

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

GUIDANCE DOCUMENTS ON DEVELOPING ANTIMICROBIAL DRUGS

GENERAL CONSIDERATIONS AND INDIVIDUAL INDICATIONS

Pages 1 thru 123

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING
64TH MEETING

ISSUE:

GUIDANCE DOCUMENTS ON DEVELOPING ANTIMICROBIAL DRUGS
GENERAL CONSIDERATIONS AND INDIVIDUAL INDICATIONS

Friday, July 31, 1998

8:10 a.m.

Hilton Hotel
Grand Ballroom
620 Perry Parkway
Gaithersburg, Maryland

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at

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1 DR. HENRY: Nancy Henry, Mayo Clinic.

2 DR. RODVOLD: Keith Rodvold, University of
3 Illinois at Chicago.

4 DR. SOPER: David Soper, Medical University of
5 South Carolina at Charleston.

6 DR. CHESNEY: Joan Chesney, University of
7 Tennessee in Memphis.

8 DR. CRAIG: The first topic this morning--in fact,
9 we are going to go through several topics, toxicology,
10 microbiology, clinical pharmacology, before we come up to
11 our last disease entity to discuss.

12 The first one is going to be a toxicology update
13 and the FDA presentation will be given by Dr. Osterberg.

14 **Toxicology Update**

15 **FDA Presentation**

16 DR. OSTERBERG: Good morning.

17 [Slide.]

18 What I would like to do this morning is briefly go
19 through the pharm-tox section of the guidance document and,
20 following that, address three questions and comments that we
21 received in response from the public.

22 [Slide.]

23 The first issue is the use of the preclinical
24 pharm-tox data. The first one would be to identify target
25 organs and tissues. This would be for monitoring during the

1 clinical trials and also for inclusion in the investigator's
2 brochure.

3 There is also a need to identify specialized
4 safety problems for monitoring during the clinical trials
5 like what the fluoroquinolones produce, Q-Tc prolongation,
6 and also to identify the toxicological profile which is the
7 complete spectrum of toxicities that the drug is capable of
8 producing in the animals so that some comparison later on
9 can be made with the human toxicities that may emerge.

10 Also, we use this data to select the starting
11 doses for the initial clinical trials and, perhaps, some of
12 the future clinical trials but definitely for the repeat-
13 dose animal toxicology studies.

14 [Slide.]

15 The types of toxicity studies that we look at in
16 the pharm-tox arena are the acute and multiple-dose who are
17 subchronic studies. We look at the chronic studies which
18 are six months or greater. We look at the two-year
19 bioassays for carcinogenicity. At least right now, we look
20 at two years. We are looking on shortening those tests with
21 specific innovations.

22 We look at genetic toxicology, both in vivo and in
23 vitro, and this, of course, constitutes mutagenicity and
24 clastogenicity effects on chromosomes. We look at
25 reproductive toxicology, specifically segments 1, 2 and 3,

1 which is impairment of fertility, teratology and prenatal
2 and postnatal toxicities.

3 We look for specialized studies on occasion.
4 Inhalation; we have look ed at tobramycin for inhalation
5 which, for antibiotics, is sort of rare. We looked at
6 phototoxicity and photocarcinogenicity for the
7 fluoroquinolones which have this potential in animals and,
8 of course, phototoxicity in humans.

9 We look also for arthropathy which we know the
10 fluoroquinolones in juvenile animals have the ability to
11 produce and, also, in the human, we know that it causes
12 tendon rupture on occasion. We look at allergenicity on
13 occasion for beta lactam antibiotics.

14 [Slide.]

15 Other studies that we utilize are safety
16 pharmacology studies which allows the drug to be tested in
17 various systems and in various reflexes, et cetera, to get a
18 better perspective on what the compound is able to do in a
19 the pharmacologic sense but, also, it gives us some signals
20 as to what types of special toxicology concerns we may have.

21 In some cases, as you know, the fluoroquinolones
22 produce convulsions and, therefore, when we see this in
23 certain types of safety pharmacology studies, we can ask
24 specific questions and design studies to see that.

25 We look for absorption, distribution, metabolism,

1 excretion which, of course, is pharmacokinetics and, at the
2 higher end of the dose-response curve, we look for
3 toxicokinetics.

4 [Slide.]

5 The purpose of the animal-toxicity studies are to
6 identify potential human toxicities to alert the clinician
7 to potential problems during clinical trials. We also use
8 this information to design special specific animal tests to
9 further define the toxicity or its mechanism. Again, the
10 convulsant activity of some of the fluoroquinolones in the
11 animal models are an example.

12 We also like to suggest specific toxicities to be
13 monitored during the clinical trials, which I have
14 mentioned, such as hearing loss that we see with the
15 aminoglycosides, neurotoxicity, again, that we see with some
16 of the fluoroquinolones and well as Q-Tc prolongation and
17 allergenicity.

18 [Slide.]

19 We also like to investigate in the animals
20 toxicities that are unethical to examine in humans.
21 Obviously, carcinogenicity and mutagenicity, clastogenicity
22 or genetic toxicology, teratology, reproductive toxicity
23 and, of course, overdosage. In these categories, of course,
24 you see information in the product labeling.

25 We also like to see the toxicity profile in the

1 animals because it is unethical to do these types of tests
2 in humans. Of course, we don't want to see extensive
3 toxicity and we certainly don't want to see mortality.

4 [Slide.]

5 I will start to address the public questions and
6 comments that we received. The first question that we
7 received was should sponsors plan to complete juvenile
8 animal studies prior to proposing to initiate single and
9 multiple-dose clinical studies in pediatric patients.

10 [Slide.]

11 The answer is on a case-by-case basis, yes,
12 because usually we know about the class of drugs and can
13 make extrapolations to juveniles based upon pharmacokinetic
14 data, body-surface area comparisons, use the rule of Clark,
15 et cetera, to help us make these dose selections. If we
16 know about the class of compounds, we are pretty confident
17 in the toxicity and what it may do in juveniles.

18 But, for new and unique chemical classes, we may
19 request juvenile studies. If we have never seen the
20 chemical before in a unique class, then we should ask for a
21 lot of studies in juvenile animals to see what it may do in
22 an immature enzyme systems, et cetera.

23 We also suspect adverse reproduction effects if we
24 see it in the animal model which utilizes, of course, the
25 juvenile or the young-adult animals, things like testicular

1 toxicity. We of course, are concerned for the juvenile
2 because of maturation arrest.

3 One of our concerns is irreversibility, so we
4 would ask for studies to measure whether or not testicular
5 atrophy was reversible in the juvenile animals. We also
6 suspect juvenile susceptibility on occasion; arthropathy
7 with the fluoroquinolones, ototoxicity, of course, with the
8 immunoglycosides, and immature blood-brain barriers.

9 This would ask us to, perhaps, request a juvenile
10 toxicity study.

11 [Slide.]

12 The second question is does the Division of Anti-
13 Infective Drug Products currently accept the ICH guidelines
14 on the topics of reproductive toxicology and mutagenicity or
15 should sponsors rely specifically on the FDA guidelines.

16 [Slide.]

17 I thought I would mention just what is the ICH at
18 this point for those of you who may not be familiar with it.
19 The ICH is really an international conference on
20 harmonization of technical requirements for registration of
21 pharmaceuticals for human use. Now you know why we call it
22 the ICH. Its purpose is to increase drug development among
23 three major drug development regions of the world,
24 specifically the United States, Japan and Europe, by
25 reducing duplication of efforts, thus saving time in the

1 development and approval of drugs.

2 It also harmonizes and updates technical
3 requirements, requests early exchanges of data and meetings
4 on emergent issues to address situations before they become
5 problems.

6 [Slide.]

7 With response to whether or not we use ICH
8 guidelines or the FDA guidelines, CDER has had historical
9 toxicity guidelines but they are fairly old and they are not
10 up to date. Therefore, over the years, we have used the
11 Center for Food Safety and Applied Nutrition's reproductive
12 toxicity guidelines in the Red Book and the Center for
13 Veterinary Medicine's genetic toxicity section and its
14 threshold assessment guideline.

15 These are somewhat up to date and are being
16 improved right now. However, the Center for Drugs is a
17 signatory to the ICH. It has helped to write the safety
18 guidances and, therefore, it is expected to implement them.
19 So when the expert working group on a particular guideline
20 and the steering committee, which is the governing body of
21 the ICH, finally signs off on the step-4 document and the
22 document is published in the Federal Register in this
23 country, and the similar documents in the other two regions
24 at step 5.

25 Everybody is expected as signatories to implement

1 them.

2 [Slide.]

3 The last comment that we received from the public
4 is that preclinical toxicity tests should identify the
5 complete spectrum of toxicities of a drug in animals.
6 Interspecies differences in pharmacologic properties of the
7 drug give rise to toxicities in humans that are not seen in
8 animals.

9 Adjunctively, one may see toxicities in animals
10 that are not seen in humans. This is true. However, CDER
11 recognizes that differences in pharmacokinetics and enzymes
12 in receptive populations, et cetera, can account for
13 toxicities seen in humans but not seen in animals and vice
14 versa. So we agree with the statement.

15 Furthermore, ethical reasons will not allow higher
16 drug doses to be given to humans to produce the complete
17 spectrum of toxicity in humans. This is unethical, as we
18 discussed before. Therefore, CDER requires sponsors to do
19 what they can do to provide useful safety data as long as
20 there is good common sense and good science involved in it.

21 Thank you for your attention.

22 DR. CRAIG: Any comments, questions, on the
23 material that was presented?

24 If not, thank you very much.

25 We will move on to the next topic which is

1 microbiology and the FDA presentation will be given by
2 Sousan Altaie.

3 **Microbiology Update**

4 **FDA Presentation**

5 DR. ALTAIE: Good morning.

6 [Slide.]

7 This morning, I am going to try to answer all the
8 questions that were given to us by industry and that we were
9 not able to incorporate in the individual indications. Most
10 of my comments have been incorporated with their answers in
11 the individual indications and you have been listening to
12 them for the past two days.

13 These are the remaining issues that could not fit
14 within the indications and I am addressing them separately.

15 [Slide.]

16 The question from industry was raised about the
17 certification and qualification of the labs and what kind of
18 certification for the outside-the-United-States laboratories
19 is accepted.

20 [Slide.]

21 We do recognize that, outside the United States,
22 there are several bodies of regulatory agencies and we don't
23 know what kind of regulations they have or the
24 standardization or how they compare to each other across the
25 continent.

1 So we recognize this fact and we just say that if
2 you use an outside laboratory to, at least, submit the
3 quality-control/quality-assurance programs and their
4 protocols in as much detail as you can for us to be able to
5 validate their results that come out of these laboratories.

6 [Slide.]

7 There was another comment independently and it
8 encouraged the division or the FDA to cooperate with NCCLS
9 and to prevent disparities in setting breakpoints and
10 quality-control ranges for susceptibility testing.

11 [Slide.]

12 In fact, the two divisions, at least that I know
13 of, the Division of Anti-Infective Drug Products and the
14 Division of Special Pathogens and Immunological Drugs
15 members do have a presence in NCCLS committees as observers,
16 as voting members and as consultants. Members of the
17 Division of Anti-Infective Drug Products do attend the semi-
18 annual meetings where these breakpoints for quality control
19 and the drugs are set.

20 So we do have an appearance and we are doing the
21 best we can in trying to collaborate with NCCLS on these
22 disparities.

23 [Slide.]

24 There is another comment referring to HCFA
25 licensure being not required in the U.S. for the

1 laboratories to be able to operate. And that would prevent
2 the College of American Pathology Certified labs to be
3 included in the laboratories that are accepted by the FDA.

4 I have good news and bad news. I will give you
5 the good news first. CAP has obtained a deemed status and
6 now is accepted by HCFA to certify laboratories.

7 [Slide.]

8 The bad news is, unfortunately, it is in the law
9 that the laboratories who test human specimens must be
10 certified under CLIA '88. There are few exceptions. That
11 is the VA hospital and the NIDA which is the National
12 Institute on Drug Abuse that are exempt. Also, the research
13 labs are exempt and the forensic labs are exempt.

14 For the NIDA only the section that does the drug
15 testing is exempt, not the rest of the laboratory. So you
16 still need to be under CLIA certification before using a
17 laboratory as a qualified lab.

18 [Slide.]

19 I need to give you a little bit of background
20 before I go into the next comment. The background is this;
21 in the general document guidelines, under the microbiology
22 issue and in the study design section, we address the
23 antimicrobial susceptibility testing and that the patient
24 isolates should be stored until the clinical outcome is
25 known so that isolates from patients who failed can be

1 studied further.

2 We also state in the same paragraph that it may be
3 appropriate for a systematic prospective sample of all
4 strains to be retested by the sponsor or by a reference
5 laboratory just to do a spot check on the results and the
6 comment.

7 [Slide.]

8 So the comment came from industry saying that such
9 retesting gives value only in limited situations. For
10 example, they list the non-U.S. laboratories where the
11 testing was done on the site abroad. They state, however,
12 that routine testing, even if for a prospective sample, is
13 an unnecessary expense.

14 [Slide.]

15 Our response to that is that we recognize that and
16 we reworded the document to read as follows: "If the
17 antimicrobial susceptibility testing is performed in a non-
18 U.S. laboratory, it may be appropriate for a random sample
19 of clinical strains to be retested by the sponsor in order
20 to assure the validity of the antimicrobial susceptibility
21 test results."

22 This statement currently does not exist in the
23 document you have in your hand, but it will make its way
24 into the document before it is published.

25 [Slide.]

1 The next question from industry was in regards to
2 dilution testing. This particular quotation was taken out
3 of the document, "What do you mean by full range of
4 dilution? Does this mean clear endpoints?"

5 [Slide.]

6 The actual statement in the document does state
7 that yes, we need clear endpoints. And the statement reads
8 as follows: "A full range of dilution should be tested to
9 yield on-scale rather than off-scale endpoints," which means
10 clear endpoints.

11 [Slide.]

12 Background. Before we go into another question, I
13 need to give you a little bit more background. To be
14 evaluable for microbiological assessment, the pathogen
15 should be susceptible to the study and control drugs." This
16 is the result of the way we write the labels. In the
17 labels, we say the drug is working against susceptible
18 strains of such-and-such organism in such-and-such
19 indication.

20 That statement is correct because we label the
21 drugs that way.

22 [Slide.]

23 The comment from industry came, "This situation
24 really does not allow for complete evaluation of the drug
25 which will be used empirically for treatment of all

1 pathogens, not just the susceptible ones." And the
2 suggestion was made that the pathogen susceptibility
3 requirements for evaluability be deleted from all
4 indications.

5 [Slide.]

6 It is easier said than done. There is an ethical
7 issue with that; how can an investigator be asked to keep a
8 patient on study knowing that the cultured isolate is
9 resistant to the study or the control drug. It may be okay
10 in an UTI but it won't be ethical in a meningitis study.

11 [Slide.]

12 Despite that, we realize the value of including
13 all patients if they are doing well. So we are trying to
14 put the following or a variation of this following statement
15 in all indications which says, "If the patient is judged by
16 the investigator to be responding well clinically to the
17 therapy, then the patient may be kept in the study and
18 counted evaluable if they meet all the other evaluability
19 criteria."

20 Actually, as a microbiologist, I am pretty pleased
21 that we finally may be able to get some resistant isolates
22 in setting up our breakpoints which will give us a much
23 better understanding of how the drug in vitro breakpoints
24 can be set having those resistant isolates and the clinical
25 outcome with them.

1 [Slide.]

2 With this one, I would like to conclude my talk.
3 I think this would address all the microbiological issues
4 that we received from the industry and other bodies. I
5 would like to thank my colleagues in the clinical micro
6 group in the Division of Anti-Infectives, Dr. Albert Sheldon
7 for his continuous support of the group--he is our team
8 leader--Fred Marsik, Harold Silver, Peter Dionne and James
9 King.

10 Thank you.

11 **Panel Discussion**

12 DR. CRAIG: Comments? Questions? I must admit
13 that I still find it difficult when you are doing a double-
14 blinded study and you have got an organism that is resistant
15 to one drug and not to the other, and you don't know what
16 drug the patient is getting--it makes it difficult, or I'm
17 sure you are going to have situations where certain
18 physicians, no matter how the patient is doing, is going to
19 pull the patient out of the study.

20 So it is still going to make it difficult to be
21 able to obtain information on resistant organisms when you
22 are doing it in a trial comparing it with an agent that has
23 significant problem against those resistant organisms. A
24 class-A example would be for drugs against drug-resistant
25 Strep pneumo and using some of our standard ones which I

1 think there are clearly problems with many of those drugs.

2 It just makes it more difficult to get adequate
3 numbers. Already, it seems that the resistant organisms
4 disappear when everyone starts a clinical trial. Secondly,
5 the difficulty in being able to enter the studies; the
6 question is, do you decide certain ones like sinusitis where
7 you are not going to see deaths occurring, whether that
8 situation, you just let it go ahead and document it better,
9 or do you do studies like we have talked about before, doing
10 retap studies so you find out the information relatively
11 soon so you can at least get some bacteriologic efficacy?

12 We just need to think of other ways that we can
13 eventually design trials so that we can make it easier to
14 get that information which I know is what you are hoping is
15 going to be the plan for the October meeting.

16 DR. CHIKAMI: I think those points are sort of
17 right on target. Part of it is a judgment of the risk of
18 the result in failing therapy, as Dr. Altaie pointed out.
19 It will be different for a study in meningitis versus the
20 study of UTI.

21 The other issue is designing the protocols so
22 that, in fact, there is a safety valve, if you will, in
23 following the patients carefully enough so that if there is
24 evidence of clinical failure that there can be appropriate
25 change in therapy. That is adequately designed in the study

1 and all that information is captured.

2 So those are some of things we need to consider.

3 DR. ALBRECHT: As you commented, it seems like
4 sometimes the resistant organisms disappear when you are
5 doing the clinical study. But in cases where we have had
6 these situations come up, some of the options that were
7 entertained, as Dr. Chikami said, if the patient were
8 clinically doing well, there was a high level of attention
9 to this discordance between clinical and resistance and the
10 patient would be carefully followed.

11 But other approaches have been that the patients,
12 actually, then get excluded from the blinded study and put
13 on an open arm and followed to gather all the information
14 because sort of the paradox was, when we were developing
15 some of the cephalosporins for the bugs the penicillins
16 didn't treat, it was like, "Well, I'm using the appropriate
17 control and yet how do I prove my case this covers those
18 organisms?"

19 So, having clear criteria of what would be
20 collected on the patients in this sort of open sidearm was
21 one of the ways we got at it.

22 DR. CRAIG: The other question that I would have
23 relates more to breakpoints. NCCLS has gone ahead and put
24 together their criteria that they require from industry and,
25 at least the criteria on which they are going to base

1 breakpoints, the M27 document.

2 Do you have similar things that industry knows
3 that you require? Are they similar at all to what NCCLS
4 requires?

5 DR. ALTAIE: Yes. We have a document in progress
6 of being published that was put together with the
7 microbiologic groups in the Division of Anti-Infective and
8 Antiparasitics and Special Pathogens. So we do have a
9 document that is going to come out and outlines our needs
10 for the way we need the microbiological data to be
11 presented, analyzed and documented.

12 The big issue, the difference, is that NCCLS,
13 under the CBC influence, I think, is steering away from
14 predicting clinical efficacy of a drug by setting those
15 breakpoints versus predicting resistance. That is a
16 philosophical difference and the breakpoints can be very
17 different.

18 I think one big issue that needs to be solved
19 between FDA and the NCCLS is that what are we setting the
20 breakpoints to predict, clinical efficacy or rising of
21 resistant organisms? I think that is the philosophical
22 difference between the two agencies.

23 DR. CRAIG: That is a debate internationally as
24 well. Some countries have set their breakpoints primarily
25 just to pick up resistance and others do it more for

1 clinical purposes. So you are right. It is a debatable
2 issue. Both are important.

3 DR. ALTAIE: And we have to find a medium happy
4 place to not have disparities with NCCLS.

5 DR. RELLER: I wonder if the revision of the
6 wording having to do with the ability of an individual
7 patient to be continued who is doing well doesn't have a--
8 whether or not it should be recognized, the real reason for
9 doing that.

10 I have questions about doing it to get information
11 on breakpoints for the following reasons. If the patient is
12 doing well, and, in fact, the organism is resistant by
13 current breakpoint criteria, what the NCCLS sees presented
14 is that the breakpoints are wrong, based on a paucity of
15 data and that they should be loosened.

16 So it works the other way around, that it doesn't
17 have to be as susceptible as what the breakpoint is to still
18 get a good clinical outcome. The numbers are never large
19 enough to make firm conclusions. I fail to understand how a
20 clinical trial that is ethical, based on inclusion of
21 patients who have a reasonable probability of benefit could
22 likely generate sufficient numbers to give you crisp data on
23 failures related to resistant organisms because the numbers
24 are so heavily stacked for susceptible ones.

25 Rather, the ability to continue a patient who is

1 doing well, despite possible in vitro resistance at
2 currently set breakpoints has more to do with recognition of
3 good patient care and a little bit of flexibility in the
4 process for carefully assessing the patient clinically and
5 that the revision of the breakpoints, at least from what I
6 have seen over the years at the NCCLS meeting, comes more
7 from development of resistance that was not recognized
8 earlier and seeing clinical failures that then one comes
9 back and looks at patients who have failed, for example,
10 patients with fluoroquinolone-resistant gonococci and then
11 revision of breakpoints, or enterococci that the breakpoints
12 weren't appropriate and have to be tightened up because
13 patients are not doing well despite apparent in vitro
14 susceptibility, or a methicillin-resistant staphylococci,
15 coagulase-negative staphylococci, that there is a mismatch
16 between some clinical outcomes and going back where the
17 breakpoints were inappropriate and have to be adjusted.

18 But to get that information up front from a
19 clinical trial that is predicated on giving patients drugs
20 to which their organism is susceptible, I simply don't see
21 how--it is not possible to have it both ways. It is not
22 possible to do the right thing for the patient and get
23 enough numbers of those that are truly not susceptible to be
24 able to give you clinical failures which you would need to
25 have to validate resistance.

1 So, theoretically, there may be a few mismatches
2 but the very mismatches that someone would be likely to
3 continue the drug would be where the patient is doing well
4 and you would end up with a resistant-organism patient doing
5 well, therefore, let's loosen the breakpoints and be more
6 inclusive, which I think is not the wisest idea based on
7 some of the--it gets us into the situation in this country
8 of having too generous a criteria relative to, for example,
9 what the Europeans look at in some of the breakpoints that
10 have been said already.

11 Just another viewpoint.

12 DR. CRAIG: I understand the concern. My view on
13 it, though, is that we have had breakpoints or we have had
14 doses of drugs that we have used that have been real
15 overkillers for what really has been required. So there is
16 some fluff underneath there that can cover many of the
17 resistant organisms.

18 Should we, though, still just call those resistant
19 and entirely go to new, more expensive, agents and abandon
20 drugs that have been around for a long period of time? I
21 think that is when you have to weigh it.

22 If you are talking about a very expensive,
23 potentially toxic, drug, playing around with breakpoints in
24 that situation, I would agree with you. That is not the
25 scenario that I would support as well.

1 But when we have tried and true, narrow-spectrum,
2 relatively highly effective drugs that we have tended to
3 dose too much in the past, at too high a dose, then I think
4 there is some room to look at changing the breakpoints. So
5 we try and get clinicians to use agents which we think are
6 more narrow spectrum which result in less side effects than
7 forcing clinicians to go and use newer drugs.

8 So I think you have to take both aspects in there
9 and try and find a medium that everybody can come to a
10 consensus.

11 DR. RELLER: Bill, could you give some examples of
12 the cites--

13 DR. CRAIG: Let me just cite for amoxicillin.
14 Amoxicillin is a drug which, if we use penicillin MICs for
15 it, we would have a very high degree of resistance and we
16 would not be using that drug. Most of the great majority of
17 Strep pneumo would be resistant.

18 So what happened was, the first time around, we
19 pushed the breakpoint from the penicillin breakpoint up to
20 0.5 for amoxicillin. Now, recently, NCCLS has been looking
21 at it with additional data and moving it up a little bit
22 higher.

23 So that is a drug which is a narrow-spectrum agent
24 and one that has been around for a long time, has been the
25 recommended drug of choice for many clinicians. So what we

1 are trying to do is be able to use this drug as rationally
2 as we can because of our good experience with it in the
3 past.

4 So I think, for trying to find the right
5 breakpoint for that drug, is a goal that we should look for.

6 DR. RELLER: For, like, respiratory-tract
7 infections.

8 DR. CRAIG: Yes.

9 DR. CHESNEY: Which NCCLS is working on.

10 DR. CRAIG: Yes. But I agree with your point,
11 too. But it needs to have some clinical data to back it up.
12 That is oftentimes the hardest thing to get if you eliminate
13 all resistant patients from clinical trials. It is very
14 difficult to find good clinical data.

15 That is why the kind of data we have been able to
16 model has been much more on bacteriologic data which comes
17 from otitis media, sinusitis, those where double punctures
18 are done, where there are diseases where, even with
19 resistant organisms, you are oftentimes going to see a fair
20 degree of clinical success.

21 But pneumonia is a much harder area to try and get
22 that kind of data.

23 DR. ALTAIE: If I might chime in here. I also
24 think that the breakpoints that were being set previously,
25 we tended to set more drug-class breakpoints. Within the

1 limits of the error of the test, 1-2 dilution being
2 acceptable from day to day, that was a practice that would
3 not have put us in this situation as much as we are in it
4 now.

5 The drive for that is this percent susceptible for
6 marketing purposes that drives companies to come to NCCLS
7 with a limited amount of data and say, "Well, I don't think
8 0.25 is appropriate. If you put me at 0.5, my
9 susceptibility is going to shoot up."

10 I think that game of one-dilution change and
11 raising falsely the susceptibility or percent susceptible
12 organism for a given drug has driven us into a situation
13 where we really don't know what we are dealing with anymore
14 in these breakpoints.

15 I think we should steer away from a one-dilution
16 difference, changing the whole breakpoint, raise the
17 susceptibility to what the company is happy with, and stick
18 more with class breakpoints, if applicable. I understand
19 that sometimes it is not. But when it is, I think that is a
20 solution to put an end to this game.

21 DR. CRAIG: Any further comments?

22 If not, let's move on to the next one which is on
23 clinical pharmacology. The FDA presentation will be given
24 by Philip Colangelo.

25

Clinical Pharmacology

FDA Presentation

1 DR. COLANGELO: Good morning.

2 [Slide.]

3 This morning, I will discuss the major revisions
4 that we have made to the draft guidance under section 6,
5 now, clinical pharmacology and biopharmaceutics.

6 [Slide.]

7 Just to back up a bit, in the previous draft
8 guidance document which was known as the evaluability
9 criteria document, the section that we had was entitled
10 pharmacokinetics under clinical issues.

11 [Slide.]

12 Currently, now, in the new draft guidance, the
13 entire section has been renamed to clinical pharmacology and
14 biopharmaceutics. The reasons for this change were really
15 twofold. One, we felt that this more accurately reflects
16 the content of the revised second and, secondly, it also
17 reflects the approach that we, as reviewers in the Office of
18 Clinical Pharmacology and Biopharmaceutics now take when we
19 review submissions.

20 When I say submissions, I am speaking for all
21 drugs and not just any infective drugs.

22 [Slide.]

23 So, to expand on the concepts of clinical
24 pharmacology and biopharmaceutics a bit further, the
25

1 biopharm component of a submission can be thought of as a
2 characterization of the drug product, itself, or the
3 formulation, if you will, and also assessment of the drug
4 product quality.

5 I have listed here primary areas of focus for
6 biopharmaceutics. This really isn't anything new. It is
7 sort of standard fare, if you will, for a submission. It
8 includes evaluation of bioequivalence, bioavailability, the
9 effect of food on systemic availability, evaluation of in
10 vitro dissolution, and, perhaps, correlation between in
11 vitro dissolution and in vivo bioavailability and other
12 formulation issues that may arise.

13 There have been no changes with this section from
14 the previous draft guidance.

15 [Slide.]

16 The clinical pharmacology component of a
17 submission can be viewed as the characterization of the drug
18 substance in humans. Again, I have listed the major areas
19 of focus and they include evaluation of mechanism of action,
20 pharmacokinetics, PK, pharmacodynamics, PD. If applicable,
21 PK/PD evaluation. Evaluation of certain patient
22 characteristics or demographics--that is, as covariates to
23 explain variability in either PK or PD or both.

24 Evaluation of special populations and their effect
25 on kinetics or dynamics, and this would include the elderly,

1 pediatrics, renal and hepatic impairment. Evaluation of
2 relevant drug-drug interactions and also a population
3 approach. Population approach can be used to explore for
4 relevant covariates again or to also discover or explore the
5 influence of the covariates on variation in PK or PD.

6 Also, a population approach can be useful when
7 there is sparse sampling such as in phase 3 trials to
8 estimate pharmacokinetic parameters in the target
9 population.

10 If I could just back up a bit, with respect to
11 kinetics, pharmacokinetics, this, of course, is a
12 characterization of the absorption, distribution, metabolism
13 and excretion of a drug. This has already been discussed by
14 Dr. Frank Pelsor in the previous advisory committee that was
15 held for the previous draft guidance.

16 So there have been no real substantial changes to
17 this section, either.

18 With respect to pharmacodynamics, in very general
19 terms, pharmacodynamics seeks to describe the relationship
20 between drug dose or drug concentration and pharmacological
21 effect. For anti-infective drugs, here we are speaking of
22 the rate of kill or the suppression of growth of
23 microorganisms.

24 A combined PK/PD evaluation attempts, then, to
25 relate an oftentimes mathematically model, the temporal

1 change in the response with concentration. In other words,
2 we are trying to quantitate the time course of the response
3 with concentration.

4 [Slide.]

5 We have included a discussion of the PK/PD
6 evaluation of antimicrobial drugs in the current version of
7 the draft. Really, this represents the most substantial
8 change that we have made to our section.

9 This discussion was included, in part, because of
10 comments that were made to the previous draft guidance by
11 the Society of Infectious Diseases pharmacists. Really, to
12 summarize what they have said, they actually supported the
13 use of PK/PD analysis as part of the drug development
14 program for anti-infective drugs.

15 Also, we at the agency also recognize that this is
16 an evolving area and that there has been rather extensively
17 investigated in in vitro and in animal models of infection
18 and increasingly in patients to assess antimicrobial
19 activity.

20 So the literature in this area continues to expand
21 and, in some instances, supports the use of this type of an
22 approach.

23 [Slide.]

24 So what could be some of the benefits for PK/PD
25 evaluation? One would be that it could facilitate the early

1 selection of a lead candidate. This would be such as doing
2 preclinical screening to evaluate either an in vitro model
3 of infection or an animal model of infection, the PK/PD
4 relationships.

5 Another benefit, and a very important one that we
6 see, would be that PK/PD evaluation can lead to the
7 selection of an appropriate dosage regimen. This would be
8 such as during your phase 1, phase 2 trials and, in turn,
9 then would provide very valuable information to design your
10 later phase 3 trials to assess pivotal efficacy and safety.

11 Another benefit is that a PK/PD evaluation may
12 help you better understand either clinical or
13 microbiological or maybe both outcomes. This would be such
14 as during your confirmatory phase 3 trial. And outcome
15 would be construed as either a failure or, perhaps, success.

16 So the net benefit would be a more efficient drug
17 development program.

18 [Slide.]

19 In the revised section, we discussed the PK/PD
20 parameters that have been examined the most. These relate
21 antimicrobial drug concentration or some metric of exposure
22 to in vitro susceptibility of the target microorganism--that
23 is, the MIC.

24 This is a table that I have taken from Dr. Craig's
25 recent review article that appeared in Clinical Infectious

1 Diseases which shows the common PK/PD parameters that have
2 been related to antimicrobial efficacy with particular drug
3 classes or certain drugs, parameters such as above the MIC
4 which is the time that the drug concentration relative to
5 the dose interval spends above the MIC may be related to
6 beta-lactam-type antimicrobials.

7 Then you have the 24-hour area-under-the curve-to
8 MIC and peak-concentration to MIC ratios which may be
9 related to concentration-dependent killing type
10 antimicrobials.

11 [Slide.]

12 These parameters have been correlated with
13 antimicrobial efficacy mainly in in vitro models and in
14 animal models. I think that is an important point is that
15 they have been mainly correlated here with in vitro and
16 animal systems. They have recently been related, in more
17 limited cases, though in the clinical setting.

18 There are other approaches and markers that can be
19 used and have been experimented with. The bottom line, at
20 this time, is that more data is needed from clinical trials
21 to really adequately validate these parameters and markers
22 and this would be especially as reliable predictors of
23 clinical and/or microbiological outcome.

24 [Slide.]

25 So, to summarize, we have stressed again the

1 importance of adequate clinical pharmacology and
2 biopharmaceutics data. In the context of that, we have
3 added a discussion of the PK/PD evaluation of antimicrobial
4 drugs. Currently, we view it as an evolving science and,
5 really, like pharmacokinetics, as a tool for providing an
6 additional level of certainty and especially with respect to
7 the selection of the optimal dosage regimen.

8 We would encourage increased utilization of PK/PD
9 evaluation especially prospectively and, also, we would
10 encourage sponsors to incorporate this type of analysis
11 throughout their drug development program.

12 Finally, we also would encourage frequent
13 discussions with the agency regarding these issues.

14 [Slide.]

15 Lastly, I would like to also acknowledge Dr. Frank
16 Pelsor and Dr. Funmi Ajayi who have coauthored this section
17 with me and have been involved in helpful discussions for
18 this presentation.

19 Thank you.

20 DR. CRAIG: Any questions and clarification?

21 **Committee Presentation**

22 DR. CRAIG: Obviously, this gives me a chance to
23 discuss my bias. I think this is a significant addition or
24 at least a first step in the right direction in terms of
25 changing or altering some of the guidelines. When one talks

1 about validating PK/PD parameters, the ones that I show
2 there, to find out which parameter is actually important,
3 what you have to have is a lot of different dosage regimens.

4 If you primarily look at one dosage regimen and
5 look at a higher dose and a lower dose, all the parameters
6 are going to increase. You are going to get a higher peak
7 level, higher area under the curve, higher time above MIC.
8 So it is exceedingly difficult to try and pull out which is
9 the parameter that is most important.

10 The only way that you can really do it is by doing
11 multiple dosage regimens because then you vary the
12 parameters and to do that in human clinical trials is going
13 to be very difficult. But, clearly, what can be done is
14 parameters can be determined in animal models of infection.

15 One of the things that is appearing to occur, at
16 least I think it is fairly well documented now with the beta
17 lactams is that the magnitude of the parameter required for
18 efficacy in an animal model appears to be not species
19 dependent. It appears to go across a whole variety of
20 different animal models and also appears to be related to
21 the magnitude required in human infections.

22 So the potential is to use animal models, and
23 maybe this will also work out for in vitro models, to at
24 least get a magnitude parameter that would fit with whatever
25 MIC one is picking and using the MIC as your potency

1 indicator and at least come up with the dose that people are
2 using, what kind of MIC could you tolerate.

3 So I think it can be useful for helping to set
4 breakpoints. I think it is going to be especially helpful
5 as was mentioned in early drug design, to try and find some
6 of your best candidates. I think it is also going to be
7 important in drug development.

8 But, as was mentioned, what we really need is not
9 just more animal data. What we need is a lot more clinical
10 data. I think that is where we really need the partnership
11 with industry for them to incorporate some of these
12 pharmacodynamic studies into their early trials with new
13 drugs.

14 Obtaining PK data, oftentimes population
15 pharmacokinetics, is very nice because then, oftentimes, to
16 generate that, you don't need a huge number of samples for
17 individual patients. Then, with population
18 pharmacokinetics, it is a very good tool that one can then
19 use that to actually predict fairly accurately what kind of
20 pharmacokinetics one is going to see in other individuals,
21 and then start correlating that with response.

22 Many of you saw the article that Dr. Drusano put
23 together in JAMA this year using such a technique with
24 levofloxacin and, again, showing what parameters came out
25 and correlated with the efficacy of that drug.

1 So the earlier this is done, I think, in the
2 clinical trial, like in early phase 2, the earlier the
3 chance it has to be useful to the pharmaceutical companies
4 later on. I know what many of us that have our biases on
5 that this might be able to do, but I think we are going to
6 have to have more clinical data before to make the agency
7 more confident with the use of pharmacodynamic PK/PD
8 parameters before they will be able to start using them more
9 in terms of the possibility of being able to reduce the
10 number of patients that are required in order to put the
11 whole document and get the whole drug through the agency and
12 the review process.

13 We know that everything is very expensive to put a
14 drug through and any tools that we can use to still make
15 sure that the drug is safe and effective but to reduce some
16 of the cost I think is a goal worthwhile trying to achieve.

17 So I think PK/PD right now is a potential chance
18 to do that but what we really need is the clinical data. So
19 I am pushing and suggesting that industry try and, whenever
20 possible, incorporate some of these. I know many of the
21 companies are starting to incorporate PK/PD studies into
22 their early phase 2 trials in order to gain such information
23 in the hope that, eventually, this will broaden our overall
24 knowledge on this in the clinical arena and be able to be
25 helpful for getting the drug approved.

1 DR. COLANGELO: Let me also add that FDA is
2 putting together a workshop to discuss this issue and it
3 will be upcoming.

4 DR. CRAIG: We also would let the people in the
5 audience know that the International Society for Anti-
6 Infective Pharmacology will be having a symposium at ICAC
7 this year. It will be on Wednesday, September 23, the day
8 before ICAC starts and the title of the symposium is going
9 to be The Use of Pharmacodynamics for Drug Delivery and Drug
10 Development.

11 This is a symposium, as I said, that will be at
12 ICAC. So I think there are going to be these workshops and
13 things around that I think, in the long run, will expand our
14 knowledge and, hopefully, get more people up to snuff on
15 what we are talking about.

16 **Committee Discussion**

17 DR. MURPHY: Thank you very much for your comments
18 because I think you have put it very much in perspective for
19 everyone. This is an exciting arena. Certainly this whole
20 area has enabled us to move pediatric drug development along
21 and I think it is an area that we would look into.

22 We always like data that enhances us and forms us
23 and directs us. We just can't make quantum leaps and we
24 need that clinical information.

25 DR. CRAIG: As the drug companies will say, there

1 are always, among physicians, risk takers and those that are
2 more conservative. Obviously, I am a risk taker but I think
3 what you have to do--it is good to have both to make sure
4 that a consensus comes up and there is good science that
5 backs it up.

6 DR. GOLDBERGER: You were just talking about risk
7 a second ago. Obviously, one of the ways to minimize it is
8 to use some of the in vitro and animal models of which you
9 spoke a few moments ago.

10 Since you have a lot of expertise in those areas,
11 I was curious, are there any particular caveats we should be
12 thinking about with particular models, particular drug
13 classes, as we try to interpret that data or make
14 recommendations to companies, for instance, in terms of
15 using it?

16 DR. CRAIG: In terms of the magnitude of the
17 parameter that is required for efficacy, I think there is
18 fairly good concordance between animal models and what we
19 have tended to see in humans in terms of the time above MIC
20 that is required for penicillins and cephalosporins,
21 carbapenems--not as much either animal or clinical data just
22 with carbapenems.

23 What you need in order to really be sure that the
24 magnitude is correct is you need failures. It wasn't until
25 the penicillin-resistant pneumococci came around that we

1 started to see failures. So then things started to look
2 fine.

3 We have had many bacteriologic failures for a long
4 time with Hemophilus but that is in otitis media, oftentimes
5 in older kids where I have told you before the bacteriologic
6 failure is infrequently translated into a clinical failure.

7 But there are magnitudes, I think, for certain
8 drugs that have come out very well and it appears to be
9 model-independent. By that, I mean what is required for
10 pneumonia is similar for what is required for peritonitis
11 models, the soft-tissue models, bacteremia models, so that
12 the data is relatively tight.

13 It is very interesting. You can just go back to
14 the old data in the literature and, as long as they give
15 pharmacokinetics, you can sit down and calculate from the
16 old studies in the literature. It is amazing how close and
17 along a very nice line one finds all the drugs and multiple
18 drugs within the same class fitting.

19 I would say that at least from the data that we
20 have been able to put together, free drug levels appear to
21 be the levels that one needs to look at. If one looks at a
22 highly protein-bound drug, one finds that it requires a
23 higher time above MIC than a drug that has low binding.

24 But if you correct for it and look at only free
25 drug levels, then they seem to be roughly the same. So that

1 would be one of the caveats that I think have come out of
2 what levels should we be looking at. At least with the beta
3 lactams, it looks like it is the free drug levels.

4 I can't tell you that is the case with the
5 fluoroquinolones. There hasn't been enough data yet and it
6 is only recently that we have started to have
7 fluoroquinolones with higher degrees of protein binding. So
8 that area is still a little unclear.

9 DR. GOLDBERGER: Is the degree of protein binding
10 sort of species-independent? Is it constant across species?

11 DR. CRAIG: No. It clearly varies in species but
12 you can use tricks. We are able to produce pretty close to
13 human binding in mice by injecting human albumin and getting
14 human albumin concentrations in the mice.

15 So there are ways of getting around that and
16 showing that you can start to approximate what you see. But
17 if you look at free drug levels in both species and look at
18 its parameter, then that sort of takes away the problem with
19 protein binding and the magnitude of the parameter seems to
20 be the same.

21 So that is what is nice about it. If it was the
22 total drug level, that was the parameter that was really
23 correlating, then the degree of protein binding would really
24 affect what the total drug level would be and make it much
25 more difficult to look at that among animal species.

1 That still may be the case with fluoroquinolones.
2 As I say, it is just more work needs to be done.
3 Macrolides, while we know what the parameter is, the
4 magnitude of the parameter required for efficacy is not as
5 clear. So there are a variety of drugs still in which a lot
6 more work needs to be done.

7 Keith and I are right now looking at a paper that
8 has been submitted in vancomycin for glycopeptide. It is
9 very difficult to try and figure out what the parameter is
10 that is important for efficacy.

11 So I agree with you. We are far from being at the
12 end of the tunnel and knowing exactly what we are doing, but
13 I think there is enough data now at least, for beta lactams
14 and fluoroquinolones, to suggest that the magnitude of the
15 parameter found in animal models is very similar to what one
16 sees in humans, that is is something worthwhile to proceed
17 on and get more information.

18 I think NCCLS has sort of bought into it and now
19 has added it as one of the other characteristics besides
20 clinical data, population distributions, things like that
21 that they will be looking at for breakpoint determinations.

22 DR. RODVOLD: One of the questions I had for your
23 presentation, and maybe it is in the documents and it just
24 didn't come across in your slides, is that--and we talked
25 about this yesterday with one of the disease states--is the

1 aspect of tissue levels. That would be another area that,
2 if you don't have it, I would encourage you in the future to
3 address, even in giving guidance to the sponsor of a
4 compound as well as interpretation of that data.

5 There are lots of ways. It is important in the
6 sense of knowing whether or not drug is in the tissue or in
7 the fluid, but where do you go from there and what kind of
8 guidance that they should collect, shouldn't collect, how to
9 do the studies.

10 I am sure Bill would tell you that the literature
11 is riddled with all kinds of data that you can twist the way
12 you want it to say, but it may not be meaningful if it is
13 not looked at the proper way. So I would encourage that
14 because it is coming into some of the disease-state
15 documents, not so much in abundance but it is still out
16 there.

17 So if you haven't, I would encourage that as
18 another thing. Actually, the approach that you have is
19 probably the better way of looking at it at this time so you
20 may want to use it as to get it out of the other places, but
21 I think you will still be approached by, we are going to do
22 this study, collect these, and we want it in our
23 advertisement or--I think you have to be ready to look at
24 that.

25 DR. CRAIG: I think you have worded it very well

1 in here in what you are looking at in tissue distribution.
2 Where you also say this does not imply that the adequacy of
3 such testing methodology has been verified for all infected
4 sites or that the relevance of all such data to clinical
5 effectiveness has been established.

6 So I complement you on the way it is worded but--
7 yes; I think we do need tissue distribution studies. There
8 are new techniques now for looking at extracellular fluids,
9 microdialysis. Some people now are even starting to do
10 microdialysis in humans so there are ways of looking at
11 concentrations at sites of infection that don't involve
12 grinding up the tissue and mixing all the intracellular with
13 the extracellular gemisch.

14 So, again, this is another area where technology
15 is expanding and where we will have more information, and I
16 am sure the kind of information you will eventually require
17 will also vary depending on how the technology changes.

18 DR. SANDHAUS: Sandy Sandhaus, Nexstar. I had a
19 pair of submitted questions, the first of which I think is
20 most relevant right now. Basically, I am going to posit a
21 theoretical drug.

22 [Slide.]

23 This theoretical drug is a liposomal
24 aminoglycoside. The most important aspect of is probably
25 the last one there; it has the potential to reduce class-

1 related toxicities, this hypothetical drug, dramatically
2 alter PK with an elimination half life of about nine days
3 following a single intravenous administration, human safety
4 at 1500 mcg/ml plasma levels of the parent drug, and
5 efficacious in animals and some data in humans.

6 But the MIC is not measurable and not predictive
7 of the efficacy in these animal studies.

8 [Slide.]

9 So the question then is a simple one. What are
10 the scientific considerations in designing clinical trials
11 for antibiotics that cannot be evaluated by classic in vitro
12 susceptibility testing?

13 It seems like the discussion they just had was
14 extremely relevant to this.

15 DR. CRAIG: I can comment about another liposomal
16 product, liposomal gentamicin, that we looked at in an
17 animal model. Again, it didn't have as long a half life as
18 nine days--was it nine days that you had there? But it had
19 a much longer half life in the animal than the other drug
20 did, probably about, say, 15 minutes to about four hours.

21 So it is quite a multiple increase. But when we
22 calculated out area under the curve and looked at it in that
23 regard for the parameter, the two drugs actually came out to
24 be roughly the same. So that is the kind of thing that I
25 would do in an animal model with this is try and find what

1 magnitude of a parameter do you find for efficacy.

2 Oftentimes, people just study a drug so that it is
3 efficacious but they never find the limits of where it
4 starts to fail because when you start to find the limits of
5 where it starts to fail, then it starts to give you a clue
6 as to what the magnitude of the parameter is that might
7 determine that and see if it is all related to what one sees
8 that is required with a more standard formulation of the
9 regular drug.

10 I think those are the kinds of things that can be
11 done in animals ahead of time to try and get some
12 information that might, then, be able to be looked at in a
13 human clinical trial from the pharmacokinetics of the drug.
14 The question is is what MIC do you use for the parameter.
15 Do you use the MIC for the compound?

16 If it turns out, when you analyze the data, that
17 you can use the MIC for the compound in the absence of the
18 liposome preparation, then that is a clear advantage for
19 you. Then you don't have to do separate MICs with this kind
20 of drug.

21 So I think there are some things that can be
22 looked at in animal models and using a variety of them to
23 try and get a little bit better handle on what you might
24 need to look at in a human clinical trial.

25 Any other comments? Keith?

1 DR. RODVOLD: No.

2 DR. CRAIG: What are the scientific considerations
3 in designing? As I say, if you know what is required in an
4 animal model in order to get efficacy against the pathogens
5 you are going after and you know what that parameter is,
6 then, theoretically, it will help you select what kind of
7 dose you are going to go after.

8 Then, in an early phase 2 study, you can collect
9 some kinetics in your patients, correlate your kinetics with
10 the outcome in the patients in that dose and then start to
11 get some initial PK/PD evaluation results. Hopefully, this
12 will, then, enable you to decide on your final dosage
13 regimen that you are going to use throughout the rest of the
14 clinical trials and then things sort of fit into the regular
15 ball game.

16 At least that is the way I would look at trying to
17 take this kind of a product and work it on through and get
18 it into the clinical arena.

19 DR. GOLDBERGER: I have a question. Have you
20 shown, then, in other words, that this drug will work
21 against organisms that a conventional amikacin dosing
22 regimen would not work again, obviously, the amikacin dosing
23 regimen to be given much more often.

24 One should probably distinguish between the issue
25 of resistance and the issue which has been floated a lot

1 with the liposomal compounds about an infection in an organ
2 site or somewhere else where the distributional differences
3 between liposomal and non-liposomal might play a role.

4 But, fundamentally, have you shown that it will
5 work against highly resistant or resistant organisms where
6 clearly conventional amikacin wouldn't work?

7 DR. SANDHAUS: The answer to that is that that is
8 in process. The place that we are most actively
9 investigating is--first of all, let me say that no organism
10 has been identified that amikacin does not treat in vitro
11 that this drug treats.

12 So, in other words, it has not changed the
13 characteristics of the parent compound. But there are drugs
14 an aminoglycoside treats in vitro that it is not used
15 against clinically because of the low therapeutic index
16 between where you get toxicity and where you can actually
17 treat the drug; for instance, Gram-positive agents.

18 And this theoretical drug appears to be able to
19 allow that therapeutic index to be greatly expanded. That
20 is kind of the way I would put the current state of our
21 knowledge.

22 DR. GOLDBERGER: Listening to that, it is a little
23 less clear to me whether the issue, then, of using
24 conventional MICs as a starting point won't actually work
25 out. In other words, it seems that if you are not saying

1 that we can treat highly resistant organisms, then it would
2 seem as though the conventional MICs would at least be a
3 starting point in terms of thinking how to proceed with the
4 development of the drug.

5 DR. SANDHAUS: I can say that we have treated
6 highly resistant organisms effectively in humans that have
7 failed conventional aminoglycosides but the numbers have
8 been extremely small. I am not willing to make claims for
9 this drug that we can't support at this point.

10 DR. CRAIG: But, again, I would come back--I would
11 think that there would be some PK/PD data that could be
12 generated in animals that could be useful in looking at your
13 Gram-positive organisms, finding out how much dose, what is
14 the area under the curve, the peak level, all those kinds of
15 things that are required for efficacy.

16 The problem that many people tend to do with
17 animal models is to do one organism and, essentially, base
18 everything on one organism while, in a clinical trial of 100
19 people, we may have 100 different organisms. So it is very
20 important, I think, when one looks at animal models, that
21 one looks at a variety of different bacteria so one can take
22 in some of the variation that one would expect to see in a
23 clinical trial.

24 DR. MURPHY: I would say that I think this fits in
25 very well to what was my second slide with I think ongoing

1 meetings with the FDA in your drug-development plan is a
2 good idea.

3 DR. CRAIG: Yes.

4 If we have nothing more, it's break time.

5 [Recess.]

6 DR. CRAIG: We will move on to our last topic
7 which is empiric therapy of febrile neutropenia. The FDA
8 presentation will be given by Dr. David Ross.

9 **Febrile Neutropenia**

10 **FDA Presentation**

11 DR. ROSS: Good morning.

12 [Slide.]

13 As the last speaker, I was trying to explain to my
14 son last night what batting cleanup means, but I am not sure
15 I did a good job. At any rate, my name is David Ross. I am
16 a medical officer in the Division of Anti-Infective Drug
17 Products. I am going to be speaking on the proposed
18 guidance for clinical trials of empiric antibacterial
19 therapy of febrile neutropenia or ETFN.

20 One point I want to make at the outset is that I
21 am only going to be speaking about empiric antibacterial
22 therapy. Certainly, we recognize that antifungal therapy,
23 given empirically for fever in the neutropenic patient, is
24 an important issue but I will not be dealing with that in
25 any great substance during this presentation.

1 [Slide.]

2 What I would like to do is talk about some disease
3 definition and endpoint issues, describe the proposed
4 criteria for conducting clinical trials for this indication
5 and then finish with questions for the committee.

6 [Slide.]

7 Let me start by tracing the kind of shadowy
8 outline of how the regulatory definition for this indication
9 has evolved. Initially, this started out as the
10 "immunocompromised patient," a phrase which appears in the
11 labeling for drugs such as ceftazidime.

12 The problem is that we know that not all
13 immunocompromised patients are alike. The solid-organ-
14 transplant patient is not the same as the HIV-infected
15 patient who is not the same as the patient on steroids who
16 is not the same as the elderly, malnourished patient from a
17 nursing home.

18 So, more recently, we have moved to the term
19 "febrile neutropenia." This terminology has been used in
20 drug labels for products such as cefapime and ciprofloxacin,
21 but the process of defining this is still evolving, in part,
22 in parallel with evolution in our understanding of the
23 concept of fever and neutropenia.

24 For purposes of this presentation, I am simply
25 going to refer to this entity as fever and neutropenia, or

1 FN.

2 [Slide.]

3 Why is it so hard to define this entity? What I
4 would like to do is just describe some clinical scenarios
5 that illustrate some of the problems in defining why it is
6 hard to define these patients, both in terms of treatment
7 and especially in terms of the setting of clinical trial.

8 As the first clinical scenario, I would like you
9 to consider a 24-year-old woman with Hodgkins disease, an
10 absolute neutrophil count of 0, and a temperature of 39
11 degrees centigrade. She is enrolled in a trial of empiric
12 therapy of fever and neutropenia. Despite an intensive
13 workup, no infectious source is found.

14 She remains febrile and neutropenic. Her
15 antibiotics are discontinued after fifteen days. The
16 patient defervesces two weeks later following bone-marrow
17 recovery. And, following further chemotherapy, she obtains
18 complete disease remission.

19 The question I would like you to think about is is
20 this patient evaluable for efficacy.

21 [Slide.]

22 As a second example, a 47-year-old man with acute
23 myelocytic leukemia develops fever while neutropenic. He
24 also is enrolled in an ETFN trial. This patient promptly
25 defervesces although, again, no infectious source is

1 identified despite intensive workup.

2 Eight days into empiric therapy, the patient
3 becomes febrile and hypotensive. He grows out multiple
4 cultures of vancomycin-resistant *Enterococcus faecium*. The
5 patient's antibiotic regimen is modified, but he dies from
6 sepsis two days later. Is this patient evaluable for
7 assessment of efficacy?

8 [Slide.]

9 Finally, on the next slide, consider a 70-year-old
10 woman with stage 4 rectal carcinoma who is receiving
11 irinotecan and 5-fluorouracil and who presents with a
12 temperature of 37.1 degrees centigrade while neutropenic.
13 She is screened for an ETFN trial that has an inclusion
14 criteria of 38 degrees centigrade for fever.

15 She is enrolled by mistake. Blood cultures drawn
16 at study entry grows *Pseudomonas aeruginosa*. Repeat blood
17 cultures at the end of therapy are sterile and the patient
18 is clinically well. In a setting of this trial, is this
19 patient evaluable for efficacy?

20 [Slide.]

21 I think that these scenarios, while they may not
22 be typical, illustrate some of the problems in defining this
23 disease state. Fever is not a perfect marker for infection
24 in neutropenic patients. Not all patients with neutropenia
25 and fever will be infected. Not all neutropenic patients

1 with infection will have fever.

2 Blood cultures are an imperfect marker for
3 infection in neutropenic patients. The majority of patients
4 in recent series of neutropenic patients with fever have not
5 had positive blood cultures. In addition, the
6 interpretation of blood cultures can sometimes be
7 problematic in the neutropenic host since these patients
8 frequently do not show classic signs of inflammation.

9 Finally, fever is frequently not associated with
10 positive blood cultures, as I have said.

11 [Slide.]

12 I think it is helpful, in some ways, to think
13 about fever and neutropenia as a spectrum in which, at the
14 top, we have situations where we have the strongest evidence
15 for infection in which there is microbiologic documentation
16 of infection, either with bacteremia or without bacteremia.

17 Below this, in terms of the strength of evidence,
18 are those individuals where there are signs of inflammation
19 or other signs of infection but we don't have microbiologic
20 documentation, we simply have clinical documentation of
21 infection.

22 Then, finally, there are those patients who have
23 fever for which the etiology is uncertain. Sometimes, you
24 will see this described as fever of uncertain origin. We
25 know these patients may be infected. We know they have to

1 be treated empirically to avoid early mortality, but we
2 don't know if they truly are infected.

3 Finally, there are those patients who have fever
4 that is felt not to be due to an infectious source, a bone-
5 marrow-transplant patient with venous thrombosis, a patient
6 with drug fever.

7 I think it is also useful to keep in mind that I
8 am showing you a one-dimensional spectrum here in terms of
9 bacterial infection. It is important to keep in mind that,
10 in the real world, this spectrum has more than one dimension
11 and that patients may also have fungal, viral or parasitic
12 infections.

13 [Slide.]

14 This situation has led to a problem in defining
15 febrile neutropenia for trials. There is a lack of
16 consensus on who should be enrolled. In addition, the
17 question of how you define the disease for efficacy
18 assessment is unclear. Do you base this on those patients
19 who you know have infection, on the basis of culture
20 results, or everyone who enters on the basis of fever and
21 neutropenia, which is the situation in the real world, after
22 all.

23 [Slide.]

24 This has also led to a situation in defining
25 endpoints for fever and neutropenia trials. There is a lack

1 of consensus on how long patients should be treated before
2 you can say whether the drug has worked. Should the primary
3 endpoint be survival, regardless of what it takes to get
4 there, so the patient can get their next round of
5 chemotherapy or should we consider fever, the surrogate
6 marker, as the primary endpoint.

7 The role of secondary endpoints is also unclear.
8 What do you do with a patient who responds to treatment, as
9 in the second case I presented, but then develops a serious
10 superinfection. What do you do about new episodes of fever
11 that may or may not be due to infection?

12 How are we to regard addition of other
13 antimicrobial agents, in particular antifungal or antiviral
14 agents or even other antibacterial agents with a different
15 spectrum of activity. There are other secondary endpoints
16 that one could imagine that I haven't put on here; for
17 example, time to resolution of fever.

18 [Slide.]

19 To show the kind of problems that can arise if the
20 outcomes are not clearly defined in advance, let me present
21 some data from Joseph Pater and his colleagues at the
22 National Cancer Institute of Canada. They took data from
23 actual clinical trials and said, "Let's see what happens if
24 we change the outcome."

25 They defined one outcome as resolution of the

1 initial episode with no new infection with a susceptible
2 isolate. Under this definition, patients who developed an
3 infection subsequent to resolution with a resistant isolate
4 were still considered successes.

5 Outcome 2 was resolution of the initial episode
6 with no new infection. And then, finally, outcome 3 was
7 survival regardless of whether the patient needed to have
8 modification of the initial regimen. So, for the first two
9 outcomes, if you modified the initial regimen, you were
10 considered a failure. For the third, it didn't matter as
11 long as you survived the infection.

12 [Slide.]

13 They looked at three different regimens in a total
14 of 283 patients. They found that the response rates for
15 each regimen varied dramatically depending on what outcome
16 you chose. The differences were also quite impressive.

17 For the first outcome measure, regimen C was
18 clearly superior. For the third outcome measure, all three
19 regimens did better than with the other outcome measures and
20 the differences really weren't that great.

21 So one conclusion from this is that you really
22 have to be careful of what you are asking in order to get
23 usable information.

24 [Slide.]

25 To make the situation more interesting or

1 confusing, this is not a static entity. There have been
2 trends in empiric therapy of fever neutropenia that really
3 have made life much more difficult for everybody. The
4 microbiologic patterns of infection have changed.

5 There has been a shift at many centers from
6 infection with Gram-negative organisms to infection with
7 Gram-positive organisms. There have been changes in the
8 practice of empiric antibiotic coverage with many clinicians
9 using monotherapy in selected circumstances and, for
10 selected patients, treatment with oral agents.

11 There has been an increasing use of growth factors
12 which shorten the duration of neutropenia. Finally, there
13 is data on treating selected patients who are felt to be at
14 low risk for overwhelming infection as outpatients.

15 [Slide.]

16 In terms of how we can kind of put this altogether
17 and try and aim at a moving target, I would just like to
18 quote David Sackett here from a paper published almost 20
19 years ago in which he says, in part, "The answer to the
20 question, 'Which events should be counted and which there
21 should be blamed?' depends on the nature of the question
22 posed."

23 I think we have to decide, when you are designing
24 a trial for this indication, what it is we are asking the
25 drug to do.

1 [Slide.]

2 Going back to the spectrum for this disease state,
3 we know that, for microbiologically documented infections,
4 we want bacteriologic eradication from the blood and
5 clinical improvement. Going down to situations where you
6 have fever alone, we definitely want to see defervescence.
7 In all situations, we want to see prevention of mortality
8 from the infection.

9 [Slide.]

10 So trying to put this together into a guidance
11 framework for this indication, let me start out with the
12 points-to-consider document which is incorporated in the
13 current draft guidance. That suggests that an adequate and
14 well-controlled multicenter trial in the setting of
15 previously established effectiveness in at least three
16 specific deep infections.

17 In addition, the IDSA guidelines published in 1992
18 made recommendations about the population to be studied,
19 what modifications of the initial regimen would be allowable
20 and what endpoints should be used and how data should be
21 analyzed.

22 [Slide.]

23 So I think, to start out, in terms of who should
24 be studied, clearly patients who have fever and neutropenia.
25 We would define fever as an oral temperature of 38 degrees

1 centigrade or more on at least two occasions or a single
2 oral temperature of 38.3 degrees centigrade or more on at
3 least one occasion.

4 The guidance refers to rectal thermometry. While
5 we would not say that someone who had a rectal temperature
6 taken that showed fever is not truly febrile, I want to
7 emphasize that, on the basis of patient safety, this is not
8 a method for taking temperatures that is appropriate for
9 this patient population in general.

10 In addition, I want to emphasize that modalities
11 such as tympanic thermometry raise issues about sensitivity
12 with regard to detecting fever. There have been a number of
13 reports in which patients who were obviously febrile were
14 regarded as afebrile by tympanic thermometry.

15 With respect to neutropenia, a neutrophil count os
16 less than 500 cells per microliter within 48 hours of study
17 entry would be considered evidence of neutropenia. Patients
18 who are not neutropenic at study entry but have their ANC
19 fall below 500 within this time period would be regarded as
20 having neutropenia for study purposes.

21 In addition, the neutropenia should be due to an
22 underlying malignancy or recent chemotherapy for such a
23 malignancy.

24 [Slide.]

25 Additional information that we would want on these

1 patients, and some of these factors are potential factors
2 for stratification, would include patient age, would note
3 that the IDSA guidelines call for stratification of studies:
4 pediatric and adult populations; severity of depth of
5 neutropenia; the nature of the underlying disease;
6 hematologic malignancy; leukemia; lymphoma versus solid
7 tumor as well as disease status; the use of growth factors,
8 the presence of absence of an indwelling vascular catheter;
9 the use of prophylactic antibiotics, and I will say a little
10 more about this later on; if the patient is a bone-marrow-
11 graft recipient, when they received it and what sort of
12 transplant they received.

13 [Slide.]

14 Who did we not want to enroll in these studies?
15 Patients should not be getting antibiotics at the time that
16 they are on therapy. We don't want to have the already
17 confused situation with regard to treatment effect
18 confounded by prior antibiotics within 72 hours of study
19 entry.

20 This raises the issue of oral-antibiotic
21 prophylaxis. In keeping with the IDSA guidelines, what we
22 would recommend is that if oral antibiotic prophylaxis is
23 used in a clinical trial, the regimen should be specified
24 prospectively, the same regimen should be used for all
25 patients who receive prophylaxis.

1 The study should be stratified prospectively
2 according to whether or not patients receive prophylaxis.
3 Finally, we would absolutely discourage the use of
4 parenteral prophylaxis in the absence of a compelling
5 rationale.

6 [Slide.]

7 Who else would we not want to routinely enroll in
8 these studies. Patients with HIV infection represent a
9 special category. I have put this in parentheses. It is
10 not that we don't want information on these patients who
11 represent an clinically important subgroup. It is important
12 to keep in mind, however, that these are patients who
13 frequently have clinically manifest immunosuppression due to
14 their underlying HIV infection.

15 So unless the study is specifically set up to look
16 at questions related to HIV infection as part of the study
17 protocol, patients with HIV infection should not be
18 routinely enrolled.

19 Patients with low-risk syndromes; for example,
20 chronic benign neutropenia who represent a different
21 population should not be routinely enrolled. Patients who
22 are about to die from their underlying disease for whom
23 assessment of therapeutic efficacy would be problematic at
24 best should also not be enrolled.

25 Then, finally, situations where the pathogen has

1 been identified prior to entry where it is not truly empiric
2 therapy would also represent a patient population that
3 should not be routinely enrolled.

4 [Slide.]

5 In terms of assessments, I think that these are
6 fairly straightforward. Certainly, we want to know history,
7 relevant review of systems with regard to signs and
8 symptoms, physical examination. Culture data, obviously, is
9 very important. Blood cultures including cultures from
10 indwelling vascular devices and other cultures is indicated.
11 Chest X-ray and other diagnostic tests is indicated.

12 [Slide.]

13 Assessment should be carried out at study entry
14 before therapy is received with an initial efficacy
15 assessment at 72 hours when culture data should be available
16 and a treatment effect might reasonably be expected to be
17 manifested.

18 You would normally expect, in terms of subsequent
19 assessments, that for inpatients, daily assessments would be
20 carried out. For patients who are treated as outpatients
21 under a protocol, the scheduled assessment should be
22 discussed with the division in advance.

23 There should be an end-of-therapy assessment and
24 then, finally, a test-of-cure assessment at seven days after
25 the end of therapy.

1 [Slide.]

2 In terms of analysis considerations, assessment of
3 efficacy should be done in a blinded fashion to avoid
4 introduction of bias. This is true whether the assessor is
5 within the agency or from the sponsor side. Analyses should
6 include both intent-to-treat and per-protocol analyses.

7 Assessment of clinical response should be based on
8 consistent application of objective criteria to the extent
9 possible. All episodes should be analyzed if patients are
10 permitted to be reenrolled. However, because episodes in an
11 individual patient may not be completely independent of one
12 another, a separate analysis should also be done for first
13 episodes of fever and neutropenia.

14 [Slide.]

15 In terms of the populations to be analyzed, and I
16 would just remind people of the discussion back on Wednesday
17 by Dr. Lin and the committee, really, I think it is helpful
18 to look at a number of different populations, especially in
19 this indication where we may be interested in a number of
20 different questions, so that no single population may give
21 the answers that we need.

22 We would take all randomized patients and define a
23 modified intent-to-treat population, and I will just remind
24 you based on Wednesday's discussion, that by MITT, I mean
25 that any exclusions are based solely on free randomization

1 characteristics so as to preserve the randomization scheme.

2 We can also define a per-protocol population which
3 is a less heterogenous population and, depending on how one
4 wants to view it, a potentially more defined population.

5 [Slide.]

6 The MITT population would consist of all enrolled
7 patients who receive at least one dose of the study drug,
8 are febrile at entry, are neutropenic within 48 hours of
9 entry, and do not have non-infectious fever at entry.

10 [Slide.]

11 A per-protocol population would take those
12 patients who satisfy the MITT criteria and analyze those
13 patients who had at least seven days follow up, those
14 patients who received the original regimen for at least
15 72 hours without modification. Patients who were modified
16 prior to 72 hours would not be considered evaluable under
17 this analysis.

18 In addition, patients who die prior to 72 hours
19 would be regarded as unevaluable in this analysis but
20 considered failures under the intent-to-treat.

21 In addition, patients where there was modification
22 for an adverse-drug reaction would also be considered
23 unevaluable. If the patient had a fever of uncertain
24 etiology and they receive antifungal, antiviral or
25 antiparasitic agents, they would be considered evaluable

1 only if that agent was given after they defervesced.

2 If they received these agents prior to
3 defervescence, they would not be considered evaluable.
4 Again, there would have to be absence of non-bacterial
5 infection at entry. Finally, if the patient died before the
6 test-of-cure, they would be regarded as evaluable only if
7 you can attribute death to infection.

8 [Slide.]

9 In terms of endpoint analyses, let me just quote
10 from Walter Hughes and his colleagues in the IDSA
11 guidelines. "It is optimal to use multiple parameters for
12 the assessment of patients including clinical response to
13 therapy, evidence of microbiologic efficacy and survival."

14 [Slide.]

15 I think what we would propose is to examine
16 different endpoints as a matter of routine with the size of
17 the analyzed population kept constant for any given endpoint
18 for which success would correspond to specific clinical
19 goals--i.e., survival, clinical and microbiologic response,
20 the need for antibiotic modification and for protocols in
21 which there was an IV to oral switch, what the effect of
22 sequential IV oral therapy is.

23 [Slide.]

24 Definitions of response could include the
25 following. The initial episode resolves with modification

1 with no febrile episodes or infection before the test-of-
2 cure visit. Under this definition, even if you defervesced,
3 if you developed a fever before test-of-cure, you would be
4 scored as a failure.

5 A less restrictive definition would simply look
6 for resolution of the primary episode without modification
7 of antibiotics. Under this definition, a new fever would
8 not be counted as a failure.

9 Finally, the most lenient, or least restrictive,
10 definition would be survival of the infection with
11 modification allowed; in other words, prevention of early
12 mortality from infection.

13 [Slide.]

14 Other study considerations which should be
15 discussed with the division in advance include the
16 comparator to be used, treatment modifications that would be
17 allowed during therapy, the use of oral antibiotics to
18 complete therapy, protocols involving outpatient treatment,
19 and planned subgroup analyses such as analysis of patients
20 by severity and depth of neutropenia.

21 [Slide.]

22 Questions we would like to receive guidance from
23 the committee on are first, are these entry criteria
24 appropriate for studies of empiric therapy of fever and
25 neutropenia, and how should protocols incorporated different

1 analyses and different endpoints.

2 Thank you.

3 DR. CRAIG: Thank you, David.

4 I would like to acknowledge one other person that
5 is at the table now and that is Dr. Arthur Brown, Professor
6 of Medicine and Pediatrics, Memorial Sloan Kettering Cancer
7 Center in New York. We clearly appreciate his being here
8 because we do, as I say, need some expert help in this.

9 Maybe, Arthur, you might want to start off with
10 what you think about the criteria that have been put forth.

11 **Committee Presentation**

12 DR. BROWN: I appreciate being invited to be here
13 and to be a part of the discussion of this and will try and
14 add what little I can to this. I first would like to say
15 that I think that David's presentation has really brought
16 together a lot of very complex issues and he has tried to
17 put them, and I think quite successfully, in plain view for
18 us.

19 So, David, I would like to acknowledge that it is
20 obvious you have done a lot of work. I think it is very
21 well done, at least put in front of us.

22 As far as Bill's question to me about these
23 criteria and so forth, I would like to just comment that,
24 unlike the other infectious kinds of definitions and things
25 we use, as is plain to everyone, is an exceedingly complex

1 thing because we are talking about a physiologic state.
2 Even the definition of what is fever and neutropenia is so
3 different, as we all know, than just the idea of having a
4 microbiologically documented or defined infection such as
5 pyelonephritis or such as--well, pneumonia, I won't get into
6 because we could argue about that--but other kinds of
7 infections, certainly meningitis or something like that.

8 From an oncologist's point of view, as well as an
9 infectious-disease person's point of view, really, one of
10 the things that, as David just pointed out, the survival of
11 the episode is certainly a valid clinical accomplishment,
12 where you want to get to and so forth.

13 But, from a regulatory point of view or design
14 point of view or from a scientific point of view, that,
15 obviously, is not all there is and there is a lot in
16 between. So that is why this is so complex.

17 If I may, I actually want to comment on the
18 wording, not David's wording because he was careful about
19 it, but there is, in the literature, this term "febrile
20 neutropenia." David got away from that and I would like to
21 encourage us to get away from that because, to me, it
22 doesn't make a whole lot of sense.

23 Neutrophils don't have fever. We should be calling
24 it "fever and neutropenia" but not febrile neutropenia, or
25 F&N or something like that, but not febrile neutropenia. I

1 don't want to get into semantics too much, but I would like
2 to encourage us to be using terminology that really is
3 correct.

4 Another point is I would agree with David and I
5 would encourage us not to even suggest that rectal
6 temperatures should ever be a part of the evaluation of
7 these patients because to put it in a guideline suggests
8 codification and suggests that that is practice, and so
9 forth, even though we may have "in parentheses" or an
10 asterisk at the bottom of the page, we don't recommend this.

11 So if we don't recommend it, we shouldn't have it
12 in there at all.

13 I am very in favor of the idea of multiple
14 analyses as has been presented. I think it is very
15 important to do it that way. I think there are, as has been
16 said, multiple ways of looking at this that are essential
17 from a regulatory point of view, from a scientific point of
18 view and, obviously, from a clinical point of view as to
19 what the outcome might be.

20 So it would seem to me appropriate that we
21 recommend or try and structure, in terms of guidelines, the
22 types of populations that would give the right kinds of
23 accrual of numbers into the studies that would allow for the
24 proper power of the study to be evaluated for these multiple
25 analyses.

1 I will leave the design of that or how that is
2 accomplished to the biostatistics people how we do that.
3 That may be how we kind of come into some conflict of how
4 this might be accomplished.

5 I am kind of the old-fashioned school that I sort
6 of rely on the idea of a microbiologically documented
7 infection even in the fever and neutropenia kinds of studies
8 has to show me that, indeed, a certain regimen, regimen A,
9 might be as good or better than regimen B.

10 I would bet that most ID people would subscribe to
11 that kind of thing. But we all know that there certainly
12 are the patients who, as was presented, don't fit. It just
13 doesn't work out that way. That is the way the world works.
14 It is not necessarily so.

15 So someone who defervesces but doesn't have even a
16 clinical documented infection, that is sort of the next step
17 down. Are they to be just tossed aside and not included?
18 No; I don't think so. As I said, I think those people are
19 just as important. So I think the multiple measures of the
20 multiple analyses at those levels is appropriate, as David
21 has presented them.

22 I think the question of not excluding HIV people
23 from studies was well-handled by David and I said that I
24 would agree that there are specific questions to be asked
25 about these patients, especially the patients who have

1 question. I'm sorry, Dr. Craig. Were you addressing that
2 to me or to Dr. Brown?

3 DR. CRAIG: You can respond. I am addressing it
4 to whoever wants to respond.

5 DR. ROSS: Oh, boy. I spoke too soon. I
6 certainly think that, because this is an important clinical
7 entity in this patient population, we need to look at those
8 patients. I think there are a number of ways of doing that.
9 I think that it may be helpful, as a planned subgroup
10 analysis, to say how does a particular drug perform in
11 patients who have line infections.

12 One thing I think we would want to see is a set of
13 consistent results so that you had evidence of efficacy in
14 the patient population with microbiologically defined
15 infection, whether it was due to line-associated blood-
16 stream infection or pneumonia.

17 I do think that that is a significant proportion
18 in some oncologists' practices and maybe just about
19 everybody will have these catheters. I think we need to
20 look at those patients as a defined group.

21 DR. BROWN: Bill, that would be my thought as
22 well. It is the exception rather than the rule that they
23 would not have catheters. Almost everyone in the management
24 of these patients now have devices of some sort for venous
25 access. So, clearly, it would be an unreal world to

1 separate them from the population being studied.

2 I understand your question. In other words, is it
3 a different kind of infection from the point of view of the
4 clinical kind of thing. It generally tends to resolve
5 easily. It is managed easily and so forth and so on. So I
6 think it would be a matter of designing things to take into
7 account this type of infection, just like we might say the
8 clinically documented or the microbiologically documented,
9 the bacteremia, and then the bacteremia that is related to
10 catheters without another source.

11 DR. NORDEN: I also want to complement David. I
12 have one question and that is the test-of-cure timing. I
13 think you proposed initially and said that whatever you do
14 in this, it is relevant to ask what are we looking for, what
15 are we trying to accomplish.

16 I am not sure that we are--frequently, what we are
17 trying to do with the antibiotic therapy is to get the
18 patient through, to, indeed, have them survive, to suppress
19 whatever infection is there until their neutrophils were
20 covered.

21 So, if that is accomplished--but if we wait seven
22 days to evaluate it--this is different from strep
23 pharyngitis or other infections where we are really going
24 for eradication.

25 I think what often happens, at least in our

1 patients, is they become febrile again in that seven-day
2 interval and you can't assess what it is due to. Then I
3 think you get into the real difficulty of what do you say
4 was the outcome of, or the response of, the initial course
5 of therapy.

6 So I would propose, or at least raise as a
7 question, whether one should shorten that period
8 significantly.

9 DR. CRAIG: Isn't it a little dependent on when
10 you stop therapy, if you stop it when the white cells are
11 coming back as compared to stopping it when they are still
12 neutropenic?

13 DR. NORDEN: Yes.

14 DR. BROWN: It certainly is and the other
15 complicating factor is the growth factors at the same time
16 because that has made even shorter the period of neutropenia
17 in many, many of these patients. So there are multiple
18 kinds of stratifications that you would have to do here to
19 evaluate this--in other words, yes, getting growths, not
20 getting growth factors, and so on and so forth.

21 I agree with you, Carl, that that was one of the
22 areas where I didn't say it but David and I went back and
23 forth in terms of a little bit on test-of-cure, really where
24 is our endpoint in that regard and isn't it really the idea
25 that patient is alive and well and moving on to the next

1 round of chemotherapy or they achieved remission at the end
2 of the day.

3 DR. ROSS: Dr. Norden, let me ask you--and I agree
4 with you, that is a very real concern. One question I have
5 is, given that you may want to put the test-of-cure--the
6 time where you see a relapse may be influenced, in part, by
7 the pharmacokinetics of the drug. Is there any way to take
8 that into account?

9 This was one reason for picking that figure of
10 seven days, but I certainly take your point that we are
11 liable to have an unrelated event occur between the end-of-
12 therapy and a seven-day test-of-cure.

13 DR. CRAIG: I can just tell you one of the
14 interesting things working with animal models that you find,
15 you can take Klebsiella and put it in the lung or put it in
16 the thigh with a normal or a neutropenic animal and give the
17 maximum drug you can give, you won't sterilize that tissue.

18 The organism still stays there. That's true
19 whether you have got white cells or whether you don't have
20 white cells. So the antimicrobial effect is essentially the
21 same. But when you stop therapy, and the animal is still
22 neutropenic, those organisms can come back while, if you
23 have got adequate white cells around, they are sufficient to
24 prevent that infection from coming back.

25 So that brings up, as Carl is saying, the

1 evaluation period. If the patient is no longer neutropenic,
2 I have no trouble looking at it out at a little longer. On
3 the other hand, if you are stopping the therapy when the
4 patient is still neutropenic, and you are looking at the
5 seven days while they are still neutropenic, depending on
6 what type of organism was the initial infection, there is
7 going to be a good likelihood that you might see a relapse
8 during that period of time and that, then, that is really
9 not saying that the drug wasn't working.

10 It was working just as well as probably in the
11 patient that doesn't have a relapse. It is just that the
12 environment at the time that the therapy is stopped is a
13 little different when you have white cells around and in the
14 other one, you still don't.

15 So it makes it a little tricky. But if most of
16 the studies are done and the therapy is stopped and the
17 white cells are coming back, I do not have a problem with
18 going out to a little longer time for evaluation.

19 But if it is that they are stopping the antibiotic
20 relatively early and then one is looking at evaluation while
21 the patient is still neutropenic which might happen in bone-
22 marrow transplants, those kinds of situations where the
23 neutropenia may be around for a longer period of time, then
24 I think it does become a little trickier.

25 DR. GOLDBERGER: Have you noticed any meaningful

1 differences, at least in the models, in how different
2 classes of antibiotics or antimicrobials might perform once
3 the drug is stopped in terms of the period of bounce-back of
4 infection?

5 DR. CRAIG: No; we have not seen any different
6 between beta lactams, aminoglycosides or fluoroquilolones.

7 DR. HENRY: Dr. Craig already touched on this, and
8 following up on Dr. Norden's comment about when you do the
9 test-of-cure, actually I think the greater question is when
10 do you define end-of-therapy? Again, you can stratify for
11 whether or not white cells are there, but it gets very
12 complicated if you have a predefined end-of-therapy
13 assessment and you think someone's white count is coming
14 back.

15 We have all seen it happen. All of a sudden, you
16 see the monocytes come back and you think, "This is it.
17 Tomorrow, there are going to be neutrophils," and then you
18 find out that it cycles back down. So how do you define
19 end-of-therapy?

20 I think you are going to have to stratify by
21 whether or not white cells are present or not present and
22 not say, "Well, it is 48 hours and we think they are coming
23 back." So you can't even talk about test-of-cure at seven
24 days because I don't think you have clearly defined when you
25 can end therapy without, again, taking into account what the

1 white cells are.

2 DR. RELLER: Is it possible to put up slide 22?

3 It is the timing of assessment.

4 [Slide.]

5 The terminology here is similar to what we have
6 had for other infections where we had a site and an
7 organism. Do we need a whole new paradigm or different
8 paradigm for these assessments, the end-of-therapy?

9 I know there are some variations in practice, but
10 the commonest scenarios, I think, are the patient becomes
11 afebrile and then there is some duration of therapy and some
12 people are willing to stop if there has been a period of
13 being afebrile before the white cells come back.

14 Others, that is a great outcome and would continue
15 it especially if there has been a response in terms of
16 defervesce until white cells come back. I think the
17 commonest endpoint is to change, ideally, if one has
18 disclosure of infection that you usually don't have, but
19 that the commonest endpoint is when the white cells come
20 back.

21 I wonder if it wouldn't be more reasonable to have
22 assessment periods related to what actually is looked at.
23 Defervescence is one; some period after defervescence.
24 Return of white cells above some number. And then a test-
25 of-cure at seven days post-therapy.

1 Again, it depends on what the endpoint for the
2 therapy is. I don't know if there can be a test-of-cure if
3 you don't have something that you have potentially cured. I
4 look at this whole process of being a therapeutic
5 intervention that everyone accepts works, of if you don't do
6 it, it is a grave risk for the patient.

7 But it is a holding action, a salvage, a
8 forestalling, a hanging-on until the important elements
9 return that we enable one to cure something if it were
10 present with antimicrobial adjunctive help.

11 So I think it might be better to try to define
12 reasonable assessment points based on objective events that
13 happen having to do with temperature or white-cell return.

14 Art, what do you think?

15 DR. BROWN: Barth, I think you raised it in a
16 very, very nice, clear, crisp way. What I was saying in the
17 beginning remarks was that this is a more physiologic kind
18 of disease state rather than defined always by specific
19 pathology.

20 If I can use an analogy, we, the clinicians, are
21 the Dutch boys with our finger in the dike holding back the
22 sea. Essentially, when the neutrophil counts comes back, we
23 take the finger out of the dike, stop the antibiotics.
24 Usually, it works out well then.

25 So, really, your point about saying maybe we ought

1 to have a different paradigm or a different way of looking
2 at this in terms of what is not the classic test-of-cure as
3 represented in the other kinds of things, it is probably a
4 reasonable thought.

5 I like the idea. I think it requires some sitting
6 down and trying to work it out. The details might be a
7 little more cumbersome but the concept is a good one. It
8 fits a little more, I think, how Carl and the rest of us
9 have sort of been talking about this and it brings it
10 together in the nice way.

11 So I would be for it.

12 DR. RELLER: One of the purposes, I take it, of
13 this sort of forum is to not just say yes or no but to think
14 about what the options would be. For example, in other
15 infections, recognizing that there are different durations
16 of therapy, and this may be a dramatic case of widely
17 differing and, appropriately so, durations of therapy but
18 for different reasons, of looking from the initiation of
19 treatment and then some time period instead of after so many
20 days after completion of therapy, so many days assessment
21 after beginning of therapy. This has come up with other
22 indications.

23 One possibility would be how long do these
24 patients literally last after initiation of empiric therapy
25 whilst neutropenic, so days below 500 that one survives

1 after initiation of empiric therapy, because the empiric
2 therapy may be a week, ten days, 14 days, empiric therapy
3 cetera.

4 What one is really trying to do, it seems to me,
5 is to acquire more days without neutrophils that one
6 survives with or without fever, ideally without fever,
7 because it just makes us more comfortable, until the
8 stimulation of the marrow facilitates return that may be
9 accompanied by fever, itself; that is, the therapies, the
10 interventions.

11 But, in the end, it is keeping people alive who
12 don't have neutrophils without which we know that,
13 ultimately, we can live.

14 DR. BROWN: Where it gets very complicated and I'm
15 sure I'm not saying anything that is news to anyone at the
16 table is just let's take and AML patient who is going to be
17 neutropenic for, potentially, as long as four to six weeks,
18 which is not uncommon in our institution where people get
19 very aggressive chemotherapy, and in other institutions as
20 well.

21 So while you might start with regimen A at time 0
22 when they became febrile and neutropenic and by day 3 or 4,
23 you have made some kind of modification, maybe adding a
24 glycopeptide and then, by day 4 to 7, you have moved on to
25 the antifungal therapy, perhaps amphotericin B or something

1 like that.

2 They are going to remain neutropenic and there are
3 going to be the superinfections, all through this time of
4 many, many weeks. How do we score that? Again, in the
5 spirit of just putting things out on the table--I don't mean
6 to make things more complicated--that is where this gets
7 very, very messy.

8 It is ont going to be a nice, neat kind of--and
9 there will be much variation from patient to patient.

10 DR. RELLER: One possibility is recognizing that
11 is what actually happens, is assessment points at times when
12 people are getting only this intervention without additive
13 therapies, and days. I think one of the differences, in
14 terms of response, is whether or not one defervesces and you
15 buy more days until you have to do something else.

16 That might be a measurable endpoint--not a
17 measurable endpoint but a measurable assessment point.

18 DR. BROWN: I like that in the sense that--I agree
19 with you. In other words, if you had regimen A compared to
20 regimen B that was started empirically initially, and it
21 turned out you didn't have to modify at the third, fourth,
22 sixth, seventh day but extended that, that might well be a
23 measure of some validity of that regimen having been better.
24 There is no question about that.

25 When we talk about test-of-cure and further down,

1 it may well be that you are going to talk about somebody who
2 does survive the six weeks and you wait for seven days after
3 you stop something like that, is that really measuring what
4 happened from the first time 0 to whatever time until the
5 modification was made?

6 I don't know. It just gets messy. And are we
7 going to have enough homogeneity in the study population to
8 be able to say, "Yes; we had significant numbers in each of
9 these regimens, and so forth, to compare A and B."

10 DR. NORDEN: I think what Arthur just said is very
11 important, but just flip up slide 29, which is the
12 definitions of response.

13 [Slide.]

14 As you look at them again and what are the goals,
15 sort of the working definition--and, Arthur, correct me--
16 that ERTC has used with some success, I think, is No. 2
17 which is that the episode is resolved without modification
18 of antibacterial therapy but you are allowed to add
19 amphotericin or whatever else it is because that is the real
20 world.

21 You can't prohibit amphotericin therapy in a
22 clinical trial. To me, if you can define the primary
23 episode which is the febrile episode and then resolved is
24 usually the patient has become afebrile. I think the first
25 definition is impossible because you are not asking whatever

1 antibiotic you are giving to prevent further episodes.

2 The third is, I think, as important; survival,
3 also. But I think if you have modified the regimen, then
4 how can you say that it worked, or didn't work. So I think
5 your No. 2 is where I would go.

6 DR. ROSS: I take your point. I think that part of
7 the intent of definition--and I absolutely agree with you--
8 definition 1 is really asking a lot of the drug. It is
9 asking it to have a prophylactic role which is a can of
10 worms that I won't even begin to open because it is
11 impossible to get them back in the can.

12 I think the idea with survival of infection is
13 really prevention of early mortality. That is really the
14 goal there and maybe we need to think how we would--

15 DR. NORDEN: As you said, you can have more than
16 one endpoint. Survival is certainly something we want to
17 look at. Resolution of infection. Death is not as good an
18 outcome, obviously, as resolution and survival. So I don't
19 think that either of those are mutually exclusive.

20 DR. MURPHY: That is also very important in
21 looking at the other side of the equation which is the
22 safety-toxicity issue that you may be picking up here also.

23 DR. GOLDBERGER: Also there have been some
24 products reviewed and at least one approved, a lipid
25 amphotericin product for a similar indication. One of the

1 things that we tried to do during the analysis of that data,
2 from actually a couple of different products, was to get a
3 better handle on the data, we tried to look at the groups of
4 patients, for instance, who did not require modification of
5 antibacterial therapy while on the lipid amphotericin
6 product or the control arm.

7 Also, I think, perhaps, more importantly, we tried
8 to look at the group of people whose white count did not
9 come back up to the normal range during therapy. There are
10 problems, obviously, with doing all these subsets but, first
11 of all, you get a better feel for what is in the data.

12 If you had a clinical trial where 80 to 90 percent
13 of people had their white counts return to normal during
14 therapy, you might not be sure how effective whatever the
15 new intervention really was. We found it helpful to get a
16 feel for how much data there was for some of the patients,
17 in fact, who didn't really return to normal.

18 With at least one drug, there were some patterns
19 that suggested that, perhaps, in those groups of patients
20 which were a harder test for the drug, it did not perform as
21 well.

22 One of the tricks with the lipid amphotericin
23 products is one is not entirely sure what is the appropriate
24 or equivalent dose, say, to amphotericin. That is probably
25 less of an issue, hopefully, with some of the antibacterial,

1 or at least it is easier to study with the antibacterial.

2 But that may be something else to consider about
3 at least thinking about some of these subgroups in terms of
4 getting a better handle on what the investigational therapy
5 is actually doing.

6 DR. BLACKWELDER: With regard to the second
7 endpoint and the discussion about it, I wonder if it would,
8 then, make sense to think of the evaluation as being
9 something like the time until there is no longer a fever
10 rather than at some arbitrary time such as seven days.

11 Is there any thought about that?

12 DR. SOPER: One of the objective criteria we have
13 used in treating post-operative infections has been the so-
14 called fever index which is the time of which the
15 temperature is greater than 99 degrees and it is calculated
16 through a formula when temperatures are taken, I think,
17 every four or six hours. That might be another way of kind
18 of looking at overall response.

19 DR. CRAIG: The title is "fever and neutropenia;"
20 am I correct? At least, that is what we are trying to cure,
21 isn't it? I think it is always hard. These patients can
22 vary so much in their response, probably, to the same
23 infection in terms of their febrile response that it may be
24 difficult.

25 But if you have large enough numbers and they are

1 randomized, that might fall out.

2 Other comments?

3 DR. GOLDBERGER: Going back, again, to the follow
4 up on what you were just saying with regard to the lipid
5 amphotericin drugs, one of the obvious original endpoints in
6 those trials was resolution of fever. One of the problems,
7 of course, not surprisingly, we discovered is that because
8 there were so many causes, we couldn't really get a handle
9 on to what was going on and you would see similar degrees of
10 resolution of fever.

11 But, in the first drug to be studied, the trials
12 were small and actually we got very few microbiologically
13 confirmed endpoints. A larger clinical trial was done. It
14 was done by the Mycosis Study Group with more rigorous
15 endpoint criteria. Actually, there, we found a noticeable
16 difference in microbiologically confirmed endpoints, which I
17 think people were somewhat more comfortable with than just
18 relying solely on changes in fever during the course of the
19 clinical trial.

20 DR. CRAIG: It is a chance, obviously, to get
21 information on response in some of the diseases, the other
22 diseases we see, pneumonia, things like that, in neutropenic
23 patients which are, oftentimes, excluded from other clinical
24 trials. So it is, I think, useful to try and incorporate
25 that into the evaluation somehow, of looking at those where

1 it is clearly both disease and microbiologically identified.

2 DR. CHESNEY: One of the advantages of having St.
3 Jude nearby, or disadvantages, is that the rest of us no
4 longer manage these patients. So this may be a question
5 that everybody knows the answer to, but what is the quality
6 of the neutrophils that are induced by the growth factors?
7 Are they of the same quality in terms of responding to
8 infection as the patient's own neutrophils without growth
9 factors?

10 DR. ROSS: I think I will defer to Dr. Brown on
11 that question.

12 DR. BROWN: I don't know if I can comment on this,
13 from the literature on this, for you, Dr. Chesney, but I
14 don't have any reason to believe that there is any
15 qualitative difference. I am struggling a bit here. I am
16 looking to my colleagues around the table to see if they
17 have any recognition of any laboratory data that supports or
18 doesn't support that notion.

19 Carl, does it come to you?

20 DR. NORDEN: No. I have no data, but that never
21 stopped from saying something. It is, just, again,
22 reasoning by analogy which is that, in general, most
23 hematologists say that if you have a neutrophil, it
24 functions, and that we give--there, obviously, are diseases
25 where it doesn't, but you give transfusions, for example--

1 you used to give transfusions from leukemics and the mature
2 white cells do function as mature white cells.

3 I can't speak specifically, Joan, to your
4 question, though. I don't know the answer.

5 DR. BROWN: The only reason I was wincing, Carl,
6 was not in response to your comment but I have had many
7 oncologic colleagues who have told me they have
8 "functionally neutropenic" patients, not receiving a growth
9 factor, but they say, "We want to start them on antibiotics
10 because they are functioning neutropenic even though they
11 have the numbers."

12 I think that is probably where Joan's question
13 comes from. I don't know how they know this.

14 DR. CRAIG: Let's look again. I think, at least
15 in terms of entry criteria, everybody was satisfied with the
16 entry criteria.

17 DR. HENRY: Just one question as far as
18 clarification. You just said two temperatures above 38.
19 Are you going to put a time frame on that?

20 DR. ROSS: The time frame that I think is in the
21 guidance right now, I believe, is 24 hours.

22 DR. HENRY: So it was just not on the slide, but
23 it is not changed from the guidelines.

24 DR. ROSS: Correct.

25 DR. BROWN: In the IDSA guidelines, was it a

1 little shorter than that? Was it within six or eight hours?

2 DR. ROSS: Twelve.

3 DR. BROWN: Twelve? Anyway, it is written down
4 somewhere that it is within a certain time frame. Apropos
5 of talking about time intervals, David, can you help me?
6 The 48-hour interval that you have to have a neutrophil
7 count less than 500, is that also prescribed in a specific
8 guideline or is it 24 or--

9 DR. ROSS: I do not believe it is in the IDSA
10 guidelines. It should be in the guidance document.

11 DR. BROWN: I have my sort of gut reaction to this
12 that it should be shorter. But I would be interested in
13 other comments. In other words, you enroll somebody and you
14 would like them to have their neutrophil drop down to below
15 500 within a certain period of time. 48 hours sounds a
16 little long to me, but I wouldn't quarrel with it.

17 DR. RELLER: The IDSA guidelines simply say,
18 "expected to fall," but it doesn't say how swiftly.

19 DR. ROSS: The derivation of that was to avoid a
20 situation in which--we have seen where a patient is febrile
21 at study entry but not neutropenic and then their
22 neutrophils don't cross that magic barrier until four or
23 five days later.

24 I agree. I think it is difficult to know where to
25 draw the threshold.

1 DR. BROWN: For continuity, for homogeneity, for
2 study purposes, four or five days in my mind is too long. I
3 think that is easy to say. In our institution, the way we
4 do it is we use 1000--just plain use 1000 because everyone
5 is on this steep curve and they are sliding down very
6 quickly. That is because the next morning, when you do the
7 next CBC, after admission, they all have counts that are
8 down 200, 300, even though they were just, say, 899 on
9 admission.

10 They are down that low the next morning. So I am
11 looking to a period of time--I think the point that was made
12 just now about the time intervals, we ought to say discrete
13 time intervals. Even if we have to be arbitrary, it
14 probably ought to close in a bit.

15 DR. ROSS: So you would advocate a shorter
16 interval of 24 hours.

17 DR. BROWN: Yes.

18 DR. RELER: Another reason for doing that is the
19 studies going back to Carpenter, Wintrobe, others, the half
20 life of a circulating neutrophil is very short; five hours,
21 six hours, something like that? It is very short.
22 Particularly if one is looking at duration of neutropenia,
23 it actually becomes very unfair if the drug evaluated has
24 already got two days when the patient is not at risk versus
25 another patient who plummets within six hours.

1 And there could be substantial differences where
2 days and hours become important. So what, Art, do you think
3 would be the most sensible time period when you are
4 anticipating?

5 DR. BROWN: 24 hours.

6 DR. CRAIG: So 24 instead of 48?

7 DR. BROWN: Yes.

8 DR. CRAIG: Good.

9 DR. HENRY: Bill, I had just one other question
10 about inclusion criteria.

11 DR. CRAIG: Sure; let's work on the criteria.

12 DR. HENRY: Talking about blood cultures, we talk
13 about at least two blood cultures of which one comes from a
14 peripheral site. What do you do about all these patients
15 who have double-lumen catheters? I think, if you have got a
16 double-lumen catheter, you should be sampling both ports
17 and, if you want to do a peripheral on entry--I guess if we
18 are going to try and come up with things that are at least
19 specific, now is the time to do that.

20 DR. ROSS: I think that is an excellent point. I
21 agree with you. I was thinking of this primarily in terms
22 of devices such as Port-a-Caths. But if you are thinking
23 about double-lumen Hickman, I absolutely agree with you.

24 DR. BROWN: I am going to bring up something that
25 has to do with the economies of things in terms of

1 bacteriology laboratories and so forth. I am hoping Barth
2 will come in on this, too.

3 When we have triple-lumen catheters, we end up
4 having four blood cultures. This has ended up being viewed
5 as an unnecessary expense--well, "unnecessary" may be a
6 strong word--but an expense that people would like to
7 control in view of the times that we are in.

8 So it is discouraged, these days, from that point
9 of view, at least in our institution. That has been
10 discouraged, actively discouraged, to draw multiple
11 cultures.

12 One could say the initial set of cultures maybe
13 you should do this, but, certainly, to keep sampling again
14 and again and so forth--in fact, one suggestion had been
15 that people combine a sample from all these so at least you
16 would know whether there was a positive culture.

17 I was an advocate of doing this years and years
18 and years ago. I have to sort of close my eyes to this a
19 little bit. I wonder, Barth, you are mainly a lot in the
20 clinical microsphere, are you under similar pressures?

21 DR. RELLER: Yes.

22 DR. BROWN: Or do you pressure your clinicians to
23 not draw as many cultures?

24 DR. CRAIG: He does the pressuring.

25 DR. RELLER: I wanted to come back to comment.

1 Here is where I would like to be educated. I am not aware
2 of any rigorous assessment of the utility of sampling
3 multiple lumens in a multi-lumen catheter. There, clearly,
4 is a relationship between volume of blood culture and
5 sensitivity, but what does one do with the information if
6 one lumen is positive and the other lumen is not positive
7 and, given the continuity and the way these things move,
8 particularly the organisms that are associated with these
9 catheters in terms of biofilms?

10 In pediatric patients, who may have multiple
11 lines, they are all touching each other. It is hard for me
12 to imagine that what is in one lumen is not in contact. So
13 I don't know where the data are that sampling one or the
14 other or both or all--there are patients who literally are
15 transfused to be able to obtain the blood cultures that are
16 obtained when one gets a customary volume from each of the
17 lumens and does it repeatedly of what is tantamount to
18 surveillance cultures.

19 The volume blood that we receive on some of these
20 patients is startling in amount and, literally, if you
21 calculate it out, they have to be transfused, particularly
22 in the children. So there has been a dramatic cutback in
23 our bone-marrow-transplant units.

24 Frankly, when we get multiple lumens in our own
25 laboratory--now, admittedly, I don't necessarily have the

1 data on the other side, although this is something that we
2 are in the process of analyzing now, we report it as the
3 catheter-positive and do not issue reports from different
4 lumens even if they are collected that way.

5 So there is a composite report, this patient's
6 catheter, or blood drawn through the catheter, is positive
7 for whatever organism. And then one gets into the dilemma
8 of how those data are interpreted. Sometimes, the
9 interpretation, I think, is dependent on corroboration with
10 a peripherally obtained culture.

11 There are multiple, multiple scenarios and, also,
12 it depends on what the organism is. If one grows from one,
13 two, three or all lumens in repeatedly bacillus or yeast, I
14 think the die is pretty much cast as to what needs to be
15 done. The spotty intermittent coagulase-negative
16 staphylococcus from one or the other lumens in someone who
17 is otherwise doing--I mean, it becomes exceedingly difficult
18 to interpret.

19 But I don't know of data that documents the
20 utility of independently assessing different lumens and how
21 that is all put together. But I would be delighted to be
22 educated if that has been done and how well it has been done
23 and where it is peer-review published.

24 DR. HENRY: Having been trained in blood-culture
25 methodology and blood-culture studies by John Washington, I

1 guess I brought an approach to my taking care of hem-onc
2 patients with fever and neutropenia perhaps a little bit
3 differently than some of my colleagues, and certainly
4 different than some of the oncologists.

5 It really is a bit confusing and there really
6 isn't anything that I am aware of published in the
7 literature. It really, to some extent, may be common sense
8 in trying to integrate the variables, especially of volume
9 and number of blood cultures, in trying to best define how
10 to take care of a patient.

11 Certainly, the house staff in pediatrics has heard
12 me get up on the soap box about blood-culture methodology
13 because, for so long, in pediatric patients, they weren't
14 even taking sufficient volume that you had a credible
15 culture.

16 So I think you bring up a number of issues. Not
17 to belabor the point, I will try and address some of them.
18 I think that in patients, and, again, we certainly see this
19 among the bone-marrow-transplant patients and the AML
20 patients, they have double-lumen catheters.

21 My own feeling is I want to know what is in the
22 blood, so I want a certain volume and I want a certain
23 number. I, personally, would be fine with both those blood
24 cultures coming through ports in the line, not just because
25 it is easier for the patient in terms of eliminating a

1 venepuncture, but it satisfies the criteria of volume and
2 number.

3 It also tells me whether or not one port or the
4 other may be the colonized port which may be academic in the
5 end, but we certainly have seen that where someone comes in
6 and we will have a peripheral and both lumens cultured and
7 only one lumen is positive.

8 It becomes important, as a reminder to the nursing
9 staff as well as the house staff, that they have to
10 alternate lumens in which the antibiotics are infused.
11 Sometimes, that gets to be a little bit difficult if there
12 is something running in a line like TPN that is not
13 compatible with the antibiotic and you have to remind them
14 that they have to switch and put infusions of antibiotics in
15 both ports, whether they infuse on a daily basis or an
16 every-other-dose basis.

17 So I think it is important, at some point, at
18 least when they first come in, to know what is in both
19 lumens. As far as once they are on therapy and we need to
20 sample blood to see if they are bacteremic with another
21 febrile episode, personally, I don't want a peripheral blood
22 culture.

23 Again, it comes back to wanting blood, wanting the
24 volume, wanting the number. You can certainly separate when
25 you draw those blood cultures by several hours because I

1 don't want blood through a lumen that just got a dose of
2 antibiotic.

3 So I think that goes into your question or concern
4 about how much blood we are drawing. John Washington
5 established, back in the late '70's, that there was an upper
6 limit to how many blood cultures could be drawn from a
7 patient. Certainly, in pediatric patients back in 1991, we
8 implemented guidelines that the volume of blood drawn is a
9 function of the weight of the child.

10 You can, certainly, by physician discretion, say
11 that you want a lesser volume based on the hemoglobin of the
12 patient which, certainly, fits in well with the oncology
13 population. So you can get the variables of number. Maybe
14 you are compromising volume but you are still able to get, I
15 think, more useful information.

16 Going back to your original question is there data
17 published that says you have to sample both lumens and how
18 do you report this, no; I don't know of any.

19 DR. CHESNEY: 'If I could just add a comment, now,
20 about the febrile neutropenic child, but we have followed
21 many children who had most of their bowel removed at birth
22 and who are now 12, 15, years old who are totally dependent
23 upon double-lumen catheters.

24 I have followed a number of children who had one
25 lumen infected and not the other, and we could easily

1 reproduce that with repeated cultures, and peripheral
2 cultures were negative. So if that is true for the febrile
3 neutropenic patient, then it might be important to get
4 cultures from each lumen at initiation.

5 That's just a comment.

6 DR. RELLER: I am a realist about the difficulty
7 of access. I think it is better to have the appropriate
8 volume of blood culture through a catheter than to not have
9 a culture, to document interpretable pathogens.

10 What I have questions about is what one can tell
11 from the commonest scenario, by far, by a log of having a
12 coagulase-negative staphylococcus, sometimes a viridans
13 streptococcus, from one or the other lumen with or without
14 any peripheral blood culture and what one practically does
15 about it.

16 There is no question that the best practices, best
17 clinical practices, in the care, the infusion, the way the
18 catheters are maintained as lifelines are exceeding
19 important.

20 The numbers of organisms are small, and whether
21 the positivity of one lumen or the other is a function of
22 distribution of organisms, whether one can systematically,
23 you might say, sterilize one lumen and treat a lumen as
24 opposed to treating the patient, this is where it gets to be
25 more complex as opposed to saying, "This patient has a

1 catheter. We have a coagulase-negative staphylococcus from
2 one lumen. This catheter is infected. We are going to take
3 this approach and see how this patient does," and use the
4 catheter as an access for repeat adequate-volume blood
5 cultures to assess superinfection with *Candida glabrata* or
6 whatever it is, whatever the resident most-common
7 superinfection in patients that break through the empiric
8 therapy or even the specific therapy for coagulase-negative
9 staphylococci that may be added when there is a reproducible
10 isolation of that organism which, I think, is the accepted
11 grounds for intervening with vancomycin nowadays.

12 DR. HENRY: I would say that we don't say, "This
13 is a red-lumen catheter-associated bacteremia." It is a
14 catheter-related bacteremia. The point about sampling both
15 lumens is so that you might know what is being harbored
16 because, you are right; if it is in one lumen, ultimately,
17 you can end up getting the other lumen colonized, just like
18 if it is in the lumen, then you might have a peripheral
19 blood culture as positive.

20 I don't feel any sense of comfort having just a
21 lumen-drawn blood culture positive and a peripheral being
22 negative. Positive is positive. That person is still at
23 risk for that organism. So I don't think we differentiate
24 in that regard. I think it does serve as a vehicle in which
25 to obtain a blood culture specimen.

1 You are right. You can better satisfy, perhaps,
2 the criteria of volume by drawing it all through one or both
3 lumens. But, again, I also think it serves a reminder to
4 people caring for the patient that you have to infuse the
5 drug through both ports, whether or not you find that one
6 port is positive or not.

7 DR. RELLER: I agree with you completely on this
8 point. That is why, frankly, in our place, and we work very
9 close with, particularly, the bone-marrow transplant unit,
10 and that is it makes sense to me--it is fine to sample the
11 catheter, what I would frankly do. It achieves the volume.
12 It doesn't defeat the sensitivity.

13 Sample all lumens. Put them in the same bottle.
14 Culture the thing and call it a positive catheter. What I
15 don't think there are data for, or a least I would like to
16 see, is that delineating which color lumen yielded the
17 positive gives information that enables lumen-specific
18 interventions that are lasting; namely, it is the catheter
19 that is colonized and it doesn't make any difference from
20 which lumen the colonization originated.

21 DR. HENRY: Ultimately, it doesn't.

22 DR. RELLER: The implications of trying to keep
23 all these separate and the poor sampling that derives and
24 the number of cultures and the costs that are amplified, it
25 gets to be counterproductive, I think, as opposed to saying,

1 "This catheter is colonized. This patient is at risk and
2 this is a grounds for when reproducible, intervening, over
3 and above the empiric therapy that is already underway.

4 DR. CRAIG: Same reason as I mentioned earlier. I
5 would still feel that you have to have the peripheral
6 because if you don't have the peripheral, in my mind, the
7 case is tossed out. It is not a real bacteremia.

8 Sure; you are going to toss out some that may be
9 true bacteremias. Volume might have been a problem or there
10 was a relatively low-grade bacteremia, but I think if we are
11 trying to look at this entity, we have to have the
12 peripheral blood culture.

13 DR. BROWN: I would agree with you, Bill, that you
14 need the peripheral. The original recommendation was a
15 peripheral and a catheter blood; right, David? I would
16 suggest that we stay with that and the reason would be that
17 the question you raised earlier, how do we differentiate and
18 do we differentiate these catheter-related bacteremias from
19 other kinds of bacteremias, we would be lost if we didn't
20 have those two different things.

21 DR. RELLER: I would like to amplify on that. To
22 me, in reality, the biggest problem, far and away, is
23 coagulase-negative staphylococci in relation to these
24 catheters, having, I think, reached a consensus on the
25 meaning of the lumens, recognizing that it has not been

1 rigorously looked at and published.

2 But they are taking the next step. The solitary
3 isolation of a coagulase-negative staphylococcus from a
4 catheter, whether it was from one or all lumens, to me, is
5 good evidence that the catheter is colonized. Whether the
6 catheter has resulted in or is the victim of a bacteremia
7 with that organism, I think, for coagulase-negative
8 staphylococci depends on corroboration.

9 It doesn't mean that the colonization of the
10 catheter is not important or that it is not colonized. But
11 I don't know how one can say that the patient has
12 bacteremia, escaped bacteremia, if you will, with coagulase-
13 negative staphylococcus without documenting it with a
14 peripheral blood culture given the affinity of this organism
15 for the plastic.

16 I don't think that is true for other organisms.
17 If one got a *Pseudomonas auruginosa* out of a catheter,
18 regardless of lumen, whether or not one, in that patient,
19 had a corroborating peripheral venepuncture, I think one can
20 accept that.

21 It would be nice if you got it out of the
22 peripheral blood culture, but I don't think it can be
23 discounted because it is not the sort of thing that we see
24 with contaminants. Contaminants, as everyone here knows,
25 are a real issue and they are a common issue and, in most

1 laboratories, nowadays, account for at least as many
2 positive blood cultures as all other organisms put together.

3 DR. CRAIG: You have gotten a lot of comments on
4 blood cultures, at least. You may want to change that.

5 The other aspects that you had were new, different
6 analyses. I think, Barth, you mentioned some. Do you just
7 want to review those again that you had suggested, or don't
8 you remember?

9 DR. RELLER: I remember perfectly. I just thought
10 I've said enough.

11 DR. CRAIG: Just to summarize is because I am not
12 sure I can.

13 DR. RELLER: The issues that clinicians caring for
14 these patients faced each day and the decisions made, I
15 believe, are based on persistence of fever and neutropenia,
16 and that assessments related to the duration of those, as
17 Dr. Soper has mentioned, possible objective ways of
18 assessing or counting the days of temperature, would be, to
19 me, important assessment points that would be useful.

20 They are, of course, correlated with the analysis,
21 No. 2, duration before modification required because most of
22 the modifications that come about in terms of added
23 antibiotics have to do with persistent fever in the presence
24 of neutropenia in these patients.

25 So they are related, but it is ways of measuring

1 things that could compare the study drug with the
2 comparator. For example, if I had a new compound that, in
3 the presence of neutropenia in a patient who was febrile,
4 could either get the fever to go away sooner or extend the
5 days and the two would be related, of course, to when one
6 had to intervene with another drug--it may be an antifungal
7 agent--and, at the end of the day or the month or the return
8 of granulocytes, there was also improved survival.

9 I think, simply living, is an important endpoint.
10 It may not be a precise one but it is an important one,
11 nonetheless.

12 DR. HENRY: It is one of our more easily
13 measurable.

14 DR. RELLER: Seriously. If you had an agent that
15 extended the time for you to intervention and bought more
16 time, that would be an important consideration--bought time
17 to modification. Ultimately, it would probably be
18 associated with greater survival because not all of these
19 people are going to survive their neutropenic episode or
20 episodes.

21 So I think it is a matter of trying to make the
22 assessment points match up with those objective markers that
23 clinicians are currently using to decide intervention or
24 modification of points, and that there really isn't a test-
25 of-cure in these patients in whom you buy time, but there is

1 not an entity that one can, for sure, have an objective way
2 of knowing that you have eradicated it.

3 So it is measuring time and it is measuring
4 forestalling interventions as opposed to measuring an entity
5 that one has eradicated.

6 DR. CRAIG: But, would you want to have it
7 relatively standardized as to how long the people would
8 continue the drug in relationship to the neutropenia? You
9 could give the drug for a short period of time and then
10 stop, even while they are still neutropenic, or you could
11 continue it until they are neutropenia resolves.

12 The latter would probably, if it works as a
13 prophylactic agent as well, potentially look better than the
14 first drug because, when you stop the therapy, you then open
15 the patient up to getting another antibiotic.

16 DR. RELLER: Arthur's comments here--I don't think
17 these drugs are used for finite periods of time. They are
18 not used in a three-day course or a five-day course. There
19 may be drugs that come along that are effective used that
20 way, but that is, in reality, now how the drugs are used.

21 They are used until something happens.

22 DR. CRAIG: By that, I mean, would be continuing
23 it until neutropenia resolves.

24 DR. BROWN: My inclination would be continue until
25 neutropenia resolves, would be the most common approach, I

1 think, used by most people.

2 DR. RELLER: Right.

3 DR. BROWN: We all know there are lower-risk
4 patients and subsets of subsets that we have begun to
5 dissect out because of the pressures on us, and appropriate
6 pressures, in managed care and so forth to find out which
7 patients might not truly need to do this.

8 But the majority of patients, the majority of
9 patients, really, should continue on antibiotics until their
10 neutrophils resolve. That needs a definition, too, by the
11 way. Usually, that is when it is crossing the 500 mark on
12 the way back up.

13 DR. RELLER: If that is the commonest reality,
14 then it is a matter of how many days does one agent or the
15 other go--

16 DR. BROWN: Exactly.

17 DR. RELLER: --before one has to modify. Usually,
18 the modifications are based on persistent temperature or
19 some other clinical parameter. But, for the patients whose
20 white cells are not coming back for a long time are the
21 patients that one has the most rigorous test.

22 If one had an agent that forestalled modification
23 longer than another agent, over the long haul, I would think
24 this is the drug that people would want to use.

25 DR. CRAIG: But wouldn't you have to divide the

1 number of days, as I say, by the total number of neutropenic
2 days because there may be variation--

3 DR. RELLER: Exactly. That is the sort of
4 analyses that I was trying to get at because it is consonant
5 with practice. If we have a group-A streptococcal
6 pharyngitis, we have got something that we can measure and
7 endpoint on because it is also consonant with what people
8 are trying to measure for the clinical entity.

9 I am just trying--rather than arbitrary durations
10 and time points of getting the ratios and the proportion of
11 days and so on to match up with the things that people are
12 following and making decisions on clinically.

13 DR. BROWN: I would just like to throw something
14 in here. I don't know why it didn't occur to me earlier,
15 and it probably has occurred to all of you so it will be
16 nothing new, if we were sitting here in 1970 and having this
17 discussion, survival would be a very clear endpoint
18 measurement, not that it is unclear now.

19 But we would be talking about regimen A versus
20 regimen B and there would be lots of deaths and so forth and
21 so on. We have the full expectation that 90 percent people
22 with fever and neutropenia survive right now. I don't think
23 there is any question about that. We have come a long way.
24 We know what we are supposed to do.

25 It is because we do it quickly, effectively, and

1 so forth. But we will have to have a survival--we have to
2 follow survival to make sure that regimen A and regimen B
3 don't have differences in survival. But the expectation is
4 that they will all be in the 90 percent range.

5 So the differences we are looking at now are the
6 things that Barth is talking about, that everyone else is
7 talking about, indeed, is the time of defervescence
8 different, is the time of--you might even talk about length
9 of staying in the hospital, time until you switched, until
10 oral antibiotics, if we are going to use an outpatient
11 approach to things in the future and so forth.

12 These are going to be the shorter-term
13 measurements and we should be looking at all of these as
14 other forms of analyses, subset analyses, and so forth,
15 along the way. But we can't, as Dr. Murphy said, discard
16 the survival thing even though we expect everyone, or we
17 hope everyone, is going to have this high survival.

18 I don't know whether I am saying anything new.
19 I'm probably not. It is just that it occurred to me, as we
20 were talking about dissecting out these little parts here,
21 the little parts may well be the differences in the quality-
22 of-life issue as well as in the efficacy kinds of things
23 that are most important now, as we have become very
24 successful at this process.

25 DR. CRAIG: What we have tended to do is look at

1 those, but we tended to do them more as percentages in terms
2 of patients instead of trying to use some other form of
3 measurement like number of days, fever indexes, things like
4 that, which give a little bit more quantity to it but also
5 need to be validated, that they are appropriate endpoints
6 and that they cannot be affected by other things that are
7 unrelated to the drug therapy.

8 DR. MURPHY: Basically, I think what you have said
9 is that, as we have improved, we are able to refine what we
10 are able to look at, not just survival. Survival is
11 important because, as I said before, it may tell us other
12 things. We assume these drugs are equally efficacious and
13 have other things that we do that we need to also look at.

14 But this discussion has been really very good. We
15 really appreciate it.

16 DR. CRAIG: Anything else that anybody wants to
17 bring up?

18 DR. ALTAIE: It could be a bit late at this point.
19 I was trying to chime in as far as the blood cultures were
20 concerned, but I am going to get it in anyway. Dr. Henry
21 was concerned about the volume of the blood for detection of
22 the organisms in the bloodstream.

23 To credit the industry that had worked very hard
24 to develop techniques and media and detection methods that
25 can work with lower volume of the blood, I would urge not to

1 sacrifice the peripheral blood for getting more volume
2 because then we have a problem with distinguishing and
3 interpreting coagulase-negative staph.

4 So, I think concern about the volume was
5 appropriate probably twenty years ago, but, since then, the
6 sophistication in the blood-culture media and detection
7 method has alleviated some of that volume need.

8 DR. HENRY: Let me make just one last comment. I
9 guess I just wanted to clarify that. As far as a study is
10 concerned, I think that a peripheral blood culture is
11 warranted as well as blood cultures through the lumens.

12 We were sort of getting off-track talking about
13 day-to-day practice and once a patient is in the hospital
14 with fever and neutropenia, do you always have to sample
15 peripheral blood. My point there was no, but I think for
16 purposes of the study, you obviously have to, especially
17 with this idea of trying to sort out those that are line-
18 associated bacteremias.

19 DR. GOLDBERGER: John, could you put up slide 22.
20 While John is doing that, just a comment about using as an
21 endpoint the time to modification of therapy. We should
22 keep in mind that has the potential to be a composite
23 endpoint; that is, on one hand, a difference in efficacy
24 and, on the other hand, a difference in toxicity.

25 On occasion, those two may move in different

1 directions--I'm sorry; slide 12--we need to be aware that
2 combining the two of them together may not be ideal because,
3 in fact, they are going in opposite directions.

4 The other comments was everyone has been talking
5 about our expectation that mortality will be up in the 90's
6 et cetera, and we ought to be looking at the other
7 endpoints.

8 [Slide.]

9 If you take a look at this slide here, and we look
10 at outcome 3, which is mortality, regimen C and regimen A, I
11 would submit, are, from a point of view of survival, quite
12 different from one another. The absolute difference is
13 5 percent. If you were just to crudely estimate the
14 relative risk, the relative risk of death would be 2 for
15 regimen A versus C.

16 If you were to produce a confidence interval
17 around that, it would be up at the high end, to 3 or 4. I
18 think that, although we say that we are expecting it to be
19 in the '90's, we need to be careful that, when we are
20 talking about a relatively common phenomenon, several points
21 difference in survival still represents a noticeable
22 difference in the impact on patient care. So we do need to
23 be careful about that.

24 DR. DOERR: Mary Beth Doerr, Rhone-Poulenc Rohrer.
25 We have a compound that we think will benefit patients with

1 fever and neutropenia. We are very grateful that the FDA
2 has put together these guidances.

3 However, our compound doesn't fit easily into the
4 guidance in that our compound is directed against Gram-
5 positives. In 1997, the IDSA published guidelines which
6 would limit the use of compounds directed against Gram-
7 positives to modification therapy except in specific
8 circumstances.

9 So we have a little bit of a dilemma in that we
10 are not 100 percent sure how to take these guidances and
11 apply them to a modification therapy design. So that is one
12 question.

13 The second question is how do we power our study.
14 You have mentioned three different populations. If we are
15 looking at empiric therapy, would it be more appropriate to
16 power the study on the modified intent-to-treat or is it
17 more appropriate, as Dr. Brown has suggested, the
18 microbiologically defined patient is the one that we want to
19 make sure we can understand the outcome, is it more
20 appropriate, then, to power the study on that criteria.

21 DR. CRAIG: Do you want to consult with them?

22 DR. MURPHY: I was going to say that I think that
23 we are not here to do that today, to develop specific drug
24 programs. I think that there is no way these guidances will
25 ever fit all drug programs. Even it were more

1 generalizable, obviously, each drug is going to have its own
2 profile for efficacy, toxicity.

3 One needs to think of these, if you will, a
4 template upon which you fit your specific needs. I do think
5 that Dr. Lin would like to comment on the power issue. I
6 think that might be wise. She is raising her hand. I am
7 not sure. We will find out.

8 DR. LIN: My comment is a general comment. I
9 think there is power for both.

10 DR. CRAIG: And, again, I would just comment that
11 things have changed a lot since the FDA guidelines were
12 written and there are, clearly, a lot more Gram-positive
13 infections than were present then and also with more
14 resistant organisms.

15 So I think, clearly, it is difficult to use those
16 guidelines exclusively. Talking to the agency is clearly
17 the thing to do.

18 DR. FOX: Barry Fox from Bristol Myers. I would
19 like to just readdress the issue of inclusion criteria with
20 respect to the absolute neutrophil count of 500 and the now
21 24 hours requirement for onset to less than 500.

22 Dr. Brown told us that even at his institution
23 they used 1000 as the criterion. My concern is, by going to
24 500 within this 24-hour period, now, it just seems to me
25 that we are going to have patients that come in with an

1 absolute neutrophil count of, say, 1600 or so. They get
2 started on empiric therapy because it is anticipated that
3 their counts will be less.

4 The next day, their count will be 600 or 650. It
5 seems to me that we are going to lose 25 or 30 percent of
6 patients by the inclusion criteria by having this 24 hours.
7 What my suggestion potentially would be is, if the count is
8 greater than 1000, have it be between 500 and 1000 within 24
9 hours and then less than 500 within the 48-hour period.

10 Any comments regarding this?

11 DR. BROWN: Yes. I would have a comment about
12 that. I don't think anyone whose count is 1600 should be
13 started on antibiotic therapy, anticipated or not. 1600 is
14 not neutropenic by any measure of any kind of study or any
15 clinical parameter used by clinicians in this country.

16 I think that is stretching things out of the
17 boundaries of what I have thought, and I am open to thoughts
18 of other people. But as I recall the way this is written,
19 it was supposed to be there was disagreement among people
20 who wrote guidelines of whether it was 500 or 1000.

21 I don't remember anyone who was saying that, well,
22 if you are 1500 or 2000 or 2500--you could go up and up and
23 up and say, yes, it is anticipated that I gave chemotherapy
24 today and ten days later, this person is going to be under
25 500. So I think that is stretching the point a bit.

1 I was trying to get, in saying this and throwing
2 it out, to get some uniformity here and some homogeneity in
3 terms of making sure the population that we are looking at
4 here is more of the same and not spread out and so forth.
5 We are talking more about the same kind of apples, so to
6 speak, not just apples and pears but the same kind of
7 apples, and so forth.

8 So I would say that it is supposed to be between
9 500 and 1000--you can measure it on the day that the patient
10 is febrile and it is 500 and 1000. But if it is anticipated
11 to drop less than 500 within 24 hours, that is an inclusion
12 and, indeed, after the study, the patient is entered and,
13 indeed, it turns out to be they are, then they would be
14 counted. If they didn't drop to that level, they wouldn't
15 be counted.

16 DR. CRAIG: I think our indications of what we
17 have tried to say is that we are not writing guidelines here
18 for the use of the drug in clinical practice. What we are
19 trying to do is look at it for safety and efficacy and so we
20 have tended to, oftentimes, tighten up on the inclusion
21 criteria so that we are clearing looking at fever and
22 neutropenia to insure that the population is what they are
23 supposed to be so we can see if the drug really works in
24 that population.

25 DR. FOX: Thanks.

1 DR. RELLER: Art, could you comment on patients
2 with fever and neutropenia. What we heard was the white
3 count is coming down and you stuck with 24 hours until it
4 plummets below 500. Theoretically, what would happen is you
5 would plummet below 500 before the fever came about.

6 Are we anticipating the fever as well as the
7 neutropenia with these early interventions or should a
8 patient have--I think we need to emphasize that it is fever
9 and neutropenia.

10 DR. BROWN: Yes; it is.

11 DR. RELLER: Because the creep goes such that
12 patients who are afebrile, who have a normal white count,
13 are started on antibiotics in anticipation that they are
14 going to have neutropenia and the anticipation that they are
15 going to have fever. One gets so much anticipation that it
16 ends up being everybody who has the entity; that is, the AML
17 gets temperature and anticipation that somebody they are
18 going to get chemotherapy and be neutropenic.

19 DR. BROWN: Both.

20 DR. RELLER: It is slippery.

21 DR. BROWN: It is both. It seems to me that, at
22 time 0, when the patient--presumably, a patient calls up and
23 says, I have fever, because they were told that when their
24 temperature is about X, they are to call in.

25 They come into bed holding, emergency room, ...

1 whatever, and, indeed, they still have fever. So there are
2 your two measurements above 38 within--did we decide how
3 many hours?

4 DR. ROSS: Twelve.

5 DR. BROWN: A certain period of time.

6 DR. CRAIG: So it is 24, isn't it?

7 DR. BROWN: Their white count is measured at that
8 point and the neutrophil count, indeed, let's say, is
9 between 500 and 1000 but it is anticipated that it is going
10 to drop below 500 within 24 hours of that entry time. All
11 the fever for that time would count.

12 I don't think it can be done for anticipated
13 fever. I agree with you.

14 DR. RELLER: The reason I emphasize this is
15 because, it seems to me, that the issue of--that it
16 reinforces sticking with the 24 hours because the fever, in
17 these patients, we are assuming is related to the
18 neutropenia. If they have fever that is not associated with
19 the neutropenia, then that is not the body of patients that
20 is being studied in these trials so that it would not be an
21 issue of being below 500 within 24 hours if it is patients
22 with fever and neutropenia that are being studied as opposed
23 to patients who have an underlying disease that are febrile
24 who then get chemotherapy.

25 DR. CRAIG: I guess the only the only question I

1 would ask is we did have the open public hearing. Did the
2 person from Nexstar feel that--did you want to finish up
3 what you had said or are you done?

4 DR. SANDHAUS: I think the questions have been
5 answered.

6 DR. CRAIG: Okay. Thank you very much.

7 I would, then, say we are adjourned.

8 DR. CHIKAMI: I just wanted to make a couple of
9 comments as we have wrapped up this two-and-a-half days of
10 meeting. First of all, I would like to thank the committee
11 members and our consultants and guests for really reviewing
12 lots of material in a relatively short period of time,
13 particularly for the discussions that have gone on.

14 They have been very helpful and sort of right on
15 target in terms of how we will use the discussions to modify
16 these draft documents over the next 90-day comment period
17 and include comment from the public.

18 I would also like to thank the audience who stuck
19 it out for these two-and-a-half days and for questions and
20 input because we also feel that is important as we modify
21 these documents.

22 Most importantly, I would like to acknowledge the
23 staff within ODE 4 and the divisions for all of the hard
24 work that they have put in in producing these documents over
25 the past couple of months and the time that has been put in

1 in preparation for the presentations.

2 I think the presentations have been of very high
3 quality and have really been right on target in terms of
4 identifying the issues that needed to be discussed for each
5 of these documents.

6 Then, most of all, I would like to acknowledge
7 Renata Albrecht who has really been the coordinator for this
8 entire effort and has really been sort of the driving force
9 in getting all this work done.

10 So thank you very much.

11 DR. MURPHY: I did have one last comment for the
12 committee. When we told people we were going to review
13 eighteen guidances issued by the FDA, eyes would glaze over,
14 people would become limp. I would like to say to both the
15 Division and the Advisory Committee, and the audience, you
16 have taken these boring, dull guidances and have not only
17 made the discussion simply informative; it has been really
18 stimulating, reinvigorating and, Barth, it makes me realize
19 my fellowship was some of the best days of my life in your
20 microlab.

21 Thank you all, and we will see you again.

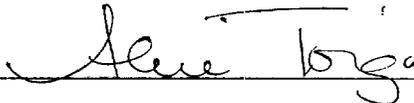
22 DR. CRAIG: We are adjourned.

23 [Whereupon, at 11:40 a.m., the meeting was
24 adjourned.]

25

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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