organism from it. But how do we know that there's  
15 inflammation when it's a central line, and how do we know  
16 for sure that the catheter is infected? Obviously, trying  
17 quantitative cultures. But that's not very sensitive. And  
18 so how are we going to know except by pulling the catheter  
19 and --

20 DR. MERMEL: The quantitative cultures have a  
21 sensitivity, if you look at Barry Farr's recent study, of  
22 over 90 percent. And the inflammation is very insensitive.  
23 You'll see it 80 percent of the time with a peripheral  
24 I.V., but maybe 20 percent of the time with a central line.  
25 So we can't depend on that or it will exclude a lot of

1 patients.

2 DR. CRAIG: So you think that you would be able  
3 in the studies -- because I think the usual standard of  
4 practice is not to remove them for coagulase-negative staph  
5 and to try and --

6 DR. MERMEL: Yes, I think the sensitivity is  
7 good enough with some of the methods --

8 DR. CRAIG: So that you wouldn't lose huge  
9 numbers of cases.

10 DR. MERMEL: No.

11 DR. CRAIG: And would be able to use that as  
12 your criteria for diagnosis of catheter infections.

13 DR. MERMEL: I think so. Yes, for including  
14 patients in the study.

15 But one other quick point to a question you  
16 raised. At the endocarditis session at ICAAC, I can't  
17 remember if it was Dr. Karshmer or there was another  
18 speaker, they presented some older animal data with right-  
19 sided endocarditis, catheter-induced, where they removed  
20 the catheter and the animals got better with just catheter  
21 removal. So I think there was some animal data to support  
22 what you were saying about case reports with enterococcus.

23 DR. CRAIG: Dr. Murray?

24 DR. MURRAY: We discussed things like pulse  
25 field at the meeting looking at the guidance document and

1 debated the issue of requiring or suggesting that, to  
2 define failure of the same organism, but didn't go that  
3 far. But I think for analysis, I think that should be  
4 required. I agree with Barth completely, and it could be  
5 done in a single site. Isolates can be collected and done  
6 by a single site that applies uniform criteria.

7 DR. CRAIG: And again, are we talking two  
8 positive blood cultures, at least one peripheral?

9 DR. MURRAY: That was one thing that was said.  
10 Dennis even said two positive peripherals and same species  
11 from a catheter. I guess I would say if it's one positive  
12 peripheral and one positive from the catheter, and then  
13 they agree by pulse field, fine.

14 DR. MAKI: I would agree with that, exactly.  
15 You have positivity in a peripheral blood culture with the  
16 device and you've excluded clinically other potential  
17 sources.

18 DR. CRAIG: And then we would have the  
19 quantitative from the catheter as well.

20 DR. MAKI: And you could also --

21 DR. CRAIG: So do we need two peripheral in  
22 order to enhance the specificity there?

23 DR. MAKI: Well, if you're going to require DNA  
24 subtyping, then you don't need two positive peripheral, but  
25 you need to have concordance with a peripheral blood

1 culture and the device.

2 DR. CRAIG: No, but I'm talking from a  
3 quantitative to if you're trying to prove that the  
4 catheter --

5 DR. MAKI: Are you talking about quantitative  
6 blood cultures or quantitative catheter cultures?

7 DR. CRAIG: Quantitative catheter cultures.

8 DR. MAKI: Quantitative blood cultures, paired  
9 blood cultures, if you have huge numbers coming from the  
10 catheter and very small numbers peripherally but  
11 peripherally they're positive, I guess you could require  
12 DNA concordance, but I think that's probably overkill. If  
13 you've got  $10^3$  coming from the catheter and you've got 7  
14 per colony peripherally --

15 DR. CRAIG: The question I was trying to ask  
16 is, is your sensitivity better or your specificity for it  
17 being truly a catheter infection if you have two peripheral  
18 cultures as compared to one comparing with the catheter?

19 DR. MAKI: The paired quantitative technique,  
20 Bill, relies on the gradient. About eight or ten studies  
21 have studied this -- and Barth probably knows these data  
22 better than I do -- and have shown an aggregate sensitivity  
23 and specificity in the range of 90 percent as long as the  
24 blood cultures are drawn before you start the anti-  
25 infective therapy. Once that's been done, their utility

1 just plummets.

2 DR. CRAIG: Yes.

3 DR. RELLER: Dennis or Leonard, or both, if one  
4 has a peripheral within 24 hours, preferably closer than  
5 that, from a catheter and one has pulse field concordance,  
6 are quantitative cultures from the catheter necessary?

7 DR. MAKI: No.

8 DR. RELLER: And if the patient then is entered  
9 into a study and is successful, you won't have the catheter  
10 tip to culture. If they fail, it might be of interest to  
11 culture it. But for the terms of diagnosis of catheter-  
12 related BSI with coag-negative staphylococci, actually the  
13 catheter tip cultures are sort of not a central issue, are  
14 they? I mean, you would only have them if they were a  
15 failure of the putative drug if you had used rigorous entry  
16 criteria in the first place.

17 DR. MAKI: First of all, Barth, I think it's  
18 important to distinguish. There's two types of catheters  
19 we're talking about. We're talking about non-cuffed  
20 temporary catheters that are not intended to be left in  
21 indefinitely. That's a very large proportion. They cause  
22 probably 75 percent of the bacteremias in the hospital.  
23 Then there are the cuffed permanent catheters in the  
24 subcutaneous ports. They cause substantial bacteremias but  
25 their risk per device day is much lower than the temporary

1 ones. But they cause substantial bacteremias.

2 Now, you can diagnose catheter sepsis one of  
3 two ways. One is you can remove the device and show  
4 there's large numbers of the same organism in association  
5 with the device, whether it's the tip, whether it's the  
6 lumen of the port, whether it's the hub of a catheter,  
7 that's concordant with peripheral blood cultures ideally by  
8 DNA subtyping. Alternatively, on permanent devices you can  
9 do paired quantitative blood cultures, one drawn through  
10 the device, one from a peripheral vein, and if one  
11 demonstrates a marked step-up in positivity and there's  
12 concordance between the organisms in the peripheral, you  
13 don't have to remove the device and you can feel quite  
14 confident that you have a device-related bloodstream  
15 infection without necessarily removing it. Whether the  
16 clinician wants to remove it or not is a judgment call, but  
17 you can feel confident that you've diagnosed the device as  
18 the source.

19 DR. RELLER: Are you any more confident -- and  
20 I ask this thinking ahead to clinical trials and the  
21 practicality, and expense, and availability, and so on.  
22 Many centers, because for other purposes they were not  
23 necessary, don't do quantitative cultures anymore.

24 So my question very specifically -- I  
25 understand and agree with everything you've said, but if

1 one has and utilizes for entry criteria denoting the  
2 catheter as the source of coag-negative staphylococci and  
3 concordance by pulse field gel electrophoresis of a  
4 catheter, a minimum of a catheter and peripheral obtained  
5 within a finite and short period of time, regardless of the  
6 kind of catheter in place or access in place, does  
7 quantitation add anything more in terms of specificity of  
8 catheter-associated bacteremia than simply the paired  
9 cultures with pulse field?

10 DR. MAKI: Are you talking about standard  
11 qualitative blood cultures? Basically, you're talking  
12 about a catheter-drawn and a peripheral-drawn?

13 DR. RELLER: Yes.

14 DR. MAKI: Well, Len has shown that a shorter  
15 time to positivity in the catheter-drawn, which is a  
16 surrogate marker for large numbers of organisms, has some  
17 utility in identifying the line as the cause. But I'm  
18 always a little uncomfortable. One of the most common  
19 fallacies I think in clinical practice is the clinician  
20 draws the blood culture through a catheter, draws one from  
21 a peripheral vein, the peripheral one is negative, the  
22 catheter-drawn is positive, and they say, "Ergo, line  
23 sepsis." It's probably, "Ergo, contaminated blood  
24 culture."

25 DR. RELLER: I agree with you completely. But

1 when that peripheral is positive and the catheter is  
2 positive, do you need a quantitative culture from the  
3 catheter to prove it?

4 DR. MERMEL: The question has been answered.  
5 First, the question has been answered because Barry Farr's  
6 huge meta-analysis suggested that there wasn't much  
7 difference. I think your point is correct, that there was  
8 no statistically significant difference in this huge number  
9 of studies in the specificity with the qualitative versus a  
10 quantitative culture in this sort of setting that you're  
11 talking about.

12 I think we can improve specificity. We looked  
13 at -- a French group has published -- we just had it at  
14 ICAAC -- if the catheter-drawn blood culture grows out, if  
15 they are continuously monitored, drawn at the same time,  
16 two to four hours quicker than percutaneously, as Dr. Maki  
17 mentioned, as surrogate marker of the level of bio-burden  
18 of organisms, that appears to increase specificity if it's  
19 catheter-drawn. But even without that, Barry Farr's meta-  
20 analysis has already answered the question that there  
21 really was no measurable difference in specificity when  
22 they were both positive.

23 A very important thing I want to remember that  
24 we've not touched upon is that most of the data on  
25 quantitative blood cultures and those that Barry included

1 in his meta-analysis, the vast majority were long-term  
2 catheters where maybe the hub has more of a role in terms  
3 of intraluminal colonization of the catheter. So I think  
4 we may learn something. There's maybe a little bit of a  
5 learning curve, and I'm not sure what Dr. Maki feels about  
6 this, when we study intensively short-term catheters and  
7 use the quantitative methodologies. I don't know if there  
8 may be a little tinkering with the specificity.

9 DR. MAKI: We don't allow quantitative  
10 techniques to be used for short-term catheters in our  
11 hospital because you can always pull it out to culture the  
12 tip. We're just not convinced it is cost-effective to be  
13 doing paired cultures. If you suspect a central line in an  
14 ICU patient as being a source of sepsis, a patient is  
15 septic, we think, rather than just drawing paired blood  
16 cultures, you ought to take it out. You can always culture  
17 the tip and get the information. You can always get access  
18 elsewhere.

19 DR. MURPHY: Dr. Craig, let me summarize. I  
20 just want to make sure -- I've got three gold standards  
21 right now. I've got a gold standard -- the first one is  
22 two cultures, one peripheral, one a minimum of one  
23 peripheral with pulse field typing.

24 DR. CRAIG: That's correct.

25 DR. MURPHY: That's really what we want to

1 know. What does this committee think is its gold standard?

2 DR. CRAIG: That's what I was trying to get at  
3 and see whether any additional -- I think what came up was  
4 that we thought there needed to be two blood cultures, at  
5 least one of them peripheral, and that we should have pulse  
6 field electrophoresis to show that they're the same  
7 organism.

8 DR. MURPHY: Okay. And then the second gold  
9 standard was two peripheral positives with same species,  
10 basically.

11 DR. RELLER: I think, Dianne, the discussion is  
12 that -- what Bill just said takes care of it. Those other  
13 things were other options. But if somebody wanted to do a  
14 peripheral and a quantitative culture from a long-term  
15 catheter that was positive but they also had quantitation,  
16 that would be great.

17 But my own view is I'd like to see the data  
18 that it for certain adds more specificity than we already  
19 have. But what I'm delighted to see everybody agreeing on,  
20 I think no matter what you do with a catheter, whether you  
21 culture it when you take it out, whether you culture it  
22 quantitatively while it's in place, in the absence of a  
23 positive peripheral culture, a diagnosis of catheter-  
24 related bacteremia sepsis one cannot make. It doesn't mean  
25 that it's not there, but one can't make the diagnosis for

1 the purposes of clinical trial for the approval of a site  
2 organism-specific indication for an existing or a new anti-  
3 infective.

4 DR. MURPHY: And the last thing I heard was  
5 that one peripheral, one pulled quantitative. In other  
6 words, he said, I thought --

7 DR. CRAIG: Peripheral. If you didn't cut it  
8 through the catheter but you pulled the catheter and did a  
9 quantitative culture that was positive, that would also be  
10 potentially a case.

11 DR. MAKI: I think we're honing in on three  
12 criteria. One is if the catheter is pulled out and we  
13 culture large numbers of the organism from the catheter and  
14 we get it from a peripheral blood culture and have  
15 concordance, that's line sepsis. If we've drawn a blood  
16 culture through the catheter and have one positive  
17 peripheral and we have concordance, that's line sepsis. We  
18 don't necessarily have to draw it out. If we have  
19 quantitative blood cultures through a permanent device that  
20 shows a marked step-up with the same organism as  
21 peripheral, that's line sepsis.

22 PARTICIPANT: I'd like to make a comment on  
23 that, Dr. Craig, if I may, please.

24 DR. CRAIG: Yes.

25 PARTICIPANT: I get nervous when I hear

1 quantitative cultures through the catheter and a step-up.  
2 Is there a consensus about what is a positive catheter  
3 culture, what colony count you're going to consider as a  
4 step-up that is appropriate and it gives everybody an equal  
5 playing field?

6 DR. MAKI: The ten studies or so that have  
7 looked at this have looked at a gradient that has ranged  
8 from about five to ten times greater through the catheter  
9 than through a peripheral.

10 DR. MURRAY: Assuming the same mils are drawn.

11 DR. MAKI: Yes.

12 DR. MURRAY: I guess I might have pushed the  
13 golds maybe to the platinum standard of two peripheral  
14 positives drawn over time. I'll just throw that out. I  
15 mean, a transient blood culture due to some organisms on  
16 the tip --

17 DR. MAKI: Well, I don't know if it's  
18 necessarily transient or not. We've heard data and seen  
19 data presented here that one positive blood culture can be  
20 true bacteremia.

21 DR. MURRAY: Oh, I agree with that.

22 DR. MAKI: That clearly occurs. And having  
23 studied this area and done a lot of DNA subtyping, we've  
24 seen our share of patients where they're septic, there's no  
25 question, there's no other source, and we get the

1 coagulase-negative staph, the same DNA subtype from the  
2 catheter in large numbers and from one peripheral blood  
3 culture, and one is negative. I've always interpreted that  
4 as simply being it's not a real high, great degree of  
5 bacteremia, they're not all positive.

6 Ideally, you'd like to have both positive. But  
7 when you're saying you have to have two positive  
8 peripherally, you're having a higher standard, and that's a  
9 reasonable higher standard if you don't have DNA subtyping.

10 DR. MERMEL: I think Dr. Murray is trying to  
11 differentiate transient where the patient is going to get  
12 better without the antimicrobial intervention, and someone  
13 who may not.

14 DR. CRAIG: That's why we want some clinical  
15 signs as well.

16 DR. MERMEL: So we're not talking about just  
17 two separate cultures. You're talking about separating  
18 them over time. You're talking about the next day. I  
19 think that's a laudable goal with coag-negative staph. But  
20 I'm worried, for example, if someone has staph aureus and  
21 you say you've got to wait, don't initiate therapy, you've  
22 got to wait another day. We have the data to show that if  
23 you don't remove a catheter in 48 hours, they have a  
24 threefold higher risk of dying. So I think with more  
25 virulent pathogens, separating over time becomes less

1 important in terms of your specificity, and there's a  
2 greater urgency to treat, maybe for a potential skin  
3 contaminant.

4 DR. MURRAY: I guess I'm just getting a little  
5 nervous with the coag-negative staph, since I think in the  
6 old days we did just take out the catheter and didn't treat  
7 them.

8 DR. MAKI: The thing is that taking out the  
9 catheter is the logical thing to do with any non-cuff  
10 temporary catheter. But it isn't always so easy with a  
11 cuff catheter. It's very expensive to put it in.

12 DR. MURRAY: Yes. I'm sorry. I meant in the  
13 sense of they make it better without treatment once you've  
14 taken it out, and now we're adding on that it seems  
15 possibly that we could be entering patients that would also  
16 just have the transient bacteremia. So I'm just expressing  
17 a little insecurity that we've taken the organism that we  
18 were in doubt about doing, and now we're lowering the bar  
19 maybe a little too far.

20 DR. MERMEL: I think the only potential problem  
21 there, and I think Dr. Maki would agree, would be someone  
22 with a fresh valve or, let's say, a vascular graft where  
23 you'd want to eradicate the bloodstream infection as quick  
24 as possible. As we know, a third to a half of nosocomial  
25 endocarditis is catheter related. Most of those are staph.

1 Some of them are coag-negative. Probably most of them are  
2 staph aureus. But I think you might have to exclude  
3 certain groups who have had vulnerable intravascular  
4 hardware. If you're going to wait more time, you might  
5 jeopardize the patient.

6 DR. CRAIG: I think, again, by having clinical  
7 signs and symptoms that go along with an inflammation and  
8 it's related, it's much more likely that it's not going to  
9 just resolve on its own, as compared to if you didn't have  
10 any clinical signs.

11 Dr. Reller.

12 DR. RELLER: Dennis, for entry criteria in a  
13 proposed study, although a heavily colonized positive  
14 culture of a catheter tip that's removed properly,  
15 processed properly, that is positive with the same organism  
16 by pulse field with a single peripheral culture is, I  
17 think, reasonably solid.

18 One certainly, in a practical sense, at least  
19 for the purpose of adjunctive therapy of catheter-related  
20 bacteremia with a coag-negative staph, wouldn't remove a  
21 catheter based on a single peripheral positive that was not  
22 accompanied by another one, as Barbara wanted, or by one at  
23 least drawn through the catheter that for the purposes of  
24 study should be one and the same by pulse field.

25 So from a practical standpoint, although

1 heavily colonized with a peripheral of the same organism by  
2 pulse field would be pretty solid, from a practical  
3 standpoint, you'd be in the dilemma if you hadn't already  
4 had a positive from the catheter or a second peripheral,  
5 that you'd be removing a catheter for a reason that would  
6 be based on a single positive, which is just the dilemma  
7 that we don't want to get into, I don't think. What do you  
8 think?

9 DR. MAKI: First of all, a single positive  
10 blood culture, we haven't removed the catheter, is  
11 uninterpretable as far as I'm concerned. I can't agree  
12 more fully. And I think your statement that if somebody  
13 gave me a nickel for every gram of vancomycin that we've  
14 given and has been urinated in the sewers of this country  
15 for treating contaminated blood cultures, I'd be pretty  
16 wealthy, because single positive blood cultures are one of  
17 our biggest problems with overuse of vancomycin. We tried  
18 to promulgate the concept, except in the patient who's got  
19 a prosthetic valve or a fresh vascular implant, that a  
20 single positive blood culture for coag-negative staph  
21 should not prompt immediate therapy but rather additional  
22 blood cultures and observation, and maybe replacing the  
23 lines and culturing the catheters.

24 But if you pull the catheter out -- let's say  
25 you've pulled the catheter out. The patient had a fever,

1 and you've got one positive blood culture for staph epi,  
2 it's grown heavy on the catheter tip, I think 9 out of 10  
3 clinicians and infectious disease consultants would  
4 probably consider that as probable line sepsis and would  
5 seriously think about treating that.

6 DR. RELLER: But for the purpose of the study,  
7 what I'm trying to do is to come back to Dr. Murphy's query  
8 about what criteria would be used. So something that could  
9 be reproducible and clear and up front for the purposes of  
10 recruitment into such a study --

11 DR. MAKI: Are you talking about clinical or  
12 microbiologic?

13 DR. RELLER: Both. One or two or three of  
14 SIRS. But just talking now about the microbiology side, to  
15 be quite specific, it seems to me one would state that the  
16 diagnosis of catheter-related bacteremia would require --  
17 not necessarily sufficient for but necessary for entry --  
18 two positive cultures, one peripheral and the other of  
19 which -- it could be two peripheral, but --

20 DR. MAKI: It could be two peripheral, exactly.  
21 Don't get caught up in saying one has to be from --

22 DR. RELLER: Two positive cultures, of which  
23 one must be peripheral, because that gives you the entry  
24 criteria rather than clouding the issue. Now, if somebody  
25 goes ahead and as part of the therapy removes the catheter

1 right away and gets quantitative cultures, or they get  
2 quantitative cultures through the line, or peripheral, or  
3 both, all of that is fine. Just pulse field them all, et  
4 cetera.

5 But you would end up with absolute -- the gold  
6 standard or the minimum would be two cultures, one of which  
7 must be peripheral, both of which must be positive before  
8 entry into a trial.

9 DR. MAKI: I could not agree more fully. I  
10 think that we need rigorous criteria, absolutely.

11 DR. CRAIG: You're saying that whether we're  
12 talking about primary bacteremia or catheter-related?

13 DR. MAKI: We're talking about catheter-related  
14 bacteremia. Just catheter-related bacteremia is all we're  
15 talking about.

16 DR. CRAIG: Because I still don't know if I  
17 have two peripherals that the catheter is infected.

18 DR. RELLER: Bill, if you have two peripherals  
19 and there's no TEE with a known or native valve  
20 endocarditis and it's unknown, no prosthetic joint in which  
21 you've entered someone as a subset of a joint infection  
22 with prostheses, et cetera, you've got --

23 DR. CRAIG: But if it's staph aureus?

24 DR. RELLER: See, I think staph aureus,  
25 ascribing it to the catheter -- it can be coming from the

1 catheter, or the catheter may be the victim. But I think  
2 we're on very treacherous ground in facilely ascribing  
3 staph aureus bacteremia to the catheter. Not that it  
4 doesn't occur, but there are patients with catheters in  
5 place who have staph aureus bacteremia where the catheter  
6 is no longer the issue.

7 DR. MURRAY: Have we lumped the cryptogenics  
8 back with the catheter-related?

9 DR. CRAIG: No, we're still separate.

10 DR. MURRAY: But if you don't have quantitative  
11 cultures or the cath tip, then how do you call it catheter-  
12 related?

13 DR. CRAIG: That's what I'd like to know. I  
14 agree that for certain organisms, it's very likely that  
15 it's still going to be catheter-related.

16 DR. MURRAY: But Dennis is still calling those  
17 50 percent cryptogenic.

18 DR. CRAIG: What I still think we need, you  
19 need for entry to be sure that it's catheter-related.

20 DR. MAKI: Let me summarize. If we want to  
21 really be rigorous, the most rigorous things we can do is  
22 require concordance between the removed device and  
23 peripheral blood culture by DNA subtyping, or we have  
24 quantitative blood cultures drawn through the device  
25 showing a marked step-up with concordance through the

1 device and through peripheral.

2 Now, Barth is suggesting, and it's clinically  
3 sound, that just standard qualitative blood cultures drawn  
4 peripheral and through the device, or simply two peripheral  
5 and they're positive -- the patient has a device and no  
6 other source of the bacteremia whatsoever, 9 times out of  
7 10 that's a device-related bacteremia. It's softer. It's  
8 more of a clinical type of a judgment that the clinician is  
9 going to use. That's softer. I'm not uncomfortable with  
10 using it, but it's not as rigorous as the first two. But  
11 I'm perfectly willing to use it if the committee thinks  
12 it's acceptable.

13 DR. RELLER: I'm happy with either, as long as  
14 there's pulse field concordance and there are at least two  
15 of them.

16 DR. MURRAY: But you voted against the second  
17 one being the criteria, the cryptogenics.

18 DR. RELLER: No, no, no. I just don't want all  
19 of those -- see, I'm only happy, for practical purposes,  
20 with coagulase-negative staphylococci and device-related  
21 infections. I am not at all comfortable with bacteremias  
22 owing to other organisms in the cryptogenic category, and  
23 that's why I voted as I did. I think it's a mistake not  
24 keeping them linked with other things, or in the  
25 neutropenia category, or discussing the issue further.

1 DR. CRAIG: What percentage of your catheter-  
2 related are staph aureus?

3 DR. MAKI: About 10 to 12 percent.

4 DR. CRAIG: That's a significant number.

5 DR. MAKI: Probably less than 1 out of 5, 1 out  
6 of 7.

7 DR. CRAIG: I guess I would feel more  
8 comfortable with knowing that the catheter is definitely  
9 infected. So I would prefer the first two, at least having  
10 one through the line that's positive, or pulling it and  
11 showing that it's positive, or, again, doing a step-up.  
12 But at least having the peripheral ones, as you say, but  
13 still requiring something through the line.

14 DR. MAKI: So you're accepting Barth's  
15 suggestion of a qualitative blood culture drawn through the  
16 line and peripheral that match, but you aren't accepting  
17 two peripheral without anything out of the line.

18 DR. CRAIG: Just to call it clearly associated,  
19 I would feel better, a little more stricter, if we had  
20 it --

21 DR. MURRAY: If you have true bacteremia --  
22 well, okay, that gets back to the coagulase-negative staph  
23 issue. Because if you have true bacteremia, you're going  
24 to get it out of the catheter. But then that circles  
25 around to if it's coagulase-negative, it's almost always

1 from the catheter. But you are going to get it without  
2 quantitation for another organism. You can't distinguish.

3 DR. CRAIG: If somebody had studied it and  
4 showed me that if you get two and you pulled out the bunch  
5 of catheters or did the other tests, that 100 percent of  
6 them were the case, then I --

7 DR. MAKI: Well, I guess the best way of  
8 putting it, Bill, if patients don't have catheters, they  
9 virtually never get staph epi bacteremia unless they have a  
10 ventricular systemic shunt. That's about the only other  
11 condition.

12 DR. CRAIG: But the question is they frequently  
13 have multiple catheters.

14 DR. MAKI: That's right.

15 DR. CRAIG: And which one are we talking about?

16 DR. MAKI: That's why I agree, the first two  
17 are the most rigorous.

18 DR. RELLER: That's why that peripheral, at  
19 least one of which is peripheral, is very, very important.  
20 It is crucial because we're looking at it all the time.  
21 One out of this lumen and that lumen, and two lumens  
22 positive, and this and so on, and you've got two -- I mean,  
23 you've got 17 blood cultures, 11 of which are positive, but  
24 not a single one of which is positive from a peripheral.  
25 And then what do you do with it?

1 DR. CRAIG: Dr. Gerding.

2 DR. GERDING: I've certainly been listening  
3 with interest to this conversation and trying to put it  
4 into perspective when you see consults with these problems.  
5 I have to agree with Dr. Reller. If I saw a patient with  
6 two peripheral blood cultures positive for staph aureus and  
7 the patient had an I.V. in, I would not attribute that  
8 infection to that I.V. without documentation. I would be  
9 very reluctant to do that because I'm going to make  
10 critical duration of therapy decisions based on whether  
11 that's an I.V.-related bacteremia or not.

12 So, clearly, the pathogen here is playing a  
13 role. The same situation with a staph coagulase-negative,  
14 I would probably make the judgment that it's related to  
15 that catheter and recommend that it be taken out  
16 immediately. But I would not be making the same kinds of  
17 critical judgments about how I'm going to treat the  
18 patient, for example, because the data are different in  
19 terms of coagulase-negative staph duration of therapy and  
20 staph aureus.

21 And the same applies for those rare gram-  
22 negative rods that cause device-related bacteremia. I  
23 would really want some documentation from the device itself  
24 to go along with the attribution to it being an  
25 intravascular device-related infection.

1           So it looks like coagulase-negative staph is  
2 such a uniquely associated organism with intravascular  
3 devices that you might make decisions differently based on  
4 those infections with that organism. But I would not leap  
5 to other organisms because of the clinical implications  
6 that that might have.

7           DR. RELLER: Just a brief comment to follow up  
8 on Dale's. We presented at last year's ASM 1,000 catheter  
9 tips that were removed and cultured by the method published  
10 by Dennis, and if I recall correctly, I think it was 156  
11 that were at greater than 15, done the right way, and not a  
12 single one of them that was not coagulase-negative staph,  
13 and that was the minority. But of those that were E. coli  
14 pseudomonas or staph aureus, all of them, though it may  
15 have started with the catheter, other things were going on  
16 at that time, and to have ascribed it to the catheter would  
17 have been a clinical mistake. Just reinforcing what you  
18 have outlined.

19           DR. MAKI: I would just add one caveat, and  
20 that is that when you study devices, those who have studied  
21 the pathogenesis of devices realize that it's a complex  
22 phenomena and that infection can come from the skin and go  
23 down the tract, they can come from the hub, and  
24 occasionally, rarely they can contaminate the infusate. So  
25 I think if one has concordance with any aspect of the

1 device and peripheral blood cultures and you have  
2 clinically excluded other potential sources, that would be  
3 a device-related bloodstream infection. Not just culturing  
4 the tip, but it may be the hub, it may be fluid as well.

5 DR. CHIKAMI: So then, if I may try and  
6 summarize here.

7 DR. CRAIG: I can try and summarize it. I  
8 think we said that clearly we feel that it's very important  
9 that we have at least one peripheral blood culture, and  
10 that we actually have to have two blood cultures as entry,  
11 one of which needs to be at least a peripheral. I think  
12 the conclusion came up that if it's coagulase-negative  
13 staphylococci, we would probably be happy even with two  
14 peripherals without necessarily documenting something with  
15 the line.

16 On the other hand, for other organisms like  
17 staph and for gram-negatives, we felt that the line needed  
18 to be looked at and that probably just getting the culture  
19 through the line by itself is probably not sufficient.  
20 What you'd like to have is a step-up with those kinds of  
21 organisms, or to culture the organism from a removed  
22 catheter. And the standard of practice I think with staph  
23 aureus right now, if you thought that was around, would be  
24 to remove the catheter so one would have a chance then of  
25 clearly proving that that was the organism.

1 DR. MURPHY: I'd like to compliment the  
2 committee. Not only have they seen it, they know it, and  
3 now they've defined it.

4 (Laughter.)

5 DR. MAKI: Could I offer just one minimal  
6 amendment to that, Bill?

7 DR. CRAIG: Yes.

8 DR. MAKI: I'm not convinced it's necessary to  
9 do DNA subtyping on organisms other than coagulase-negative  
10 staph or perhaps Bacillus species or Corynebacterium, other  
11 skin commensals where it is essential. But I think for  
12 things like staph aureus, enterobacter, these others, I  
13 don't think it's necessary to do DNA subtyping. We do it,  
14 but we have never seen an organism that we thought, for  
15 instance, was an enterobacter or staph aureus bacteremia by  
16 our criteria. We excluded other sources, we got large  
17 numbers, we had a different clone that was involved.

18 DR. CRAIG: I don't think there's any way that  
19 we're going to be able to put together the clinical  
20 criteria now. I think first when Dr. Danner even mentioned  
21 some of the criteria, that would be data that I think would  
22 be interesting for us to look at, but I think the committee  
23 is uniform in that we need some clinical signs and symptoms  
24 that there's inflammation going on associated with the  
25 infection. Whether that's using some multiple of the

1 different SIRS criteria, or just simply fever leukocyte, we  
2 need something, and I think we need to have a little  
3 stronger idea of what would be the best data to use.

4 DR. MAKI: Dr. Mermel and I have a paper we  
5 actually worked on last night that we'd be happy to share  
6 with the committee if they're interested. We're about to  
7 submit it. It's over a thousand -- it's a very large  
8 number of bacteremias that are clearly secondary  
9 bacteremias and clearly line-related bacteremias. We want  
10 to know what's different about those two in terms of  
11 clinical presentation, microbiologic features, duration of  
12 bacteremia, all of this sort of information.

13 What astounded us was you could not discern  
14 line sepsis from non-line on average in terms of mean temp,  
15 white counts. They just didn't fall out very differently.  
16 There's a little more left shift, but there's left shift in  
17 both. And the most critical discerning point was duration  
18 of bacteremia. Much longer bloodstream infections with  
19 lines, intravascular infections, and the microbiologic  
20 profile was really the critical thing. We'll be happy to  
21 share that if it may be of some use to you in looking at  
22 clinical features.

23 DR. CRAIG: Okay. Anything else?

24 DR. CHIKAMI: And for cryptogenic bacteremia?

25 DR. CRAIG: Oh, cryptogenic. How about blood

1 culture criteria for that? I think, again, we'd say that  
2 we still need two. But now the question is how do you  
3 disprove that you don't have line sepsis? I think for  
4 coagulase-negative staph, you have to have evidence from  
5 the pulled lines that the rolled cultures were negative.

6 DR. MAKI: Or you can say that the techniques  
7 that were advocated here for diagnosing line sepsis had  
8 been done and had not implicated the line. That's what  
9 we're talking about. For instance, they did paired  
10 quantitative blood cultures in the port or Hickman and  
11 there was no gradient, or they removed the catheter and the  
12 tips were negative.

13 DR. CRAIG: Does that mean all catheters?

14 DR. MAKI: I think we're talking about all  
15 catheters, yes. At least an effort is made to diagnose  
16 infection with all implanted catheters.

17 DR. CRAIG: Or, then again, it would include in  
18 there patients such as staph bacteremias which come in from  
19 the community that don't have a catheter in, that don't  
20 have any discernible focus. But again, you would want to  
21 have at least two cultures. Probably here -- how many do  
22 we need? Just two?

23 DR. MAKI: Do you need two if it's staph  
24 aureus, or salmonella, or pneumococcus, or H. influenza?

25 DR. CRAIG: Good question. As long as they're

1 peripheral.

2 DR. MURRAY: We're talking about studies here  
3 too, though, where the more clearly things are defined, the  
4 better the likelihood the study will show some --

5 DR. CRAIG: Would you be happier with two or  
6 one, Barth?

7 DR. RELLER: I'm not happy with this indication  
8 in the first place.

9 DR. CRAIG: But at least help those of us that  
10 are.

11 DR. RELLER: There are two reasons for getting  
12 two blood cultures. One is, with the ordinary volumes of  
13 blood culture, to get enough volume. The overwhelming  
14 reason for having two separate ones is to sort out the  
15 contaminants, the viridans and the coagulase-negative  
16 staphylococcus. I'm perfectly happy with the documentation  
17 of salmonella typhi with a single positive blood culture,  
18 and almost always most other organisms -- pseudomonas  
19 aeruginosa. I'm happy with pseudomonas aeruginosa out of a  
20 line in granulocytopenic febrile patients. As a basis for  
21 adjusting therapy, as Dr. Bell mentioned, it's often not  
22 done, sticking with the general.

23 But I think to reinforce good practice, for the  
24 documentation of bacteremia or blood stream infection, that  
25 one should obtain a pair of blood cultures, depending on

1 the organism, not both of which need be positive.

2 DR. CRAIG: Could I ask what criteria are used  
3 now for, let's say, when you're doing associated  
4 bacteremia? Do you require two positives there?

5 DR. CHIKAMI: Usually two positives.

6 DR. CRAIG: I think one should essentially have  
7 the same criteria.

8 DR. RELLER: Bill, I don't want to speak too  
9 much, but there's a problem with that. That is, the two  
10 blood cultures got into the patients with neutropenia and  
11 fever as an important diagnostic criterion. It wasn't  
12 expected that they'd all be positive, but this was part of  
13 the evaluation of those patients to make sure that if a  
14 specific organism was obtained, et cetera. It's a good  
15 reason to get two blood cultures for the evaluation of  
16 patients with pneumonia or urinary tract infections with  
17 pyolin nephritis.

18 But to require two will automatically exclude  
19 -- again, I don't like bacteremia as an indication itself.  
20 But, for example, for other sites, for the secondary ones,  
21 for example, to exclude a positive blood culture for  
22 pneumonia owing to *Streptococcus pneumoniae* because only  
23 one blood culture was positive instead of two, or a urinary  
24 tract infection with *E. coli* because one was positive  
25 rather than two, or on and on and on, I think is

1 fundamentally a mistake outside of viridans and coagulase-  
2 negative staphylococci, because it's going to, right off  
3 the bat, exclude about 30 percent of the patients that you  
4 would have had the opportunity to get specificity, and that  
5 30 percent figure is not drawn from thin air. It's because  
6 it's the proportion of patients who need, on balance, from  
7 adults, 40 mL of blood versus 20 mL of blood to have a  
8 positive at all, and it has to do with the number of  
9 organisms, the number of which, the quantitation of which  
10 in the peripheral blood is of no importance having to do  
11 with the specificity of blood cultures and confirming of  
12 bacteremia associated with urinary tract infections,  
13 pneumonia, et cetera.

14 DR. MURRAY: With the pneumonia, I would have  
15 been happier with one because at least you know you have an  
16 infection. But in the cryptogenic, I would think a little  
17 more rigor were needed.

18 DR. CHIKAMI: Let me correct myself. In fact,  
19 my reviewers have corrected me that in those situations  
20 where there is a positive culture at the primary site of  
21 infection, like pneumonia and urinary tract infection, et  
22 cetera, if there is a single positive blood culture which  
23 is concordant, then that's accepted.

24 DR. CRAIG: Dr. Roberts?

25 DR. ROBERTS: I would just like to make a

1 comment. I know a lot of our discussion has been on the  
2 microbiologic diagnosis, and we certainly appreciate that.  
3 But I have some concern with respect to the clinical and  
4 some of the terminology that's come out, and using the  
5 sepsis database for the failed trials, which now, as Dr.  
6 Danner says, are over 10,000 patients to date. I'm  
7 concerned that we're talking about sepsis, and are we  
8 asking more than an antimicrobial agent can do?

9 I think it is important, if we're going to  
10 define a subset of patients where we're going to look at an  
11 anti-infective to see if they can treat the condition, that  
12 we don't -- this is a spectrum, as Dr. Ross showed, going  
13 from the asymptomatic patient with some bacteremia all the  
14 way out to the floridly septic patient in shock who has a  
15 mortality of 80 percent or greater. If we're asking this  
16 antimicrobial to do something, it's very important that the  
17 clinical criteria are defined such that you don't have that  
18 patient who is tipped over and now may need an  
19 immunomodulator and we're out in the adjunctive therapy  
20 area where we haven't had any success to date.

21 DR. MAKI: What immunomodulator are you going  
22 to use?

23 DR. ROBERTS: No, I'm not saying we're going to  
24 use it. I think we're talking about anti-infective  
25 products to treat a condition of catheter-related

1 infection, and I'm just concerned if we get these patients  
2 too sick, or especially in cryptogenic, if we get them  
3 where the anti-infective can't do its job alone because  
4 you've got the cascade, the cytokines and everything else,  
5 we may never be able to see what the anti-infective can do.

6 DR. MAKI: I couldn't agree more strongly with  
7 you because, as I said initially, I didn't think we should  
8 put a real high bar. I don't think it's necessary. If you  
9 look at all comers with bacteremia, 10 to 20 percent -- 30  
10 percent in some hospitals -- are dying, and that's the  
11 whole spectrum of people. So I agree with you.

12 I think what we were talking about, though, in  
13 terms of, say, fever, and if they don't have fever, two of  
14 the SIRS criteria is not too high. We're not talking about  
15 shock. We're not talking about organ failure or anything.  
16 I think if we were to build that into the criteria, that  
17 would be very excessive.

18 DR. ROBERTS: I just wanted to make sure that  
19 we understood that.

20 DR. MAKI: I wanted to just add one thing to  
21 Barth's comments, and that is that doing clinical trials of  
22 an infection such as bacteremia are not easy. Finding good  
23 evaluable patients is hard work, and the reality of that is  
24 that somebody has strep pneumoniae in their blood, or they  
25 have salmonella in their blood, or they have pseudomonas

1 aeruginosa in their blood, and they have one positive blood  
2 culture, I don't think you're going to find anybody who is  
3 going to say that's a contaminant in a clinical picture.  
4 If they're septic, they have true bacteremia.

5 I think saying arbitrarily they have to have  
6 two positive blood cultures, we're going to lose good  
7 evaluable patients who are just as good as the people who  
8 have two positive blood cultures. I think the rigor in  
9 terms of requiring two should be where we know there are  
10 common contaminants, such as the skin commensals,  
11 coagulase-negative staph, the cillus species, et cetera.

12 DR. CRAIG: I would hope that all those  
13 examples you gave would be ones that we would find either  
14 in neutropenic patients or with other secondary infections  
15 and not very common as primary organisms.

16 DR. RELLER: Absolutely. You know, Dennis, you  
17 made the strongest possible vignette for not having  
18 bacteremia as an indication, the salmonella typhi. If  
19 you're going after a drug to treat typhoid fever, great.  
20 The bacteris fragilis, I hope it's interabdominal sepsis  
21 associated with, or pneumonia associated with, or  
22 meningitis associated with positive blood cultures.

23 DR. CRAIG: So to summarize, then, I guess we  
24 came up with the same criteria that you used for the  
25 others, except one has to rule out that if the patient does

1 have catheters in, they have to be essentially removed or I  
2 guess you would say have the step-up to show that there's  
3 no step-up to insure that they're not infected.

4 DR. ROSS: I would just like to ask the  
5 committee to extend that issue of exclusion a little  
6 further in terms of the issue of endocarditis specifically  
7 vis-a-vis staph aureus. Frequently patients with  
8 bacteremia with unknown origin may be treated as if they  
9 have endocarditis, even if a transesophageal echo is  
10 negative. I'm just wondering if the committee could  
11 address that issue in terms of exclusion of that condition.  
12 I think staph aureus would certainly be the most  
13 problematic, but certainly coag-negative staph would be  
14 another issue.

15 DR. MAKI: I can't speak for other hospitals,  
16 but in our hospital, if a person has a cryptogenic staph  
17 aureus bacteremia, it would be very uncommon for them not  
18 to get a TEE. I mean, there would be so much concern. If  
19 they had a cryptogenic enterococcal bacteremia or  
20 cryptogenic strep bacteremia, we would be concerned about  
21 endocarditis. They would probably get a TEE in our  
22 hospital. I don't know about others.

23 DR. MURRAY: There's a good organism to worry  
24 about a single positive blood culture, however, as Dennis  
25 would well know -- enterococcus. So before we get too far

1 into the single positive blood culture --

2 DR. MAKI: I think it's got to be at least two  
3 with enterococcus.

4 DR. CRAIG: So we have one for staph. That's  
5 about it. Everything else is still open.

6 DR. RELLER: If this discussion is carried out  
7 fully, as it should be, when one gets in all the exclusion  
8 criteria to rule out endocarditis with staph and to lend  
9 specificity to the cultures, like two with staph aureus,  
10 and on and on, I suspect strongly that the number of non-  
11 neutropenic, non-positive transesophageal echocardiograms,  
12 two positive blood cultures peripherally, independently  
13 obtained, et cetera, that what we are left with is a quite  
14 small and very heterogeneous group at the moment that one  
15 would be enrolling in a trial, a cryptogenic but not  
16 necessarily with good follow-up remaining cryptogenic group  
17 of patients that would be exceedingly difficult and, to me,  
18 unwise to give an indication for.

19 DR. ROSS: If I could just follow up on this  
20 question of exclusion of endocarditis. Dr. Maki, if I can  
21 ask for those patients who have cryptogenic bacteremia with  
22 staph aureus, how are they normally treated in terms of  
23 duration of antimicrobial therapy?

24 DR. MAKI: We treat virtually all of those  
25 patients for at least four weeks, even if the

1 transesophageal echo is negative. If there's no obvious  
2 source, we can't find a source and they have a cryptogenic  
3 staph aureus, they're virtually all going to be treated for  
4 at least four weeks.

5 DR. GERDING: I share Barbara's concern about  
6 one staph aureus positive culture, because that can be a  
7 contaminant. Almost invariably when that happens, the  
8 thing that's done first is to get another culture. I mean,  
9 you might start therapy immediately afterward, but you  
10 almost -- at least I almost invariably am reluctant to  
11 launch into the whole question of four weeks versus two  
12 weeks versus I.V. or no I.V., device associated and all the  
13 rest of it. So I would propose that you have at least two  
14 positive cultures for staph aureus because of the fact that  
15 that can be a skin contaminant.

16 DR. CRAIG: But if you look at it from the  
17 clinical trial and we're talking about it as a patient that  
18 comes in from the community that's sick, toxic, septic,  
19 you're going to start antibiotic therapy. So what you're  
20 essentially doing is you're right away, from the beginning  
21 essentially saying everybody is going to need to get four  
22 blood cultures so that you can at least try and insure what  
23 you've got. I'm not saying that you're wrong in doing  
24 that, and that may be the exact appropriate way to do it,  
25 and by increasing the numbers, it's very likely that you'll

1 end up with two positive.

2 DR. GERDING: You just added all the clinical  
3 sepsis parameters to the patient, and I'm afraid that's not  
4 always present.

5 DR. CRAIG: No, but I think those are the  
6 things we said we needed in order to make them a study  
7 patient, that just somebody who is sitting there with no  
8 fever and no increase of the white count, all of a sudden  
9 you get the organism out of a culture, that would not be a  
10 patient that would meet the criteria.

11 Did you want us to say anything more, Dr. Ross,  
12 about the endocarditis question?

13 DR. ROSS: No.

14 DR. MURPHY: I've heard two things. This is  
15 cryptogenic now.

16 DR. CRAIG: For cryptogenic, I think if you  
17 wanted to get the consensus of everybody which would be  
18 close to 100 percent, it would probably be two positive  
19 blood cultures, and we're talking here -- since somebody  
20 wouldn't have a line in, I guess we're talking two  
21 peripherals.

22 DR. MURPHY: To be enrolled in the study, or to  
23 be defined, because I also heard that some people were  
24 comfortable with one for pseudomonas or --

25 DR. CRAIG: As I said, I think there were some

1 people that were willing to take that the more it was  
2 talked about. I hope that pseudomonas aren't going to be  
3 part of primary bacteremias. When you take out the  
4 neutropenics and take out the others, you're going to be  
5 talking about a small subset in a clinical trial, and you'd  
6 never get a large enough number to look at. So at least in  
7 my mind, the primary organisms you're going to be looking  
8 at are enterococcus, staphylococci, and then I think you  
9 still will have some coagulase-negative staph that you  
10 can't prove are related to the lines when you take the  
11 lines out. Then those would be the primary organisms. Am  
12 I right?

13 PARTICIPANT: And candida.

14 DR. CRAIG: Candida, again, is more of a Mark  
15 Goldberger issue, that it is the anti-infectives group as  
16 far as fungal. But that's a different entity. Again, if  
17 one was going to look at that and look at candida, again, I  
18 think since a lot of them are associated with the line,  
19 some of the same criteria that we talked about line sepsis  
20 would apply.

21 DR. MURPHY: Okay. So I did hear that  
22 alternative, and then we came back to two because your  
23 outpatient --

24 DR. CRAIG: Right, and --

25 DR. MURPHY: And they come in with these

1 symptoms, and I know we haven't defined those, you get two  
2 blood cultures. One of them is positive, they're not in  
3 the study.

4 DR. CRAIG: Again, I think for most organisms,  
5 that's what people would want. I think there's staph  
6 aureus where I think Barth would be willing to do one. My  
7 experience in seeing a lot of these patients is you usually  
8 get all the blood cultures positive in the real sepsis  
9 patients that you don't find a source for. So you're not  
10 going to lose many patients by requiring two cultures.

11 Okay? Anything else?

12 (No response.)

13 DR. CRAIG: So let's take a break, and then  
14 we'll come back to the last portion. One of the speakers  
15 is not here, so we have gained a little bit, but we're  
16 still probably only running about 20 minutes behind.

17 (Recess.)

18 DR. GOLDBERGER: When we originally set up this  
19 session, we figured that the issue of incentives would be  
20 sufficiently important that most of the industry  
21 representatives, et cetera, would stay.

22 (Laughter.)

23 DR. GOLDBERGER: I'm not sure that we were  
24 exactly correct in that. Perhaps if we had offered the  
25 incentive of one guaranteed NDA approval, we would have had

1 more success.

2 (Laughter.)

3 DR. GOLDBERGER: Perhaps it's still possible to  
4 do something like that, although the regulations are not  
5 quite that flexible, even though they are fairly flexible.

6 As everyone has heard, the problem basically is  
7 resistance, at least to some organisms, outpacing drug  
8 development.

9 Could you put up the next slide, John?

10 So if we think in terms of solutions, it's  
11 similar in essence to many issues in economics. There is  
12 the supply side, accelerate the development of new drugs,  
13 and the demand side, hopefully ultimately to preserve the  
14 usefulness of current and new drugs. I'd like to talk a  
15 little bit about both those aspects.

16 Go to the next slide, please.

17 Well, let's talk first about the accelerating  
18 development. One thing that we've been doing for a while,  
19 some of which is based upon some of the regulatory  
20 initiatives I'll talk about in a second, others we like to  
21 think is just good practice, is the idea of increased early  
22 guidance, formal and informal communication with companies.  
23 This is something we've been doing a lot in a lot of  
24 different areas. It has tremendous return in terms of  
25 efficiency on the time spent doing it.

1           Another thing which today and yesterday are  
2 good examples of is getting more advisory committee input  
3 on some important issues, and we take this quite seriously.  
4 Since last November, this is the sixth day of meetings with  
5 the Anti-Infective Advisory Committee to deal with  
6 nonproduct-specific issues -- pediatric use of  
7 fluoroquinolones, development of guidance documents for  
8 studying drugs for clinical trials, and finally this two-  
9 day meeting related to resistance issues. So this is  
10 something we take actually quite seriously.

11           In addition, there are a variety of regulatory  
12 tools that are available, a number of which you've sort of  
13 heard about or touched on at various points in the two  
14 days, and these include Subparts E and H, Fast Track  
15 designation, orphan drug designation. I'll talk a little  
16 bit about these on the next couple of slides.

17           Go on to the next slide, John.

18           Subpart E. I put in some citations for those  
19 with a strong interest in wanting to read through this, 21  
20 CFR 312.80. This is something that came out as an interim  
21 regulation. It's still an interim regulation, and it will  
22 be having its tenth anniversary I think sometime next week,  
23 I think next Tuesday. It is for life-threatening and  
24 severely debilitating illness, particularly when there is  
25 no satisfactory alternative therapy. It utilizes a

1 risk/benefit analysis in the decisionmaking process.

2 This is something that we often do. These  
3 regulations explicitly recognize risk/benefit in the drug  
4 approval process, including the recognition that patients  
5 with serious illness and physicians who are taking care of  
6 those patients may be willing to accept greater risks in  
7 return for the benefits of products.

8 Things that it offers are, again, early  
9 consultation and increased communication between the agency  
10 and the company, and an approval that is possible earlier  
11 in the drug development process. This is one of the places  
12 where one talks about approval being based upon Phase II  
13 studies, and in essence what we're basically talking about  
14 is smaller clinical trials than would otherwise be the  
15 case.

16 These regulations have been used in a wide  
17 range of areas, in almost any drug that's come in for HIV-  
18 related opportunistic infections, many products for  
19 oncology, transplant drugs, et cetera. I think clearly  
20 this is an opportunity for certain of the anti-infective  
21 indications that we've talked about, and I'll say a bit  
22 more about that in a second. Let's go on to the next slide  
23 first.

24 You've also heard a fair amount, intermittently  
25 at least, during the meeting about the concept of

1 accelerated approval, surrogate markers, et cetera. This  
2 again is Subpart H from the NDA regulations, 21 CFR  
3 314.500. This is for serious or life-threatening diseases.  
4 It deals with a surrogate endpoint that is reasonably  
5 likely to predict clinical benefit, and this is discussed a  
6 little bit in the regulations, much more in the Federal  
7 Register notice that accompanied them when they were  
8 released, which I think was in April of 1995 or 1996.

9 A good example of where this has been used a  
10 lot is CD4, and then viral load for new drugs for HIV. We  
11 have also used it, for instance, recently in the approval  
12 of a new drug for tuberculosis. Much of the discussion  
13 that you've heard about in the last couple of days when we  
14 talk about the use of preclinical data, pharmacokinetic  
15 data, pharmacodynamic data, et cetera, really goes to this  
16 issue of the surrogate endpoint, and that's why we ask,  
17 obviously, what's the data to say that it's reasonably  
18 likely to predict clinical benefit which may cure an  
19 infection, depending on the infection. In many cases it's  
20 been survival, not necessarily in all the anti-infective  
21 indications, although it certainly could be in some.

22 One thing worth mentioning about this, however,  
23 that perhaps did not come out, we talked a lot about the  
24 applicability of these types of regulations and what kinds  
25 of clinical studies should be done. There's been talk

1 about superiority studies, talk about equivalence studies,  
2 et cetera. We should remember that the regulations also  
3 talk about a meaningful therapeutic benefit over existing  
4 therapies. Now, this is not spelled out. It could, for  
5 instance, mean that the new treatment is better than what's  
6 already out there. It could mean that it's as good but  
7 less toxic. One might wonder whether in a situation in  
8 which one showed equivalence to an already-approved therapy  
9 and no other advantage, whether that type of drug would fit  
10 in under this regulatory initiative, and I think that's  
11 something that's probably worth some discussion.

12 Other things that are included in these  
13 regulations include the need to do confirmatory trials to  
14 prove the surrogate correlates, expedited withdrawal of a  
15 product when the confirmatory trials do not work out, prior  
16 submission of promotional materials, and the issue about  
17 restricted distribution or use of the product. I'll talk a  
18 little bit about a couple of these things a little later  
19 on.

20 The other thing to remember is that a  
21 development program for a product may be fairly complex.  
22 It may have multiple indications, some of which are more  
23 garden variety, others of which deal with resistant  
24 indications, et cetera. It is possible to use these  
25 initiatives for only some of the indications in a given

1 package. It is also possible in a situation where a drug,  
2 for instance, is already approved and a sponsor were to  
3 come in with a new indication, even though the drug is out  
4 there, it is possible, for instance, to approve the new  
5 indication under Subpart H, accelerated approval. In fact,  
6 the first approval that technically took place under these  
7 regulations actually fulfilled that.

8           So there is some flexibility as to how these  
9 are used. We obviously have to think ultimately about  
10 issues like serious or life-threatening disease, meaningful  
11 therapeutic benefit, et cetera, and we have to talk about  
12 the clinical entity we're talking about, of which there's  
13 been a lot of discussion over the last two days, about the  
14 clinical significance, for instance, of resistant isolates.

15           Go on to the next slide, John.

16           Another thing that you've heard about more  
17 recently is fast track designation. I didn't give the  
18 reference to the statute. The statute itself is in  
19 everyone's large package, if you care to read it. The FDA  
20 is currently developing a document to outline exactly how  
21 we intend to interpret this.

22           Fundamentally, though, it again is for  
23 situations in serious or life-threatening disease, where  
24 one expects a meaningful therapeutic benefit. It combines  
25 parts of Subparts E and H, about which I just spoke, and it

1 also includes a provision to accept for review a portion of  
2 a marketing application prior to submission of the complete  
3 package. We often refer to this as a rolling NDA.

4 Although this in many circumstances sounds like  
5 a big deal, we have been using, at least in a couple of the  
6 divisions, this approach for a considerable period of time.  
7 Nonetheless, in some other divisions, this may be a change.

8 Also, I'd briefly like to mention orphan drug  
9 designation. Remember, less than 200,000 patients qualify  
10 for orphan drug designation. It's very important to  
11 remember, 200,000 in the United States. It can be a  
12 disease that affects 100 million people worldwide, but the  
13 designation is based upon the U.S. population. It offers  
14 limited funding for clinical trials, and more importantly,  
15 seven years of marketing exclusivity for that drug for that  
16 indication. This will be used in a situation where a drug  
17 has been out for a long time, where the patent exclusivity  
18 is about to run out, et cetera, for an old drug being  
19 developed for a new indication, et cetera. So this is of  
20 some potential value and quite useful in certain clear  
21 indications, like tuberculosis, malaria, et cetera.

22 What its role would be, for instance, for a  
23 resistance indication is less clear, since that would  
24 require some consultation with the orphan drug people since  
25 they are concerned with a concept which is what they like

1 to refer to as salami slicing, in which you take a large  
2 indication and take little bits of it to keep it under the  
3 200,000. How they would view the resistance indication or  
4 resistant organism for an organism that is very common I'm  
5 not really sure, but I think if companies were interested  
6 in this, this is something we could at least explore.

7 Go on to the next slide.

8 Well, there have been a variety of scientific  
9 issues which have gotten a lot of input over the last two  
10 days. One, definitions for resistance, from basically a  
11 simple quantitative approach, and also from the methods  
12 used -- i.e., looking from a genetic point of view, looking  
13 from clinical response, et cetera. The clinical importance  
14 of some resistant isolates, and I think obviously this is  
15 fairly important. We heard some very interesting data  
16 yesterday from Dr. Klugman in terms of the effect of  
17 penicillin on penicillin-resistant isolates. Finally, what  
18 we spent a lot of time on are the issues of the role of  
19 nonclinical trial data. I think we've actually gotten a  
20 lot of useful advice, how some of that data could be  
21 utilized to assist in making decisions.

22 Do you want to go on to the next slide?

23 What about the other half of this? That is, in  
24 essence, perhaps the demand side. That is, to preserve the  
25 usefulness of current and new drugs.

1           Well, one of the reasons we tried to get a wide  
2 group of people to come to this meeting is because we  
3 recognized that educational efforts here are very  
4 important. These educational efforts need to come from the  
5 broad medical community, and that means not so much really  
6 just from FDA but from other government agencies, from  
7 nongovernmental organizations, from academia, and also  
8 really from the pharmaceutical industry, that all need to  
9 be directed, obviously with some differences, at provider,  
10 patient, and purchaser, and that certainly emphasize  
11 prudent use of antimicrobial therapy.

12           There are many ways to do that. I just put  
13 down a couple of examples. One is, which I phrased a  
14 little vaguely, maximize value of susceptibility testing,  
15 which might be to remind many physicians about looking at  
16 the susceptibility test when one chooses antimicrobial  
17 therapy and when one keeps a patient for longer term on  
18 antimicrobial therapy. Of course, the issue, certainly  
19 from a patient perspective, of distinguishing viral from  
20 bacterial infections in terms of the potential value of  
21 antimicrobial therapy.

22           Obviously, there are many other examples, but  
23 education is certainly an important component in hopefully  
24 preserving usefulness of current and new drugs.

25           Go on to the next.

1                   Well, what are other things we can do? Another  
2 thing is labeling initiatives. I was just talking about  
3 the issue of educational programs. We should remember  
4 another important way in which consumers, in which  
5 physicians, et cetera, get educated is through promotional  
6 material from the pharmaceutical companies, and this is  
7 certainly another form of education. We must remember that  
8 promotional material fundamentally comes from what is in  
9 the package label. Therefore, it's important that the  
10 package label represent some of our thinking in some of  
11 these areas if we are to expect that promotional material  
12 might have some of this information in it as well.

13                   Certainly, if we are to do anything in this  
14 area, we need to be fair. We need to have a level playing  
15 field that realistically affects companies equally and  
16 ought to apply to all products. One is simply the issue of  
17 fairness. The other is that we should remember that there  
18 would be not much point, and probably certainly not enough  
19 effect in singling out the newer antimicrobials and leaving  
20 the older ones without any statement at all about some of  
21 these issues, because many of the problems we see today in  
22 antimicrobial resistance are due perhaps to overuse and  
23 misuse of drugs that have been available for a long period  
24 of time.

25                   Well, we're sort of working on some labeling

1 initiatives now. Fundamentally, again, they emphasize  
2 prudent use, reminders about susceptibility testing as I  
3 spoke about a few moments ago, and remembering, for  
4 instance, your local epidemiology, in your setting, in your  
5 particular institution, helping to remind you of how you  
6 might want to prescribe. But I think this is an area that  
7 probably will evolve over time, but we think it's an  
8 important component overall, and we want to do it in a way  
9 that's fair to all concerned.

10 Go on to the next overhead.

11 Another regulatory initiative of which I spoke  
12 a few minutes ago relates to the issue of restrictions to  
13 insure safe use. Now, this is a statement that comes  
14 actually from the accelerated approval regulations, and it  
15 can be implemented in very many ways. It has been used in  
16 certain circumstances. For instance, when thalidomide was  
17 just approved, a very elaborate program was set up to  
18 minimize as much as possible the occurrence of any  
19 teratogenic event. It's been used in the past with an  
20 antipsychotic agent that had the risk of producing severe  
21 neutropenia, requiring weekly blood testing.

22 However, this in fact can be implemented quite  
23 flexibly through a simple statement in the label reminding  
24 individuals of some of the issues I talked about before.  
25 We should also remember that apart from, for instance, the

1 issue of thinking about restrictions to insure safe use,  
2 FDA labeling regulations currently include the statement  
3 more generally that labeling in the indications section  
4 should include information about tests used in the  
5 selection or monitoring of patients -- e.g., microbe  
6 susceptibility tests -- which in fact are the examples used  
7 in the regulations.

8           So this is really not a particularly radical  
9 step. We recognize, however, that some of these issues are  
10 extremely sensitive in terms of not discouraging  
11 development of new products, and I think it's the kind of  
12 thing we would be very interested in hearing some comment  
13 from the industry representatives who have managed to stick  
14 it out this long in terms of this issue, and, from their  
15 perspective, things they think they can do to insure  
16 prudent use of their product that they initiate on their  
17 own.

18           Next.

19           Some of the scientific issues. We've had a  
20 fair amount of discussion about improved capability for  
21 rapid diagnosis and susceptibility testing. We've heard of  
22 the potential benefits, but I think we've also heard a lot  
23 of discussion about the problems in trying to interpret  
24 this data, the link between what happens when you find a  
25 genetic locus and whether or not resistance is expressed.

1 So this is an area that has promise but clearly has not yet  
2 reached the maturity that could be perhaps widely used for  
3 clinical trials, or perhaps more importantly as a very  
4 useful tool to help practicing physicians, over time,  
5 tailor antimicrobial therapy.

6 Another issue we didn't talk a whole lot about  
7 is potential relationships between dose and duration of Rx  
8 and development of resistance in terms of thinking about  
9 dosing regimens that might enhance compliance, reduce  
10 resistance, et cetera. This might be an area that's ripe  
11 for further research.

12 Finally, an area that, again, hasn't been  
13 touched upon a whole lot in this meeting but many people  
14 recognize is important, some categories of behavioral  
15 research to again talk about issues related to why people  
16 take or don't take drugs, issues about why physicians  
17 prescribe, patients demand, et cetera. Obviously, a lot of  
18 information in this area, but I suspect the information is  
19 not entirely complete.

20 The next slide.

21 I'd like to close just by reminding everyone  
22 that one of the reasons we had some money from WHO, from  
23 other international organizations, et cetera, is that this  
24 is a global problem. This is an area that certainly links  
25 us with other parts of the world. The emergence of

1 resistance isolates has occurred all over. Sometimes it is  
2 sentinel in other parts of the world to what will occur  
3 here, but clearly this is a global problem. There are  
4 less-than-ideal usage patterns of antimicrobial therapy  
5 both in the United States and all the way around the world.  
6 This is again a problem that links all of us.

7           We at present do not have a big problem in this  
8 country or a big use of over-the-counter availability of  
9 antimicrobials. This is a significant issue in other parts  
10 of the world. As you know, there is a major problem today  
11 with drug-resistant malaria. There's a new class of drugs,  
12 the artemesins, based on the Chinese herb, that is  
13 considered by many to be the most promising new class of  
14 antimalarials available anywhere. These products are not  
15 really available at all in the United States in almost any  
16 form. They are currently available over the counter in at  
17 least two different continents. So this is again a big  
18 issue and is a significant concern.

19           You should also remember that this is more than  
20 just bacteria. Again, there has been attention paid to HIV  
21 resistance, attention paid in terms of drug development to  
22 anti-fungal resistance. We have not had nearly the same  
23 attention paid to multi-drug-resistant tuberculosis. I  
24 feel compelled to mention this, since this is an area that  
25 I'm particularly interested in, that although we had some

1 discussion about the few number of cases of multi-drug-  
2 resistant TB in the United States, we must remember that  
3 the most effective way to prevent multi-drug-resistant TB  
4 is to effectively treat susceptible TB.

5           So there is a somewhat larger market, but this  
6 is clearly important, as is again drug-resistant malaria.  
7 It's a major problem worldwide, an important problem for  
8 U.S. travelers overseas, and I might add also an important  
9 problem for the U.S. military, which is growing quite  
10 concerned about the lack of therapies for some parts of  
11 Southeast Asia.

12           Although we have had a lot of interest in the  
13 types of incentives that might be available for developing  
14 therapies for some resistance indications, sadly we have  
15 not seen quite the same interest in developing drugs for  
16 these indications when clearly these incentives would  
17 apply.

18           Thank you.

19           DR. CRAIG: Thank you, Mark.

20           (Applause.)

21           DR. CRAIG: Our next speaker is going to give  
22 an NIH perspective, Dr. Stephen Heyse, from the National  
23 Institute of Allergy and Infectious Diseases.

24           DR. HEYSE: Thank you. It's a real pleasure to  
25 be here, and I really appreciate this opportunity to talk

1 to you about our research programs in antimicrobial  
2 resistance.

3 One of the benefits of speaking so late in the  
4 day and so late in the meeting is that everyone has already  
5 said what you were going to say anyway, so I was able to  
6 throw away most of my slides, and hopefully I'll be quite  
7 brief.

8 This slide is just to remind me of who I am.  
9 I'm a medical bacteriology and bacterial resistance program  
10 officer in the Division of Microbiology and Infectious  
11 Diseases at the NIAID. In addition, I'm also the project  
12 officer for the mycoses study group and the medical officer  
13 for the clinical studies of chronic lyme disease, which  
14 will come to bear a little later.

15 I put this slide up to emphasize that where I  
16 am in the bacteriology and mycology branch is just one  
17 component of infectious diseases. Indeed, antibacterial  
18 resistance applies to diseases in other branches of the  
19 division, such as the Respiratory Diseases Branch would be  
20 where the strep pneumo research would be housed, and work  
21 on resistance to penicillin would occur there. As well,  
22 there's the gonorrhea resistance within the Sexually  
23 Transmitted Diseases Branch, but I have an opportunity to  
24 try to bring some focus to the antimicrobial resistance  
25 issues across the institute, and I find that rather

1 daunting since what is actually in my program is perhaps  
2 only about 10 percent of the whole spectrum.

3           This is a little faint but it's just a slide I  
4 whipped up to give you an idea of what's happening with  
5 respect to funding of antimicrobial resistance. I joined  
6 the institute in 1996, so you can see that there's been a  
7 great upswing since then, but it's nothing to do with me.  
8 It has more to do with the obvious importance of the  
9 problem, plus the generous funding that Congress has been  
10 giving NIH of late. It is really making a difference and  
11 it's coming at a very opportune time for this important,  
12 growing problem.

13           But there has been a more than doubling of the  
14 amount of money and the numbers of projects that are  
15 focused on antimicrobial resistance. However, these are  
16 not all antibacterial.

17           I put this in out of order, but that's okay. I  
18 found this in the workshop that you all have on your table.  
19 The very last sentence of the summary on the first page  
20 brings into focus what is needed in terms of research, and  
21 I agree fully with this statement that what we need now is  
22 additional basic research and funding for such, the  
23 clinical research to go with that, and then finally the  
24 infrastructure to move those things along.

25           In terms of what we support and how we support

1 it, we use a variety of mechanisms. Most of it, as you can  
2 see, the big white piece of the pie there is the  
3 investigator-initiated research, and the vast part of that  
4 is composed of the traditional R01 grant. There is a  
5 smattering of new grants called R03s. Those are small  
6 grants. There's also the remainders of the R29s, which are  
7 the FIRST Awards, which have been folded back into R01s  
8 now, and the R37s are Merit Awards, which we have a fair  
9 number of in this area.

10 The SBIR and STTR relate to the small business  
11 efforts that we have, and this has become a very important  
12 portion of the NIH budget in general, and in particular in  
13 antimicrobial resistance, we're finding it to be a very  
14 important opportunity to develop and move along through  
15 clinical testing novel antibacterials, novel strategies  
16 with respect to vaccines, et cetera, things that will help  
17 us in managing patients who have antimicrobial resistance  
18 patterns. We also use a variety of other mechanisms and do  
19 some training. Both the career awards and the fellowships  
20 are training of professionals in this field. Then finally  
21 we have a small number of intramural projects that are  
22 addressing antimicrobial resistance.

23 Next I tried to pull this apart by organism.  
24 The parts that relate to what I think we've been talking  
25 about here today are the bacterial mechanisms and the other

1 bacteria, as opposed to everything else that's more clearly  
2 set out. Of course, we support a lot of research on the  
3 issue of HIV resistance, and this is very important. But  
4 we see quite a bit of growth recently in staphylococcus and  
5 enterococcus relating to antimicrobial resistance, and this  
6 will make it easier to break that out eventually.

7 We do support a fair amount in TB, and also  
8 mycobacteria apium for Mark's concerns. That is a very  
9 important area that the institute recognizes, as well as  
10 malaria. Those two we are contributing quite a bit of  
11 money to.

12 This is a very busy slide, and it's okay that  
13 the parasites fall off. The point of this is to look at  
14 the center where there's sort of a hole, under "Bacteria"  
15 in particular. What I've tried to do here is identify  
16 areas where the institute specifically supports research of  
17 the categories of basic research, targeted drug discovery,  
18 preclinical testing and clinical trials. We have very nice  
19 full programs in HIV, and also in antivirals in general.  
20 However, we don't have many of those pieces under bacterial  
21 or fungal.

22 In particular, the bacteria is a little  
23 misleading. I put on the bottom next to clinical trials  
24 areas that we are supporting clinical trials through, such  
25 as the clinical studies of chronic lyme disease. I don't

1 expect you to understand what all these things stand for.  
2 I'm surprised I know. It's also the sexually transmitted  
3 diseases, and we have a tuberculosis research unit. At the  
4 bottom I put the VTUs, which is the Vaccine Treatment  
5 Evaluation Units. I put that in parentheses because they  
6 really focus more on vaccine development, and although they  
7 are in place to do some testing of therapeutics that might  
8 become available, we've never used them that way, to my  
9 knowledge.

10 What's missing here is targeted drug programs  
11 for antibacterials, particularly in the context of  
12 resistance. In preclinical testing as well, there's  
13 nothing that we have. In terms of clinical trials, we  
14 perceive that there really is a need for something like a  
15 mycoses study group, which is there as the MSG next to it  
16 in the fungal group, or the collaborative anti-viral study  
17 group, which is conducting clinical trials in antivirals.  
18 I would appreciate the reaction of the committee to whether  
19 this is an appropriate thing for the NIAID to be moving  
20 toward.

21 We have had advice from various groups that  
22 this is clearly a hole in our approach and that we do have  
23 an initiative to develop such an infrastructure. That's  
24 basically the approach we would take, bringing in  
25 opportunity for the pharmaceutical industry to bring to the

1 study group clinical trials of drugs that need clinical  
2 trials and providing biostatistical support for such, data  
3 safety monitoring, as well as regulatory monitoring, and  
4 also being able to facilitate moving through the IND  
5 process for new drugs.

6           These are some of the new opportunities that we  
7 see that we hope our researchers can take advantage of. In  
8 particular, the genomes are exciting. We've been funding  
9 an increasing number of full genomes of various bacteria.  
10 Most recently we got involved with funding the staph aureus  
11 genome at the request of the researchers in that field. We  
12 had a consultation of academia and our colleagues from CDC  
13 and the Food and Drug Administration last September, a year  
14 ago September, to begin addressing the problem of what  
15 research was needed to address the problem of vancomycin  
16 resistance appearing in staph aureus. One of the clear  
17 recommendations that came out of that meeting was to  
18 sequence the genome of staph aureus and make that available  
19 to the research community. It has already been sequenced  
20 but not available.

21           Also, the use of chip technologies will help  
22 move things along, as well as the use of information from  
23 x-ray crystallography for targeted drug development.

24           Go to the next slide.

25           Just to follow through on the staph aureus

1 issue, what we did was presented a plan to Dr. Fauci based  
2 on the recommendations from that consultation, and he made  
3 funds available from his special reserve that provided the  
4 opportunity to move ahead with the sequencing. We were  
5 also able to supplement a program announcement. That's the  
6 thing in the middle, PA-97-026, which stood for a program  
7 announcement encouraging research applications on  
8 aspergillosis, ehrlichiosis, and drug resistance, which  
9 sounds a little weird, but we used some of those funds to  
10 specifically fund applications in resistance issues in  
11 staph aureus.

12 As well, we issued a request for proposals to  
13 establish a network on resistance in staph aureus, and we  
14 have received three proposals that will be going to review  
15 next week. Depending on how much further negotiations we  
16 have, we hope to have that network up before the end of the  
17 calendar year. This will be a virtual and real network of  
18 the investigators that we are supporting in staph aureus to  
19 provide them both an opportunity to meet on a regular basis  
20 and also to have a network with Web site participation.

21 We'll be collecting isolates of particularly  
22 vancomycin-resistant staph aureus or intermediate  
23 susceptibility isolates as they become available, and other  
24 important isolates for comparative purposes, and making  
25 these available along with the clinical data. In

1 collaboration with our colleagues at CDC, we'll be  
2 attempting to collect as many, if not all, of the available  
3 isolates as they really become available.

4 We followed on the genome funding with a  
5 workshop last June where we brought together our staph  
6 aureus researchers and presented them with what was being  
7 developed through the genome projects, as well as  
8 introduced them to the various technologies they'll be able  
9 to use to exploit that information.

10 In the context of prudent use, we are planning  
11 to convene a state of the art conference on the issue of  
12 vancomycin usage both in staph aureus and enterococcus.  
13 This is still in the development stages, so I can't be any  
14 more precise on that.

15 Another public awareness type of effort that we  
16 are considering at this point is an NIH consensus  
17 development conference. The American Academy of Orthopedic  
18 Surgeons has asked Dr. Varmus to consider the issue of  
19 prophylactic antibiotics in orthopedic procedures as an  
20 important enough issue to warrant such a conference. We're  
21 working with our colleagues at the National Institute of  
22 Arthritis and Musculoskeletal and Skin Diseases and the  
23 Office of Medical Applications of Research, which is the  
24 agency which actually funds those conferences, in  
25 determining whether there is sufficient evidence to move

1 such a conference ahead, or perhaps there's another format  
2 that might be more appropriate to that.

3 In closing, I'd just like to ask again if you  
4 have specific advice or comments on the idea for what we  
5 like to call an antibacterial study group and whether  
6 that's something the institute really ought to give high  
7 precedence to. We'd really appreciate that advice.

8 Thank you.

9 (Applause.)

10 DR. CRAIG: Thank you very much.

11 Now we have a break, but we're not going to  
12 take it.

13 We now have the industry perspective from Frank  
14 Tally of Cubist Pharmaceuticals.

15 DR. TALLY: Thank you, Mr. Chairman. I'd like  
16 to thank the FDA for the opportunity to come down and talk  
17 on this subject.

18 When I looked at the subject after speaking on  
19 a different subject back in July, I found it somewhat  
20 daunting but knew I would have the advantage of having a  
21 lot of people speak before me and say most of the things.

22 Could I have the next slide, please?

23 What I'd like to do is give you the perspective  
24 of somebody that's in the biotech industry now but at one  
25 time was in large pharmaceuticals and kind of state the

1 problem as we see it in trying to come up with new  
2 antimicrobial agents and trying to enhance development, and  
3 at the same time trying to encourage the prudent use of  
4 antibiotics.

5 The problem, as I would simply state it, is  
6 resistant organisms are killing people right now, and  
7 that's why everybody's concerned. The therapeutic  
8 alternatives for some organisms, particularly VRE and MRSA,  
9 are severely limited. With what's going on, these will be  
10 limited even further.

11 Next slide.

12 What has happened in the industry is that  
13 there's been -- antibiotic development is really in  
14 transition from the era of "me too" drugs acting on old  
15 targets with multiple mechanisms of resistance. The reason  
16 is -- I think the pharmaceutical industry has done a  
17 spectacular job in looking at these drugs and improving  
18 them for resistance and less toxicity, and I think we've  
19 picked most of the low-hanging fruit, and getting to that  
20 next level is a major problem. With the old classes of  
21 drugs, as brought out by Gordon Archer this morning, the  
22 multiple mechanisms of resistance, they're already there,  
23 and all they have to do is amplify them.

24 So the improvements we make in the old classes  
25 are really not going to get us to the next quantum level.

1 Really what we need is new chemical classes inhibiting  
2 novel targets where resistance mechanisms do not exist, and  
3 then use those drugs appropriately so we don't get into the  
4 mess that we're into now with the old groups of compounds.

5 Next slide.

6 The challenge, though, is to provide the  
7 incentive to do that. We've heard this talked about, to  
8 develop new classes of antibiotics, because to do that from  
9 new novel targets is a process that takes five to ten years  
10 and a huge investment on the pharmaceutical industry's  
11 part. With some of the new techniques in molecular biology  
12 and screening, it was felt that maybe we'll have new drugs  
13 in a year or two, but that's unrealistic when you look at  
14 the process of going from the gene, which we now have  
15 thousands of them to look at, to a product that can be  
16 approved is still a long process.

17 What you're seeing right now is the evaluation  
18 of a number of compounds by a number of companies that were  
19 previously evaluated but were not brought forward because  
20 of some problems with them, and you'd call these drugs with  
21 some reduced toxic therapeutic ratios that are being re-  
22 looked at because the paradigm has shifted, because when  
23 you're looking at risk/benefit ratios with patients being  
24 infected with organisms of high virulence and high  
25 resistance, then that changes the risk/benefit ratio for

1 certain therapeutic indications.

2 Next slide.

3 Well, how do we enhance development? We've had  
4 a lot of talking on how to do that. From my point of view,  
5 having registered a drug once before, and having formed  
6 what I'd call a team between FDA and the drug sponsor, I  
7 think this is absolutely key in getting a drug rapidly  
8 developed and looking at all the initiatives we've been  
9 looking at for the last two days. I'd like to go into some  
10 things in that particular area.

11 We heard extensive talks yesterday employing  
12 animal PK and PD for dose selection, for different  
13 organisms, and we'll get into that. Finally, we just heard  
14 about fast track review, and I'd like to talk about that.

15 Next slide.

16 Forming the team really is agreeing early on on  
17 the rationale for the clinical plan and the indications to  
18 be studied, and I think one should do this before investing  
19 in a lot of different areas and trying to come in with a  
20 drug that's going to be registered for 14 different  
21 indications. That's not possible for a small company like  
22 mine. We have to really focus on our clinical plans.

23 We'd like to define the number of studies that  
24 you want for each indication also. That would be to insure  
25 that you really have the clinical data that I know is

1 needed in order for FDA to approve a drug, because the  
2 drugs we'll be approving are new chemical classes and new  
3 molecules, so we'll have to get adequate data so that  
4 safety and efficacy can be evaluated.

5 Next slide.

6 We've heard that the early review of pivotal  
7 clinical protocol design, both in Phase I, II, and III,  
8 should be done before initiation, and we've heard a lot  
9 today about what is going to be comparative therapy. I  
10 look at it based on best approved therapy that's currently  
11 available in different areas. This may change from one  
12 place to another. I was interested to hear about the  
13 Chinese menu approach. I've looked at studies that have  
14 had Chinese menu approaches, and they're very difficult to  
15 interpret after you look at them. So it would be nice to  
16 be able to pick a narrow group of comparative agents to go  
17 against the new drugs.

18 Defining endpoints for safety and efficacy, and  
19 also other points like we talked about with bacteremia,  
20 maybe to the rapidity of clearing up the bacteremia.

21 Finally, I think for all the new compounds  
22 coming along which are new classes, there has to be some  
23 pre-arrived number of patients required for safety  
24 assessment.

25 Finally, reviewing design of the draft package

1 insert versus the protocols I think is mandatory early on  
2 to speed up this process.

3 Next slide.

4 What about PK/PD for dose selection? I think  
5 what it does, it allows you to make a better guess on the  
6 effective dose for controlling different types of  
7 infections in different locations. What you do is identify  
8 key pharmacodynamic parameters, possibly even to separate  
9 efficacy and toxicity. As we've seen in the past with the  
10 aminoglycosides, going to once-a-day therapy, increasing  
11 efficacy, and actually decreasing nephrotoxicity, that may  
12 be possible with other compounds also.

13 It may be also possible with these studies to  
14 streamline, or indeed maybe even to eliminate the need for  
15 some Phase II dosing studies. This is a high-risk area  
16 because if a company invests a lot of money into a large  
17 Phase III program, they may have guessed wrong, and I've  
18 actually had experience with that, because with piperacillin  
19 tazobactam, we did do some doses where we did show that the  
20 drug was not effective in those particular areas. So it is  
21 a high-risk area that you have to think very carefully  
22 about.

23 Next slide.

24 We've heard about fast track review, Subpart E  
25 and H. I think what we want to do is to look at this

1 particular fast track review for therapeutic alternatives  
2 limited for resistant pathogens. You want to look at life-  
3 threatening infections. I listed several of them here.  
4 Finally, you want early review of CMC packages, nonclinical  
5 packages. As Mark just talked about, the clinical packages  
6 would occur with advertising and promotional material. I  
7 think this all has to go on in concert with reviewing all  
8 the other material.

9 Next slide.

10 I would also say that I think FDA, as Mark  
11 pointed out, has already demonstrated the fast tracking not  
12 only of antiviral drugs, but with a couple of indications  
13 for the treatment of resistant TB. So I think the fast  
14 tracking of important drugs that are life-saving, FDA has  
15 already demonstrated that.

16 What about the prudent use of antimicrobial  
17 agents? We've heard a lot of talk about spreading  
18 antimicrobial agents around, and if you look back at  
19 resistance, resistance develops almost on the tonnage of  
20 antibiotics you use. This was actually worked out with the  
21 aminoglycosides early on. If you're looking at tonnage  
22 used, when you go outside of humans, we use huge amounts in  
23 certain areas. So I think life-saving drugs for resistant  
24 infections should be limited to treatment in humans, and  
25 only in very special circumstances should it go outside of

1 humans. Particularly it should not go for growth  
2 promotion, because I think there are a number of  
3 alternative ways of doing that.

4 The same is true with aquaculture or fish  
5 farming, where the quinolones have been dumped into fish  
6 farms, and that's just another source of many resistant  
7 isolates.

8 We've talked about approval of drugs only for  
9 bacterial infections and not syndromes, and I think that's  
10 to remove new antibacterial agents for the treatment of  
11 viral infections. I think that's been discussed by a  
12 number of people, but I would back that up also, that we  
13 should clearly identify them only for bacterial infections.

14 Life-saving parenteral agents either given  
15 orally or parenterally should be restricted from certain  
16 applications. We learned early on that the use of life-  
17 saving drugs in skin preparations will rapidly bring about  
18 resistance, and that lesson was learned at Grady Memorial  
19 Hospital a long time ago and has been learned with others.  
20 I think if you have a life-saving drug, you should not have  
21 a topical formulation, and I would say topical both to the  
22 skin and the gastrointestinal tract. Because of the huge  
23 numbers of bacteria in the gastrointestinal tract and the  
24 high counts, I think this is an area where you can bring  
25 about resistance quite rapidly. We ought to look for

1 alternative drugs to treat these particular areas,  
2 alternative classes for life-saving systemic drugs.

3 Next slide.

4 I would limit prophylactic use too, but there  
5 are certain indications where infections with those  
6 resistant organisms, particularly in cardiac surgery and in  
7 orthopedic joint replacement, where even Bob's favorite  
8 bug, staph epidermis, causes a disaster. This may be the  
9 area where you would want to limit the prophylactic use of  
10 these agents.

11 Finally, I think what you have to do is provide  
12 commercial opportunity for the discovery of these new  
13 classes of drugs because of the tremendous cost involved in  
14 this. I think you can do that with fast track review, and  
15 I think there can be broad use of these agents for the  
16 treatment of serious infections. The reason I say that is  
17 because of the six points of empiric therapy. If you look  
18 at therapy, most of our therapy is empiric, because you  
19 cannot tell what the organism is that is coming in, and you  
20 do not know, a priori, what the resistance of those  
21 organisms are.

22 So I think one would not want to limit a  
23 physician's ability to select empiric therapy of even new  
24 agents, because that therapy is dictated by the patient's  
25 environment and the risk for mortality and morbidity from

1 the underlying infection which the patient is presenting  
2 with. I think that's a judgment of the clinician taking  
3 care of the patient, and they should have all those  
4 therapeutic options open to them.

5 Thank you.

6 (Applause.)

7 DR. CRAIG: Thank you, Frank.

8 Dr. Cassell from Eli Lilly is not here, so I  
9 guess we'll move on to the comments and questions for the  
10 committee from Dr. Chikami.

11 DR. CHIKAMI: Given the lateness of the hour  
12 and the fact that Mark made most of the comments that I was  
13 going to make, I think I won't go through my slides, but I  
14 will make a few general comments, and then we'll go  
15 basically to some questions that we'd like to have the  
16 committee comment on.

17 Over the past two days we've had discussion  
18 from the committee on some general scientific issues  
19 related to drug development for products for antibiotic  
20 resistance, and tried to paint the context of where certain  
21 regulatory incentives may be appropriate, and have tried to  
22 distinguish those in the committee's mind, in our own mind  
23 about what areas might be most appropriate; defining, for  
24 example, serious and life-threatening infections for which  
25 there are no therapeutic alternatives, and seeing how we

1 might apply those criteria to identify specific organisms,  
2 much along the lines that the CDC has done in developing  
3 their priority list. I think that's a useful model that we  
4 in the divisions, in the office, would like to apply.

5           The other area is the context of drug  
6 development. That is, those products which have a broad  
7 clinical development program or products which are already  
8 developed, and we have lots of information about their  
9 safety and activity in a number of infections, sites of  
10 infection, and for a number of organisms, including  
11 susceptible organisms that might provide the context for  
12 how much information we would additionally need to  
13 determine effectiveness; as opposed to new products in the  
14 pipeline which have a more targeted development for perhaps  
15 fewer indications and may be targeted for specific  
16 problematic resistant organisms, and how, in fact, those  
17 are the products which might really require and deserve the  
18 application of these incentives.

19           The other is sort of a process comment in that  
20 many of the specific areas of questions and discussions  
21 that we've had over the past couple of days, like specific  
22 issues with clinical trial design, with dose-response or  
23 standard of care designs, or with the discussion that we  
24 had today on bacteremia as an indication and how to define  
25 that, require internal discussion within the divisions to

1 develop guidance documents, much as we've done for the  
2 guidance documents for traditional indications that were  
3 presented back in July.

4 So those are areas which we will need to go  
5 back, discuss these, develop guidance documents so that we  
6 can consistently apply the advice that the committee has  
7 provided, and we certainly are going to need to develop  
8 those and get further committee input on those issues.

9 So why don't you go to the questions, John?

10 There are two questions we'd sort of like the  
11 committee to consider.

12 Are the current regulatory incentives that have  
13 been described -- for example, Subpart E, Subpart H, or  
14 accelerated approval, fast track as defined in the FDA  
15 Modernization Act -- adequate for the development of  
16 antimicrobial agents for resistant pathogens? Do you have  
17 any additional suggestions that might be appropriate?

18 Secondly, should the FDA consider the addition  
19 of class labeling statements for antimicrobial agents to  
20 encourage appropriate use? This should be considered in  
21 the context of the overall educational role that the agency  
22 might have in promoting the prudent use and to preserve the  
23 usefulness of antibiotics.

24 DR. CRAIG: Okay. I don't know if we're really  
25 the best people to answer the first question, but we'll let

1 Barth give it a try.

2 DR. RELLER: I wanted to, for this, ask Dr.  
3 Tally and others with industry, do you feel what Dr.  
4 Goldberger outlined gives the kind of latitude necessary  
5 for development and speeding along the process for drugs  
6 for resistant organisms? Is it there now, applied  
7 flexibly, as outlined?

8 DR. TALLY: I'll answer that two ways. In  
9 preparation for this meeting, on reading the documents that  
10 were sent to me, and then trying to think about it and  
11 approach it with a broad brush, I think there are a large  
12 number of parts in the Subpart E and Subpart H and fast  
13 tracking that allow us to take old drugs through and new  
14 drugs through. There are some parts of it, though, that  
15 will, if taken to the full extent, that it would be  
16 restricted down to a point for just the resistant  
17 organisms, that would be a disincentive, I think, for any  
18 of the companies to come forward with that strategy.

19 So it's a balance between fast tracking, a new  
20 chemical entity that maybe works against resistant  
21 organisms, but also works against other organisms, to just  
22 develop it for resistance, because I know that that's not a  
23 viable alternative with what it costs in the current  
24 marketplace where those drugs will be used.

25 But if you went back to approval of a drug for

1 serious indications, for serious infections, and whether or  
2 not those infections were resistant or not, if you've  
3 proven that that drug worked against both susceptible and  
4 resistant, then the prudent use of it in serious infections  
5 and seriously ill patients -- I think it can be done on the  
6 existing laws.

7 DR. CRAIG: Frank, let's say it had enough data  
8 or didn't have quite enough data to meet the criteria for  
9 susceptible organisms. The usual randomized clinical  
10 trials, you didn't have that, but we really had a need and  
11 the drug did have enough information, and you could get  
12 some initial clinical data so that it could be fast  
13 tracked. Would that be okay to fast track it for the  
14 resistance as long as the other was coming later?

15 DR. TALLY: I think that would be a strategy  
16 that could be discussed, yes, and bring it forward. I  
17 think with new chemical classes -- I'm only speaking for  
18 myself now --

19 DR. CRAIG: Yes, right.

20 DR. TALLY: -- that you could consider that  
21 type of strategy to bring it along. The fear is that it  
22 would then be restricted to just the resistant organisms,  
23 which I think would be inappropriate. If that happened,  
24 then that would never happen again, because no organization  
25 would be able to bring it forward.

1 DR. CRAIG: Dr. Bertino?

2 DR. BERTINO: I think that there's a dichotomy  
3 here, and I don't have an answer to this question. But  
4 we're talking about promoting prudent use of antibiotics,  
5 and yet what we're hearing is the realities, that a company  
6 won't develop a drug just for resistant organisms. So for  
7 those 14,000 people that have MRSA a year, nobody is going  
8 to develop a drug to treat 14,000 people. They want  
9 indications for other things.

10 I don't really know the answer to this  
11 question, but what I do know is that bacteria are a lot  
12 smarter than we are, and on a one-on-one basis, in your  
13 office, when a pharmaceutical rep comes and talks to you,  
14 what's going to happen is that these drugs, even if they  
15 were labeled "Do not use this for anything other than MRSA,  
16 but it's got activity against all these other things,"  
17 they're going to be labeled for that. That doesn't really  
18 promote the prudent use of antibiotics.

19 Dr. Goldberger talked about educational efforts  
20 and things like that, but it really gets down to a one-on-  
21 one basis, and it gets down to ethical issues, and it also  
22 gets down to financial issues. I don't have an answer for  
23 it. I'm just trying to point out some of the things that  
24 passed through my mind since I heard the presentations in  
25 the last 30 minutes.

1 DR. CRAIG: I understand, as you mentioned,  
2 that a lot of our use is empiric. So you oftentimes don't  
3 know about the resistant organism until the laboratory  
4 tells you about it. In fact, there is no resistance until  
5 the laboratory tells you. So in many of those situations,  
6 it's tough to use it. For those kinds of infections that  
7 produce very serious infections, it may be difficult.

8 But I agree with you. If we had an oral agent  
9 for methicillin-resistant staphylococci that could be given  
10 orally that was highly effective, I think it would be a  
11 fantastic drug and it probably would be used a lot, and I'm  
12 sure financially it would be a success. But again, the  
13 drug might also work equally well for susceptible  
14 organisms, and I think the thing that we really don't know  
15 and don't have a lot of good knowledge on is what really  
16 drives resistance and what really leads to it. Just the  
17 use of one particular agent may not be it.

18 If we look at the lesson from Iceland, it's  
19 coming so far that their incidence of penicillin resistance  
20 seems to be dropping. It's not the **beta-lactams** that  
21 they're reducing. If you look at their usage, actually  
22 it's increasing with the beta-lactams. What they're  
23 reducing is their macrolides and **trimethylsulfur** usage, as  
24 if then, because of the co-existence, some other drug  
25 unrelated to the one that **is** maybe the best one for

1 treating the infection is actually driving the resistance.

2 So there are a lot of things with resistance  
3 that we really don't have good information on.

4 Dr. Gerding?

5 DR. GERDING: I think this issue is somewhat  
6 being perhaps misconstrued because of this word "prudent,"  
7 which sort of carries with it, I think, some frugality kind  
8 of issue. For that reason, I don't like the term "prudent  
9 use." I prefer the use of good stewardship of your  
10 antibiotics. You take care of business, if we can put it  
11 in Elvis Presley's jargon, and taking good care of your  
12 business is using the right drugs at the right time.

13 It would be a huge mistake, I think, to develop  
14 drugs active against resistant organisms and then somehow  
15 try to say that it's inappropriate to use them against  
16 organisms that are susceptible to other drugs. I think  
17 that's a mistake.

18 I think empiric regimens can be done in a  
19 number of ways. We need empiric drugs and we need drugs  
20 that are very specific. We need them both, and you can  
21 develop an empiric regimen out of a single broad spectrum  
22 agent or you can develop an empiric regimen out of several  
23 narrow spectrum agents. In a situation where you suspect a  
24 resistant organism, inclusion in your empiric regimen of a  
25 drug against the resistant organism is perfectly

1 appropriate, I think, and demonstrates good stewardship and  
2 good care of that patient. When you find out it's a  
3 susceptible organism for which you don't need to use that  
4 agent, you make a judgment and you can drop off whatever is  
5 inappropriate and go on with what's appropriate.

6 So I think we really need a policy here of  
7 eliminating the obvious inappropriate usages, and who is to  
8 say that the new drug which is, say, active against  
9 susceptible staph aureus and MRSA isn't going to be  
10 superior against susceptible staph aureus? We won't know  
11 that until we test it, and the fact is that this may be the  
12 best drug across the board for staph aureus infection,  
13 maybe superior to nafcillin.

14 So I think the very idea that you would approve  
15 a drug only for use against a resistant organism I think is  
16 innately flawed in its overall approach here, and what  
17 you've really got to be looking at is just using good  
18 stewardship all around in taking care of your antibiotics  
19 and eliminating the obvious inappropriate usages.

20 DR. CRAIG: Dr. Danner?

21 DR. DANNER: I don't know if I'm jumping ahead,  
22 but I actually don't think that the current incentives are  
23 adequate, and I would favor the development or  
24 consideration of additional incentives. I base that on  
25 just looking at the emerging drug resistance problem and

1 the rate at which solutions are being developed both for  
2 resistance problems that are very central issues in the  
3 U.S. and resistance problems that perhaps don't affect the  
4 U.S. as greatly but do affect the developing world, like  
5 malaria. Being a very rich country, we have an obligation  
6 also to fulfill a need there.

7 Right now, when drug companies develop drugs,  
8 one of the questions they ask is what is the market, and  
9 how much can we make in doing this? Can we recoup our  
10 investment? That obviously has to be central to  
11 pharmaceutical companies' concerns because they are in  
12 business to make money. So it just seems to me that for  
13 some of these things where right now there is not a market,  
14 and also you don't necessarily want pharmaceutical  
15 companies to have a lot of incentive because the market is  
16 small to, in a way, create a market that perhaps shouldn't  
17 be created -- i.e., by overusing drugs that aren't needed  
18 to address resistant organisms.

19 I don't know what kind of incentives those  
20 should be, but perhaps there should be other things like  
21 tax incentives or incentives that can further increase the  
22 exclusivity issue, extend it out in time, particularly if  
23 you're developing a drug for an organism that's trivial  
24 today but is a growing problem. I could see a drug company  
25 maybe being interested in developing the drug now if they

1 know that they can have exclusivity to it longer into the  
2 future when perhaps a market will, caused by the pressure  
3 of using the existing drugs, essentially increase in size.

4 So I guess ultimately I think that the things  
5 that are available now are good, but they're not  
6 necessarily adequate to completely correct the natural  
7 market forces that exist in regards to this area of drug  
8 development.

9 DR. CRAIG: Dr. Reller.

10 DR. RELLER: Bob, I wonder if there aren't two  
11 aspects to this. One is the market that in this country is  
12 not apt to be ever substantial and what incentives might be  
13 needed there, and the market that if the indications are  
14 not too restrictive might be a sufficient market. But as  
15 Dr. Tally pointed out, it may not be a sufficient incentive  
16 if it's only a resistance indication.

17 On the latter issue, I wanted to put forth an  
18 idea that tries to address number 2 as well and get  
19 people's comments as to whether this is purist, naive, or  
20 simply wishful thinking, and pulling in some of the  
21 comments that Dr. Mermel made earlier as well.

22 Oftentimes, empirical therapy is initiated, and  
23 then when the database unfolds, people don't respond.  
24 There's not a restricting when there is actually a good  
25 database that would enable one to focus the therapy.

1           So, Frank, is it reasonable to consider that if  
2 one got some added usage for one of these putative new  
3 agents from empirical therapy for serious infections, but  
4 that in an attempt to encourage good stewardship ala what  
5 Dale pointed out, and to include that stewardship in the  
6 possible even-handed application in the package insert to  
7 something along the following lines: that one would not  
8 continue new agents once data were available that the  
9 patient in fact turned out not to have a resistant  
10 organism, unless, of course, it turns out, which may be the  
11 case, that it's a better drug.

12           So what I'm envisioning is, here we've got a  
13 new agent that is very important to get fast tracked under  
14 Subpart E, et cetera, and that it's pushed along because of  
15 its utility for a resistant organism, but it may turn out  
16 to be, say, like vancomycin, which I think all of us would  
17 agree that if an organism is methicillin susceptible, that  
18 vancomycin, in fact, is not the best agent, and that one  
19 should not use or continue to use vancomycin. I mean, the  
20 reality is that people have to start with vancomycin when  
21 you've got 30 percent resistance to oxacillin for staph  
22 aureus and 70 percent resistance to coagulase-negative.  
23 But then people don't stop. Or that one uses vancomycin  
24 because the patient is really sick, or was sick and they're  
25 responding, when in fact you've got a susceptible strain

1 and one should cut back.

2           So let's take the putative new agent. Unless  
3 it were shown to be superior in the next wave, not after  
4 the initial fast tracking but the additional clinical data  
5 showed it to be a superior agent, that one would go along  
6 with package insert instructions recommending -- it would  
7 require two things. One is the good use and availability,  
8 and maybe the NIH might think about this in terms of this  
9 infrastructure. I mean, part of the problem with drug-  
10 resistant TB was that the public health infrastructure  
11 collapsed. When the traditional methods were reinforced  
12 and money was put back into it, to directly observe, seek  
13 out and find, whether it's the homeless or whatever, but  
14 there have been comments before about the dwindling  
15 infrastructure in American hospitals for diagnostic  
16 microbiology and adequate sample and documentation and  
17 susceptibility testing.

18           But if one put the emphasis on getting an  
19 organism, getting susceptibility, and it turns out that it  
20 is a susceptible, not a resistant strain, putting in the  
21 package insert that one should change to currently  
22 available therapies unless your new drug was shown to be,  
23 in fact, with the next phase after the rapid approval, to  
24 be superior for susceptible, and not only superior just for  
25 the resistance. Do you follow the drift of what I'm trying

1 to put across?

2 DR. TALLY: Yes. I think what you're trying to  
3 say is what the second question is.

4 DR. RELLER: Exactly. I'm trying to phrase the  
5 second question issues in a way that would both be adequate  
6 incentive in terms of total numbers for empirical use for  
7 your new drug that would make it economically feasible to  
8 pursue, but yet would not get us in the dilemma of  
9 destroying the utility of your new drug by unnecessary use  
10 when it's not necessary owing to superiority for resistant  
11 organisms, that continued use that was begun in good faith  
12 empirically gets you the sales that you need to make it  
13 viable but does not put inordinate pressure on using it,  
14 unless you can show in subsequent trials that it's actually  
15 superior for the susceptible organisms.

16 DR. TALLY: I think we can go into a lot of  
17 theoretical arguments. I think what you have to do is to  
18 develop the particular drug along some lines on where it  
19 works and what its characteristics are, and then you can  
20 make the judgment on what the package insert should say  
21 because you have clear evidence. I think you have to write  
22 that with clear evidence of efficacy and safety and clearly  
23 state that in the package insert. I think that's the  
24 mandate that we have.

25 The second mandate that I think Mark talked

1 about was education on the prudent use of antibiotics. I  
2 think we're all taught the prudent use, but then it comes  
3 down to -- I'll put on my other hat, not a drug developer  
4 but a physician using that, and I would want to have the  
5 option. I mean, I could look at that and read it and say,  
6 yes, I should do that for every drug, and that should be  
7 maybe an indication for every drug for the prudent use of  
8 it, and I would encourage that for anything to select the  
9 safest, most effective drug when you have the  
10 susceptibility testing.

11 DR. RELLER: That's just as an example. To put  
12 it very specifically, do you think it's reasonable for the  
13 FDA to consider putting in the package insert labeling,  
14 when the data support that it's a reasonable conclusion,  
15 something along the lines -- and let's take as an example  
16 vancomycin. If you were writing the vancomycin package  
17 insert, that it would say that this drug is effective for  
18 oxacillin-resistant organisms, but should not be continued  
19 to be used without a reason like allergy, et cetera, for  
20 methacillin-susceptible strains of staph aureus?

21 DR. TALLY: I'm going to let (inaudible) answer  
22 that.

23 DR. RELLER: I mean, that's a clear example.

24 PARTICIPANT: That would destroy development of  
25 new drugs for resistance, and let me answer it in several

1 ways. First of all, if you take Dr. Bell's list of all  
2 resistant pathogens that he's concerned about and add them  
3 up, there are less than 200,000, including the 189 patients  
4 with TB. So immediately, all of what Dr. Bell is talking  
5 about is orphan indication. You don't fund \$250 million  
6 costs with orphan indications, number one.

7           Number two, Subpart E and Subpart H for Big  
8 Pharma are not incentives to develop new antibiotics for  
9 resistant pathogens. Marketing people tell me that it is a  
10 death knell for a new drug to go through those because they  
11 will be positioned as resistant-only, and the academics and  
12 the regulators will take every opportunity to say for  
13 resistant pathogens only for the five to seven years that  
14 we have to go through in getting it, and that will imprint  
15 on the minds of the people, and it will only be used for  
16 that, and pharmacoeconomically it does not meet the  
17 economic imperatives of the industry.

18           Now, what suggestions could be used to help us?  
19 Fast track is a good idea, and there's no question I think  
20 Big Pharma appreciates the openness of the agency to have  
21 frequent small talks trying to identify issues and get them  
22 resolved early on. However, I will say that even with that  
23 opportunity, they don't get resolved very quickly. The  
24 issue of bacteremia's indication is two years old, and I  
25 don't know if I heard it solved today. So the speed

1 certainly isn't there.

2           Now, other suggestions. The pediatrician who  
3 is from our company wanted me to ask this. Can pediatrics  
4 help us out with resistant pneumococcus? Because we heard  
5 that you've got to be white, under six, and in the suburbs  
6 if you have a reasonable chance of studying it. Can that  
7 indication spill over to adults? And also, can some  
8 adults, if there's no difference in the pathological  
9 process, cross over for package insert labeling for  
10 children?

11           I've heard no incentives today to help get  
12 increased package insert labeling to help protect  
13 pediatricians, unless we say that if there is a large  
14 experience with sensitive organisms and it's a different  
15 mechanism of action and there's an adequate safety database  
16 and there's unimodal distribution of sensitivities that we  
17 can have limited number of clinical cases. Let me tell  
18 you, Big Pharma hopes that that's going to be the case,  
19 because Sheldon Kaplan told you that there's no way that  
20 the pediatricians are going to be able to supply the number  
21 for cases for resistant organisms to be able to meet that  
22 hurdle, unless we adapt somehow in that regard.

23           Another suggestion is that most of the time we  
24 are going to have to go to other continents to be able to  
25 get the requisite number of resistant pathogens, and I'm

1 not saying that any regulatory agency in the world has an  
2 overt prejudice against data from another continent, but I  
3 think that we have to think globally and we're going to  
4 have to accept globally-generated data if there is a  
5 reasonable modicum of good clinical practice. We have to  
6 trust the people in Russia and Thailand and Chile and  
7 Canada and whatever, and we're going to have to be able to  
8 take data from a large number of places to be able to get  
9 the number of resistant pathogens.

10 Now, on the second point, we're going to have  
11 to be evenhanded, absolutely evenhanded, if we're going to  
12 start doing this number two point. You can't pick out the  
13 glycopeptides and say, boy, we're going to really make sure  
14 we give the message for those people, and then say, but the  
15 macrolides have been around for a long time and everybody  
16 sort of knows about those, so we'll forget about them.

17 Now, if you're absolutely evenhanded, what's  
18 the value? We all went to medical school. We don't need a  
19 package insert with another five paragraphs telling us do  
20 the right thing in using antibiotics. I don't know that  
21 that's going to make the impact if we're going to be  
22 evenhanded, and let me tell you, Big Pharma is not going to  
23 stand for us not being evenhanded. If the macrolides get  
24 it, the immunoglycosides get it, the erythromycins get it,  
25 the new classes of antibiotics get it, et cetera. You're

1 going to have to be evenhanded.

2 I think that I understand what you want to do,  
3 but I don't know that in the package insert is the way to  
4 do it, and if you require in the package insert that a  
5 person who is found to have a resistant organism and on the  
6 day three is found that it wasn't resistant, and then you  
7 say in the package insert that you should switch them to a  
8 different agent, I don't think Big Pharma is going to  
9 accept that either, and accepting that we have to show that  
10 any new agent is superior to old agents in order to be  
11 continued on, there are too many things in the practice of  
12 medicine -- convenience, riding a winning horse, not  
13 wanting to switch, that sort of a thing -- and I think  
14 we're opening a Pandora's box here.

15 DR. RELER: I posed the examples to get this  
16 out on the table, so that we'd get honesty in the dialogue,  
17 and I think we're hearing it. I welcome it. Not  
18 necessarily that I agree with it, but I think we need to  
19 get it out here, so that we're being realistic.

20 DR. CRAIG: Vince?

21 DR. AHONKHAI: I wanted to take a crack at the  
22 question you asked in relation to the second question  
23 there. I believe that the intent is absolutely good for  
24 implementing the appropriate use of antimicrobial agents.

25 Let's look at what the current barriers are. I

1 believe that the current problem really stems from a number  
2 of areas. There is no mechanism whereby enforcement of any  
3 lack of compliance with this can be implemented. So right  
4 off the bat, you have to ask the question how do you insure  
5 that in fact, if that's not happening, we can make it  
6 happen?

7                   There is an infrastructure in place for us to  
8 all benefit from the information that's available. The  
9 payers make a difference as to how prescribers are going to  
10 prescribe these drugs, so the exclusion of either managed  
11 care organizations or formulary committees and so on will  
12 in actual fact not work. Practice guidelines are another  
13 way that perhaps we can all, in an educational mode, get  
14 the information that is appropriate for the use of  
15 antimicrobial agents.

16                   DR. CRAIG: Yes, Dr. Bell?

17                   DR. BELL: I actually think that Dr. Reller's  
18 suggestion is an excellent one, and the response that "Big  
19 Pharma wouldn't stand for it" is to me just another way of  
20 saying that incentives may really be needed for this kind  
21 of approach.

22                   But what I really wanted to say is that since  
23 we're moving into point number two now, CDC has a major  
24 interest in the prudent use of antimicrobial drugs, and I  
25 would like to raise two issues for consideration as

1     pertaining to labeling of antimicrobial drugs for humans.  
2     I know that these issues have been discussed internally at  
3     FDA, but I would like to bring them out onto the table.

4             One of them is that labels need to reflect  
5     current data regarding drug susceptibility, not simply data  
6     that were available when the application was submitted.  
7     There needs to be a mechanism to update labels with a  
8     minimum of fuss to insure that the labels and the  
9     promotional material based on the labels are in fact  
10    helpful to clinicians as they attempt to treat resistant  
11    infections.

12            This has a number of implications, but one in  
13    particular that I would invite the committee's attention  
14    to, which is that when drugs are used empirically in  
15    cultures or in practice rarely to never attained, such as  
16    the case for otitis media, it is critical that emerging  
17    resistance in the causative pathogens, if it reaches a  
18    problematic point, that labeling for drugs approved for  
19    otitis media be modified to reflect that reality.

20            For example, drug-resistant pneumococcus, which  
21    is probably the causative agent for otitis that in reality  
22    most requires actual drug treatment, I'm aware of one case  
23    in particular where an agent is approved for treatment of  
24    otitis media that actually performs terribly for treatment  
25    of drug-resistant strep pneumo, but then it says in the

1 label for drug-susceptible strep pneumo, and in fact if you  
2 never get cultures, this is really a misleading statement  
3 in an environment where drug resistance is a problem.

4 To make it worse, promotional material based on  
5 this package insert -- most physicians don't read the  
6 package inserts all that often. What they do get hit with  
7 is promotional material. You would never get a clue from  
8 the promotional material that this was in fact a major  
9 problem with this drug. So the major point of labels need  
10 to be updatable with a minimum of fuss to reflect emerging  
11 resistance data.

12 The second point I'd like to make was actually  
13 mentioned to me as a sort of -- well, it was an idea by  
14 somebody at the FDA, and I actually thought it was a great  
15 idea, which is that consideration should be given to  
16 labeling antimicrobial drugs as a class, labeling that  
17 antimicrobial resistance is a potential adverse effect of  
18 the use of these drugs, and I say this for a couple of  
19 reasons.

20 One of them is it's a scientifically accurate  
21 statement. I think we'd all recognize at a societal level  
22 that increased drug use leads to resistance. We also have  
23 information from case-control studies of resistant  
24 pneumococcal and VRE infections that prior antibiotic use  
25 in individual patients leads to increased chance of

1 resistant infections. So it's scientifically accurate.

2           The reason I think it would be extremely  
3 helpful is that it would be an important adjunct to our  
4 educational campaigns to influence prescribing practices  
5 among clinicians, and also the public's view, and it might  
6 exert a, let's say, subtle restraining influence on  
7 occasional overexuberant pharmaceutical marketing  
8 activities if it had to be stated that drug resistance was  
9 a possible adverse effect.

10           I'm thinking, for example, now we have not only  
11 the marketing to physicians, which I don't really criticize  
12 -- I mean, this can serve major educational objectives.  
13 I've often said that nobody knows how to educate physicians  
14 better than drug companies, and I think that we should  
15 enlist their help in the campaign against resistance, but  
16 now we're also seeing, for example, drug advertisements  
17 directed at the public for antibiotics. Regardless what  
18 the issues might be in general about advertisements  
19 directed at the public, I guess advertising antibiotics, we  
20 have some potential concerns that this might conflict with  
21 messages we'd like to send that actually antibiotics are  
22 way overprescribed.

23           We're dealing with a situation where we  
24 estimate, based on our studies of drug use and  
25 appropriateness, that every year in the United States there

1 are approximately 50 million unnecessary outpatient  
2 antibiotic prescriptions. These are prescriptions for  
3 colds, for nonstreptococcal pharyngitis, for uncomplicated  
4 acute bronchitis, and so on. This is five zero million  
5 annually. This is the major driving force, we think, for  
6 pneumococcal resistance, and we'd like to reduce the amount  
7 that are prescribed.

8 Now, in fairness, I can think of one  
9 advertisement direct to the public that states something to  
10 the effect of remember to take all of the medicine as  
11 prescribed, which I guess is sort of in deference to the  
12 notion of resistance developing if you don't do it. Now,  
13 for tuberculosis, it's very important, compliance with the  
14 regimen and so on, but we think for these common  
15 respiratory infections that the driving force for  
16 resistance is the number of prescriptions. It's not  
17 somebody forgetting to take a dose or only taking seven  
18 days versus 10 days.

19 So basically, to kind of sum up, to support  
20 efforts to really encourage prudent use by reducing the  
21 number of prescriptions and encouraging physicians to  
22 scrutinize do they really need to write this prescription  
23 and is this the best use of this drug, I think it might be  
24 helpful to consider the concept that antibiotic resistance  
25 be included in the label as a potential adverse effect of

1       prescribing the drug.

2                     DR. CRAIG:  Dr. Bertino?

3                     DR. BERTINO:  Kind of a little bit of a follow-  
4       up to your comments.  In terms of the package insert, many  
5       of us over 40 can hardly unfold those package inserts stuck  
6       on the side of the bottle, much less read them.  I mean, I  
7       know that FDA lives and dies by the package insert, but I  
8       do agree.  I don't think most people read the package  
9       insert.  The people that I find read the package insert are  
10      the patients that we take care of that have the PDR.  They  
11      read the package insert, and they ask you about all the  
12      unusual side effects and things like that.

13                    Secondly, in terms of an educational effort,  
14      since the majority of antibiotic use is used as an  
15      outpatient basis, one of the things that I would ask the  
16      FDA to consider is to ban sampling of anti-infective  
17      agents.  I think that sampling of anti-infective agents is  
18      a bad thing.  There's an abstract in Pharmacotherapy this  
19      month from Geisinger that shows that when sampling  
20      occurred, and anti-infective agents was one of the things  
21      in there, that increased prescribing of that agent  
22      occurred.  It's environmentally unsound, all those little  
23      plastic bottles and cardboard boxes and package inserts and  
24      things like that, and it promotes overuse of antibiotics.  
25      So I think if we're going to do an educational effort that

1 would be something very tenable that the FDA could do.

2 I actually asked a couple of pharmaceutical  
3 manufacturers if they would consider stopping sampling, and  
4 they said, "If everybody else didn't sample, we wouldn't,  
5 because honestly it's really a big pain for us, and it  
6 costs a lot of money and that money could go somewhere  
7 else."

8 DR. CRAIG: Let me just comment a little bit  
9 about what you say reflecting current susceptibility in the  
10 package insert. The problem we have for pneumococci is  
11 that if we look at the FDA-approved break points, they're  
12 way high, and many of these organisms that are resistant  
13 would be called susceptible if we look at the current FDA  
14 break points.

15 The NCCLS is just now in the process of trying  
16 to establish break points for many of these, so right now  
17 we just don't have anything that you can really put your  
18 finger on that one could use that's a consensus for  
19 pneumococci for many of the drugs.

20 So eventually, hopefully, that will be there,  
21 but you'd have to somehow get around the FDA's break  
22 points, which were established many, many years ago, and  
23 oftentimes for many of those oral agents they were based on  
24 urinary levels and for treating urinary tract infections,  
25 and they weren't designed for specifically treating

1 pneumococci.

2           So while I applaud the goal, I think that's one  
3 of the reasons why the NCCLS is tackling this problem and  
4 trying to go ahead and give break points to all the oral  
5 agents, because of feeling that if that information is out  
6 there, so that the drug is now called resistant in surveys,  
7 so that there's a high incidence of resistance, that might  
8 affect use of some of these agents, and again, the concern  
9 being that use of an inefficient or a subtherapeutic dose  
10 may actually spawn resistance instead of at least keeping  
11 it similar or trying to even reduce it.

12           DR. MURPHY: Could I ask our remaining industry  
13 speakers to respond to some of the comments, particularly  
14 the banning of samples or the direct to consumer if it were  
15 across the board for everybody? I mean, this is someone  
16 stating his opinion and I'd like to hear what your thoughts  
17 on that are.

18           DR. AHONKHAI: I don't think we're the right  
19 folks to respond to those, because we would need to take  
20 that back to our colleagues in marketing and sales and so  
21 on. I'd be very surprised if there are individuals within  
22 R&D who feel very comfortable to comment on this.

23           DR. CRAIG: I guess I would have trouble with  
24 labeling also that had anything to do with making specific  
25 recommendations, as was talked about before. I feel much

1 of what we're trying to do with resistance is to attack the  
2 inappropriate usage in viral infections where the drug's  
3 not being used than trying to necessarily get into the area  
4 where an antibiotic is needed and getting more into trying  
5 to use the FDA as being a therapeutic decisionmaker. I  
6 think that still is something that I think belongs to the  
7 people that really have the license and are the ones making  
8 the decisions, and I think you need their education.

9 But I think clearly it's very appropriate to  
10 put things in, I could see, that reminded people that  
11 antibiotics are not active against viral infections and  
12 that many of the infections, respiratory infections, are  
13 viral, and just again reinforcing that antibiotics can be  
14 overused.

15 DR. MURPHY: What about Dr. Bell's other  
16 suggestion?

17 DR. CRAIG: Personally, if every single drug  
18 has it that it's a potential side effect, I have no trouble  
19 with that. I mean, I think it's got to be across the board  
20 for everybody.

21 DR. MURPHY: I pretty much understand that,  
22 that we can't pick anybody out to pick on.

23 DR. CRAIG: Dr. Dudley?

24 DR. DUDLEY: I don't speak officially for my  
25 company, Microcide Pharmaceuticals. We don't have anything

1 to sample or to give out as samples because we're engaged  
2 in discovery.

3 One area I would like to hear, or at least we  
4 would like to see the agency begin to address, and I  
5 touched on it briefly yesterday, was the area of  
6 potentiators of antibiotics, and for a variety of reasons,  
7 and some of them being discussed this afternoon, those  
8 would be very highly desirable agents to have out there.  
9 They are agents that would target a resistance mechanism  
10 and not necessarily be an antibiotic in and of themselves,  
11 so by definition, then, they would be compounds that would  
12 only have an effect on resistant bacteria.

13 As I mentioned, those are drugs that you're  
14 familiar with, such as beta-lactamase inhibitors, but there  
15 are other resistance mechanisms, some of which have been  
16 discussed at this meeting, for which there can be  
17 potentiators potentially developed for, but as we stand now  
18 there's no guidance for that type of activity. There have  
19 been discussions of having stand-alone agents, such as  
20 beta-lactamase inhibitors, in the past, but that has not  
21 come to fruition with any type of development programs that  
22 I am aware of in the United States.

23 So I think this deserves some consideration and  
24 certainly some guidance that would be positive would  
25 certainly I think serve as a stimulus, perhaps, for

1 industry to pursue those types of mechanisms or types of  
2 programs if it would be clear that there would be certain  
3 types of ways to actually develop those and seek labeling  
4 that would achieve mutual goals.

5 DR. CRAIG: Any other comments? Yes, Janice?

6 DR. SORETH: I want to respond to Dr. Bertino's  
7 comments with regard to the package inserts. Yes, we live  
8 and die by them. That's true, and we work very hard in  
9 hammering them out with industry.

10 We would agree. We don't think that most  
11 physicians read them, but it's kind of like democracy.  
12 It's a terrible form of government, but show me something  
13 better. So the package insert may be a terrible way of  
14 putting the information across, but as yet we haven't  
15 arrived at something better. We have had efforts within  
16 CDER both to develop a patient package insert, as well as  
17 revamping the current package insert that goes to  
18 physicians or becomes the basis for what's in the PDR, and  
19 again the important point is that with whatever package  
20 insert we draft, it is from that material that promotional  
21 materials are put together by the company.

22 Now, that represents another step, I would say,  
23 for intervention or oversight on our part, because it has  
24 sometimes happened that material is extracted in such a way  
25 from the package insert into promotional material where you

1 don't really recognize the connection between the  
2 promotional material and the package insert. So we have a  
3 Division of Drug Marketing and Advertising that oversees  
4 that promotional material to make sure that there is a  
5 genuine link between the promotional material and what is  
6 in the package insert.

7 That said, I think the promotional materials  
8 represent first, foremost, and last what prescribing  
9 physicians get for the most part about their education for  
10 a particular drug product, and that's problematic, but we  
11 at FDA don't really, as far as I understand, have easy  
12 mechanisms ourselves outside of the package insert for  
13 educating physicians on the prudent or appropriate use of  
14 antibiotics. Maybe a Surgeon General's warning on every  
15 bottle that inappropriate taking of antibiotics may be  
16 hazardous to your health, like a cigarette package warning,  
17 might do it, because I think it's still a novel idea to the  
18 layman that inappropriate use of antibiotics might be  
19 deleterious.

20 DR. CRAIG: Personally, I agree with him. I  
21 think that you'd find more patients reading them than you  
22 will find physicians reading them, so again it is a way of  
23 getting information to the patients.

24 DR. BERTINO: You might think about supplying a  
25 pair of magnifying glasses with each package insert.

1 DR. CRAIG: Dr. Bell?

2 DR. BELL: Well, maybe somebody from FDA staff  
3 could follow along on this, but my impression is what  
4 physicians get is the promotional material. Promotional  
5 material has to be based on the package insert. So I don't  
6 think we should just dismiss the package insert. I think  
7 the FDA should consider appropriate modifications to  
8 package inserts, and then making sure that that pertinent  
9 information from the package insert is in fact in the  
10 promotional material, because sometimes it's not, and it's  
11 really the promotional materials that I'm thinking mostly  
12 about if we start to modify the package insert in the way  
13 that various people have suggested.

14 Would it in fact be helpful, and does anybody  
15 have comments on this, to include the development of  
16 antimicrobial resistance as a potential adverse effect of  
17 antibiotic use on a class-wide basis? Would that help  
18 some? Would that help restrain some of the exuberant  
19 marketing? Would it be helpful?

20 DR. RIKOWSKI: I'm Alex Rikowski, FDA. Just  
21 like Dr. Dudley, I'm not sure if I represent the FDA here,  
22 but just to throw this out, I believe that we need to have  
23 a fair representation of all the data for the clinicians to  
24 decide. Firstly, one problem I see is the fact that the  
25 product is essentially a distillation of what was actually

1 reviewed. Maybe one way to get around all this is to  
2 actually publish our reviews in public journals. Just like  
3 there's a morbidity and mortality report in JAMA, why not  
4 have an FDA report and let the clinicians then decide? I  
5 know there's a lot of proprietary information involved  
6 there, but at least for approved agents, if that  
7 information is shared, it would give clinicians a more fair  
8 representation and maybe help them make their decisions.

9 DR. CRAIG: Barth?

10 DR. RELLER: One important aspect, it seems to  
11 me, of the package insert as a basis for education practice  
12 and promotion, it may not be that it's at everyone's  
13 fingertips, but to me it's somewhat like the Constitution.  
14 It's good to have it there when you need it as a basis for  
15 interpreting promotional material, educational guidelines,  
16 et cetera. So it's important as a repository for guidance.

17 DR. CRAIG: I guess the question is could it be  
18 as something that we get the lawyers involved if someone  
19 came and it was listed as an adverse reaction?

20 DR. MURPHY: I don't think we'll ever prevent  
21 that, but I did want to comment that the reviews, FOI puts  
22 them on the Web, so they're available after a drug's  
23 approved. It isn't everything, but it is the medical  
24 officer and the pharm review. So they are available for  
25 somebody to look at. I realize it's not something that we

1 all want to do as our nighttime reading, but they are  
2 available.

3 DR. CRAIG: Yes, Dr. Davis?

4 DR. DAVIS: Are there any disincentives for the  
5 improper use of antibiotics?

6 DR. CRAIG: In terms of you mean some of the  
7 general things like he was mentioning?

8 DR. DAVIS: In terms of any disincentives to  
9 practicing physicians. For example, you can almost imagine  
10 that perhaps a managed care organization or the insurance  
11 companies would not reimburse the patient, for example, if  
12 there was not a confirming lab diagnosis along with the use  
13 of antibiotics.

14 DR. BERTINO: Actually, this just came up at a  
15 Department of Medicine meeting at our place a couple of  
16 weeks ago, and generally the answer was no. In fact, the  
17 HMOs aren't paying for cultures.

18 DR. DAVIS: Well, that's encouraging.

19 (Laughter.)

20 DR. BERTINO: Well, that's American medicine.

21 DR. CRAIG: Yes?

22 DR. GOODMAN: Jesse Goodman, formerly of the  
23 University of Minnesota, still there, and also helping out  
24 at FDA now, and I certainly don't really speak for FDA, but  
25 maybe one way, rather than this being totally adversarial,

1 is we've heard a public crisis or a near public health  
2 crisis described here, and that's also a public health  
3 opportunity, and in a sense it's one for industry.  
4 Physicians mostly get drug information from promotion, and  
5 I think industry has to examine how they're promoting drugs  
6 and how they can promote them better to meet public health  
7 needs. I think that's something to really think about.

8 We heard about a quinolone today and the  
9 difficulty in these clinical trials of finding patients  
10 with resistant infections. Well, as an infectious disease  
11 clinician, one might then say that 995 of each of those  
12 1,000 patients could have been treated with a drug unlikely  
13 to shorten the lifespan of quinolones, rather than a  
14 quinolone, so that maybe what one of the things those  
15 studies were telling us is should we be promoting X class  
16 of drugs for community-acquired upper respiratory  
17 infections in certain settings?

18 So I think industry needs to work with CDC,  
19 with FDA, with academia to think about not just does a drug  
20 work for something, but is it really indicated and  
21 appropriate for it? And that was partly embedded in Dr.  
22 Reller's comments about response to sensitivity data, but  
23 for human infections there is no culture and there is no  
24 sensitivity, and then we have to go by epidemiology and by  
25 doing what's right. So I think it's a public health

1 opportunity and it's a public health crisis.

2           The other one mentioned was drug development.  
3 Yes, of course, a company has a responsibility to its  
4 stockholders to develop extremely profitable drugs, but  
5 here we have a public health crisis that may be cause for  
6 the development of some drugs that if most appropriately  
7 used might not be very profitable. Is there a way to  
8 incentivize or for different companies to work together to  
9 produce such drugs and use them appropriately?

10           This is a real need and I think we have to  
11 think a little more creatively about that, because if all  
12 we think about is that the next drug for resistant  
13 organisms needs to also be used for community-acquired  
14 infections that could be treated with ampicillin, I think  
15 we're all stuck in the same old box and we're going to keep  
16 regenerating the problem. I'm not saying I have all the  
17 answers, but I think it's a public health opportunity. If  
18 it turns into a crisis that industry and academia have not  
19 met, it will then be taken out of our hands.

20           Thank you.

21           DR. CRAIG: I guess my concern still is we  
22 really don't know a lot about what are the characteristics  
23 that lead to resistance. That's even something that people  
24 are starting to look at now pharmacodynamically in models  
25 to sort of see if we can look at that, and to pick on

1 particular agents without that knowledge, without that  
2 scientific base, I have a little bit more concern on and  
3 I'm much more apt to apply it generally to all of them to  
4 try and reduce use than to start picking on certain ones.

5 But if we had the knowledge, that we knew that  
6 certain things were clearly driving resistance and that you  
7 really knew, then I think you have a scientific basis for  
8 trying to be more specific, but I just don't think we're at  
9 that level yet. I think we just know it's increased use.

10 DR. MURPHY: That's right, and I think that's  
11 why some of the suggestions that have been made are  
12 helpful, if not in development of drugs, certainly in  
13 outreach and educational aspects of the FDA's  
14 responsibilities.

15 DR. CRAIG: Any other comments?

16 MS. YOUNG: Kathy Young from the Alliance for  
17 Prudent Use of Antibiotics. Because of the urgent nature  
18 of the problem and the multidimensional causative factors  
19 that go into it -- we've been talking about one, really,  
20 for two days, one way of attacking the problem, but there  
21 are very few, really, regulatory leverage points, and so I  
22 would encourage the FDA and any other government group to  
23 think of the leverage points they do have and how they can  
24 be used to influence the problem, because I think we need a  
25 more aggressive way of dealing with it, and so I welcome

1 the suggestions by David Bell, and I certainly think  
2 anytime we have a scientific basis we really should  
3 consider using those leverage points aggressively. I hope  
4 the FDA does consider the suggestions.

5 DR. CRAIG: The more I think about it, though,  
6 I guess I am a little concerned about if you called  
7 something an adverse reaction, when really all it may have  
8 been is that the person was in contact with somebody else  
9 and picked up the resistant organism, and it's not related  
10 to the use of the drug at all, and if that could be used by  
11 lawyers at all as a litigation thing, I'm concerned about  
12 calling it necessarily an adverse reaction. I think it's  
13 important to call it something, but if we could do it in  
14 such a way that it wouldn't have that potential negative  
15 content to it, I think would be the better way to do it.

16 Any other comments?

17 DR. LOVE: Maybe I have a question. I'm Ted  
18 Love from San Francisco, formerly at Genentech, and now  
19 with the startup. It's just a question about kind of some  
20 of the assumptions lying behind this. In all of my  
21 dealings with the FDA over the years, the FDA is very  
22 rigorous in terms of thinking about things, applying good  
23 science, and I'm just trying to understand. I'm a big fan  
24 of package inserts, and in fact think that the way a  
25 company should develop a drug is to write the package

1 insert first and then develop the drug to get to that  
2 package insert. So I'm very much in favor of that.

3 But, actually, just an anecdote. I'm a  
4 cardiologist by training, and one of the things that I  
5 think I did most commonly inappropriately was put in PA  
6 lines. I didn't put in PA lines because the manufacturer  
7 of PA lines was trying to get me to do it. I didn't put in  
8 PA lines because of any kind of promotion related to the  
9 company at all. I put it in because of pressure from my  
10 colleagues, I put it in because of other inappropriate  
11 things, but it had nothing to do with that.

12 So I'm really wondering where is the  
13 information that says that it's promotion by companies?  
14 I'm a cardiologist. I really don't know if companies are  
15 traditionally promoting to physicians to inappropriately  
16 use antibiotics. I'm just wondering where is the  
17 information that links, that makes us think that that would  
18 in fact happen.

19 DR. MURPHY: As an ex-chief of general  
20 pediatrics, I would say that promotion to the practicing  
21 physician is very heavy, and I think that we do have  
22 information in that arena. We also can't blame it all on  
23 the companies. I think we need to -- I'm not speaking as  
24 the FDA right now -- work on our parents, and we need some  
25 major efforts in that arena as to their expectations also.

1 DR. LOVE: The reason I was asking is I was  
2 thinking a little bit about some of the data that we saw  
3 showing that at least with resistant pneumococci, it is  
4 occurring in the suburbs, and it's occurring in patient  
5 populations that are different perhaps not because of  
6 promotional things, but because of physician practice, the  
7 behaviors that patients and families are dictating.

8 DR. CRAIG: Plus they can afford it.

9 DR. MURPHY: I was going to say, look at the  
10 number of visits by children to their pediatrician and  
11 family physicians for URIs and you can probably correlate  
12 it somewhat with economic income, but I just think that  
13 certainly it has to do with use of the health care system  
14 and being able to afford some therapies.

15 DR. CRAIG: Dr. Bell?

16 DR. BELL: I want to express that in my one-  
17 year tenure in this position at CDC coordinating  
18 antimicrobial resistance activities, one thing that has  
19 struck me over and over again is, number one, how  
20 multifaceted the problem is and, number two, how when you  
21 try and focus on one facet how often the reaction is, well,  
22 but what about all those other facets?

23 I see this when we talk about arenas of  
24 antibiotic use, whether it's the hospital or the farm or  
25 the outpatient pediatric setting. People say, "Well, what

1 about all those other people doing it? I don't own this.  
2 It's really the others."

3 I wonder if I'm hearing a little bit of it  
4 today in this discussion, when the question at hand is what  
5 can the FDA do regarding labeling, and there may or may not  
6 be some things -- I tend to think there probably are -- but  
7 I guess I thought that we should try and help the FDA  
8 answer that question. What should they do about labeling?  
9 And yes, we all know that there are many other factors  
10 involving promoting prudent antibiotic use and educating  
11 physicians and the patients and the public, et cetera, et  
12 cetera, but the issue is is there something the FDA can do  
13 in its labeling mechanism?

14 DR. CRAIG: Right now, I think as far as  
15 requiring -- we need some MIC break points before one can  
16 start commenting on that, plus then I think you have the  
17 legislation to require reports from the companies about the  
18 drugs that are already proved as to whether they're still  
19 current microbiology data, which I don't think you're  
20 doing, but don't you have that? The law or something that  
21 at least allows that to be done? At least I understood  
22 that that was something that had been stated in the past  
23 that you could go back to be sure that the drug was still  
24 effective against the organisms that are included in your  
25 insert.

1 DR. CHIKAMI: Companies are required to provide  
2 in an annual report all significant information, including  
3 any significant safety information, and that may include,  
4 for antimicrobial agents, any information on  
5 susceptibility.

6 DR. CRAIG: So do you get them?

7 DR. CHIKAMI: We do, actually.

8 DR. CRAIG: What do you do with them?

9 (Laughter.)

10 DR. CHIKAMI: I knew you were going to ask the  
11 hard questions.

12 That information is reviewed as part of a  
13 review of the annual report. Whether and how and if it's  
14 reflected in changes in the package insert is more  
15 variable.

16 Let me just say parenthetically that the EMEA  
17 has recently instituted a requirement in their five-year  
18 review of their products. In the EMEA, products are  
19 required to undergo recertification every five years. They  
20 are now requiring for all antimicrobial agents that there  
21 be submission of surveillance information, and that that  
22 information be reviewed and updated in their product  
23 information.

24 DR. CRAIG: So that would be something that you  
25 could do, right? I mean, if you decided to do the same?

1 DR. MURPHY: We don't have any recertification  
2 process. This is the European that he's talking about.

3 DR. CRAIG: But right now you're getting the  
4 data, but you don't have a way to --

5 DR. MURPHY: I would say that one of the issues  
6 there gets back to our fairness issue, too. You really  
7 would have to do this as a concerted effort.

8 DR. CRAIG: Everybody.

9 DR. MURPHY: Everybody at one time, and there  
10 are some pragmatics to that.

11 DR. CRAIG: Obviously, tough to do on a yearly  
12 basis. The question is it may be on a periodic time. If  
13 someone is trying to get into the package insert some of  
14 the current data on what the incidence of resistance is to  
15 that particular drug, you're going to have to get some  
16 current data to be able to do that. So there has to be  
17 some mechanism, and at least right now one of the  
18 mechanisms, it seems, is the company does provide you a  
19 report of doing that data. I don't know if that's verified  
20 data or where it comes from, but if you wanted to try and  
21 put that information in, to add that to it, there's a  
22 mechanism.

23 I think for the other things that you talked  
24 about, suggestions of having a class statement, something  
25 that doesn't necessarily call it an adverse reaction, but

1 at least comments about resistance occurring, that's  
2 something they could do with package inserts. Again, it  
3 would have to be done with all of them.

4 Yes?

5 DR. SORETH: I would venture to guess that we  
6 don't get that kind of data reliably for every drug in the  
7 annual report, so again, there's the issue of fairness.  
8 There's an obvious disincentive to update the label from  
9 the company's point of view, to update the label along  
10 those lines, and lastly, if I can use an example of safety  
11 information with regard to adverse events, let's say, with  
12 a given class of drugs, there sometimes seems to be an  
13 inordinate lag time, despite our best efforts, to get that  
14 information in the package insert, because again, there's a  
15 built-in disincentive for any company to put additional  
16 negative information into the label. So all of those  
17 factors conspire against keeping the label up to minute  
18 updated, including changes in susceptibility testing.

19 DR. MURPHY: We're not saying it's not a good  
20 idea.

21 DR. SORETH: I think it's a great idea.

22 DR. MURPHY: It's a great idea.

23 DR. SORETH: It's hard.

24 DR. MURPHY: But what she's telling you is that  
25 either we have, if not we think clear safety issues because

1 of an adverse event, it takes a lot of work and effort to  
2 get that label rewritten and out in a timely manner. To  
3 now have the companies come in and redo this for  
4 sensitivity issues, which we think also is a public health  
5 safety issue, it's going to have to be looked at both for  
6 fairness and a mechanism to make it work so that we get  
7 that information, because I'm sure it's not all coming in  
8 in the same manner.

9 DR. CRAIG: Sure. No, I understand.

10 Dr. Ross?

11 DR. ROSS: Just to extend on Dr. Soreth's  
12 remarks, I think that there is a disincentive for  
13 companies. I think that from another aspect there may be  
14 an incentive in terms of by putting adverse events or other  
15 information about problems that use of a product may be  
16 associated with, that that may have an impact on their  
17 liability, that it may be something that reduces their  
18 liability.

19 DR. CRAIG: Dr. Reller?

20 DR. RELLER: Dr. Bell's cogent comments about  
21 the multifactorial nature of this problem, you know, I  
22 wonder if the very reality of that doesn't make it  
23 imperative for at every opportunity, even though it's not  
24 the total solution, it may not even be the biggest impact  
25 on the solution of operating within spheres of influence of

1 what can be done, as was mentioned earlier.

2 For example, could it be in layers? Should the  
3 burden be on the FDA, if this is perceived as a public  
4 health issue, to rewrite the thing as regards resistance,  
5 but as opposed to saying that we are going to try to do  
6 this on an evenhanded basis, and ask for -- and it may be  
7 in layers and it may be stages, one thing this year, one  
8 thing the next year, et cetera.

9 For example, it may be that there would be some  
10 comment that the overuse of antibiotics is a major problem  
11 in promoting drug resistance, that that would go into every  
12 package insert. Therefore, these following things are  
13 given to you for individual efficacy, safety, et cetera,  
14 but also you're sort of reminding people at that point.  
15 Not that they're necessarily going to read it, but it's  
16 there, because it's a basis for promotion.

17 That one might, on the agent for respiratory  
18 tract infections, otitis or whatever, where there's that  
19 indication, to get in something -- maybe it's already  
20 there, I don't know -- saying that most respiratory tract  
21 infections are owing to viruses for which antimicrobial  
22 agents are ineffective. If you have a bacterial infection  
23 owing to Haemophilus, Branhamella, et cetera for beta-  
24 lactam X for oral therapy, and then the thing about the  
25 general use promoting resistance, then this is the way to

1 use this drug.

2 But those are the things that are within the  
3 FDA's purview if this is perceived as a public health  
4 issue, which we spent a lot and heard a lot that it is.  
5 Resistance is. The Institute of Medicine has strongly  
6 endorsed that.

7 My own experience is, in talking with  
8 physicians who are responding negatively to some of the  
9 constraints that we try to put on it from the microbiology  
10 level, there's recognition that overuse contributes to  
11 resistance. Sometimes it's twisted around to use as to why  
12 I need to have this susceptibility information, so I don't  
13 have to use vancomycin when we do not release  
14 susceptibility for vancomycin, for example, for oxacillin-  
15 susceptible staph aureus, or don't give it out based on a  
16 single positive blood culture for viridans or staph epi.

17 So people understand all that's important and I  
18 recognize it and I'm doing everything I can, but I want to  
19 use the drug in my patient or keep using it even though  
20 there is a simpler alternative. So it's in a way a commons  
21 issue, that parents may -- but when my kid has it, I want  
22 an antibiotic regardless of the basis for it.

23 So we're persisting on and we try to explain,  
24 but this is a judgement call. It's my responsibility to  
25 issue reliable reports, and we're not going to issue a

1 susceptibility for any drugs on a single isolate of  
2 coagulase. I mean, that's something that we can do. It's  
3 defensible scientifically not to issue a report on  
4 contaminants and that's what we're going to do, so that in  
5 a similar way there are many things that need to be  
6 addressed, but as individuals or agencies or task forces or  
7 whatever -- I mean, one has to operate within the sphere of  
8 influence over which one has control.

9           So it seems to me that getting started along  
10 this path, perhaps with just an opening statement for every  
11 package insert at the next go-around for antimicrobials,  
12 would be a way to start, and then one could consider some  
13 of the more controversial issues that have been brought up  
14 having to do with change from empiric therapy to others.

15           One of the most persistent problems that we  
16 have is this business of riding a winning horse, all  
17 evidence to the contrary, or the disincentives that are  
18 truly there and increasing. Actually, there are  
19 disincentives to appropriate antimicrobial use from many  
20 directions, including there are a lot of statements like  
21 "We don't need gram stain microbiology, et cetera, because  
22 you know you're going to give them vancomycin, and maybe  
23 you don't even need a lumbar puncture, for bacterial  
24 meningitis. I mean, what difference does it make? You're  
25 going to give them vancomycin and ceftriaxone anyway."

1                   Of course, nothing could be further from the  
2 truth in trying to do things right for patients, as well as  
3 for responsible antimicrobial use. So there are a lot of  
4 avenues to attack, and one is preservation of the  
5 diagnostic process.

6                   I'll stop there, but it is truly multifactorial  
7 and I think every opportunity to act should be grasped,  
8 because of what was stated before.

9                   DR. CRAIG: Okay. Anything else?

10                  DR. MURPHY: Thank you all very much. We  
11 really appreciate the comments.

12                  DR. CRAIG: We're adjourned.

13                  (Whereupon, at 6:05 p.m., the meeting was  
14 adjourned.)

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