

at

ATDEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING
61ST MEETING

Wednesday, March 5, 1997

8:15 a.m.

Ramada Inn, Bethesda

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

at

8400 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

at

PARTICIPANTS

William Craig, M.D., Chairperson
Ermona McGoodwin, Executive Secretary

MEMBERS

Virginia Banks-Bright, M.D.
Susan Cohen, B.S., Temporary Consumer Representative (II
only)
Henry Francis, M.D.
Nancy Henry, M.D.
Marian Melish, M.D.
Donald Parker, Ph.D.
Edwin Thorpe, M.D.

CONSULTANTS

Arthur E. Brown, M.D. (I only)
Barth Reller, M.D. (I and II)
Jonathan S. Serody, M.D. (I only)
Jerry L. Shenep, M.D. (I only)
Stephen H. Zinner, M.D. (I only)

FDA

Renata Albrecht, M.D.
David Feigal, M.D., M.P.H.
David Ross, M.D.
Janice Soreth, M.D.

C O N T E N T S

PART I

Call to Order	4
Conflict of Interest	6
Opening Remarks: David Feigal, M.D., M.P.H.	7

**Cefepime (Maxipime): Supplemental NDA for the Empiric
Treatment of Febrile Episodes in Neutropenic Patients
(Bristol-Myers Squibb)**

Introduction by FDA Consultants

Background--Febrile Neutropenia (ISDA Guidelines): Arthur E. Brown, M.D.	9
---	---

Febrile Neutropenia in Pediatric Patients: Jerry L. Shenep, M.D.	35
---	----

Sponsor Presentation

Introduction: Dr. Laurie Smaldone	47
Historical Perspective: Dr. Stephen Schimpff	50
Methodology: Dr. Claude Nicaise	64
Results of Clinical Trials: Dr. Reubin Ramphal	70
Summary and Conclusions: Dr. Claude Nicaise	86

FDA Presentation

Febrile Neutropenia Supplement: David Ross, M.D.	96
---	----

Committee Discussion	123
----------------------	-----

II

**Guidance Document on Evaluability Criteria for the
Review of Antimicrobials: Individual Indications**

Introduction: William Craig, M.D.	170
David Feigal, M.D., M.P.H.	172

General Section on Guidance Document:

Renata Albrecht, M.D.	183
David Katague, Ph.D.	191
Martins Adeyemo, Ph.D.	203
Sousan Altaie, Ph.D.	213
Francis Pelsor, Pharm.D.	223
Ralph Harkins, Ph.D.	239

at

Renata Albrecht, M.D.

252

Open Public Hearing

268

at

P R O C E E D I N G S

Call to Order

DR. CRAIG: Good morning. I would like to call to order the Anti-Infective Drugs Advisory Committee Meeting. I guess this is the 61st. I might as well announce right away that, for those of you that will be continuing on for the next two days, it will not be in this hotel. It will be back down the street at the Holiday Inn.

I think, at least the Chair of the Committee, had a little difficulty finding this place. For some reason, I thought it was the Hyatt so I walked all the way down to the Hyatt to find out it wasn't there and had to turn around. So maybe that is where some of our other members are.

As Dr. Feigal said, that is the reason we have consultants because they can at least find where the place is.

What I would like to do to start off is to go around the room and have everybody register officially. So if we could start down at the end there. If you would say your name and your position.

DR. SHENEP: Hi. I'm Jerry Shenep, Pediatric Infectious Diseases at St. Jude's Children's Research Hospital.

DR. SERODY: I am Jonathan Seroday, Adult

at

Infectious Diseases and Hematology at the University of North Carolina in Chapel Hill.

DR. BROWN: I am Arthur Brown from Memorial Sloan Kettering Cancer Center in New York, Adult and Pediatric Infectious Disease.

DR. ZINNER: I am Steve Zinner from Brown University, Adult Infectious Diseases.

DR. THORPE: Edwin Thorpe, OB-GYN, University of Tennessee, Memphis.

DR. HENRY: Nancy Henry, Pediatric Infectious Diseases, Mayo Clinic.

DR. RELLER: Barth Reller, Adult Infectious Diseases and Clinical Microbiology at Duke University.

DR. CRAIG: Bill Craig, University of Wisconsin, Adult Infectious Disease.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. PARKER: Don Parker, University of Oklahoma Health Science Center.

DR. MELISH: Marian Melish, Pediatric Infectious Diseases, University of Hawaii.

DR. ROSS: David Ross, Medical Officer, Anti-Infectives, FDA.

DR. SORETH: Janice Soreth, Medical Team Leader at the FDA.

at

DR. FEIGAL: David Feigal, the Acting Division Director for Anti-Infective Drug Products in the Office, Director for Drug Evaluation IV.

DR. CRAIG: Thank you.

The next item on the agenda is the conflict of interest statement.

Conflict of Interest Statement

MS. McGOODWIN: Thank you, Dr. Craig. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it had been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting.

We would like to note that there are no conflicts with the Committee members. Dr. Rodvold was unable to come today.

With respect to FDA's invited guest speakers, Dr. Jerry Shenep and Dr. Zinner have reported interests which we believe should be made public to allow the participants to

at

evaluate objectively their comments. Dr. Shenep would like to disclose that he had a grant from Bristol Myers Squibb to support education of infectious disease fellows and visiting scientists.

Dr. Zinner would like to disclose that he lectures occasionally for Bristol-Myers Squibb and is an ad-hoc scientific advisor for Bristol-Myers Squibb and several other pharmaceutical companies.

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

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

Thanks.

DR. CRAIG: Next is opening remarks by David Feigal from the Division.

Opening Remarks

DR. FEIGAL: Good morning. I would like to

at

welcome everyone here. This issue has not been discussed in front of this committee in an open session since the time that the points to consider documents were presented.

If we look back historically at the labeling for this indication, in some of the older labels for products approved more than a decade ago, there is passing reference to the use of some products in the setting of the compromised host but it wasn't until the IDSA participated in the project with the Division almost eight years ago now that we began to formally look at what would the appropriate study designs be to try and show safety and effectiveness in the common clinical setting of an empiric treatment of infection in a neutropenic host.

This application is actually the first application to actually try and conduct the studies under those guidelines and points to consider. One of the things I think that the committee will need to look at is all of the levels of detail, the additional detail, that are required once you actually have some data and studies in place to go beyond the outline of the study design and assess what is the best way to establish effectiveness in the setting where we recognize that in the majority of cases we will not even identify an infectious agent. What are the appropriate rules for an infection in that type of setting.

at

The fact that it is somewhat daunting to study this does not obviate the clinical need which is very real, and the improvements in the treatment of infections has been part of the progress that is made more aggressive chemotherapy, whether it is in the setting of bone marrow transplantation or cancer chemotherapy, possible for some of its strides.

So we look forward to the committee looking at this specific application but we will also pay close attention to the discussion of the issues as we attempt to provide guidance to companies and academic sponsors who wish to study this type of issue further and further the progress we can make in this area.

Thank you for your participation today.

DR. CRAIG: Thank you David.

I would like to remind all the speakers, both the consultants and those for the sponsors, to please try and stay within the allotted time. We have got a tight agenda to try and leave sufficient time for discussion. I think we will pick up that half an hour at the end for the open public hearing as there is nobody scheduled to speak during that period of time.

But we would like to be able to get as much time to discuss the area and for the questions that will be

at

presented.

So, we will be starting off with some of our consultants. The first one is Dr. Arthur Brown.

Introduction by FDA Consultants

Background--Febrile Neutropenia (ISDA Guidelines)

DR. BROWN: Good morning. I did bring a compass so I was able to find my way. I would be glad to lend it to the Chair at any time.

DR. CRAIG: Thank you.

DR. BROWN: Please forgive me. I just recovered my voice last night and I hope it will last through the presentation. My nasal voice is not the usual.

When David Ross called me and asked me to be involved in this, I was quite pleased so I thank him and I thank the FDA for the invitation. I thank the committee for including me. My understanding of what David and the FDA and the group wanted to come of this was, perhaps, a precis of the existing IDSA FDA guidelines and with an accent on what may have changed since they were published in '92 and, perhaps, some notions of where, in my opinion, things might be going and so forth and so on.

That is a daunting task in 20, 25 minutes. So what I have done is I have taken the guidelines and used them as an outline for the presentation and just, at my own

at

pace, decided to just highlight a few things here and there. So, if you are lost in the presentation, you can always look at the insert that was given out to us earlier in terms of the guidelines.

[Slide.]

You usually start with an introduction and that is where we are. I am going to spend a fair amount of time reviewing what we would call standards of care because that, obviously, has great impact on how we would approach studies in such patients.

The current standards, the this is a very broad brush-stroke kind of comment here, of prompt initiation of broad-spectrum anti-infective drugs, there is no way anyone could find fault with that. It is just chock full of ambiguity and so forth, appropriately so, to give flexibility in order to do this.

Perhaps, in reviewing a bit of where we have been, we can understand what constitutes broad-spectrum and what we regard as prompt.

[Slide.]

This is a slide I always use for the house staff whenever I give a talk about infections in patients with cancer, particularly with neutropenia. It shows data, the patterns of the causes of death, in autopsied patients who

at

had acute leukemia from quite some time ago, now, some 40-plus years ago, going back into the 50's. These are NCI data, data from just up the street, the first three rows going across.

These were adults and children who came to autopsy who had acute leukemia and it shows, in a very specific but, and it is contradictory, general sense of whether they died of hemorrhage, hemorrhage and infection, infection or other causes. The principle point of the slide, and I have included some data from the first part of time I was at Sloan Kettering in pediatrics, shows that, indeed, we had a problem arising as we began to more intensively treat patients with acute leukemia, that infection, indeed, was the major cause of death in these patients as proven at autopsy.

You may ask, and everyone always does, how come we don't have any data into the '90's on this. I will tell you that hardly anyone does autopsies anymore, and that is a big problem in terms of determining these kinds of data in the future. Indeed, the autopsies that are done, I would say, rather selected and probably biased and so forth and truly don't represent the population at large.

[Slide.]

So that was the setting in which things were done.

at

I think Dr. Schimpff, Dr. Klatersky and other people from whom I learned a great deal will discuss this in much more detail especially about the history of things. They have a few more grey hairs than I do.

But, in 1990, The Infectious Disease Society of American published its guidelines. These are the clinical guidelines. And these are the opening statements in the first couple of paragraphs. This was done partly because there was a fair amount of controversy which, I am sure, all of us will reiterate today to some extent, about how one should approach these patients.

In the first few paragraphs, there really were these three statements that said there was no controversy about these things. This is the framework about which we all agree. How we respond to it is where the controversy may exist.

I just will quickly mention that basically the neutropenic patient who became febrile at that time had a 60 percent or lower chance of being infected, a very high-stakes event from a clinical point of view.

If the neutrophil count was less than 100, in the many series that have been done, approximately 1 in 5 of these febrile episodes will be associated with--and the manuscript said bacteremia. I would say a positive blood

at

culture in view of today's considerations of fungemia, just to sort of add an editorialization there.

So, in other words, there was a very high likelihood that there would be a positive blood culture, especially when the counts were profoundly suppressed.

But, most importantly, if left untreated, these infections were going to be rapidly fatal. This was, indeed, the emphasis that was taken for the need to have guidelines and uniformity in how we approach these patients because people died if they were not appropriately treated. Appropriate treatment meant prompt treatment.

[Slide.]

This is Dr. Schimpff's slide from a few years ago showing the relationship of the absolute neutrophil count on the x axis as it goes down to zero and the numbers of infections per 100 days in a very high-risk group of patients, ANLL, acute non-lymphocytic leukemia, during induction to therapy, a very aggressive chemotherapeutic regimen usually applied to these patients.

As you can see, as the counts go down from greater than 1000 to less than 1000 and less than 500, and, certainly, when they are less than 100, the numbers of bacteremic infections, severe infections and the total, go way up. This is a relationship that has been shown, first

at

by Gerry Bodey but many, many other people and is accepted as pretty much fact now and the basis for how we approach these patients.

[Slide.]

Who are the players? The various organisms we need to be concerned about, if we all agree that, indeed, this is something that requires immediate action, are basically bacteria and fungi. I would suppose we are mainly concentrating on bacteria in the morning, here.

There is a range of organisms to be concerned about. This was made up in the early '80's by me, and I chose to show it again because I will get into the changes in the organisms in a few minutes. But I wanted to show you where we have been.

Gram-positive organisms included the beta-hemolytic strep, the pneumococcus, Staph aureus, common everyday organisms that affect normal hosts as well as our neutropenic host. Then, it used to be that organisms like Staph epi, viridans strep, enterococci, not so much AK and bacillus, but, certainly, these three, were organisms that patients got in the hospital back in the '70's and early '80's after they had been in the hospital for a period of time, sort of gram-positive superinfection.

That is a change that has happened now, and I will

at

point that out. Now, for instance, Staph epi is the principle organism in terms of frequency of recovery from blood culture on outpatients who are febrile and neutropenic, presenting with fever and neutropenia. I will discuss a little more of these as we go along.

The gram-negative rods traditionally have been the Enterobacteriaceae including E. coli, Klebs, Enterobacter serratia and, to some extent, Proteus. I think we would all agree, we don't see a lot of Proteus infection but it is traditionally included here. And Pseudomonas aeruginosa, although taxonomically distinct, is certainly part of the consideration in these patients.

It is these organisms that, in the past, had really contributed to the high mortality rate that we have come to know about and to be concerned about and about which we respond with broad-spectrum antibiotics.

The shift, as I have already alluded to, is more to the gram-positive side, a little less on gram-negatives. But this may depend on what side of the Atlantic you are on or, in New York, which side of York Avenue you are on. At New York Hospital, which is across the street, they have a very different range of organisms than we do at Sloan Kettering.

So, just like all politics is local, I feel that

at

if I am in Washington, I should say something like that. I think epidemiology is local. It is a very important differential point to be considered. I think that has been appreciated much more by all of us in the field in the last ten, fifteen years than perhaps it was when we were trying to get, as you might--you will have to forgive my humor. I can't help this--a managed-care approach of trying to get "one size fits all" back in the early '70's, a little premature, perhaps, given the current climate.

But there was an attempt to sort of say, "Well, this regimen will work for all neutropenic febrile patients," and I think we have come to think that it varies from institution to institution and city to city and so forth. So there are local factors that must be considered.

[Slide.]

The other group of organisms to be considered in these patients with neutropenia are, of course, the fungi. We know about invasive disease with *Aspergillus*, *Mucor*, *Candida* and we have come to learn about other invasive organisms that, heretofore, were not so much a problem, *Trichosporon*, *Rhizopus*, *Fusarium*.

I don't know if I have the slide in the right order, but there is a slide later on that lists a whole bunch of tongue-twisting fungi that, heretofore, were really

at

environmental or presumed to be non-pathogenic in humans that are now causing problems and I will get to them in a few minutes.

[Slide.]

To give you some numbers besides descriptive talk, I will show you some data from Memorial. This is an often-quoted paper by Carol Singer from the Green Journal in 1977 and represents, I think, kind of where we were as we were just beginning to use combinations of antibiotics. These were data taken over 14 consecutive months at Memorial, 364 consecutive episodes of sepsis and fungemia in patients.

Carol and Don Armstrong and Mark Kaplan analyzed this. They put in order the frequency with which these organisms recovered from the bloodstream and their mortality.

Let me be clear. This is not attributed mortality but crude mortality. In other words, there was no attempt to assign the cause of death of infection versus other causes. But I think what we have done at Memorial over the years and what other people have done as well, if you tend to do this consecutively and consistently, you can make comparisons.

Anyway, this set the stage and I'm sure everyone

at

else was familiar with this during a period of time, for the big three, as I call them, the E. coli, Pseudomonas and Klebs, were responsible for the bulk of the mortality in these patients. As you know, our direction of therapy was to make sure we were absolutely covering these three organisms very well.

I am not suggesting that Staph aureus was not a player or not to be considered, but it had a different mortality rate, certainly, at that time, roughly speaking, and that yeast in the bloodstream was a very often fatal event. And more than one bug in the bloodstream was, also, very often fatal and happened with reasonable frequency.

[Slide.]

What were the changes? I have kind of alluded to this a bit. The changes, as I have said, are increased gram-positive infections--and coag-negative staph is most common now as a bloodstream infection--followed by, among the gram-positive, streptococci and enterococci, which weren't on any of these lists that we have developed in the past.

Changes with respect to gram-negative infection. There is decrease of infections in many centers due to E. coli, increase in infection due to Klebsiella, particularly resistant Klebsiella in New York and other places,

at

Enterobacter that are somewhat resistant, serratia, which was not part of the general scheme before, and what is probably not appropriately called non-aeruginosa Pseudomonas.

This was made up years ago before the taxonomy was changed, but to just give you a flavor, these would be what I refer to down here as the water-borne gram-negative rods, Acinetobacter being among them, also what used to be called Pseudomonas multifilia, then got changed to Xanthomonus multifilia and now is called Stenotrophomonas multifilia and will be something else next week.

In any case, those organisms, because of the use of catheters and so forth, have come to play a large part in our consideration in these patients. This doesn't apply to our patients who are neutropenic but it is a change.

[Slide.]

Just to show you the change a little bit, these are data from about 20 years later at Memorial, albeit these are all pediatric data. This is now published in Cancer in February, 1996. The lead author is Lucas. These are a organisms causing bacteremia and fungemia in children with fever and neutropenia at Memorial for better than two, two-and-a-half, years in the early '90's.

The point is not so much what each organism is but

at

it reaffirms what I have said to you, coag-negative staph at the top of the list, almost a quarter of all of them. E. coli is still the number one gram-negative rod, but it has got a new contender here with Acinetobacter coming up here.

One of the things that is happened, and we will get into this, is that it is an exception for someone not to have a catheter rather than to have a catheter. Everyone has some catheter or some intravenous vascular-access device. So I think that has changed things to a certain extent.

In children, as I am sure Jerry Shenep will tell you, Strep viridans is a bigger concern than it is in adults and we are seeing, as others are, a penicillin-resistant viridans Strep.

I am not going to go through all of these but, basically, you can see the range of organisms and that some of the traditional organisms are rather far down the list.

[Slide.]

Factors promoting infection of gram-positive; well, I have alluded to this. The use of these subcutaneous tunnelled vascular-access devices is very much a factor. As you break the skin and so forth and have reason for the skin to become contaminated around the device, if it is not properly cared for, or the device is not handled

at

appropriately, there may be contamination with skin flora.

Wide use of prophylactic antibacterial agents against gram-negatives. Sulfatrimethoprim and various fluoroquinolones have been used for antibacterial prophylactic activity in neutropenic patients or in patients presumed to become neutropenic, at risk for having fever, and so forth.

And they have very potent gram-negative activity which has changed things in terms of gram-negs, but some of the gram-positive activity of some agents may not be as potent and, therefore, explain why we get more gram-positive.

Early use of empiric agents against gram-negatives. I would have to say we have taught our lessons well and people, in general, have been prompt in starting empiric agents heavily against gram-negatives leaving gram-positives to emerge.

Probably most important is the intensification and prolongation of chemotherapeutic regimens. As there have been advances in the therapy of these infectious diseases, the oncologists have been equally advancing within increasing the intensity and the length of these chemotherapeutic regimens.

As I will mention with the cytokines, they have

at

been able to shorten the time of neutropenia but the mucositis may not be as diminished and the portals of entry may remain.

[Slide.]

This was also Steve's slide from years ago. It just seemed appropriate to bring it. Just to show you, for those who don't deal with these things, what a catheter looks like. This part is out in the free world here, exposed to everything. And this is where the access site is, and it goes underneath the skin. This is the tunnel area and then it goes into one of the great vessels and, hopefully, not across the tricuspid valve but into the heart.

I have always been a little concerned. This isn't really germane to this, but this represents, in lots of ways, the laboratory model of endocarditis that many of have looked at over the years. All you have to do is just rough up the valve a little bit, shoot a few organisms in and you have got endocarditis.

It has been shown that this is not a problem, but it is always a potential. So I wanted to show you that.

[Slide.]

What are some of the other things that might cause changes, and that is use of prophylactic agents. So

at

catheters, and now prophylaxis. These are some data from mostly European studies that show, with the use of fluoroquinolone, various, and some not stated.

There have been reports in some of the major trials, from some of the major groups, of, indeed, isolets that were resistant over the isolates tested in varying percentages here. I just leave that to you. So it is something to be concerned about.

I am not picking out one versus the other. It is the class of compounds that I am concerned about and there is a lot of room for debate here.

[Slide.]

Here is our data from Memorial. This is going to be coming out in CID in, I assume, a couple of months, just comparing the EORTC data using fluoroquinolones and their sensitivity and resistance patterns compared to ours over the years, '92, '93, '94 and '95, suggesting, at least by inference--we didn't do statistical analysis of this because it wouldn't really be correct considering these were not comparative groups--that not having used prophylaxis on this side of the Atlantic at Memorial may have precluded the emergency of resistance so far.

We have institutions that have used prophylaxis in these patients and they have a fair amount of resistance

at

already in North America. It makes it easy to talk about it that way but I don't mean an exclusively American versus non-American point of view.

I just throw that out as something that will factor into our thinking of how we would design trials in the future. So my concept and my concern about fluoroquinolone prophylaxis is it not having great coverage for Strep, some Staph, perhaps some enterococci, certainly pneumococci, in some cases, and penicillin-resistant pneumococci. I am talking about available agents right now, Staph aureus and MRSA.

Vancomycin use will be increased. Vancomycin use has been shown to result in increased VRE, vancomycin-resistant enterococci, and what might the future hold. Vancomycin-resistant Staph aureus, vancomycin-resistant coag-negative staph, and so on and so on and so on, the nightmare we all fear.

This is my own hypothetical construct. I don't present it as fact but just as a concern that we should all take into consideration.

[Slide.]

That leads into the other changing pattern that we are seeing and it isn't just in compromised cancer patients but in the population at large in the world. Much attention

at

has been given in the lay press to the emergence of resistant organisms. MRSA, certainly, is well known to all of us.

Multiply antibiotic-resistant enterococci, particularly VRE, vancomycin-resistant, is a big issue and is reshaping the way we use, or should think about using, vancomycin. I am mentioned that a bit.

Penicillin-resistant pneumococci. There is now a fair amount of chatter on the internet about very broad-spectrum, third-generation, cephalosporin-resistant pneumococci as well, ceftriaxin. It is unofficial but it is being talked about. It has to be proven.

Antibiotic-resistant Enterobacter, I have referred to. Pseudomonas and Klebsiella such as Jim Rahal described in New York, the 1026, ceftazidime-resistant Klebsiella. That is not so much of concern for our neutropenic patient as MDRTB--a definite concern but not the point of our topic this morning as acyclovir-resistant herpes viruses.

[Slide.]

Then yeasts; we are mainly talking about antibacterial activity but I can't help but mention yeasts. We are seeing an increase in infectious due to yeasts, more common now than nosocomial aerobic gram-negative bacillary blood-stream infections in some centers.

at

I will show you this data in a few minutes that show you that this is so. In other words, yeast from the blood stream as a cause of nosocomial bloodstream infection in this country has been now, for about six years, more frequent than any gram-negative rod from the bloodstream. That is a change from the way it was back in the '60's and '70's and has a large impact on how we do things.

Increase in hepatosplenic candidiasis. Increase in non-albicans Candida infections. Maybe this has to do with the fact that organisms like Candida krusei or Candida glabrata or Torulopsis glabrata, depending on what you believe the taxonomy is there, are, indeed, intrinsically resistant, particularly krusei, to azoles and so it would be natural that you would expect them to be more of a problem.

The association of various organisms with venous-access devices. Some strange names, Malassezia furfur, Rhodoturula rubra, and so forth. There are many others, too.

[Slide.]

This is that list I thought I would mention. A bunch of us sat around the table at lunch one day and tried to think up how many more than-three-syllable fungi we have recovered from people that initially were thought to be contaminants and then were proven to be invasive.

at

I won't go through this but it is quite something. I now tell the house staff that when they get a call from the lab where it is on the computer, which is the more modern way of doing things these days, they shouldn't dismiss as a contaminant an organism with more than three syllables that they can't pronounce but they ought to call an ID consult.

[Slide.]

This is the data from NNIS. This is a little bit old now--it is from 1988--but it shows you nosocomial bloodstream infections, most frequently associated pathogens. As you would expect, coagulase-negative staph represents a quarter of the bloodstream infections and Staph aureus is next, 15 percent.

But virtually tied for third place are enterococci and yeast, here at 7.9, 7.7. It is pretty close, a dead heat. As you have heard, they are both organisms that we have come to expect as problems in the '90s and into the 21st Century. So it is ahead of E. coli, ahead of Enterobacter, Pseudomonas and Klebsiella. So I would keep an eye on that.

This is not in cancer patients exclusively. In fact, in these studies, they are pretty much exclusive of cancer patients. I don't believe centers include, or

at

included back then, the comprehensive centers very much at all.

Another way to look at this would be comparing NNIS data from 1980 to 1990. Bloodstream, I have alluded to, a six-fold increase, roughly speaking. Surgical-wound infections, almost trebling. Lower respiratory-tract infections, a 50 percent increase. Urinary-tract infection more than doubling, in terms of numbers per number of discharges in these patients.

[Slide.]

That you are going to have trouble reading. These are just the factors that might be associated with why we have more fungal infections. I have alluded to this prolonged mucosal damage from chemotherapy. Keep in mind that as cytokines are being used, more chemotherapy, heavier doses, dose intensification is increased, and so there may be more mucosal damage.

Also, viral infections. We are much more aware now that preexisting herpetic lesions, the mucosa and so forth, may well lead to such portals of entry for fungi. Increased use of corticosteroids in terms of supportive measures is well described. Increased periods of prolonged neutropenia, from what I have just described from more intensive chemotherapy and increased use of broad-spectrum

at

agents and central venous devices and TPN.

I won't dwell on these but these are things to think about, malnutrition being the actual thing here that that is a surrogate for.

[Slide.]

Much of this repeats itself. I will try and weave this now into what will be the second part of that introduction thing that says future trends. I have talked about cytokine use. I think that has changed the landscape quite a bit. Probably we are going to have to be concerned about how it is used.

The official documents of ASCO and IDSA have said it shouldn't be used except in extreme situations but surveys within ASCO, the Oncology Society, suggest that it is used by many of the members. So that is going to figure into how we design trials.

A new thing to be concerned about is IV antiinfective will be used in the outpatient setting. It will no longer be the strict clinical research center sort of milieu, if you will, of the inpatient setting. The controls won't be quite as stringent. It will be more difficult. It means we are going to have to make house calls or get to see these people in their home environment. It won't be as controlled and I think that has to be

at

factored in.

There will be oral antiinfective used, both as inpatients and outpatients. This is not fantasy. This is being done at M.D. Anderson and other places and we are moving towards that rather quickly ourselves as are others. So that is going to change things.

Hopefully, diagnostic techniques will be improving such as imaging that will lead us to making specific microbial diagnoses more often and, certainly, clinical diagnoses more often. We all hope that there will be more rapid microbial detection and identification with some of the new technology with PCR and so forth.

[Slide.]

One of the things that I, personally, have a problem with is the concept of empiric therapy versus directed therapy. I think that underlines some of the controversy that is before us.

Quite frankly, if we have someone who comes to us and, again, I will use the house staff way of describing things--I say to them, somebody comes in, you work them up, you do all the usual things, all the things you were taught to do in school, a history, physical and collect the lab data and then you go through it.

If, indeed, at the end of all that, and you have

at

done it rigorously, you cannot find anything that suggests a focus of infection, then you use empiric therapy. We often forget that therapy is directed when we, say, find somebody who--I will pick something out--has some element of cellulitis, even the slightest amount in a neutropenic patient, around the broviac or Hickman site.

All the argument about whether to use vancomycin or not to use vancomycin can be really modified by deciding that using vanco when somebody has redness around their broviac catheter site is what I would call directed therapy. That is not empiric therapy.

You are making sure that at least you are covering what you see, what you have found. This can get even more complicated, and so forth.

This also has led, with increased techniques, to make these specific diagnoses; in other words, we have more opportunity to do that. There are less patients who are vaguely out there and so forth, although, if you look at the numbers, it seems that there are as many fevers without a source, which may sound contradictory.

Anyway, I think this issue needs to be addressed whether we include just empiric or we call it directed.

[Slide.]

at

Design must take into consideration the degree of risk for the patients. This has been alluded to in the past when we talk about we would stratify, say, for leukemia versus solid tumor. That is perfectly reasonable. Jerry Shenep is going to talk about differences among kids and adults.

You could also talk about a newly diagnosed disease versus relapsed disease. Allogeneic transplants versus autologous; that is pretty straight forward. Patients who have received prophylaxis for bacterial infection versus those who did not.

That is probably all summed up in the last line which is the approach we are using to find out who are the patients who can, indeed, have outpatient therapy. We would call them low-risk patients, patients whom we intuitively know are low-risk meaning they don't present with shock and so forth and so on.

There have been many studies, some in Boston, M.D. Anderson, and we have done a review ourselves--and I don't mean to leave anybody out, but there are many studies that have looked at this. I think we can actually define what low risk is and that will have to figure into how we conduct the trials in these patients in the future.

I think that represents one of the biggest

at

challenges to us because that encompasses the whole idea of outpatient therapy as well. In other words, if we just took all the low-risk patients and studied them, everything is going to look good no matter what we do. That has been the problem, I think, is that we have been mixing apples and oranges in the past. I am sure others will agree.

This is an opportunity to sort that out in a more physiologic way, I think.

[Slide.]

The enrollment of patients. This is the part where I picked out a few things that I want to point out. From the document, it says, "Ideally, all consecutive patients presenting to the investigator should be enrolled in order to avoid bias. Evaluation by episode is acceptable but outcome should ideally be assessed both by episode and by patient.

I think that is done, but it has to be reinforced. But, back to this point about consecutive patients, I think this is my concern here. That is enrollment bias. Sometimes, there is a tendency for the research nurse or the principle investigator basically to enroll people Monday through Friday, 9:00 to 5:00.

Well, the kind of person who shows up in the emergency room at 3:00 in the morning, who got out of bed

at

and got in a cab or got in an ambulance and came is not, necessarily, the same kind of patient who got admitted from clinic who happened to be there and who was neutropenic and febrile.

If we don't enroll people consecutively around the clock, and rigorously, we are not going to be putting the sickest patients in our studies. I have seen this over and over again. I am guilty of it. We are all guilty of it, in a sense. So I think this is an important thing to make sure that this aspect of things is supported in doing such studies.

[Slide.]

So, in summary, the changes--and this won't cover all of them--include cytokine use which, in my mind, shortened the period of neutropenia. I think that is demonstrable and true. Allow for dose intensification, more frequent cycles of chemotherapy but leave prolonged mucosal damage there, especially when we are talking about the G's, GCSF, and so forth.

Use of indwelling vascular-access devices is very much a part of the landscape. It is exceptional that they are not used. The use of antibiotics in the outpatient setting, IV and oral. There is very good opportunity with home care to do it IV. I think with the newer agents coming

at

out orally, and some existing already, there is ample opportunity to pick our low-risk patients.

I have mentioned the changing patterns of organisms. Gram-positives are increased in many centers. Gram-negatives are decreased although I must say in our center, we still have plenty of gram-negatives. And there are the highly-resistant organisms.

Most importantly is the variation at different medical centers which, I think, needs to be taken into consideration.

Thank you very much.

DR. CRAIG: Thank you, Dr. Brown.

We will go on and have Dr. Shenep also make his comments and then we will have time for questions.

Dr. Shenep.

Febrile Neutropenia in Pediatric Patients

DR. SHENEP: Good morning.

[Slide.]

My comments are going to be very brief today. You will be happy to hear that. I am just going to focus on the issues that are unique, or at least more important, to the child with neutropenia rather than an extensive review because I think Dr. Brown's comments in general apply to the child with neutropenia. I can add just a little bit more to

at

that from our perspective in dealing with the pediatric population with febrile neutropenia.

First of all, the pediatrician loves to say that the child is not simply a small adult. But if we were arguing in this arena, we might have a hard time winning our argument because in the febrile neutropenic patient there are striking similarities between the child and the adult. My opening remarks will be just to emphasize that, that there are a lot of similarities in febrile neutropenia in adults and pediatric cancer patients.

There are some minor differences, however, and we will mention those. Then I would just like to comment about the advantages and limitations of monotherapy which, I think, is pertinent to the discussion here today.

[Slide.]

Just to emphasize the similarities; it is clear that the degree and duration of neutropenia is what determines the incidence of infection in the neutropenic child as well as the severity of mucositis. In our center, we have found that mucositis is just about as important as the degree of neutropenia, if not more important, in determining the risk of infection.

The pattern of infectious organisms that you see in children and adults is strikingly similar and the use of

at

empiric therapy in these populations is very similar. There is only one set of IDSA guidelines. There is not a set for adults and a different set for children.

Successful outcome is highly likely in both the child and the adult.

[Slide.]

There are some differences. They are minor differences but, in some cases, they might be important relative to today's discussion. First of all, fever remains unexplained in a higher proportion of children than adults. My internist colleagues like to say that that is because they are better clinicians than we pediatricians and they are diagnosing more of their patients with infection than we are.

But I would rather think that the populations are different, that, perhaps, children have more viral infections that we are unable to diagnose or have other reasons for fever.

There is one advantage in pediatrics that we have and that is our patients tolerate therapies, in general, much better than adults do so that we can get by with using aminoglycosides and get by with using amphotericin B sometimes even simultaneously better than the internist can in the adult. In general, the younger the child, the better

at

they tolerate multidrug therapy.

Another important difference is there is a slight increase in the incidence of viridans streptococcal bacteremias in children but, very strikingly, there is a huge difference in the amount of septic shock that occurs with viridans streptococcus compared to adults.

This is not explained, not well explained, why children tend to go into shock with this organism more so than is seen in adults. But it is something that would be of concern.

[Slide.]

So I wanted to spend just a little time talking about viridans streptococcal sepsis. I think Dr. Brown anticipated that I might mention this topic.

First of all, what are the factors that predispose to viridans streptococcal sepsis. Prophylaxis with trimethoprim sulfamethoxazole, which is almost universal in our population at St. Jude, or a use of fluoroquinolones which we do very seldom.

These are agents, though, that will predispose to viridans streptococcal sepsis. A profound neutropenia. Use of antacids or histamine type-2 antagonists. Severe mucositis and even beyond the degree of mucositis that it causes, cytosine arabinoside, or ara-C, is known to

at

predispose to the development of viridans streptococcal sepsis.

Again, while the child has a little bit more bacteremia than the adult, the child is much more likely to go into a septic shock or have a fatal illness with this organism.

[Slide.]

This is a study that we did now almost ten years ago at St. Jude in 101 children. This is a study in which patients were randomized to receive the combination vancomycin, ticarcillin, amikacin compared to ticarcillin, clavulanate and amikacin.

What prompted us to perform this study is, at that time, vancomycin on patent. It was very expensive. We really felt that we didn't need to use vancomycin in our patient population and we set out to prove this in a study and ended up proving the opposite for the time and the population that we were dealing with.

With the vancomycin-containing arm, we had one breakthrough bacteremia that was inconsequential with coag-negative staphylococcus on five days into therapy for febrile neutropenia in this child.

In contrast, in those patients that received ticarcillin coagulate and amikacin, we had nine

at

breakthrough bacteremias. Five of these were coag-negative staphylococci and these children were easily treated with the addition of vancomycin.

Four of these patients, however, broke through with viridans streptococcus. Two of those incidences were extremely life-threatening. One of them was fatal. This child right here, just to try to put a face on some of the these statistics, was a ten-year-old girl with leukemia who came into the hospital with febrile neutropenia.

There was no source of infection to be found at the time of admission. She promptly became afebrile after starting therapy. We were blinded in the study. This was blinded study. Dr. Brown would be happy to note that we did admit patients to this study 24 hours a day, seven days a week.

But this child came in, was randomized. At the time we didn't know it, but she was randomized to the ticarcillin coagulate, amikacin arm. Her initial blood cultures were negative. She became afebrile. She was doing quite well on day 3 of therapy. About 10 o'clock, on a Friday morning, her fever spiked up to about 41 degrees centigrade and her blood pressure dropped to about a systolic of 40.

She was immediately rushed to the intensive care

at

unit and started on vancomycin, amikacin and ticarcillin now in open-label therapy. By 2 o'clock in the afternoon, she was dead of overwhelming sepsis. She had three blood cultures that grew out viridans streptococcus so I think there is no doubt of what happened here.

What is surprising is that the organism that she grew out, while it was resistant in vitro to penicillin, it tested susceptible to ticarcillin coagulate in the test tube. Obviously, there was clinical failure but it highlights the fact that the in vitro testing may not be reliable when it comes to viridans streptococcus.

[Slide.]

Now, giving you some anecdotal experience from St. Jude, we have had literally hundreds of patients on vancomycin throughout the years. We have never had a breakthrough with viridans streptococcus on a patient who was receiving vancomycin.

We have had quite a number of patients on cefotaxime and we have never seen a breakthrough. We have had two patients who were on ceftazidime without vancomycin who did break through with viridans streptococcus but did not have shock at the time. They merely had positive blood cultures.

We have had a number of patients in a study that I

at

will briefly mention next who received oral cefixime and we have had no breakthroughs with viridans streptococcus there. So it does seem that one can adequately treat with third-generation cephalosporins, but there is some caution and the two patients that have broken through on ceftazidime keep us very alert to this possibility.

[Slide.]

Just to mention to you and, perhaps, reinforce some of Dr. Brown's comments about selection of patients, we certainly have recognized that there is a high-risk and the low-risk patient. We have designed a study that has looked at using monotherapy not at the initiation of therapy but after 48 to 72 hours of hospitalization.

So we looked at patients, children, who came in with febrile neutropenia that was unexplained. If, after 48 to 72 hours of intravenous antibiotic therapy, these patients had negative blood cultures and we had been unable to establish a source of infection, a negative chest X-ray, not colonized with *Pseudomonas aeruginosa* or methicillin resistant *Staph aureus*.

Those that had those risk factors were excluded from the study. Those that did not have that risk factor were randomized to either continue their intravenous regimen which, in most cases, would have been vancomycin, tobramycin

at

and ticarcillin, or vancomycin and ceftazidime in patients with renal dysfunction.

Or, they switched at 48 to 72 hours to oral cefixime therapy, again realizing these patients are not colonized with *Pseudomonas aeruginosa*. We randomized 200 children in this fashion.

[Slide.]

The outcome is those that recovered with an ANC over 500 without having to change therapies; there were 27 out of 100 patients that continued on IV therapy who were not successful and 28 out of 100 patients who were treated with oral cefixime therapy who were not successful.

You can see that that is statistically equivalent. But, again, these are very selected patients. These are not all comers.

[Slide.]

The reasons for failures; if a patient had become afebrile and suddenly spiked a fever, reminiscent of the 10-year-old that I told you that died, we were unable to tolerate having that child on oral therapy. We instituted intravenous therapy. So a new episode of fever would fail you for oral therapy and the equivalent of that in the intravenous therapy although, if they were on IV therapy, we would usually continue to watch them if it was early in the

at

course and we weren't worried about fungal infection, it was equivalent.

So the two therapies were about equally successful in preventing new fevers.

There was only one breakthrough bacteremia in all 200 patients. This was a breakthrough with a multiresistant *E. coli* from a patient from South America. That child had fever and a positive blood culture but did not have shock or any other worrisome symptoms.

There were new focus of infections that were not microbiologically defined in five patients in total, and so forth and so on. The bottom line is that you can treat selected patients with an oral monotherapy agent and do quite well in this setting.

[Slide.]

What are the advantages of monotherapy? Certainly there is reduced toxicity. There is ease of administration and cost savings and we are very aware of that having used very expensive regimens. One can save a tremendous amount of money with monotherapy that only has to be administered a couple of times a day.

The therapy is quite adequate for the stable patient in the absence of infection with resistant bacteria and there is an overall reduction of antibiotic usage and

at

preservation of antibiotic activity.

The other side of the coin of our heavy use of vancomycin at St. Jude is that we have now started experiencing vancomycin-resistant enterococcal bacteremia. This has led us to be much more selective in our use of vancomycin. I guess there is never an easy solution in medicine so whatever course you take, you pay a price one way or the other.

I suppose our price is that we now have some vancomycin-resistant enterococcus in the institution and we are trying to limit our use of vancomycin because of that.

[Slide.]

There are contraindication, I believe, to monotherapy. One of the concerns I had as we were going to through the material about cefepime is that there has been a lot of emphasis on what we are looking at as the endpoint. But to, again, echo Dr. Brown's comments, I think just as important or, perhaps, more important, we need to decide what is the beginning point, what are the patients that we are going to call febrile neutropenia, when are we really using empiric therapy.

I would suggest, as a starting place, that if I had a child that came in into the clinic with neutropenia and fever but they were in shock, I would not be satisfied

at

with the use of monotherapy with any agent that you can name. I would want to cover broadly with probably three antibiotics in that situation.

The same goes for the patient who is hypotensive and, perhaps, in impending shock. If there are skin lesions that make me think the child has septic emboli, if there is a life-threatening pneumonia on chest X-ray, or if you have reason to suspect, such as the example that Dr. Brown gave with the Hickman catheter that has the cellulitis about the catheter, if you have concern about Staph aureus or methicillin-resistant Staph aureus, or cephalosporin-resistant pneumococcus or viridans streptococcus that can be resistant, Pseudomonas aeruginosa, enterococcus, other resistant organisms, these may not be patients that you would want to use monotherapy in.

I would just end in saying that, again, I would think that one of the things that has to be carefully considered is that the patient that is a candidate for monotherapy should be stable and there should be no evidence of resistant infection in those patients.

I will stop there and move on from here.

DR. CRAIG: Thank you.

We are running just a few minutes behind but I will entertain a few questions for our speakers.

at

Specifically, I guess, I would have one from adult medicine. What are the trends, now, in terms of monotherapy versus combination therapy. We have heard about going to oral, but is there also a trend, now, more to go to combination, or stay at combination and more to go to monotherapy?

DR. BROWN: If we take into consideration Jerry's comments, I think the trend has been towards monotherapy. But I agree with Jerry completely that one has to select those patients carefully. To the extent that you can select the high-risk patient out of that group, I think the trend is appropriate.

DR. SERODY: I would agree with that with the exception that I think one of the problems here is you really do have to look at the high-risk versus low-risk folks. I think in the solid-tumor setting, the main emphasis now among oncologists is to use monotherapy.

In the transplant setting, we would never use monotherapy. When we looked at our last 300 transplant patients, about 15 percent were bacteremic, half of which had viridans streptococci, all of whom had mucositis. There is no way to tell who has viridans streptococci. Mortality of that, in our setting, is 20 percent.

So we would never use monotherapy for those individuals.

at

DR. ZINNER: I think the last two studies of the EORTC, at least, are suggestive--well, the last one study that we did look at monotherapy certainly did not show a difference between monotherapy with imipenem and ceftazidime plus amikacin combination.

So I am not so sure that I share all of those concerns since one can either, in the case of combination therapy where you don't need the aminoglycoside anymore, you can stop it after three days. Or similarly, one could add it after two or three days. Certainly, with respect to the vancomycin in the EORTC trial, which was predominantly an adult but not exclusively, addition of vancomycin back at two or three days if the patient was failing and had a resistant organism, showed very good success rates of that approach.

So it is really sort of complicated. But I would agree with you that monotherapy is increasing, certainly, in most of the country.

DR. CRAIG: Any other questions? If not, then, let's move on to the sponsor presentation from Bristol-Myers. Dr. Smaldone will begin.

Sponsor Presentation

Introduction

DR. SMALDONE: Good morning.

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

at

[Slide.]

Dr. Feigal, Dr. Craig, members of the committee and the FDA, we are here this morning to turn our attention to the point of discussion today which is cefepime, or Maxipime, and the supplemental NDA for the empiric treatment of febrile episodes in neutropenic patients.

[Slide.]

I would like to briefly go through the chronology of Maxipime. Maxipime was officially approved in the U.S. in January of 1996. Shortly thereafter, we had a pre-NDA meeting with the agency to discuss the possible filing of the febrile neutropenic supplement in April of '96 which brought us very quickly to the advisory committee here today.

[Slide.]

Cefepime is an injectable cephalosporin which has been developed by Bristol-Myers Squibb Company and has some critical features important to the treatment of febrile episodes in neutropenic patients. It has very broad coverage of gram-positive and gram-negative organisms and there is a very extensive clinical experience both in clinical trials and in practical experience for treatment of a variety of indications.

Cefepime is currently indicated in the U.S. for

at

treatment of moderate to severe pneumonia, complicated and uncomplicated UTI, uncomplicated skin and skin-structure infection and bacteremia associated with some of these conditions.

[Slide.]

Cefepime, as was mentioned earlier, is the first antibiotic to be officially reviewed for this indication based on the 1992 IDSA guidelines. You will hear today a very extensive evaluation of cefepime used both as monotherapy and combination therapy in this indication.

[Slide.]

I would like to introduce our international panel of consultants with whom we have had many active discussions on the data and this indication. I would like to point out Dr. Thierry Calandra and Dr. Howard Gold who served as the independent blinded reviewers of the data.

[Slide.]

This is the outline of the presentation from the company. My name is Laurie Smaldone. Dr. Stephen Schimpff from the University of Maryland will present for us the historical perspective of febrile neutropenia.

The methods used in our analyses will be presented by Dr. Claude Nicaise from the Antiinfective Clinical Group. Dr. Rubin Ramphal from the University of Florida will

at

present the results. And we will conclude at the end with Dr. Nicaise and entertain questions at that point.

Thank you.

I would now like to present Dr. Stephen Schimpff who will present the historical perspective.

Historical Perspective

DR. SCHIMPPFF: Good morning.

[Slide.]

I was very honored when Bristol-Myers Squibb asked me if I would give an historical background on the area of infection in neutropenic patients. I think, probably, I should give you just a 30-second background on myself for those of you who do not know me.

I am the Executive Vice President of the University of Maryland Medical System and I a professor of medicine, oncology and pharmacology. My background is in internal medicine and I have boards in infectious disease and medical oncology.

For a long number of years, I was involved pretty much exclusively in the area of infections in the cancer patient but, in recent years, I have been more involved in medical-center management, if you like. But this is still my first love.

What I would like to ask you to do is, in your

at

mind, go back about 30 years. For me, I want to go back to about 1969 which was when, having left medical school, I finished my residency and I was fortunate enough to get chosen to the National Cancer Institute. They assigned me to the Baltimore Cancer Research Center which was a center primarily for the very aggressive treatment of cancer patients with new agents.

[Slide.]

When I got there, I was assigned, unlike my colleagues who were doing the direct care of patients, to the intensive care unit and asked if I would initiate some studies into septic shock.

Now, septic shock and infectious death, as we have all heard, were very common among neutropenic cancer patients. The reason I ask you to go back in your mind and just recall that the way we were all trained was you don't start antibiotics unless you know what the infection is, you know the site of infection.

That was drilled into all of us. At that point in time, empiric therapy was not the standard. As Dr. Shenep said, trying to get sort of a sense of a picture of the patient in your mind might help, so I want to present a patient to you. It is a true patient although I have changed the patient's name and I had a colleague stand in in

at

these photographs.

[Slide.]

We will call this Mr. Miller. He had just retired from the railroad. During his retirement exam, they found that he was a little bit anemic and had some funny cells in his blood count and so they referred him to us.

[Slide.]

He got some tests done.

[Slide.]

He found out that he had acute leukemia. He was not pleased by that. He was treated very aggressively with cancer chemotherapy.

[Slide.]

As it turns out, once he got the chemotherapy in a couple of days, he started feeling reasonably well. He usually wore street clothes, as you can see here, and he would kind of wander around the hospital. My point is, of course, that he looked and felt relatively well.

[Slide.]

On the tenth day of his hospitalization, about 4 o'clock in the afternoon, he developed a temperature to about 100.6 degrees. When his physician went to see him, he was found laying on the bed, over the covers, not under. He said, "You know, I just don't feel quite right. But that is

at

all I can tell you."

The rest of the history was negative. The physical exam--a very good physician, incidently--a very careful physical exam was completely negative. Urinalysis was negative, looked at by the physician. The chest X-ray was negative.

He had just had a platelet transfusion about 2:00 in the afternoon. The physician made the decision, "Maybe it is a platelet-transfusion reaction. Let's just watch it." By 7 o'clock that evening, his temperature was down a little bit. It looked like maybe that was the right decision. The doc went home.

It turns out in the middle of the night, his temperature started to come back up again. It is recorded in the chart, but no physician saw him in the evening.

[Slide.]

When morning rounds occurred, around 8:15 in the morning, he was in obvious septic shock. At that point, a reexamination showed that, in fact, he had a very subtle, but very real, perianal cellulitis, the inflammatory response being so poor in these patients. Remember, he has no circulating granulocytes in aplastic marrow, but, nevertheless, minimal but clearly there perianal cellulitis.

At this point, he gets multiple broad-spectrum

at

antibiotics, fluids, blood, pressors and so on.

[Slide.]

But, by noontime, he has met his maker, only 20 hours from the time of that first low-grade fever. It turns out that the blood cultures came back *Pseudomonas aeruginosa*. The two cultures both--we were doing some quantitative cultures then--both had more than 200 colonies per cc which is very high for gram-negative.

But here was a guy that looked relatively well and just said, "I don't feel quite right."

[Slide.]

I think there are some implications to Mr. Miller's story, obviously that fever is frequently the only early evidence of infection in these patients. If you repeatedly reexamine them, tomorrow or the next day, repeat X-rays, exams and so on, frequently, although not always, define the site of infection.

The patient may have bacteremia yet, as Mr. Miller showed us, may appear relatively well initially and, very importantly, the patient will progress to sepsis and shock and death quickly if not treated rapidly.

I will take you back to myself, just having gotten to the cancer center and having been assigned to the intensive care unit, I was starting to see a number of

at

patients like this. It seemed like maybe the thing to do was, rather than try and treat septic shock, why not try and treat something earlier.

But, again, the approach was not to treat until there was more evidence. I went to the senior physician and just asked him what his experience was. It was just what Arthur presented earlier. He said, "Well, there are about four bugs cause most of the problems. It is E. coli, Klebsiella, Pseudomonas and Staph aureus."

I went and asked the nurses. They said, "Yeah. But it is really Pseudomonas. That is what brings them in and knocks them off." Those were their words.

I decided I would ask some of the patients. They seemed to know, too, at least the patients who had been around for a while. They said, "Well, it is Pseudomonas something. We don't know just what it is but we do know this. If you get it, they take you down to that intensive care unit and there is only one way out. It is through the morgue."

So it seemed like everybody seemed to know what the issue was and what the problem was.

[Slide.]

So I decided to do a little chart review of the Pseudomonas bacteremias that had occurred in the previous

at

year, 1968 and the first half of 1969. It turned out there were 22 episodes among neutropenic patients. They had not been treated empirically but, to the extent they did receive an anti-Pseudomonas antibiotic, it was one of the polymyxins.

As you can see, 21 of those 22 patients died and half of them died before the results of the blood cultures were known. This seemed to clearly have the implication, then, that empiric therapy was the right thing to do.

Gerry Bodey had been talking about it and writing about it for a number of years but, again, there was this really strong feeling that this was not the right thing to do. It just wasn't the standard of the day.

These were the days when gentamicin and carbenicillin were investigational. They were available to us. The idea was, at that point in time, "Gee; gentamicin should cover that waterfront of those four key organisms." You could add on the carbenicillin for the extra activity against Pseudomonas which would, also, have some synergy and maybe that would be useful.

So, the study was put together but, frankly, it took five months to convince my first-year clinical associate colleagues that it was appropriate to try empiric therapy. Frankly, they just needed to see a number of Mr.

at

Millers before they would be convinced to go ahead and do this.

[Slide.]

But, anyway, we got it put together. Patients with advanced cancer receiving chemotherapy, many--not all, but most--had acute leukemia, granulocytopenia, febrile. We treated 75 consecutive patients day and night, weekends, with carbenicillin, gentamicin.

[Slide.]

If we just look at the Pseudomonas here. This is the curve of the 22 patients I just showed you. Here are the patients using carbenicillin and gentamicin. It is not a controlled trial. It is historical data. It is the only uncontrolled trial I was ever involved with.

Nevertheless, it was pretty striking. As it turns out, it got written up in the New England Journal of Medicine and I think because of where it got written up, it sort of helped push the idea of empiric therapy. Again, as I say, I was clearly not the first one. There were others and I am going to talk about that more in a few minutes.

[Slide.]

I presented Mr. Miller to you. Is he an aberration? Was that just really an unusual patient? I kind of look at what I call the rule of 20 percents which is

at

if you look at a large number of patients who were febrile and neutropenic, you can generally divide them up more or less into these categories, that about 20 percent will have a bacteremia, 20 percent will have a microbiologically documented infection without a bacteremia, another 20 percent clinically documented, 20 percent FUO. 20 percent, in retrospect, probably were not infected.

This is based on now you have examined the patient multiple times. The cultures are now back and so on. These percentages change dramatically. I think both Arthur and Gerry have pointed that depending on if you like the local epidemiology. It really varies from institution to institution based on how many bone-marrow-transplant patients or acute leukemia patients versus solid tumor, and so on.

Combination therapy, beta lactam, aminoglycoside, was the standard for quite some time going on into the early 1980s and still is a common standard today. The changes over time were more potent, if you like, more broad-spectrum, beta lactams with the various aminoglycosides.

But then, in the early 80's, and mid '80's, came some studies of monotherapy.

[Slide.]

at

Let me just go through the obvious rationale. Avoid the toxicity of the aminoglycoside, both nephrotoxicity and ototoxicity. Ototoxicity; we don't think about that much but it is actually pretty important in these patients who come back time after time after time for repeat chemotherapy. Pretty soon, they say, "I can't quite hear what you are saying, Doc."

Simplify the therapy for patients and caregivers. But, truly, the issue here is that the advent of broad-spectrum--and I should have put up here more potent--beta lactams with good bactericidal activity. Appropriate pharmacokinetics; what I mean by that is that there is a bactericidal activity in the serum that is effective against the commonly infecting organisms and a good safety record.

[Slide.]

Let me just very briefly show you ceftazidime versus a combination and imipenem versus a combination, just picking out two examples. There are many in each case.

[Slide.]

This is from the National Cancer Institute. It is a little fuzzy down at the bottom there, but Phil Pizzo's study. Jim Hathorne who was involved in that is here. The study was fever granulocytopenia, randomized to a

at

combination of three agents versus ceftazidime.

[Slide.]

There were a large number of patients. 282 got ceftazidime, 268 got a combination. Here are the documented infections. I think many of you are probably familiar with the definitions that have been used there; success without modification--in other words, only the original combination; equivalent success rate here.

Many patients had a modification. That might be the addition of amphotericin, the addition of vancomycin, the addition of acyclovir. Again, equivalent response. And failure, around a 10 percent failure rate. So a very similar response in the two regimens.

[Slide.]

If you look at those patients who had unexplained fever, 190 and 240, the same thing, equivalence between the two regimens. This was printed also from the New England Journal of Medicine and it really, I think, got the ball rolling on the idea of monotherapy, particularly ceftazidime.

There are now a good number of studies that have been published about ceftazidime. I wrote 1,000 here but it is probably closer to 2,000 patients that are in randomized, prospective controlled trials that have been published

at

comparing ceftazidime monotherapy to various combinations in all of them, no detectable difference in efficacy for response or survival.

There is a large metaanalysis that has been published and a large study by Dupaw in the Annals of Internal Medicine that looked at ceftazidime versus piperacillin/tobramycin. Again, no differences. So there is, I think, a lot of data showing the equivalence of monotherapy with ceftazidime versus combinations.

Briefly, let me just talk about imipenem here. A study that was done at the University of Maryland Center by Jim Wade. Again, cancer, fever and granulocytopenia, randomized, double-blind study to imipenem versus combination.

[Slide.]

If we look at the bacteremias, equivalence, 57, 60 percent. Without bacteremia, again equivalence. Clinically documented, equivalent. There are no statistically significant differences here. Overall, 78 versus 75 percent.

The definitions here are different than the Pizzo definition. They are very close to the IDSA definitions where any change equals a failure. So clinical deterioration, death or a change in antibiotic regimen would

at

be a failure.

[Slide.]

What is current practice today? This is my opinion of what current practice is of talking to a lot of people around and some marketing surveys that Bristol has done, but, principally, it is my own survey of people that I know around the country, both practicing in the community and in academic centers, that monotherapy with a potent, broad-spectrum beta lactam such as ceftazidime or imipenem is now considered appropriate initial therapy, for most--for most--febrile neutropenic patients.

Again, however, there is the issue of local epidemiologic considerations which may favor the addition of another agent. That might be an aminoglycoside. It might be a glycopeptide. And it really depends upon the patient. I think it is the point that Arthur made before about directed versus empiric therapy.

When you have data, you use the data.

[Slide.]

The point about the changing spectrum of infections. Down here, EORTC, International Antimicrobial Therapy Cooperative Group, a group that was put together by Dr. Klastersky who is here, Dr. Tattersall from Australia, Dr. Gaya from London and myself back in about 1972. The

at

first study started in 1973.

What you see here is, looking at the bacteremias from that study and a study that started in 1992, to just give us some time spread here, that back in 1973, 71 percent of the bacteremias were gram-negative. 29 percent were gram-positive, so just basically a reversal of that; now 33 percent gram-negative, 67 percent gram-positive.

Here is what they are. I won't read them to you. The increase in streptococci, coagulase-negative staphylococci, decline in E. coli. Again, a very great variation from institution to institution, the type of therapy, and so on.

Steve Zinner, as he walked in this morning, looked around and said, "It looks like the meeting of the Neutropenia Club here," and then reminded John Klastersky and myself that almost exactly 20 years ago, the three of us were staying--well, we were in a room upstairs here. I heard some slight negativism about this hotel, and that is the way we remember it, also, from 20 years ago.

But that is when we put the data together about this first EORTC study. I kind of blanked out that particular room.

[Slide.]

Just quickly to summarize; prompt empiric

at

antibiotic therapy has proved to have a major impact on the survival of febrile neutropenic patients.

[Slide.]

Secondly, fever is frequently the only sign, initially, of infection in these patients although if you repeatedly examine them, I believe, that in most patients, you will find the site over time.

As Arthur pointed out, and I didn't show a slide on this, but infection, incidence and severity is inversely related to the granulocyte count. A fairly limited number of organisms cause most infections which means that it is possible to cover the bulk of the waterfront with empiric therapy.

[Slide.]

Finally, large comparative clinical trials do demonstrate that a potent beta lactam is adequate initial therapy for both--again, most febrile neutropenic patients.

[Slide.]

We are going to go on to methodology but we can take a moment, if you have questions at this point.

DR. CRAIG: Any questions from members of the committee or consultants?

DR. SCHIMPF: In that case, we are going to go

at

on. Dr. Claude Nicaise from Bristol-Myers Squibb is going to go through the methodology.

Methodology

DR. NICAISE: Good morning.

[Slide.]

I will try to present in a few minute how the methodology applies to the clinical studies that we are including in the cefepime submission. But first, let me summarize some of the data that Dr. Schimpff just presented. Clearly, the empiric use of antibiotic therapy in febrile neutropenic patients is associated with a significant clinical benefit.

We have seen that potent beta-lactam antibiotics are adequate initial therapy in this indication. This was particularly illustrated for ceftazidime which has become the standard therapeutic approach in this indication.

[Slide.]

If one looks at the intrinsic properties of cefepime, it has the characteristic necessity for successful treatment in febrile neutropenic patients. Cefepime is a beta-lactam antibiotic. It is bactericidal and it has a broad spectrum of activity that encompasses gram-positive and gram-negative pathogens that are frequently identified in neutropenic patients, in particular the

at

methicillin-susceptible staphylococci, most of the streptococci and *Pseudomonas aeruginosa*.

Finally, cefepime has an excellent safety record demonstrated from the clinical-trial program as well as from post-marketing experience.

[Slide.]

The database supporting the role of cefepime in these indications comprise seven randomized studies conducted between June, 1989 and June, 1995. These studies were conducted at multiple sites in Europe and in the United States.

[Slide.]

In order to ensure consistency in disease definition, evaluability criteria and outcome measures, a blinded evaluation was performed by an independent reviewer. This assessment was done across all studies and became our primary evaluation.

All criteria were derived from the Infectious Disease Society of America and the Immunocompromised Host Society guidelines and were applied to all studies except one which included cefepime in combinations with amikacin and this study will also be described later.

This study was, however, independently reviewed by the principle investigator who assessed all patients who

were randomized and treated.

[Slide.]

The definitions used in our analysis are illustrated on this slide. Fever was defined as a temperature greater than 38 degrees celsius. There was a requirement for two consecutive measurements for temperature between 38.1 and 38.3. Neutropenia was defined as a granulocyte count below 500 per microliter and severe neutropenia corresponded to a granulocyte count below 100.

The diagnosis of the primary infections leading to the neutropenia are listed here and were broken down into hematologic malignancies including leukemia, lymphoma and myeloma; solid tumors; and other hematologic malignancies.

[Slide.]

The causes of fever were also defined according to the IDSA guidelines and consisted of microbiologically documented infections with or without bacteremia, clinically documented infections and fever of unknown origins.

Among patients with bacteremia, a single positive blood culture for usually acceptable with the exception of coagulase-negative staphylococci for which two separate blood cultures were required. There were also a number of cases of non-infectious fever for which a definite cause such as thrombophlebitis could be identified.

at

[Slide.]

A number of prognostic factors were characterized in our studies. They consisted of the cause of fever, essentially microbiologically documented infections, clinically documented infections and fever of unknown origin, the underlying cancer diagnosis--and we looked specifically at hematologic malignancies versus solid tumor, the bone-marrow transplantations, the severity of neutropenia, especially patients with less than 100 neutrophils versus 100 to 500, the duration of neutropenia is of less than 10 days or more than 10 days.

We also look at the effect of the use of the indwelling catheter and its impact on treatment management.

[Slide.]

Three outcomes were considered; success, failure and mortality. The criteria for success were strict and were constructed around the outcome of the original empiric regimen. Success was defined as the resolution of fever and the signs and symptoms of the infections where they were present.

They also required eradication of the pathogen in patients with microbiologically documented infections. In addition, no change in the antibiotic therapy were allowed and the response had to be maintained for five to seven days

at

post treatment.

[Slide.]

Failure consisted of at least one of these criteria; fever persisting for more than three days, a clinical deterioration, a bacteremia that persisted more than 24 hours from study therapy, and the isolation of resistant pathogens.

We also considered as treatment failure all death due to the primary infection. As indicated earlier, any modification of therapy was also considered a treatment failure in our analysis of eligible patients.

[Slide.]

An analysis of infectious-disease mortality was also performed. This analysis provides further information on the overall outcome. We included in this analysis all patients who died of infectious causes, either the primary infection or a new infection.

[Slide.]

In our analysis of efficacy, we look at two populations, the evaluable patients and the eligible patients. As indicated earlier, our primary analysis was based on the first febrile episode.

[Slide.]

The eligible population consisted of all patients

at

who had documented fever and neutropenia as defined earlier and who received at least one dose of the prescribed antibiotic. Patients who received systemic antibiotics for an established infection within three days prior to entry and those who had evidence of non-infectious cause of fever were excluded from our eligible populations.

[Slide.]

The evaluable populations included all patients who met the eligibility requirement and for whom viral infections were ruled out. These patients had to be treated for a minimum of three days unless there was clear evidence of treatment failure. No changes in the antimicrobial therapy were allowed during the first 72 hours unless those changes were justified by clinical deterioration, a resistant pathogen or a persistent bacteremia.

Finally, the adequate follow up was also part of the evaluability requirement.

[Slide.]

The issue of treatment modification is fairly complex. These modifications are frequently performed although, in many cases, these modifications may be disputable. In the current IDSA guideline, it is proposed that the empiric regimen be maintained unmodified for a minimum of 72 hours.

at

Current medical practice does not necessarily reflect this guidance and complicate the outcome assessment.

[Slide.]

The primary analysis of outcome was performed within each treatment comparison of UFC in the background document, mainly cefepime versus ceftazidime, cefepime versus combination therapy and each of the cefepime combinations versus the corresponding ceftazidime combinations.

The analysis of outcome in the comparison of cefepime to ceftazidime was adjusted for multiple protocols using the DerSimonian and Laird method. For each comparison, rate differences and two-sided 95 percent confidence interval were estimated. In this efficacy analysis, the equivalent region was defined as plus or minus 20 percent based on response rate less than 80 percent, and these are definitions that apply from the FDA Points to Consider.

All other comparisons of treatment outcome were based on the Cochran-Mantel-Haenszel method specifically for outcome assessments.

This will be the end of the method section and I would like to introduce Dr. Ramphal from the University of Florida who will summarize our results.

Results of Cefepime Clinical Trials

DR. RAMPHAL: Good morning.

[Slide.]

I am Reubin Ramphal from the University of Florida. I was involved in the cefepime monotherapy trials in the United States and I have been involved in the past in other monotherapy trials, for example, ceftazidime.

I will now discuss the results of the cefepime trials that were conducted worldwide.

[Slide.]

We have performed an extensive evaluation of cefepime in febrile neutropenic patients. It included a total of 1412 patients who were enrolled in 1549 treatment episodes since some trials allowed for the multiple febrile episodes to be enrolled. However, the primary analysis will concern only the first treatment episodes.

[Slide.]

The studies can be divided into four categories; non-comparative studies which enrolled 114 patients, comparative studies of cefepime versus ceftazidime in 600-plus patients, comparative studies of cefepime to combinations of antibiotics in 187 patients and studies of cefepime in combination with an antibiotic compared to ceftazidime in combination with that same antibiotic.

at

The 114 patients that were accrued in the two non-comparative trials provide limited clinical information to demonstrate the activity of cefepime for this indication and, therefore, will not be discussed further.

[Slide.]

I will first present the data on cefepime versus ceftazidime. Three randomized studies were performed at multiple centers in the U.S. and Europe. Cefepime was used at a dosage of 2 grams intravenously every eight hours and ceftazidime was used at similar doses and a similar dosing frequency. These trials were conducted between August of 1989 and June of 1995.

[Slide.]

The studies have been combined for assessment purposes because the dose and dosing interval of cefepime was consistent across the clinical trials. The comparator, ceftazidime, is an accepted standard for the treatment of febrile neutropenic patients and has demonstrated clinical benefit as discussed earlier in Dr. Schimpff's presentation.

Each patient in each trial was assessed by an independent blinded reviewer using criteria from 1992 Infectious Diseases Society of America guidelines coupled with those of the Immunocompromised Host Society.

[Slide.]

at

In these trials, 327 patients were enrolled in the cefepime arm and 320 patients were enrolled in the ceftazidime arm. The pretreatment characteristics with regard to sex, race and age in these populations were quite similar.

[Slide.]

The distribution of the prognostic factors alluded to earlier by Dr. Nicaise was similar in the two arms with similar numbers or similar percentages of patients having hematological malignancies--i.e., leukemia--bone-marrow transplant, and the length and the depth of neutropenia.

[Slide.]

Antimicrobial prophylaxis was used extensively in these studies. However, there were no differences between the cefepime arm and the ceftazidime arm. About 40 percent of the patients overall received antibacterial prophylaxis, but the prophylaxis was not standardized with fluoroquinolones and trimethoprim-sulfa being the most commonly used agents.

[Slide.]

Looking at the infectious diagnostic categories, the majority of the patients, or about 50 percent of the patients, I should say, had fevers of unknown origin. About 20 percent of the patients had bacteremias and I will show

at

that on another slide. Let's say, overall, about 50 percent of the patients had documented infections, the majority being microbiologically documented with a smaller percentage being clinically documented.

[Slide.]

When examining microbiological documentation, the distribution of gram-positives and gram-negative organisms is similar to what has been reported in other large centers, in other large studies, as alluded to earlier by Dr. Schimpff.

However, when one looks closely at the organisms in the two different arms--this is the cefepime arm and this is the ceftazidime arm--we can see that it was in excess of cases of Staph aureus and Pseudomonas aeruginosa in the cefepime arms.

[Slide.]

The median duration of treatment in the two arms was about seven days with ranges as shown. Antibacterial modification occurred in about 30 percent of the patients in each arm with fewer numbers of patients receiving antifungal or antiviral modifications.

[Slide.]

If one looks at the nature of these antibacterial modifications, one can see that the majority of the

at

modifications consisted of glycopeptides with only about 3 percent of the patients actually requiring an aminoglycoside in this population of over 600 patients.

[Slide.]

If one looks at catheter use in treatment modification, one can see that patients with catheters had more modifications than patients without catheters and that glycopeptides, again, were responsible for most of the modifications in these patients.

[Slide.]

If one looks at the outcomes, in terms of a successful clinical outcome in the evaluable patients, and just in case this point gets by too quickly, I will stress that these are evaluable patients, one sees that the percentage of patients having a successful clinical outcome was quite similar in the two arms.

[Slide.]

If one looks at the individual studies, now, one can see that there was consistency from one study to another in terms of outcomes, whether the patients were treated with ceftazidime or cefepime and, in general, there was consistency from one study to another.

Looking at these studies and applying the Gail-Simon test for lack of qualitative interaction supports

at

the pooling of the data from these three studies.

[Slide.]

The metaanalysis of all three studies also demonstrates the comparability of cefepime to ceftazidime. Overall, the point estimate was -2 percent with a 95 confidence interval ranging from -11 percent to +7 percent with a lower boundary well into the region of equivalence.

If one looks at the individual studies, the point estimates range from -7 percent to +12 percent showing good consistency in outcome across these clinical trials.

[Slide.]

If one examines the successful clinical outcome by infectious diagnostic categories, we see that the outcomes were also quite similar in the two arms with about 50 percent of the microbiologically documented infections having successful clinical outcomes and about 60 percent of the patients with fevers of unknown origin also having successful clinical outcomes.

[Slide.]

Among the patients with microbiological documentation, the outcomes for gram-positive infections and gram-negative infections was comparable for cefepime and ceftazidime. The differences in these subpopulations were not statistically significant.

at

[Slide.]

Looking now at outcome by prognostic factor, we see that the various subsets, as defined by the underlying cancer diagnosis or the occurrence of bone-marrow transplantation, were comparable. As expected, solid-tumor patients did better than patients who had underlying hematological malignancies and patients with bone-marrow transplants did poorer than patients without bone-marrow transplants.

[Slide.]

Similarly, the analysis, according to the length and the depth of neutropenia, supports the comparability of the two treatment arms with similar success rates for cefepime and ceftazidime in each subset.

[Slide.]

Turning now to analysis of all eligible patients--that is, 314 patients treated with cefepime and 306 treated with ceftazidime--one, again, sees that the clinical outcomes were similar with a successful outcome in 42 percent and 41 percent of the patients receiving cefepime and ceftazidime, respectively.

It should be noted that in this analysis, patients who had their treatment modified at any time prior to the control of the infection were considered as treatment

at

failures whether or not those modifications were clinically justified.

[Slide.]

The metaanalysis now conducted in the eligible patients also demonstrated the equivalence of cefepime to ceftazidime. Overall, when all 620 patients were included, the point estimate was 0.1 percent with a tight confidence interval. There was also good consistency across studies in terms of point estimates and 95 percent confidence interval.

Of note, for all three studies as well as for the pooled analysis, the lower boundary of the confidence interval was within the equivalence region, all less than -20, demonstrating the equivalence and comparability of the two treatment options.

[Slide.]

If one looks at successful clinical outcomes in this eligible population by infectious diagnosis, one, again, sees that the outcomes were similar for cefepime and ceftazidime in patients, microbiologically documented infections, clinically documented infections, and fevers of unknown origin.

[Slide.]

Turning now to mortality, one sees that the mortality in both arms were essentially equivalent in the 2

at

to 3 percent range due either to primary infections or new infections.

[Slide.]

The next set of clinical trials I will describe are the trials concerned with cefepime versus combination therapy.

[Slide.]

Two trials were conducted. The first trial was done at two centers in the United States when cefepime was compared to piperacillin plus gentamicin. These patients were accrued over a two-year period, from 1989 to 1991.

The second study compared cefepime to mezlocillin plus gentamicin and these patients were accrued over a two-year period. This study was intended to accrue patients who had undergone bone-marrow transplantation.

[Slide.]

A total of 187 patients were accrued in these two studies and all prognostic factors were equally distributed in the two arms. Of note, the length of neutropenia in these studies was longer than those reported in the monotherapy studies since most patients had hematologic malignancies and more than a third of the patients had bone-marrow transplantation.

[Slide.]

at

Looking at the infectious diagnostic categories, we see that microbiologically documented infection, clinically documented infection and fevers of unknown origin were distributed in a similar way across the two treatment arms. About 50 percent of the patients, overall, had a documented infection and one-third of the patients had microbiologically documented infections, mostly bacteremias.

[Slide.]

The duration of treatment and treatment modifications were fairly comparable in the two treatment arms, 8 days in terms of duration and antibacterial modification about 39 to 45 percent of the patients. These antibacterial modifications mostly consisted of the addition of vancomycin with 30 percent of the patients in the cefepime arm and 37 percent of the patients receiving combination therapy.

[Slide.]

I will now go on to the results. These are the results in the evaluable patients. As judged by a successful clinical outcome, 59 percent of the patients were treated successfully in the cefepime arm and 56 percent of the patients in the combination arm.

[Slide.]

The outcomes in each individual study were also

at

similar for cefepime and for the combinations. So, from one study to another, these outcomes were similar. The Gail-Simon test for lack of qualitative interactions supports the pooling of the data from these two studies.

[Slide.]

If one now turns to the eligible patient population, a larger population, one sees that the outcomes, in terms of clinical success, was comparable between the two treatment arms.

[Slide.]

If one looks at infectious-disease mortality, one sees that the deaths from primary infection occurred in about 2 percent of the patients in each arm.

[Slide.]

To summarize the results of the monotherapy studies at this point, cefepime monotherapy was comparable to ceftazidime monotherapy and also to combination therapy.

[Slide.]

During the remainder of my presentation, I will summarize two studies which involve the use of cefepime in combination with another antimicrobial versus ceftazidime in combination with the same antimicrobial. These studies were conducted in Europe.

[Slide.]

at

In the first study, cefepime was combined with amikacin and, in the second study, cefepime was combined with a glycopeptide. This was vancomycin.

[Slide.]

The first trial was a multicenter trial conducted at 31 institutions in France. Of note, cefepime was used at a dosage of 2 grams every 12 hours, which is quite different from all the trials that I have reported on earlier, and ceftazidime was used at a dosage of 2 grams every 8 hours in combination with amikacin. This study was done over a two-year period.

[Slide.]

A total of 353 patients were accrued in this trial. There was a two-to-one randomization of cefepime to ceftazidime. Almost all the patients had hematologic malignancies and more than 40 percent of the patients had bone-marrow transplants. Consequently, most patients were profoundly neutropenic with prolonged durations of neutropenia.

In addition, indwelling catheters were almost universally used. These characteristics illustrate that these patients accrued in this study had a potentially more serious prognosis than those previously described in the

at

cefepime monotherapy trials.

[Slide.]

The diagnostic categories were equally distributed across the two treatment groups. Two-thirds of the organisms were gram-negative, predominantly staphylococci and viridans streptococci, and E. coli represented half of the gram-negative pathogens isolated.

[Slide.]

The treatment duration and percentage of patients with treatment modifications was similar in both arms. However, importantly, 55 to 57 percent of the patients received antibacterial modification which is a substantially higher proportion than what was reported in the other trials.

Among these modifications, the addition of a systemic antibiotic was especially frequent, in particular, a glycopeptide, either vancomycin or teichoplanin which were added to 49 percent of the patients receiving cefepime and 52 percent of the patients receiving ceftazidime, of course in combination with the aminoglycosides.

[Slide.]

The outcome in evaluable patients in this trial was assessed by the principle investigator and not by the blinded external reviewers. Overall, the outcomes in the

at

two treatment groups were similar with no statistical difference. The response rates were lower than those previously described in the cefepime monotherapy trials. This was largely due to the fact that all treatment modifications were considered failures and it is also likely that the more serious prognostic factors in these patients was associated with slow control of fever and a more frequent need for treatment modification leading to treatment failures.

[Slide.]

However, when one looks at mortality in this patient population, one, we see that the mortality rates in the cefepime arm versus the ceftazidime arm were really not different, either in the categories of primary infection or new infection and, secondly, we see that the mortality rates are really quite low comparable to those in the monotherapy trials.

[Slide.]

The second combination study was done in Belgium. Cefepime was combined with vancomycin and compared to ceftazidime combined with vancomycin. This combination was designed due to the high prevalence of gram-positive infections in the four institutions where the study was performed. The study was completed over a one-year period

at

between 1993 and 1994.

[Slide.]

About 50 patients were enrolled in each arm. The majority had hematologic malignancies and most patients had profound and durable neutropenia with a median duration of neutropenia in excess of 10 days.

[Slide.]

The infectious diagnostic categories were fairly well distributed across the study arms although there were slightly more bacteremias in the ceftazidime arm. In this study, 34 organisms were isolated and 29 were gram-positive primarily coagulase-negative staphylococci and viridans streptococci.

[Slide.]

As in the other studies, the duration and modifications were similar in the two treatment groups, 11 to 12 days duration of therapy, antibacterial modifications between 50 and 55 percent of the patients.

Interestingly, although vancomycin was part of the empiric treatment, more than half the patients received additional antibacterial agents. This consisted primarily of aminoglycosides and macrolides. Antifungal and antiviral agents were also frequently added very early, usually as extended prophylaxis.

at

[Slide.]

Comparable clinical outcomes were observed in the two treatment arms with success rates of 63 percent in the cefepime/vancomycin arm compared to 56 percent in the ceftazidime/vancomycin arm. The results were consistent across the various diagnostic categories including those with microbiological documented infections.

[Slide.]

Looking at mortality rates, infectious disease mortality in these two small studies, we see mortality rates between 2 and 3 percent, both in the case of primary infections and new infections.

[Slide.]

To summarize these studies overall, cefepime monotherapy is as efficacious as ceftazidime monotherapy or combination therapy when used for the empiric treatment of febrile episodes in neutropenic patients. Importantly in these monotherapy trials. Deaths resulting from primary infections occurred in 2 percent of patients treated with cefepime, ceftazidime or combination therapy.

Cefepime in combination with either amikacin or vancomycin was equivalent to the respective ceftazidime combination.

Dr. Claude Nicaise will now present the

at

conclusions and some information on the adverse events.

Thank you.

Summary and Conclusion

DR. NICAISE: Thank you.

[Slide.]

Earlier in our presentation, Dr. Schimpff demonstrated that the empiric therapy of febrile neutropenic patients was associated with a clinical benefit. In addition to the clinical benefit of these historical data, he highlighted the need for adequate coverage initially with a combination therapy and most recently with new broad-spectrum beta-lactam antibiotics.

Among these antibiotics, the activity of ceftazidime was well characterized in a number of well-controlled clinical trials.

[Slide.]

We initially presented the activity of cefepime monotherapy when given at a dose of 2 grams every eight hours. This activity was demonstrated in three randomized studies comparing cefepime to ceftazidime. In the pooled analysis of these studies, we demonstrated the equivalence of cefepime to ceftazidime in more than 600 patients.

This slide actually demonstrates to you the point estimates and the 95 percent confidence interval in a

at

variety of populations included in these pooled analysis. This equivalence was actually established for the entire patient population, the entire eligible population, also for the evaluable populations, as well as in a subset of microbiologically documented infections and patients with bacteremia including those that were evaluable.

[Slide.]

We also performed an analysis of cefepime versus all controls combining ceftazidime and the two combination regimens. In 795 eligible patients, cefepime was comparable with all controls with a very narrow confidence interval. The comparability of cefepime in this control was also identified in patients with microbiologically documented infection as well as those with bacteremia.

[Slide.]

No safety issues were noted in these clinical trials and the excellent safety profile of cefepime was confirmed. This was seen both with cefepime monotherapy and cefepime combinations.

Finally, the assessment of overall mortality, all-cause included, was similar for cefepime, ceftazidime and the various combinations.

[Slide.]

The most frequent drug-related adverse event noted

at

in our comparative monotherapy trials are presented on this slide. No differences between cefepime and ceftazidime were detected. Rash was the most frequent adverse event in these trials with an incidence ranging from 3.8 to 5.5 percent.

All other adverse events, as well as significant or clinically relevant laboratory abnormalities in terms of renal or hepatic functions were noted in about 1 percent of the patients or less.

[Slide.]

In conclusion, the data presented today demonstrate that cefepime is safe and effective when used for the empiric treatment of febrile neutropenic patients. The activity of cefepime was demonstrated at a dose of 2 grams every eight hours as well as in combination with an aminoglycoside or a glycopeptide.

Thank you. At this point, I will answer any questions from the committee or the FDA.

DR. CRAIG: Questions from members?

DR. PARKER: I am not sure to whom I address this. I was interested in knowing which technique you use in computing your 95 percent confidence intervals, the exact technique or the P1T1? It depends on whose package you pick up, I understand. I just wondered which one.

DR. GRECHKO: My name is Janis Grechko from

at

Bristol-Myers Squibb. The technique that we use from the StatExac package, the exact intervals from StatExac.

DR. ZINNER: I just wonder if you look at the bacteremias, the gram-positive and gram-negative separately, in the document that we have been presented, there were data shown for all microbiologically documented infections for gram-positives or gram-negatives.

If you break that down to just the bacteremia episodes, gram-positive, gram-negative, how does monotherapy with cefepime compare with ceftazidime?

DR. NICAISE: The data in bacteremia patients actually mimic the data in the microbiologically documented infection. Actually, bacteremias represent more than 80 percent of the microbiologically documented infections.

DR. SHENEP: In your studies using either cefepime or ceftazidime monotherapy, did you include patients with septic shock? Did you include patients with hypotension or what were your criteria for including or excluding patients.

DR. NICAISE: Patients with septic shock were specifically excluded.

DR. SHENEP: Other exclusions? Hypotension?

DR. NICAISE: Essentially, those patients with a known unfavorable prognosis where death is a fairly expected outcome were excluded; septic shock, hypotension,

at

overwhelming sepsis. Those patients were not accrued. And I think that, in these patients, monotherapy, as you indicated, would not be indicated.

DR. SERODY: It appears from your analysis that approximately 15 percent, or 65 patients, in the total of all the studies were transplant recipients. Do you feel that this is an adequate number of individuals analyzed in this manner to recommend cefepime as either monotherapy or combination therapy for these individuals?

DR. NICAISE: These studies were not specifically designed to look at a subset analysis. What we have done is to look at the homogeneity of populations and report the data in specific subsets. So these studies were not designed to demonstrate equivalence.

DR. SERODY: But you are specifically asking for an individual for the treatment of all patients with febrile neutropenia; is that correct?

DR. NICAISE: That's correct.

DR. CRAIG: Any other comments?

DR. MELISH: Among the microbial agents we have covered, what proportion were resistant to cefepime?

DR. NICAISE: Maybe I can show you the susceptibility data. Can I have slide B(5).

[Slide.]

at

This slide summarizes the susceptibility in the comparison of cefepime to ceftazidime but, actually, the data can be very similar in the other comparison.

[Slide.]

If we look at the gram-positive organisms, we see that 81 percent of the organisms isolated were susceptible to cefepime or at least in the organisms tested versus 69 percent in terms of ceftazidime.

If we look at some specific organisms, what we see is that the susceptibility was 100 percent for Staph aureus and there was still adequate susceptibility for the majority of the methicillin coagulase-negative staphylococci as well as the viridans streptococci.

If we look at the gram-negative, the susceptibility, overall, was 98 percent for cefepime and 91 percent for ceftazidime. This is a breakdown for the most frequent organism, essentially. No resistance detected in vitro.

DR. CRAIG: Other questions? Do we have any idea, in these studies, how consecutive these patients were or how selected they were of what was being seen at the different centers.

DR. NICAISE: These patients were consecutively accrued but I do not have a count at each institution to

at

confirm that.

DR. RELLER: Could we return to the susceptibility slide?

DR. NICAISE: Yes; we can.

[Slide.]

DR. RELLER: What were the criteria for susceptibility of these agents for methicillin-susceptible coagulase-negative staphylococci and viridans streptococci.

DR. NICAISE: These used the NCCLS method and the NCCLS breakpoint, essentially, 8 microgram per ml or lower.

DR. RELLER: For which organism?

DR. NICAISE: For the staphylococci and also for the streptococci. These are the NCCLS breakpoints.

DR. RELLER: For MICs.

DR. NICAISE: For MICs; that's correct.

DR. RELLER: Something is amiss there. I don't have the document right in front of me but I think most infectious-diseases clinicians would not consider a viridans streptococci of an MIC of 8 as susceptible to one of these cephalosporins nor would they consider methicillin, any methicillin-resistant, coagulase-negative staphylococci susceptible to them.

I question the data on the susceptibility for methicillin-susceptible coagulase-negative staphylococci.

at

DR. NICAISE: I think that Dr. Kessler, who is a microbiologist in our company, can address these breakpoints as they are currently defined. Then I would like to give you a further answer on the clinical.

DR. RELLER: And how the testing was actually done. The NCC list does not recommend testing these agents directly against any staphylococcus.

DR. KESSLER: Bob Kessler from Bristol-Myers Squibb, Microbiology Department. The testing that was done would, of course, have been done in the labs at the site. It would have been done by NCCLS standards. The testing for viridans strep, in particular, would have been done--I can tell you that the MIC seen for the viridans strep across the board were 4 micrograms per ml or less, as far as I remember. I don't have the data in front of me.

Whether organisms were methicillin-susceptible or methicillin-resistant would have been done by the standard oxacillin-disc test.

Is there anything else?

DR. NICAISE: Can you give me the first slide, B(1).

[Slide.]

These are data from a recent microbiological survey that was done by the group in Iowa. These are not

at

the organisms in our study but will answer some of these. If we look at the viridans streptococci, we have an MIC 90 which is way below 8. It is actually 0.5 and 2 in terms of MIC 90. As you can see, in terms of staphylococci, we retain some activity in terms of the Staph epi and specifically the Staph aureus.

So when you asked me the question what were the breakpoints, these were actually the breakpoints but these were not the MIC noted. When we look at the clinical data, the MIC were, in general, for the viridans streptococci, 2 and lower.

DR. RELLER: But given the pitfalls and susceptibility testing, the NC test specifically says that if one has an oxacillin-resistant staphylococci, it is resistant to all cephalosporins, period. It is not accurate to do the in vitro susceptibility testing with the cephalosporins.

DR. NICAISE: We do not claim that cefepime is effective against methicillin-resistant staphylococci.

DR. RELLER: Let's go back to the slide on susceptibility data.

DR. NICAISE: These are the crude results of the susceptibility testing as they came to us. They were, obviously, more staphylococci that were isolated. We do not

at

claim that methicillin-resistant staphylococci are susceptible to cefepime. We do not.

DR. RELER: But that slide says otherwise. It says that the data presented are in accord with NCCLS testing and, I presume, reporting which is simply not the case. It is easy to say, "done by NCCLS criteria." It sounds great. It is a sort of imprimatur or a stamp of approval. But it is not so.

DR. NICAISE: Again, I can only realize that we do not claim that cefepime is effective against methicillin-resistant staphylococci. These are the numbers. They were reported to us. We do not claim the effectiveness against these strains.

DR. CRAIG: So they are not included in your efficacy data?

DR. NICAISE: These patients are largely considered treatment failures.

DR. CRAIG: All of them? Even those for which you say that the drug was susceptibility?

DR. NICAISE: The only ones that have been considered a treatment success were those who were successfully treated without treatment modifications.

DR. CRAIG: Do we know how many of those were methicillin-resistant Staph epis?

at

DR. NICAISE: There was one example and, at pretesting, the resistance was doubtful.

DR. CRAIG: Any other questions? If not, it is time for our break. I would like to thank Bristol for an informative presentation and for all the speakers staying one time. We will get back together in about 15 minutes.

[Break.]

DR. CRAIG: Our next speaker will be the FDA presentation by Dr. Davis Ross.

FDA Presentation

Febrile Neutropenia Supplement

DR. ROSS: Good morning.

[Slide.]

My name is David Ross. I am a medical officer with the Division of Anti-Infective Drugs with the Food and Drug Administration. I am going to be speaking to the committee today about the FDA's analysis of the Maxipime, cefepime, application for empiric therapy of febrile neutropenia.

[Slide.]

What I would like to discuss are, first, issues involved in reviewing new drug applications for empiric therapy of febrile neutropenia, next discuss a specific supplement to a new drug application for Maxipime seeking

at

approval for this indication and then, finally, present questions for the committee's consideration.

The major questions which we would present to the committee are, first, what endpoints are appropriate measures of outcome for this indication. Secondly, are the data presented for cefepime sufficient to support the claim of safety and effectiveness for empiric therapy of febrile neutropenia?

[Slide.]

Let me start by reviewing the current regulatory status of febrile neutropenia as an indication. Currently, there are no antibiotics approved for this indication. Some antibiotics do carry usage statements with related language. For example, ceftazidime carries a label which says that it may be used concomitantly with other antibiotics in the immunocompromised patient.

However, there is no antibiotic which carries specific language for empiric therapy of febrile neutropenia. This results in a situation in which we have no precedence for regulatory decisions for empiric therapy of febrile neutropenia. As I will show with some cases, it may lead to a less than clearly defined situation.

[Slide.]

Let me present two cases which are not typical but

at

are certainly not atypical. In the first case, a 24-year-old woman with Hodgkins disease who is neutropenic is started on empiric therapy for fever. Despite multiple cultures and physical examination, no infectious source is found.

She remains febrile and neutropenic, on antibiotics which are discontinued after a 15-day course. The patient remains febrile, off antibiotics and defervesces two weeks later following bone-marrow recovery. She goes on to be treated successfully for her underlying disease.

The question I would ask in this case is did the antibiotic fail? The patient did not defervesce. However, she survived, to be treated successfully for her underlying disease. Had she not been started empirically on antibiotics, she might have died of overwhelming infection.

You should keep in mind that this sort of patient, the cause of fever may change during the hospital course from infection to drug fever, to other etiologies.

[Slide.]

In the second case, a 47-year-old man with acute myelocytic leukemia develops fever while neutropenic, is started on empiric monotherapy and promptly defervesces. Again, no infectious source is identified. Eight days after empiric therapy is initiated, the patient again becomes

at

febrile and hypotensive. Multiple blood cultures grow vancomycin-resistant *Enterococcus faecium* with high-level resistance to gentamicin.

This is a patient that bears some similarity to the case of the ten-year-old girl described by Dr. Shenep. The question I would ask here is did the antibiotics succeed in this case. True, the patient defervesced, but we have a situation, after eight days of therapy, that may be due to the antibiotic in question and which is less than optimal.

[Slide.]

These cases illustrate some of the problems in reviewing new drug applications for this indication. Fever is not specific for infection in these patients. We know, as presented by earlier speakers, that these patients must be started in empiric therapy to avoid unacceptable mortality rates.

However, we don't know, a priori, if these patients are infected. Secondly, fever is frequently is not associated with positive cultures. This is not a microbiologically driven infection leading to further doubt for particular patients as to what we are treating.

Because of this, a wide variety of clinical-trial designs is possible and is found in the literature.

[Slide.]

at

With regard to evaluability criteria, there is a lack of a consensus in the literature on the duration of therapy required for a patient to be considered evaluable for efficacy. Should it be 72 hours? Should it be any patient who receives therapy? Is this a meaningless criterion if you say that it doesn't matter how long the patient is treated without modification as long as the patient survives.

How would we evaluate patients who receive concomitant antifungal therapy in the absence of a defined source of fever? Or patients who continue on prophylaxis after empiric therapy has begun.

Finally, in an era of managed care, how should we evaluate or view for evaluability patients who receive oral antibiotics to complete their course of therapy when these antibiotics may differ from the original antibiotics that were used for initial therapy? Or how should we view patients who were started on home IV therapy or PO therapy, particularly low-risk patients?

[Slide.]

Similarly, there has been a lack of consensus in the literature on what endpoints to use. Should the primary endpoint be survival from infection regardless of what it takes to get there or should we consider defervescence to be

at

the issue alone and consider treatment modifications to represent failure.

Similarly, the treatment of secondary endpoints, bacterial or superfungal infections, new episodes of fever without a defining source, an empiric addition of other microbiological agents such as antifungals or antivirals when there has not been a response to the initial regimen, represent endpoints that are not consistently treated in the literature.

[Slide.]

As an illustration of how variation in these parameters can affect response rates, let me cite a study by Joseph Pater and his colleagues at the National Cancer Institute of Canada. They examined, retrospectively, 283 patients who had been randomized to one of three treatment regimens.

I will just note that the third regimen listed is the one with the broadest antimicrobial spectrum. They then defined three different measures of outcome. Under the first measure, the primary episode resolved. No new infection with a sensitive isolate occurred, and no modification occurred to achieve this outcome.

Under the second outcome, success was defined by resolution of the primary episode with no new infection at

at

all. Under either of these outcomes, modification of the initial regimen was scored as a treatment failure.

Under the third outcome definition, survival was the definition of success. Treatment modification did not represent failure. The results were quite instructive. Under outcome definition 1, and that is, resolution of the initial episode, no superinfection with a sensitive isolate.

The third regimen was clearly superior with a p value of .001. Under a stricter definition of success, response rates dropped. The p value changed somewhat although significance was still demonstrated.

If survival was the criterion for success, then all the regimens look pretty much the same and there were no significant differences between the groups. So the question of how to review these applications really depends on what endpoints we choose as well as other criteria such as evaluability criteria.

[Slide.]

So, with these problems in mind, we set the following goals: to design consistent evaluability and efficacy criteria that would allow us, in a flexible way, to review different applications with similar, yet non-identical, trial designs from empiric therapy of febrile neutropenia; to use these criteria to analyze the safety and

at

efficacy of empiric therapy for febrile neutropenia relative to a scientifically and clinically accepted comparator; and then, finally, to use the data from this analysis to construct a clinically useful and scientifically sound label.

I should mention that, at this point, there is no Divisional policy with regard to the evaluability criteria that were designed. These were designed by review of the literature and there was no preexisting agreement between the Division and any sponsors as to what criteria would be used.

[Slide.]

The regulatory framework for meeting these goals is contained in the Divisional points to consider document which has suggested applicants provide data from one statistically adequate and well-controlled multicenter trial in the setting of previously established effectiveness for three specific deep infections which are shown here.

This stipulation implies that effectiveness for these infections will have been shown for specific designated microorganisms.

[Slide.]

As material to build on this framework, we have the Infectious Disease Society of America guidelines which

at

give information on conducting clinical trials for this indication, particularly with regard to the study populations that should be included, inclusion and exclusion criteria, selection of comparators, what modifications are allowable, endpoints to be used, and data analysis.

It should be noted that while the IDSA guidelines provide an enormous amount of information, there are areas in which enormous variation is still possible within studies.

[Slide.]

We started with a statement from the guidelines. Walter Hughes and his colleague wrote, "It is optimal to use multiple parameters for the assessment of patients including clinical response to therapy, evidence of microbiologic efficacy and survival.

[Slide.]

Complementing this and, perhaps, as a more general statement is the approach taken by David Sackett and his collaborators with regard to metaanalysis and other features of analyzing clinical trials. The answer to the question, which event should be counted and which treatment should be blamed, depends on four elements of the individual trial; the nature of the question posed, the perspective from which the question is posed, the consideration of why the

at

experimental maneuver might be abandoned or violated, and the avoidance of specific bias.

Put more simply, what is the question we are asking? What are we asking drugs to do for this indication.

[Slide.]

So our strategy was as follows. We analyzed both intent-to-treat in strictly evaluable subsets and we examined the data from multiple perspectives by coding outcomes in a descriptive way and analyzing differences in survival, clinical and microbiological response to the initial regimen, the need for modification of the initial antimicrobial regimen and the effect of sequential intravenous oral therapy, particularly when the oral antibiotic differed from the initial regimen.

This is essentially the approach taken by Pater et al.

[Slide.]

Let me move from these general issues to a discussion of the specific application at hand for cefepime. This is a cephalosporin antibiotic, the structure of which is shown here, with a serum half life of a little over two hours in adults. It is active in vitro against gram-negative and gram-positive organisms commonly affecting neutropenic patients.

at

[Slide.]

Currently, cefepime is labeled as approved for uncomplicated and complicated urinary-tract infections, uncomplicated skin and skin-structure infections, and moderate to severe cases of pneumonia due to susceptible strains of designated microorganisms.

[Slide.]

The application has proposed the following addition to the labeling; empiric therapy in neutropenic patients. Cefepime has been used successfully as monotherapy or in combination with an aminoglycoside or a glycopeptide in this indication.

The dosage that is proposed is 2 grams given every eight hours intravenously for seven days or until resolution of neutropenia. This is the maximum dosage for indications that have already been approved.

[Slide.]

The application in question contains, as we have heard, data on 1549 febrile episodes in 1412 accrued patients. The studies presented in the application fall into four groups; cefepime monotherapy compared to ceftazidime monotherapy comprising three studies, two of which were multicenter, all of which were randomized, with 743 episodes; cefepime compared to a beta-lactam

at

aminoglycoside regimen, two studies comprising 187 episodes; a third group comprising cefepime in combination with amikacin or vancomycin compared to the corresponding ceftazidime combination; then, finally, two small noncomparative studies.

Because review of this third group of studies is ongoing, I will only present results from our analysis of these two studies.

[Slide.]

Our methods used for review were as follows; to avoid bias, patient assessments were done blinded to treatment group assignment. In addition, we consistently applied objective criteria to score a patient evaluability and outcome.

If the meaning of a clinical scenario was unclear from the data in front of us, additional data was requested from and provided by the sponsor. The goal with these two methods was to have as little subjective judgment by the reviewer as possible.

In addition, all episodes were analyzed. Patients were eligible for reenrollment in some studies. We analyzed all episodes rather than just initial episodes. When we looked at initial episodes separately, results did not significant differ.

at

Finally, we used different endpoints and I will describe these in a minute. Two points that I would like to make with regard to this method. First, success for any given endpoint corresponded to a specific clinical goal. Secondly, in order to avoid selection bias by including and excluding patients and going from one endpoint to another, the size of the patient population that was analyzed was kept constant in looking at different endpoints.

[Slide.]

We used two sets of evaluability criteria to construct two datasets for analysis; a modified intent-to-treat analysis and construction of a strictly evaluable population.

All patients enrolled were analyzed. MITT criteria were applied and an MITT population was defined that essentially consisted of individuals who had the condition in question--that is, febrile neutropenia--and who did not clearly have a noninfectious source of fever.

The second population was constructed by taking the MITT population, applying additional criteria to define a strictly evaluable population.

[Slide.]

The MITT evaluability criteria were as follows: patients who were enrolled were included in this analysis if

at

they were febrile at study entry, if they were neutropenic within 48 hours of study entry and they did not have a well documented non-infectious source of fever.

This population corresponds roughly to the eligible population of the sponsor with the difference that the eligible population also required that patients received at least one dose of study drug and that patients in the eligible population had not received treatment for another infection, or preexisting infection, within 72 hours of study entry.

These criteria formed part of the strictly evaluable population criteria which are shown on the next slide.

[Slide.]

To construct the strictly evaluable population, we included all MITT patients who received at least one dose of study drug who were not receiving treatment for another infection within 72 hours of study entry, who did not have any modification of the empiric regimen prior to a 72-hour assessment point or who had not had discontinuation of empiric therapy due to an adverse drug reaction at any point during their course.

To be included in this analysis, patients also could not have a nonbacterial infection. They had to have

at

follow up for at least four days after end of therapy. And they could not have had clinically unjustified modifications of therapy.

The major difference in evaluability was this criterion; patients who were modified for any reason, even clinical deterioration, were excluded from this analysis and analyzed under intent-to-treat.

[Slide.]

The results with regard to evaluability of the populations are shown on this slide. The red bar represents the strictly evaluable population. The yellow and red portions represent the MITT populations. Orange represents patients excluded from both analyses.

The number of enrolled episodes for each study are shown here. I will just comment that, for one study, and actually this number should be 308 not 316, I apologize, 16 patients are excluded from our analysis simply because data is being reviewed, additional data is being reviewed.

For the combination studies, the evaluable population sizes range from roughly 40 percent to something over 60 percent of the enrolled patient population. For the studies comparing cefepime alone versus ceftazidime alone, the evaluable population was roughly similar for each study.

For the pooled cefepime versus ceftazidime

at

monotherapy population, the number of evaluable patients was roughly 60 percent of those enrolled. For intent-to-treat analysis, the number of patients evaluated was roughly 90 percent for each study.

[Slide.]

Reasons for nonevaluability; I won't spend a great deal of time on this, but they were comparable between the cefepime arm and all control arms with regard to overall attrition rates and reason for modification.

The most frequent reason for viewing patients as being unevaluable under the strictly evaluable population was modification prior to 72 hours.

[Slide.]

The demographics of the evaluable population were analyzed. A detailed table with numbers will be found in your revised briefing package. The treatment arms were balanced for individual studies and for the overall treatment groups by age, sex and race, by the distribution of diagnoses of the underlying disease, for severity and duration of neutropenia.

The majority of the patients had neutropenia with less than 110 neutrophils per microliter. Overall, 50 percent of patients were neutropenic for a week or longer.

at

The arms were balanced with regard to prophylactic antibiotic use, the category of infection that the patient was eventually assigned, microbiologically documented infection either with bacteremia or without, clinically diagnosed infection or fever of uncertain origin. The groups were also balanced with regard to the presence or absence of indwelling venous catheters and history of bone-marrow transplantation.

[Slide.]

The definitions of success that were used, and I will spend a little bit of time on this, were three, with some categorization. These form a spectrum going from most strict to least strict.

The first definition of success required that the initial episode resolved without modification of the empiric regimen and that no new febrile episodes or infection developed during therapy or during the follow-up period. Thus, to be a success under this definition, a patient had to succeed on the initial regimen alone all the way through with no new events occurring.

The second definition required for success that the primary episode resolved without modification with subsequent episodes being censored. In other words, if a

at

patient defervesced and subsequently developed a bacteremia, that was not regarded as a treatment failure.

There were two subclassifications for both these definitions, A and B. A was the strictest. Under this classification, no oral antibiotics were allowed to complete therapy. In addition, no antifungal or antiviral modifications were allowed. The patients who received these were scored as failures.

Thus, definition IA would be the absolute strictest. Unless a patient defervesced and survived without any modification whatsoever, they were scored as a failure. Category B allowed for the use of oral antibiotics as well as nonantibacterial modifications if the initial episode had resolved.

In other words, if a patient had defervesced and subsequently developed a thrush and they were started on amphotericin, that was allowed. So these two definitions form a spectrum with IA being the strictest and II being the most lenient in this group.

The third definition was survival of infection regardless of modification. The only criterion for success was that that patient not die of an infection. So these form a spectrum, IA being the strictest, III being the most lenient.

at

Simply as a starting point, definition IB was applied to the strictly evaluable population. The more conservative definition was used as a starting point for the MITT analysis, IA. So IA was used as the starting point for the intent-to-treat analysis. IB is the starting point for the strictly evaluable population.

[Slide.]

The results are shown on this slide. Cefepime is shown in red. Control values are shown in yellow. These represent response rates as a percentage with a number evaluable patients--that is, strictly evaluable--shown above each study.

These are the different study arms, cefepime monotherapy versus combination here versus ceftazidime here, and a pooling of the cefepime versus ceftazidime results here. For the combination studies, when cefepime was compared to piperacillin and gent, cefepime had a response rate of roughly 53 percent, combination therapy had 64 percent.

When compared to mezlocillin and gentamicin, in a different study, cefepime had a response rate of 47 percent, mezlocillin and gentamicin had a response rate of roughly 13 percent. So there was considerable disparity between these two studies.

at

Because of differences in the design of these two trials, they were not pooled during further analysis.

For the studies comparing cefepime monotherapy versus ceftazidime monotherapy, results are shown here and range from slightly under 30 percent to the 50 to 60 percent range. Although the response rates varied from study to study, cefepime and ceftazidime were within one to seven percentage points of each other for each study.

For the pooled analysis, the response rates were 46 percent of cefepime, 50.5 percent for ceftazidime. Again, detailed figures can be found in the revised briefing package.

[Slide.]

To analyze what this meant with regard to therapeutic equivalence, confidence intervals were calculated as shown here. Again, this is for the strictly evaluable subset. This bar represents the difference in response rates. So this is a response rate where cefepime was 20 percent worse than comparator. Here it is 20 percent better than comparator.

For response rates in the ranges that I have shown, the Divisional Points to Consider Document gives, for therapeutic equivalence, a criterion that the 95 percent confidence interval be no more than 20 percent; that is, it

at

would be 95 percent confidence that the true difference in response rates was no greater than 20 percent.

For the combination therapy studies, the results are shown here. The confidence interval, obviously, has to cross zero for therapeutic equivalence to be demonstrated. All the confidence intervals do cross zero here.

When compared to piperacillin and gent, the confidence interval does cross zero. However, the lower bound is less than -20 percent. When compared to mezlocillin and gentamicin, the confidence interval is shown here. It only marginally includes zero; that is, this is on the verge of showing statistical superiority to mezlocillin and gent with regard to therapeutic equivalence.

For each of the monotherapy therapies, the confidence intervals were quite similar. They all cross zero. The lower bound in each case fell just outside of -20 percent. As one would expect from pooling studies, the confidence interval narrows and, for the pooled study, the lower bound of the confidence interval was -14.7 percent.

[Slide.]

We next ask is this result true only for this definition or can this be applied, is this result obtained with other definitions. We, therefore, applied the different definitions of success that I showed in the

at

previous slide with IA being the strictest and III being the most lenient. This requires that the patient be successfully treated with no modification. This simply requires that the patient survive regardless of modification.

Again, cefepime is shown in red. Ceftazidime is shown in yellow. I should mention these are pooled results from the cefepime versus ceftazidime studies for the evaluable subset. As I mentioned earlier, we did not pool the combination studies.

Similar results were obtained with regard to equivalence for each definition although the absolute response rate differed. As one would expect, as one loosened the definition of success, response rates gradually rose. At each level, therapy equivalence was found between the treatment arms for the given response rate.

[Slide.]

The same analysis was done for intent-to-treat and the same result was obtained. Again, cefepime in red, ceftazidime in yellow. Again, IA has the lowest response rates but the arms are equivalent with regard to the confidence interval. This is true for each other definition that is used.

[Slide.]

at

The results, overall, for the pooled cefepime versus ceftazidime evaluable subset is shown here. Response rates range from the 30 percent range to over 95 percent. There was no significant difference between treatment arms under this analysis regardless of the definition of success.

[Slide.]

We also analyzed outcomes according to specific pathogens since these are the patients who have the strongest evidence for infection. The results are shown here. Before going into these, I want to add a note of caution. These represent a post hoc analysis. The studies were not designed nor intended to demonstrate therapeutic equivalence for these subgroups.

Therefore, no conclusions should be drawn from these specific data. For all pathogens examined, E. coli, gram-negatives and well as gram-positives, there was no significant difference between treatment arms for cefepime and ceftazidime.

Again, I would note that the numbers here are small. These results should be interpreted with caution.

[Slide.]

We also analyzed other subgroups. Again, these are post-hoc analyses. They should not be used to draw conclusions but simply to generate hypotheses. There was no

at

significant difference between cefepime and ceftazidime in patients with severe neutropenia, prolonged neutropenia. those individuals with leukemia, those with a history of bone-marrow transplantation or those with indwelling venous catheters, nor were there differences in patients who had received prophylaxis between treatment arms or patients who had not received treatment with prophylaxis.

We also analyzed patients who were hypotensive. The number of patients from that analysis was too small to draw statistical conclusions.

[Slide.]

Safety analysis was performed for the studies looking at cefepime monotherapy. No difference was seen between cefepime and controls with regard to overall mortality or mortality due to infection. Looking at patients in all the studies, including those where cefepime was used in combination, there was no difference between cefepime and controls with regard to adverse clinical or laboratory event rates.

Finally, a Kaplan-Meier analysis did not reveal any difference in the time-to-bone-marrow-recovery between cefepime and control arms.

[Slide.]

So, with discussion of these issues and results of

at

these analyses before the committee, we would present these questions to the committee. First, which clinical endpoints are appropriate measures of outcome for the indication of empiric therapy of febrile neutropenia? Secondly, do the data support the claim of safety and effectiveness of Maxipime for empiric therapy of febrile neutropenia?

[Slide.]

I would just like to thank the many members of the Division who helped in preparing this presentation. If I left anybody off, you can come yell at me later.

[Slide.]

I will just leave these questions for the committee and I will be happy to answer any questions.

DR. CRAIG: Are there any questions from the members? Any questions on the FDA presentation?

DR. RELLER: Of the categories of granulocytopenic patients, those with leukemia, solid-organ malignancies and bone-marrow transplant, the only group for which there were insufficient patients for analysis is bone-marrow transplantation?

DR. ROSS: Are you referring to the table in the briefing package?

DR. RELLER: The analyses that you presented. There was some cautionary note having to do with the numbers

at

of bone-marrow-transplantation patients.

DR. ROSS: For all of the subgroup analyses, I think the numbers were quite small. The numbers were small for bone-marrow-transplant patients. They were also too small for patients with hypotension to draw any meaningful conclusions.

DR. ZINNER: Just as a matter of a routine question about the methodology that you had. How many patients could not be evaluated into the different outcome categories that you describe? Did you have to exclude or discard any because you were unable to categorize them properly?

DR. ROSS: Let me see if I understand your question. What were the relative attrition rates--

DR. RELER: In terms of your definition.

DR. ROSS: --in terms of the definition of diagnosis? That analysis we just looked at superficially. There were no obvious differences between the groups.

DR. CRAIG: Anything else?

DR. PARKER: I am trying to find my numbers in my book here. There has been some modification between that and what I was handed; is that true?

DR. ROSS: Yes; there should be a revised package for you.

at

DR. PARKER: It has February 26.

DR. ROSS: Yes; there is another one. Dr. Soreth has the revised package for you.

DR. PARKER: That accounts for it. But I still have the question. There were the three studies that you pooled together; is that correct?

DR. ROSS: Yes.

DR. PARKER: In one of those studies, its success rate for both arms was certainly much different from the other, yet you included it; is that correct?

DR. ROSS: Yes.

DR. PARKER: You cited the Breslow-Day in the document that I had a chance to read before I got here as your reason for doing it.

DR. ROSS: Yes.

DR. PARKER: In some sense, including it would probably tend to wash out differences so I am not objecting to the inclusion. But I would, from my own judgment, not have included it in that. The Breslow-Day is a great way to prove you shouldn't pool, but it is not very good to say you should.

The absence of evidence is not the evidence of absence, that old cliché. I would think that an analysis not including that one, using just those other two studies,

at

which look very comparable, might be a more accurate way to display results.

DR. ROSS: I think it is interesting that the two studies to which you are referring, which are numbered 189 and 204, have very, very similar designs. 131 was an earlier study which had generally comparable design but I think that the difference in response rates reflects that.

The other point I would make with regard to 131. 189 and 204 are multicenter trials. 131 is a trial carried out at a single center. Since local practice patterns can greatly influence how patients do--one investigator may, for example, institute modifications for different criteria than other investigators. Therefore, with a single center, if there is a particular practice pattern, that may account for it being an outlier.

DR. PARKER: Everything you said makes me say I wouldn't include it.

DR. ROSS: I hear you.

DR. CRAIG: I guess I would just add if you just looked at those two, would the percentage still fit within the 20 percent for the confidence limits?

DR. ROSS: I don't have an answer for you on that.

DR. CRAIG: Any further questions? If not, it is lunch time. We will break for lunch and we will be back

at

here and start precisely at 1 o'clock.

[Whereupon, at 11:55 a.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:15 p.m.]

Committee Discussion

DR. CRAIG: This time has been set aside for committee discussion, then, also a consideration of the questions. Then, eventually, these are the questions that we will be voting on. Just to go over the questions again, since I don't think we have them on a transparency, let me just read them.

Specifically, the first question that I think we need to address is which clinical endpoints are appropriate measures of outcome for the indication of empiric therapy of febrile neutropenia.

I guess that I would try and see if we could at least get some initial thoughts from our high-paid consultants. I know at least some of you have been involved in some of the IDSA thoughts on this and the guidelines they have put forth and can also look at some of the modifications that have been put forth here, suggested by, the FDA.

DR. ZINNER: I think that the difficulty dealing with this whole area from a regulatory standpoint--i.e., the fact that it really hasn't been done before--reflects the difficulty in answering that question, what are the

at

appropriate clinical endpoints.

The group that I have worked with for the last 20 years looks upon the success rate as disappearing signs and symptoms associated with infection with the absence of modification. Yet, when you think about it from the doctor's standpoint at the other end of trial, if the patient survives that additional episode, regardless of what is modified, what is added to the therapeutic course, that is a success of the empiric therapy because you are getting the patient over that hump of the initial fever.

So I must confess, and I said this to Dr. Ross after his presentation, that the way the data were analyzed here, I think it would be nice to get incorporated into the standard operating procedure for the groups that were doing these kinds of studies because then you see the whole spectrum of the question, all sides of the issue.

It has been difficult to compare, for example, studies that were done by the group that uses the response to initial therapy without the availability of modification. It is very difficult to compare outcomes for those trials than for trials done, say, at NCI where success with modification was the bottom-line criteria.

So it is a very difficult and very complicated area. But I do believe that this analysis as presented

at

covers the whole waterfront and is very useful in making the decision that has to be made.

DR. CRAIG: So, in summary, then, it is that you think we need multiple endpoints, that there is no way that you can do it with just single one?

DR. BROWN: If I had to pick one single discriminator, it would be bacteremia because there is the most objective measurement. You have a bug. Is the bug eradicated, yes or no. But you only have bacteremia in 20 percent of the patients. The difficulty in doing these kinds of studies is that when these trials go out in multiple centers and the investigator has the slightest bit--or the clinical caring for the patient--has the slightest bit of concern about the fever still being present after 24 or 48 hours, they will rush to add another drug, usually a glycopeptide.

It is very difficult to control. The level of anxiety in the presence of persistent fever which may or may not reflect failure of initial antibiotic choice is what has made this area so difficult to cleanly evaluated. I think that the evaluation that was proposed here, with all the different classes of response, basically considers all of those things. That is why I am attracted to it.

While I have the floor, I might as well just make

at

a comment about the glycopeptide, itself. I don't believe, quite frankly, that everyone shares Dr. Shenep's view on the use of up-front or early empiric vancomycin at the start.

Certainly, there are at least three large published trials, one from NCI, one from Florida and one from the EORTC, that suggest that the results--most of the patients were adults which would suggest that one could add the glycopeptide on day 2 or 3 if the patient is either failing therapy or there is documented resistant infection to whatever empiric regimen.

So I wouldn't want to prejudice this discussion by thinking that vancomycin was necessary up-front in all patients. I don't believe that it is.

DR. BROWN: I would agree with Steve in many ways. I don't think we can limit it to just one outcome measurement. If I could call the two kinds of a traditional, meaning the pre-NCI 1986 study, and then, say, the NCI 1986 study, criteria where you looked at success with modification, I think, indeed, Davis Ross' analysis of this opened our eyes to things that we may not have seen as clearly before.

By the way, I congratulate him on a very, very crystal clear presentation. But I would add one other thing to that and that is that I think that all the difficulties

at

that are correctly presented by Steve and certainly implied by all that you have heard today may well be not eliminated but somewhat more easily dealt with if we are putting more apples in the apple bin and pears in the pear bin.

I get the feeling that the problem really of why this is difficult in particular is that what I was saying earlier about low-risk, high-risk, and so forth, this has all been put into one area before. And then, afterward, in an ad-hoc way, we sort of say, well, this was a low-risk person, this was a high-risk person, and so forth and so on.

If we could get our entry criteria very crystal clear as best you can--this isn't like doing UTIs or doing other site-specific infections. That is really the problem. But if we could get our entry criteria to be more uniform, more homogenous and so forth, then I think the outcome measures would be a little more clear and, certainly, the comparability to other trials and interpretation of that comparability would be made easier.

So I would say I would want at least have two endpoints open for discussion. I would have the traditional and then the success with modification endpoint and, of course, the microbiological kinds of things that are also traditional.

But I would want to put a lot of emphasis on

at

clear-cut entry circumstance and spend some time working on that.

DR. CRAIG: So to summarize I think what we have heard so far, then, one thinks that the resolving of the episode without modification obviously is an important endpoint to look at. The question I would have is they looked at two of them. Do you feel that one should also look at two, one in which they looked at also no subsequent new infection while on the drug and then they also looked at those in which there was--someone could have a subsequent bacteremia and still be counted as a success.

Is there a difference between the two and would members see preference of one of those over the other?

DR. ZINNER: I think that from the vantage point of having done some of these studies, I think that the bottom line is the one that doesn't deal with the subsequent infections and the subsequent infections can be looked at separately.

On the one hand, unless it is clear that the subsequent infection is related to drug A or drug B as opposed to the fact that you still have the neutropenic patient who has received any antibiotic, you don't want that event to prejudice the original comparison.

DR. CRAIG: Couldn't that clearly be the case?

at

DR. ZINNER: I think it could be a secondary endpoint. It is a secondary endpoint but I wouldn't want to exclude or prejudice a drug because of that fact because unless it was so overwhelmingly clear that drug A versus drug B really influenced and selected for an excess in superinfections or subsequent infections, as they are sometimes called, then I don't think that should be used to determine efficacy or non-efficacy, unless there were a very dramatic difference.

In some cases, you see a small difference of 3 or 5 percent with drug A versus drug B. It is very difficult when you just have that end statistic to know what all the variables were that led to those infections in the first place. And there may be many. So it is very, very complicated. It is cleaner to do it the other way.

DR. BROWN: I would be in favor of this discussion about the subsequent infection sort of thing not including it as an endpoint as such, not calling it an endpoint. I may be using the wrong term here at FDA, but something more under the level of ADR or something like that; in other words, as an adverse drug reaction or something like that.

That is probably not the right term. Somebody here will correct me but something like that as opposed to outcome because, I think it is what Steve said earlier.

at

Basically, you want to give the clinician a safe, effective, empiric regimen to get started.

The one thing we have all learned is that you have to be ready to modify as you go. This doesn't mean that if you start with regimen A, that if you don't finish with regimen A at the end of 12, 14, 16 days or whatever it is--some of these people are neutropenic for as long as six weeks and hardly ever are you on what you started from.

That doesn't mean it was a failure. The evolution of what goes on in the hospital and so forth and so on. It is too complicated to lay that on as an outcome measure in terms of superinfection.

DR. CRAIG: So you would see it more as a safety issue.

DR. BROWN: It may be a little bit of wiggling out of it but that is how I would like to see it rather than calling it part of an outcome measurement. But it obviously has major importance because if you found a regimen that had a very high superinfection rate with it, that would certainly influence whether or not you chose it.

DR. CRAIG: Any other comments?

DR. SERODY: I think that that is a difficult area. When we have looked at our institution in terms of the differences between a glycopeptide and a cephalosporin

at

versus a cephalosporin alone as monotherapy, the major differences in the rate of superinfection specifically due to gram-positive organisms in the monotherapy arm, I don't see how you can discriminate from the initial therapy and defervescence versus the selection of gram-positive organisms by a cephalosporin at day 5, day 6, day 7 and consider that to be a beneficial outcome.

So I would disagree with the notion of that being in an ADR category or subsequent category. I think that it all should be considered together. I think that the only way you are going to know in the future if monotherapy arms select for these types of problems is to include them as endpoints.

DR. CRAIG: Just to bring this up, how are superinfections treated in most other indications? Are they considered as overall a therapeutic failure? Yes? So, for most of the other indications that we have, those would be classified as a therapeutic failure. So you could treat your pneumonia, get rid of it. But if you had a superinfection with another organism, that would be classified as a therapeutic failure.

DR. BROWN: Not to beat this to death, but I will.

DR. CRAIG: Well, we need to beat it down.

DR. BROWN: Let's make a situation up where

at

someone comes in, they have gram-negative sepsis, Klebsiella pneumoniae, bacteremic pneumonia. They are neutropenic and febrile the way they are supposed to be. You start them on a broad-spectrum coverage of, say, an aminoglycoside beta lactam.

On the tenth hospital day, after having defervesced, while still neutropenic, they spike again and they have a pulmonary infiltrate--sorry; let's say a rash. I will make it easier. They have a rash and it turns out to be Candida tropicalis fungemia expressed as a rash clinically and documented.

Is that a failure of the original regimen?

DR. CRAIG: So you are trying to differentiate between something that might not be related at all to the drug as compared to something that might be--

DR. SERODY: And I would state that superinfections with viruses, fungi, or parasites not specifically covered by an initial antibacterial regimen would not be considered a failure.

But, in my eyes, if that individual at day 10 developed a coagulase-negative or Staph aureus bacteremia from their line while on a beta lactam and aminoglycoside, I would consider that a failure of the initial regimen.

DR. CRAIG: Although you could turn it around and

at

say that the reason you got the fungus was that the drug affected the flora and allowed the fungus to colonize. So you can still sort of tie them all in.

DR. ZINNER: It is not necessarily prejudicial to the initial drug unless there is a statistically significant difference that is fairly impressive and dramatic that one drug would select out, be it a fungus or another resistant bacteria compared with another one.

If it is just part of the fact that you still have a potential pool of infecting organisms to selectively infect a compromised patient who has had an additional pressure of antibiotic added to their milieu, that may just be what you would expect from the nature of the beast.

That is what is hard to determine without prejudice to the initial drug.

DR. CRAIG: The data we saw was just a few percentage points different than you presented. I guess I would ask either the FDA or the sponsor were those primarily bacterial infections or were they mostly fungal or viral infections in those that tended to come on later.

DR. NICAISE: I will see if I can give you the answer. I am Dr. Nicaise from Bristol-Myers Squibb. We looked specifically at the breakthrough bacteremia. There were 2 out of 337 in the cefepime group. One was

at

gram-positive, one was gram-negative. There were 9 in the ceftazidime group out of 320 patients. Most of them were enterococci, actually 5 out of these 9. The others were Candida albicans and Klebsiella.

We also looked at the combinations with vancomycin, specifically, and there were 3, irrespective of the two treatment groups, 3 out of 111. One was a streptococci. One was a Corynebacterium and the last one was Hemophilus.

DR. CRAIG: So still a fair number of them were bacterial.

DR. NICAISE: Yes; the majority were bacteria.

DR. CRAIG: So how about comments from other members as to whether they think those should be--let's start off--do people feel fairly confident that one endpoint should be response to the initial therapy? Do you have a question, Dr. Thorpe?

DR. THORPE: No. It sounded like you were posing the question that one endpoint would be the determinate.

DR. CRAIG: No; I am just trying to get points that people may feel--as I say, it may not be one that we are going to be able to use, but multiple ones. The question we are being asked is what would be appropriate clinical endpoints to measure response to the drug.

at

I think that is what I was trying to get at, is the defervescence of the fever with the initial regimen without modification an appropriate clinical measure of response to the drug?

DR. THORPE: In answer to that, yes. But here, again, it is a much bigger spectrum than that alone. I think that is the purest way that you can determine efficacy. However, we have a much bigger spectrum, in this situation, in which we would need other endpoints. I think that the way it has been designed here, where we go from the purest endpoint where you have eradication of bacteremia all the way to survival, I think gives you the best opportunity to look at how well these drugs perform.

Survival, certainly, is the ultimate endpoint. That is ultimately what we want to get to.

DR. CRAIG: Again, the question that I come back to, is we can do one in which we look at response to therapy and we do it all the way through, like the FDA did, where there is no other infection that occurs. It is also useful to include the other type of response, looking at it in terms of efficacy there.

It would decrease it there because you would have some patients that would have responded that would then develop an infection later. I have heard some people say

at

that isn't going to be useful, that that maybe should be put back as a superinfection. And then I have heard some people say that that is still a useful indication for efficacy that is a little different so that both of them should be looked at.

DR. ROSS: One thing I just wanted to add to that discussion of superinfections as an endpoint and is related to the question of how fever and defervescence should be treated. In our analysis of reasons for treatment failure which is found on page 19 of the briefing package, for patients who had a new episode, the most common reason for failure was a new fever without a clear source.

The differences were not statistically significant between the treatment arms. I just throw that out because, given that all the uncertainties surround the meaning of fever as the initial episode, I want to confuse the issue a little more and just mention that there is also the population of patients who develop fever as a second episode but, again, you don't quite know what is going on.

DR. CRAIG: Is that from table 10?

DR. ROSS: Yes; that's correct.

DR. CRAIG: But you have it written there as persistent fever. Is this actually fever that came down and then came back up again?

at

DR. ROSS: That's correct. The four columns that say "new."

DR. CRAIG: Okay; new FUO. So it is more fever than it is in terms of actually finding some other etiology.

DR. ZINNER: I think that, really, to answer the question, you have to look at it all because you won't know that there is a dramatic difference unless you do it this way because you might miss a significant difference in terms of risk of superinfection if one exists if you don't look for it.

So I think it is better to do it all just as David did.

DR. CRAIG: It would be appropriate to be discussed in the package insert, too, in terms of these endpoints. What we are hopefully going to be doing by having these endpoints is to at least be able to have them eventually to define the response in the package insert and give useful information to clinicians.

I think that what you are saying is that some of these patients may have other episodes that may occur after and we should at least look to see if they are somewhat similar in frequency in terms of whatever comparative agent one is using.

DR. ZINNER: Yes; but those data are not routinely

at

available. I think, on a going-forward basis, studies should be designed to gather those data so that future submissions and considerations could be related to those categories. Otherwise, we are never get out of this argument.

DR. CRAIG: No question.

DR. BANKS-BRIGHT: Could I ask you a question about table 10? I am sorry--the gentleman that was talking about table 10.

DR. CRAIG: Dr. Ross.

DR. BANKS-BRIGHT: I know my eyesight is not that great anymore, but what is the difference between the second, poor microbiological response, resistant isolate?

DR. ROSS: I apologize. There is nothing wrong with your eyesight. There is something wrong with my word processor.

DR. BANKS-BRIGHT: Is that "sensitive?"

DR. ROSS: That is sensitive. I apologize.

DR. BANKS-BRIGHT: And which one is which?

DR. ROSS: The first one is sensitive.

DR. BANKS-BRIGHT: So does that mean, then, that you have a persistent bacteremia with an organism that is still sensitive to the antibiotic that you have the patient on? Is that right?

at

DR. ROSS: No. The meaning of that category was simply that the isolate was susceptible to the initial regimen. It may have been a different organism entirely. It was not, necessarily, the same organism. There actually were, from my recollection, no cases in which an individual showed temporary eradication and then had a recurrence. There were cases, obviously, of persistence but not of relapse with temporary microbiologic improvement if one would define such a category.

DR. BANKS-BRIGHT: Which one is that one here, the persistent bacteremia?

DR. ROSS: That would be poor microbiologic response susceptible isolate. In other words, the second one. That should read "susceptible."

DR. BANKS-BRIGHT: But not necessarily with the same organism.

DR. ROSS: I'm sorry; I was thinking of the other category. That would be with the same--

DR. MELISH: So that is a repeat positive blood culture?

DR. ROSS: That is correct.

DR. CRAIG: Are those all blood cultures there? Some of them could be--

DR. ROSS: Some of those could be from other

at

sites. The numbers are, obviously small. The majority of those would be blood cultures.

DR. BROWN: Could I ask David a question. Just from my own satisfaction here, when we are talking about last four categories, new MVI, new MVI CDI, if you will, apropos of your response, John.

Are these strictly new bacterial infections eliminating viral, fungal--

DR. ROSS: No. The MDI may also include fungal infections as well which would be included under resistant. That was a function of how they were coded.

DR. BROWN: Is that how the committee wants it to be, though? It would strike me absolutely unfair to put an antibacterial to the test of eradicating or controlling of fungal infection, or a viral infection. And that is why I proposed that superinfection kind of category.

DR. CRAIG: I thought we heard that most of those isolates were actually bacteria.

DR. BROWN: If they are bacteria, fine. But I am wondering that if they are other than bacteria, should they be called new infections and regarded as treatment failures as such, as opposed to another category entirely?

DR. ROSS: If I may address the rationale behind scoring the patients in that way. In fact, the majority of

at

those cases were bacteria. The question that was being asked, or the concept that I wanted to capture, was what risk was there for any kind of infection that might be due to factors such as changes in colonization resistance, and so on.

Clearly, there is not going to be a prophylactic effect by an antibacterial against an antifungal. I just want to emphasize that I did not intend to ask that of the drug in this analysis. It was primarily in terms of the risk of a fungal superinfection.

DR. BROWN: I appreciate that. I wasn't trying to imply that you were trying to attribute other characteristics to antibacterial. But I would ask the chair or the committee to consider the idea that the concept is correct but wondering whether, indeed, other than bacterial infections that they might not be tallied in there.

I know for David's summary for this presentation it was, but I am thinking for what we are asking in the future.

DR. CRAIG: Personally, I think I would have to look at them, especially fungi. I probably could say that viral may not be as important although I am sure there is probably a link there as well. But I think, clearly, if you change the flora, you can clearly make a fungal infection

at

more likely.

I could see an agent which has a much more anaerobic coverage changing flora even more than what we have seen with these agents and possibly having a greater incidence of fungal superinfection and then the other.

So I personally would think it would be good to include them so you would keep looking at them so that you would be able to see whether there was a difference between the standard regimen and now.

At least we know with what has been looked at with ceftazidime and now with cefepime, fungi don't appear to account for much in the way of failures here.

DR. BROWN: I wouldn't suggest we shouldn't look. I just was, again, using the yardstick of--

DR. CRAIG: My feeling is that if you get too restrictive, then you may miss something that may be an important observation and at least it doesn't appear right now to cause a major confusion to the data. And so, at least for the time being, my position would be that it should be continued to be looked at that way.

DR. SHENEP: I would like to make a couple of points. One is I would like to assure Steve that in the era of vancomycin-resistant enterococcus, I certainly wouldn't advocate using vancomycin on all febrile-neutropenic

at

patients. On the other hand, there are patients that I would not advocate using monotherapy on either. I think we have made that point pretty clear.

The other point is getting back to David Ross' presentation which I thought was very educational and enlightening to show that you can look at data in so many different ways and come up with different conclusions. But this is also bothersome to me from the standpoint of having multiple endpoints to a study and not having one primary endpoint.

Then we are getting into issues of multiple looks at data. If we are having multiple looks at data, we should really adjust the p value to a smaller p value that we would accept a difference as being statistically significant. And then our studies are so underpowered that they have very little meaning.

So while I appreciate that we need to have multiple endpoints to help us appreciate the data, I think we also better be cautious that we don't come out of here with the feeling that all the studies should now look at multiple endpoints without correcting for p values.

That is a conflict and probably why this is such a difficult issue.

DR. FEIGAL: It may not be quite as bad as it

at

looks, though, because one of the issues with multiple endpoints is if you win on all of them, then the math is very similar to just having picked a single one and called that in advance and won it.

These are highly correlated endpoints and there is kind of a fine line between looking for robustness of the analysis and looking for sensitive subgroups versus the thing which I think you are more concerned about which is that by specifying enough different endpoints, there would be so many different ways that you could be a winner and could claim that that was the effect of your drug without anticipating it in advance.

I think, to come back to a point that Dr. Craig was making, I think really what you are grappling with and is very helpful is there are a lot of things we will do to see how robust an analysis is and to see how well a study hangs together, but when it comes down to the way of trying to describe that study clinically, we don't want that same level of detail.

So your comments are very helpful in terms of helping us prioritize which of these analyses should be mentioned in the product labeling.

DR. CRAIG: Again, I guess I would come back to it because I don't think I am clear on what people think in

at

terms of labeling. I think clearly from what I have understood so far, the response to the single drug without secondary infection was one of them that I thought people indicated. Did they think that the one also which would include those patients that have a secondary infection on it should be addressed in the package insert or should they, if that percentage is relatively small like it has been with these studies, essentially not be one of the major ones to be discussed in the package insert.

DR. ZINNER: I think since the incidence of superinfection remains low in most of these studies, under 5 percent, usually, I think that your statement makes some sense and to make it as simple as possible for the practicing physician. I would not overcomplicate the labeling issue.

DR. RELLER: To me, it is precisely because of the labeling that one would like to see the multiple-endpoint analysis as Dr. Ross presented. What does one really want to do in an ideal situation with the package insert, the labeling.

I would think it would be an active description of the expectations. So if these drugs are better than 90 percent in terms of survival, one could expect the patient, given appropriate empirical, early-on, therapy to

at

survive the episode.

But if there is a substantial number of organizations that may become apparent, or after the fact become apparent, like the poor microbiological-response-resistance isolates which was actually in the order of 10 percent of patients, that one would heighten alertness to this, that if a certain agent is more frequently associated with emergent of resistant fungi, that one would be alert to that.

It may affect when one would add a second drug so that everyone doesn't have to get vancomycin, for example, up front with all of the pressures that that entails, and a realistic expectation that one is going to be able to give one of these agents and that is the end of it and nothing else will be done until the neutrophils come back, that realistic expectation may be down in the order of 30 percent.

I think that is what one wants to describe in the package insert, not that someone does, but that one wouldn't be misled, that one gives the drug and that is the end of it because this works in febrile granulocytopenic patients, neutropenic patients.

So I think the multiple endpoints are helpful to put the appropriate boundaries around the expectations of

at

performance of a given agent relative to another agent and, also, the exclusions up front in the study or what becomes apparent from that analysis would be important caveats to put in so that patients who had this constellation of clinical findings that would be excluded from the trial, that that would be clearly delineated because the implication is if someone is very sick that they might not be appropriate patients for monotherapy drug empiric therapy in the first place, or the numbers are too few at the point that a drug would be potentially approved to exclude them.

This has been brought up earlier, for example, with bone-marrow transplantation patients, granulocytopenia, neutropenia in that setting. So I think the multiple endpoints are very important to give an accurate description of expectations to anticipate potential problems that would warrant something other than mono-drug therapy.

DR. BROWN: I think Barth is describing an educational process for the physicians, clinicians, out there which I think is a great idea, and so forth, but people have to learn how to read these things properly and how to interpret them.

I think the truth of the matter is that too many people don't read them and don't look at them at all. We shouldn't be making our decisions on what they don't do but

at

what they should be doing. So I applaud that.

Could I ask the committee one thing in regard to this whole idea of the last four categories. How would you categorize C-dif positivity? David, I will ask you first.

DR. ROSS: That was categorized as a new microbiologically documented infection with a resistant isolate.

DR. BROWN: How do other people feel about that?

DR. ZINNER: It could also be interpreted as an ADR.

DR. BROWN: That's right. What I am concerned about, and I am going to be a little bit of a devil's advocate here because I think that is our role, we are supposed to play it both sides. Let's say we have a combination or a monotherapy that has--it is just the greatest thing since sliced bread but it happens to be very high on, let's say, the C-dif list.

There is going to be a combination drug A with metronidazole given all the time to people because that is the way practitioners practice. I don't know that that is what we want to encourage, in a way. I am being very extreme in saying it to just bring up the point, but I wonder about that.

It is interpreted as being a new infection as

at

opposed to being a result of a complication of therapy. I think there is a fine line, but there is a line.

DR. CRAIG: How is that with other drugs? Is it considered a superinfection?

DR. SORETH: I think we have generally thought of it in terms of adverse events.

DR. BROWN: That's right. I'm pretty sure you have.

DR. SORETH: Drug-related adverse events. And we have tried to include that information within the label.

DR. CRAIG: So how many were there, one or two, in the group or several, Dr. Ross?

DR. ROSS: The number of C-dif second episodes that represented C-dif colitis--and let me just say parenthetically, in order to make that determination, what I required of the data was that there be a positive assay for C-dif cytotoxin not simply a clinical impression.

That was a minority of the data. I don't have the specific figures offhand, but, in general, a new microbiological infection with a resistant isolate was something along the lines of a new bacteremia with a resistant bug, somewhere along those lines.

But I certainly take your point in terms of how does one regard that. I primarily had to make a decision in

at

terms of how regard those for purposes of this review alone.
So I take your point.

DR. BROWN: But, again, we are using this review to talk about the issue. But, if we are going to set a precedent to do this in the future, that is a big burden.

DR. CRAIG: I guess I would still come back to if the majority of them are still new bacteremias, that is information that I would think would be important to know and to discuss. If they were all C-dif, I would agree. I would be happy to have that just be considered as an adverse reaction.

DR. BROWN: Although I would come back to the idea of saying if it a nonbacterial, perhaps it not be lumped in this new category. I am sorry to be so stubborn about it.

DR. BANKS-BRIGHT: Not to further confuse the issue, but what about the VRE issue, the emergence of VRE, now, with its association with the use of cephalosporins, not just vancomycin now but with cephalosporins. Where does that put VRE? Where does that put VRE now and where will it put VRE, vis-a-vis that case that was just presented earlier, the man who developed VRE after being in empiric therapy.

DR. CRAIG: That would probably be a new MDI with a resistant isolate?

at

DR. ROSS: Yes.

DR. CRAIG: If it grew out of blood. If you were just getting stool or something for no special reason and you grew it out.

DR. ROSS: There were more stool cultures that I looked at than I--I won't share the results of those stool cultures with the committee in detail, but yes, there were a large number of stool isolates. Unless there was a clinical scenario that was consistent with infection, those were not regarded as evidence of infection.

DR. BROWN: So you made a differentiation between colonization and infection based on your interpretation of the data.

DR. ROSS: Correct.

DR. RELLER: Dr. Feigal, what is the definition that the agency uses for adverse drug reactions? Specifically, is it limited to physiological, biochemical aberrations in the human host?

DR. FEIGAL: No; I think it is the whole spectrum of things that would be considered an untoward event. I think if you look at the methodology even of how things are looked at in trials, it varies from trying to categorize every adverse outcome that the patient experiences and trying to see if there is an excess of those.

at

So, for example, in the study of foscarnet, initially, there appeared to be a small excess of seizures that was just seen by--some of it was clearly drug-related, but there was an attempt to find every seizure that the patients had during that time period and see if there was an excess.

There are things which are clearly prospectively planned and looked at, like laboratory findings and follow-up cultures. Then there are things which are event-related such as the appearance of worsening clinical condition or an apparent new infection or some other organ complication.

But the attempt is to make it as broad as possible. There are times when success and failure are simply mirror images of each other, as well. Death and survival are--one is an adverse event and the other is a treatment success. So there are times when the kinds of things--there is some arbitrariness in terms of where the are placed.

Part of this is relevant because, historically, there is very little description of efficacy in product labels. There would be an indication and there would be an adverse-reaction section.

It has only been in the last decade or so that we

at

very commonly put clinical-study reports in the labels that actually describe the totality of the efficacy. There was really no attempt to say how well something worked. The logic in some of the antibacterial labels is that it works for susceptible organisms which is somewhat circular when you think about it. It worked where it worked and where the organism was sensitive.

So I think that this is kind of an issue that we grapple with. The product labeling, although as they have gotten longer they are even less likely to be read, they do form the basis of the promotional materials for the company so they are often not read as the label, per se, but they are read as the monographs that are prepared, as the educational materials, as the slide sets and so forth.

But I think your question is very good one. We have quite a bit of latitude as to whether we take something like the superinfections of whatever type and whether we place them with the description of the drug's efficacy as we evaluate failure in the context of efficacy or whether we separate it out and put it in adverse reactions.

Part of the argument for not putting it in adverse reactions, per se, is that is often a long list of systems review of things which are sometimes infrequent complications of drugs. Some of them are well-known

at

complications of drugs and they don't really get at the kinds of untoward things that occur in a specific clinical setting, that you wouldn't see in another setting where the use of the drug would be much more successful, for example.

DR. RELLER: It seems to me that this may be not settled necessarily this afternoon, but to, perhaps, rethink the issues we have been discussing relative to adverse drug reactions which I consider as something that you didn't expect to happen or that you didn't want to have happen--whereas most of the things that we are talking about now, a Candida or vancomycin-resistant enterococci.

Depending on the pressure, they are expected ecological consequences of doing the right thing. The first thing is to maintain the light. But then it is to anticipate the complications. You can count on them. They are going to happen. It just depends on how much and how long the pressure is.

That doesn't mean to me that they should be, therefore, not considered. I think they should be considered, maybe not as adverse reactions but as expected consequences that may differ by the agent that one is using and would be worthwhile delineating to the extent that objective data are available because it could make a difference in what one chose initially.

at

It might make a difference in what the agency approved for empiric therapy. And it could have a lot to do with how a conscientious clinician, what they would look for and what additional steps would be taken at what pace.

For example, one of the terribly confusing things to me about vancomycin in relation to this topic early on was because of the recognition of coagulase-negative staphylococcal isolates from blood that there was a swing toward adding vancomycin to every one.

Then, as complications came up, people thought, "Wait a minute." And then the clinical pace is different. Given that even in these patients, if we are honest with ourselves, most of those coagulase-negative staphylococci don't mean anything.

The pace of the infection with a coagulase-negative staphylococcus versus some of the resistant viridans streptococci or Steve's presentation early on of *Pseudomonas aeruginosa* that happened to be resistant from the outset is very, very different.

I think many places, not all, would consider that it is not necessary, at least for the purpose of coagulase-negative staphylococci--one is not compelled to add vancomycin until one can show that it is there. Let's face it. It is not hard to find coagulase-negative

at

staphylococci. It is harder to know which ones mean something. But to find them, we have got an oversensitive test particularly with our current blood-culture systems which are very much more sensitive for these coagulase-negative staphylococci, some of the old ones.

So it seems to me that in infectious diseases, the ecological implications of therapy may warrant descriptors that are different from what is used for prolonged prothrombin time or whatever because the approach is different.

DR. ZINNER: I agree with that but that should be applied to all antibiotics.

DR. RELLER: Yes.

DR. CRAIG: I guess the only other question that I would have, then, regarding some of the break points was where they also tended to look at subcategories in terms of those that received no oral antibiotics or those that were switched to oral antibiotics. Are those important subgroups to look at?

DR. ZINNER: I would say they are important but not necessary.

DR. CRAIG: So not something that you would feel needs to be--

DR. ZINNER: Absolutely done for everyone? I am

at

not sure. But I think one can anticipate, as we have heard already today, that we will be more likely to see more of these studies that go from an IV to an oral. So I think that the future will be full of those but I don't think that that is a requirement.

Again, it is another descriptor. It is useful but not necessary.

DR. SERODY: I would agree. I would state that I think that for the practitioner out there--and I know at our institution, there was a big push to get folks out of the hospital on oral drugs, that, as part of the package insert that would be quite helpful to clinicians to know that these drugs had been evaluated in that setting and that a certain percentage of patients can be safely put on an oral antibiotic and have them followed in that way.

I think that pressure is going to increase logarithmically over the next five years. So I would state that that ought to be included in everything after this meeting for drugs approved for this indication.

DR. CRAIG: Let me just bring up the question of entire oral therapy. Is that going to be a problem because we are looking at a different population, a much lower-risk population, or are we going to see some of these things even being used in higher-risk patients.

at

DR. ZINNER: I think all things are possible as we get more managed care. So I think they will be looked at but I am not sure we have an answer to that yet.

DR. CRAIG: But the same things that we have been talking about would be applied to the potential of somebody who had a superoral agent that wanted to use that. It would be the same thing, I would assume, for combinations. If somebody wanted to get approval in combination with another agent, the same criteria that we have been talking about would apply.

DR. ZINNER: I would agree.

DR. CRAIG: Everybody is sort of in conjunction on that. So let me summarize and you may want us to vote on it. At least what I am getting as the sense of the committee is, in terms of specifically trying to identify which clinical endpoints are appropriate measurements, we felt that the response or the primary episode resolved without modification.

No new febrile episodes of infection was an appropriate endpoint all the way to survival of infection also being an important endpoint that should be looked at.

The other question where I saw there was a little question was the group where the primary endpoint resolves but where you can get a secondary infection. I think more

at

it was where that should be included as to not that it is not important information, whether it should be considered as an adverse reaction, an adverse effect of the drug, or whether it should be included as part of the overall efficacy of the drug.

Am I correct on sort of that summary for everybody? Do you need us to specifically vote on that?

DR. FEIGAL: No. I think that is one of those questions where the discussion is very helpful and gives us a sense of the committee in terms of what is important.

DR. CRAIG: Does anybody want to have anything else to add on that specific question? If not, let's go on, then, to the second question which is obviously of interest to the sponsor, and that is do the data support the claim of safety and effectiveness of Maxipime for empiric therapy of febrile neutropenia.

I would comment right at the beginning here that, over the lunch break, both Dr. Ross and the sponsor recalculated the intervals for the pooling of two studies instead of the pooling of all three, and they found that it did fit within the 20 percent criteria. The lower boundary limit was at -17 percent.

So pooling the two instead of pooling the three still fit within the current guidelines as included in the

at

points to consider.

DR. PARKER: Once again, which technique did you use to compute your confidence interval?

DR. CRAIG: Don't ask me. Ask Dr. Ross.

DR. CHAKRAVARTY: We resorted to the quick and dirty. It is a small program written in Excel but sits on Dave's laptop.

DR. PARKER: Those are the same numbers I got. I was just trying to check and see--

DR. CRAIG: So you got the same.

DR. PARKER: Within the ballpark.

DR. CRAIG: Does anybody want to start off the discussion here?

DR. ZINNER: I think if we accept that ceftazidime has, by tradition, I guess, been an acceptable gold standard against which--I hate to use that word "gold standard," but at least standard against which to judge other drugs, certainly, the data are comparable and I would have to say the answer, then, would be in the affirmative.

DR. PARKER: I guess I am asking for clarification rather in this because my understanding is that this be within 20 percent as a criterion when we are measuring against an already approved drug. That is my understanding. When we are comparing against placebo, we have got to be

at

better than placebo.

Since we don't have an approved drug to compare against here, what is a strike, what is a ball and who is on first? What are the rules by which I am playing the game?

DR. FEIGAL: I think, although it was addressed just briefly by one of the presentations in the sponsor's presentations, you would have to be convinced based on historical data that ceftazidime would do better than no treatment and that it is an acceptable therapy, that it is not a therapy that has been artificially chosen as something that is easy to beat and something that wouldn't be used in clinical practice.

In this kind of setting, the product that is the community standard is also able to submit a literature-based application for that indication to us. That has been done with some indications. But we often find ourselves in the situation where a product has become the community standard even though it is not in the label.

Off-label uses are perfectly legal. Companies are just not allowed to promote them. If a second company wants to use it, then the second company's burden is to show that the first therapy is reasonable. So, to rephrase your concern, I think it would be whether or not you feel--are the comparator arms reasonable comparator arms.

at

Could you link those back some way to historical literature that would say that patients should be treated with antibiotics and that these are reasonable antibiotics in those settings.

DR. CRAIG: Does that help you? I think, clearly, one would say that, in terms of trying to provide that link, ceftazidime has sort of become, in a way, one of the standard compounds.

DR. BROWN: What I would ask the FDA people, in one of David's slides, I think it was his third slide, where it describes the labeling for ceftazidime and says, "Labeling for ceftazidime state that it may be used 'concomitantly with other antibiotics in a unicompromised patient.'" Does that affect the way we compare?

DR. FEIGAL: This is an example of another common problem for us which is that there were many clinical situations in some of the older labels that were virtually described just in passing. For example, cystic fibrosis is mentioned in passing in some of the labels without any data about trials in that patient population or any specific evidence.

I think with the process that began with the IDSA guidelines and the points to consider, the proposal was made that this could be a much more formal indication that would

at

have much more description than just a passing mention.

Part of what you have grappled with are what kinds of information should be in such an indication in order to provide a good clinical sense of how a product would perform in that kind of a setting. So we are not talking about just using that old language.

That old language is something we would not allow for new products to have. They would have to do studies to get the indication of febrile neutropenia along the current guidelines.

DR. BROWN: Part of the reason I ask is that if I gather the data from the sponsor being presented this morning, most of the patients entered would not fall in the high-risk category that most of us would call high risk. That sounds redundant, but I think you know what I mean. Basically, most of the patients who were entered were low risk. I am willing to be reinforced on that if that is not so by the sponsor.

DR. CRAIG: Why do you say--I thought there were very few that were solid tumor, that these were mostly hematologic malignancies with a fair number of bone-marrow transplants. What makes you think--

DR. SERODY: There certainly weren't a fair number of transplant recipients. I think 15 percent of the overall

at

population were transplant recipients, approximately 65 in each arm which I would argue is not sufficient power to discriminate between a good outcome and a bad outcome.

Certainly, there weren't a large number of hypotensive individuals in this trial which would be one of the higher-risk groups. The predominant makeup of this trial was hematologic malignancies with a period of neutropenia of 7 to 10 days, specifically in the monotherapy arm, 7 days, which, in my estimation, is not a high-risk group but a medium-risk group.

DR. ZINNER: I am not sure that the monotherapy versus combination therapy choice is really terribly germane to this discussion because the option always exists for any clinician to use a drug alone or in combination. I think that, as we learn more about the risk factors for "high risk" and be able to predict those going forward, one could design studies that might better answer that question.

For the time being, monotherapy is an accepted way of treating these patients with some caveats, that the various investigators and bodies such as the IDSA are dealing with in terms of recommendations for guidelines.

So not every patient needs to be treated with combination and the corollary of that is that not all patients would be optimally suited for "monotherapy," given

at

the available issues.

But when you look overall, I think these patients are "typical" for most of the studies, at least, most of the drugs that have been used in these trials. So I don't think that they have selected a particularly low-risk population at all.

DR. BROWN: But I thought, in the discussion when the sponsor took questions from the floor, I recall this and someone correct me if I got it wrong, that specifically people who were hypotensive, people who were in septic shock, and I think even the term "high risk," those people were excluded from entry. Am I wrong?

DR. CRAIG: Are we, then, dealing with febrile neutropenia or are we dealing with septic shock, then, at least, in my mind, starts to be the question because then it may be an entirely different disease that you are looking at.

DR. MELISH: I was uncomfortable with that as well, although I wouldn't consider that these were typical patients with the exception that they didn't represent children. I think that it would be important to describe that this was a population in which hypotension and septic shock was uncommon, less than 2 percent--well, less than 3 percent had a low blood pressure.

at

So if you would give that description of febrile-neutropenic patients with--or not in septic shock, I think that describes the population very well.

DR. BROWN: For monotherapy.

DR. MELISH: Yes; for monotherapy.

DR. CRAIG: But do we have data for the other?

DR. MELISH: You could even say clinicians would be advised to use broader coverage in the event of septic shock which would include antifungal therapy, I would think. The EORTC trials do has not excluded patients with septic shock.

DR. BROWN: The number of patients who present out of the pool of febrile neutropenia in a predominantly leukemic population present with hypotension or shock is very low. It is, again, under 3 or 4 percent. So I don't believe this was a biased sample.

DR. MELISH: No; my concern was not that it was biased, just that if we are looking at this data with good outcome in patients who were generally not in septic shock, that that should be conveyed to the clinician, that there might be situations where they don't want to use monotherapy even though febrile-neutropenic patients can be treated with monotherapy.

DR. CRAIG: This specific addition to the labeling

at

that they proposed was, it says, "It has been used successfully as monotherapy or in combination in this indication." So they do bring that possibility up.

DR. SHENEP: I think it would be very appropriate to expand that labeling when you get to the labeling issue. I certainly think cefepime is an appropriate drug to use in the febrile-neutropenic patient, in some cases as monotherapy and in some cases as combination therapy.

But what I am very concerned about is if it has a label as proposed, the nonexperienced clinician might take the patient who is hypotensive and cover them with monotherapy thinking that they are in compliance with the labeling of the product and they can use that as their defense of why they did this.

I think it would be helpful. I can't see any reason not to expand the labeling to make it clear that it could be used as monotherapy in the nonhypotensive patient without high-risk features or in combination therapies in patients who do have hypotension or high-risk factors.

DR. CRAIG: I guess, unless there is some data out there that I am clearly unaware of, I am really not much aware of much data in terms that combination specifically of aminoglycoside and, let's say, a beta lactam is going to give significantly better response in this indication.

at

I think there is data out there that conflicts on both sides. You are giving me what your feeling is. I am not sure that there is good science out there to entirely back it up.

DR. SHENEP: I would argue that, for Pseudomonas, for example, there is quite a bit of evidence--

DR. CRAIG: If you look at those studies, that is aminoglycoside versus aminoglycoside plus beta lactam, not beta lactam versus combination. I will agree with you 100 percent that, clearly, combination is better than an aminoglycoside alone but, in terms of looking at beta lactam alone, there is where the data is not really clear in the literature.

So, in my view, I don't think we have good data that I can argue and say that we have to put in the package insert that people should use combinations when I don't think the data that is present in the literature supports that.

DR. SHENEP: But the data that has been presented to us has excluded these patients with hypotension.

DR. CRAIG: I think that is fine. Getting back to what Dr. Melish said, specifying what the population is and saying that this was a population that had a very low incidence of septic shock and hypotension is a way of trying

at

to get that across.

DR. FEIGAL: We often have the problem that the studies that are adequate for an initial approval don't paint the entire spectrum. So there is often a study in the clinical-study section, sometimes even in the indication, that says, "This approval is based on," and then describes the patient population.

So we said the monotherapy indication was based on studies which excluded patients that were hypotensive of whatever else would be appropriate to get the sense of what was observed as opposed to what wasn't observed so it wouldn't overstate the case.

It is also possible to put in broad caveats that suggest to identify high-risk patients that might require more intensive therapy not only with antibacterials but we can even extend our editorial comments in that setting to antifungal coverage, for example.

These are important concerns and we are glad you are addressing them. There are ways that we have done this in past labels.

DR. RELLER: It seems to me that not only should the population that was studied be delineated with the exclusion criteria for what data the approval is based on, but it would also, it would seem to me, to be simple to fuse

at

the specific approval indications to encompass that reality, something along the lines of approved for monodrug therapy for patients who are not hypotensive at the initiation of treatment.

If that is who was studied and that is what the drug shows efficacy for, it seems to me one could simply say that. It doesn't, in any way, exclude adding other things. It doesn't include doing others. But it says this monodrug therapy is for patients who are not hypotensive at the initiation of therapy.

DR. CRAIG: We are going to need that for pneumonia and everything else as well, then?

DR. RELLER: If you are using a drug that excludes patients up front and you do not include patients who are hypotensive when one starts treating them for pneumonia, I think that is reasonable to point out.

DR. FEIGAL: In fact, we do something that is similar to that although not often that specific when we attempt to describe some infections and moderate to severe and some mild to moderate when, in fact, the severe infections haven't been studied or the results weren't adequate.

I think what would be helpful to us is not to try and negotiate the final wording but to get a sense of the

at

committee of what the important issues are that we can bring back to the company if we have an overall sense of what you think the important issues are.

DR. RELLER: It seems to me from the sense here that people do think that it is important to point out that the potential differences in severity of infection at the outset. But what is moderate to one clinician may be severe to another and vice versa.

So if I think there are specific measurable, generally known, physiologic parameters that have been delineated and people, looking at the data, think may be important, the more specificity one can include without being restrictive, the more helpful it might be--if anyone reads it.

DR. SHENEP: I also wanted to point out that before our break, in the presentation this morning, even the sponsor said that they would not favor using cefepime monotherapy in the severely hypotensive patient. So I don't think even the sponsor would disagree with that. They want to see their drug used appropriately.

It is not that one wouldn't use their drug. One would use their drug in combination at that point.

DR. CRAIG: Fine. Any more comments? Can we sort of take a vote? We can do this very quickly. I haven't

at

heard much conflicting looks at the data so why don't I just ask, all of those that feel that the data support the claim of safety and effectiveness of Maxipime for empiric therapy of febrile neutropenia raise their hands.

[Show of hands.]

DR. CRAIG: We have five. And I am one, too, so six. So, six out of seven. Dr. Parker?

DR. PARKER: I was just waiting for you to tell me the definition. Do you mean does it meet the criterion as--is it within 20 percent?

DR. CRAIG: Within that 20 percent.

DR. PARKER: That is the question.

DR. CRAIG: Yes.

DR. PARKER: Then I will vote yes.

DR. CRAIG: Okay. We got him in some way, through the back door.

Does that satisfy the answers that you were hoping to get from the committee, then?

DR. FEIGAL: Yes; it has been very helpful. Thank you very much.

DR. CRAIG: I would close, then, this first session. Remember, we need to get immediately on to the second session but we might have a five-minute stretch.

[Break.]

Part II

Guidance Document on Evaluability Criteria for the Review of Antimicrobials: Individual Indications

Introduction

DR. CRAIG: What we are going to be doing this afternoon is starting part of a three-day session that will continue hopefully not past about 1 o'clock on Friday, on looking at a guidance document of evaluability criteria for review of antimicrobials specifically with individual indications.

I might comment that, you may not know it, but the 3:00 to 3:15 break you already had. It is gone. We do have people that are going to talk on the open public hearing and we will sort of see how we are going. We had a little bit of leeway so that if we start to get a little bit too long, we can just stop and bring it up tomorrow.

But I do want to make sure that we can at least get the open public hearing portion done this afternoon. So we may stop somewhere in the presentation in order to be able to get that so that we can at least try and finish on it in a timely manner.

So, to start off this session, Dr. David Feigal will begin.

DR. FEIGAL: I would like to welcome everyone

at

here. I think one of the issues that has come up in planning all of this that often gets asked is what is the difference between points to consider, guidance, guidelines, regulations and whatever happened to the Food, Drug and Cosmetic Act? Wasn't that the law that Congress intended to create?

[Slide.]

It is hard not to have a session as broad as this without going back all the way to the roots. If you go back to the time before there was an FDA, the Postal Service did have some interest in detecting fraud, but there was a time, nearly a century ago, when there was a great deal of concern about whether or not larger government could help with things.

Some of this was generated by the muckrakers. Upton Sinclair was part of the movement to look at that quality of food and some of his comments on what went into sausage have been repeated and paraphrased as jokes ever since.

If you look at that era, there was a time, at this time, when there was a creation of a series of institutions including formalizing the Bureau of Census, creating a National Bureau of Standards, developing vaccine and serum licensing for the first time, transforming the Hygienic

at

Marine Hospital into the Public Health Service, for the first time instituting controls on narcotics.

And then, of course, there is our own personal favorite, the Pure Food and Drug Act of 1906.

[Slide.]

One of the things that happened was that there had to be a basis for exactly how involved were we going to be. Where was the government and its faithful employees going to be in this whole process. One of the other themes, I think, in terms of inspiration for regulatory reform has been that many of the specific acts that have evolved have involved tragic things happening the children including the ten children who died from contaminated tetanus in 1902 that lead to vaccine laws.

The first Act was actually an exercise in simplicity. One phrase, just to illustrate sort of where the need for some of these different types of guidance was, was the description of what should go into a label. Back then, the simplicity; a label must not put any statement in the label that was false or misleading in any particular. This is quite a relatively simple statement.

The only problem is that Congress did not define what a label was. And they didn't define what could be in statements and the exact meaning of these terms, "false and

at

misleading."

[Slide.]

So what they did at that time was they created the process for creating regulations which were to implement the law and to develop the definitions that were needed to really interpret all this.

And, although the rulemaking process has evolved quite a bit, and I don't actually even know the history of what happened between this early first version and our current version, at this time, they took the Secretaries of Agriculture, Commerce and Treasury and they were the rulemaking authority.

The three-person panel was chaired by Harvey Wiley who was a muckraker, himself, a physician by training but also someone very interested in the adulteration of food and was the first Chief of the Bureau of Chemistry in the Department of Agriculture which was the home of the original FDA, which wasn't even called that.

They had public hearings but a comment that was quoted in White's book called the Medical Messiahs, a druggist wrote into the FDA just a year after the law and after the start of the regulation process and said, "I can't figure out what it's about, this new law. The law is just too complicated for poor devils to understand."

at

What this is is just an extension today of the process of educating poor devils. I am glad that you have come and I am glad that we will put this into transcripts and continue to work on the guidance so that we can make this more transparent.

[Slide.]

Of course, in 1938, we had the changes in the law that made the law much more complicated and required safety testing before marketing approval.

[Slide.]

Just to quickly bring us up to date, we had the thalidomide tragedies which, actually, did not affect the United States. There were exposures in the United States, but there were relative few cases because, fortunately, the drug was not used very often in pregnancy in the United States.

As someone quipped, it resulted in the only gold medal given to an FDA employee and this was a gold medal given for blocking the approval of a product. No one has ever gotten a gold medal for actually approving a product. We would like to do something about that, actually.

The only other perverse thing that I did with this photo was that J. Edgar Hoover was in the background and I airbrushed him out.

at

[Slide.]

In 1962, we had a whole series of other things that we needed to address for first time. The Kefauver Act required the demonstration of effectiveness and safety before approval. There was quite a bit of discussion at that time about how stringent that standard should be. It clearly was not going to be that it had to be shown to be effective beyond a reasonable doubt, the criminal standard for guilt.

[Slide.]

It was not also going to be even the standard of the preponderance of the evidence which is the civil-trial requirements which doesn't require a unanimous jury. In fact, the level of evidence was that the evidence required substantial evidence which, in a legal sense, doesn't even require a majority vote. It just requires that some people would think that there is evidence.

But where this was balanced was that it stated that the evidence must come from adequate and well-controlled trials. That was the crux of many, many changes in drug development, I think many of them for the positive in terms of the process of the development of pharmaceutical science.

But the challenge for us has been how to define

at

the link between the design of the study and the specific indication and then, once we have conducted the study, how to analyze it.

The first part of this process in earlier years has helped us. So, we have this hierarchy, if you will. We have the Food, Drug and Cosmetic Act with its major revisions. And that can only be modified by Congress. We have the Code of Federal Regulations which is modified by the FDA through rulemaking and that currently is a rather involved process including publishing proposed rules in the Federal Register, having a comment period, commenting on the proposed rules.

It is complicated enough that even the Waxman-Hatch Act, which is an Act that enabled the creation of generic drugs and patent-term extensions, still has portions of that Act that are still proposed rules and still not finalized because of the complexity.

But what we are here to talk about over the next couple of days is to get your help and consultation on the topic of guidance. One of the things that we have been asked is what, exactly, is guidance.

One person phrased this as, it is our best advice. It is our best current advice and it is often developed in consultation with advisory committees, sometimes with the

at

hearing process. Other times, it has been done with expert consultants such as IDSA process.

There is also the process of international harmonization of technical specifications where there has been a partnership between the regulatory bodies in the three major commercial areas of the world and industry from those areas to try and make our drug development processes more similar to avoid unnecessary duplication of effort.

So there are a variety of very useful things that occur in guidance but the thing I remember about guidance is that when we asked general counsel what happens if someone follows guidance, what can we tell them? General counsel's answer is, "We would be less likely to prosecute them than if we didn't follow the guidance."

So that is far as you get. It is our best advice but the caveat is that general counsel knows all too well that we can give bad advice from time to time and we need to do what is best for the public health.

The guidances that are in place and I think have been very useful, and we will probably go through a process in the not too-distant future of updating them as they begin to age, have been the ones that have laid out the bones and the structure of the study-design issues that IDSA and this committee have been very helpful, along with those of you

at

who have commented.

[Slide.]

But, for the next couple of days, we will take a look at evaluability criteria. I wanted to just make some very broad comments that we will come back to and go over again and again in the specifics to kind of look at the paradigm of why these evaluability criteria and counting rules are necessary.

If you look at the paradigm for an indication for an antiinfective, we begin, often, with describing the site of infection. There are two setting where that is done. Often the organism is known. Other times, it is an empiric treatment.

Sometimes, the indication is based on treating a syndrome and sometimes, although less commonly, a specific organism. There are indications which are designed to prevent infection either broadly or narrowly.

[Slide.]

If you begin to look in a little more detail at each of these paradigms, you can see where the issues are that lead to disagreements when we look at studies that have been submitted to us in terms of counting rules of who should be in the analysis and who would be out.

Probably the most common paradigm for our

at

infections is there is a site of infection, the severity or the clinical setting may be specified. And then it is indicated for sensitive organs. So we may have an indication that is nosocomial pneumonia "due to sensitive strains of," or urinary-tract infections, uncomplicated due to specific strains.

And you begin to see the type of information that is needed to be able to evaluate these claims. You need to know something about how to define the site of infection, how to define severity, the rules for capturing the organism and microbiologic evaluability.

[Slide.]

With empiric therapy, we have a similar paradigm although here we have to decide which are the important organisms that really need to be covered if you trust the therapy to be given empirically. But this is the situation that often happens clinically in such settings as otitis media or one that we considered this morning on febrile neutropenia.

[Slide.]

There are times when we will consider the indication turned backwards, rather than starting with the site, starting with the specific organism. And this committee, in fact, during the last year, has recommended

at

that this may be the only way that we can actually learn enough about uncommon organisms such as penicillin-resistant Strep pneumo or vancomycin-resistant enterococcus in order to provide some guidance in the labels as to how to treat these types of infections.

[Slide.]

Then, of course, there are times when there are syndromes and settings that involve prevention. Again, I have picked examples that the committee has discussed and there are many others.

[Slide.]

Now, part of where this interacts with is tied into the way that most antibiotics are studied and approved. Because antibiotics are effective and because infections usually need to be treated and not simply observed, even for short periods of time with very few exceptions, we typically do not have superiority trials.

In a superiority trial, where you can use no treatment or you have a therapy which is clearly going to be better than existing therapies, the most conservative thing to do from an analytic standpoint and the easiest thing to justify from a design standpoint is to plan your analysis so that, if you include everyone who is randomized, the study that is superior will be superior by a standard hypothesis

at

test, typically a 0.05, two-tailed p value.

But, as you well know, we are very often, including earlier today, looking at similarity between products or, as it is said sometimes, equivalence. The difficulty that we have and the reason why evaluability criteria become so important is that what we end up doing is including some patients that make the drugs look falsely similar.

So if we include patients in both arms who don't even have the disease that you are treating, they are going to do the same, or who didn't get the drug, who weren't followed long enough to contribute a unique outcome or endpoint or who were followed but were not adequately evaluated or who were treated with an inappropriate comparison drug or got some other active drug.

Many of these things are things which are determined after randomization and some of them are things which are inherently tied up with the nature of the infection, themselves. They get us into a slippery design slope of needing to exclude patients who were randomized in order to get a fair comparison between two drugs in a hierarchical sort of fashion.

I think, again, referring back to this morning, that was actually part of what was done with the multiple

at

analyses in the setting of febrile neutropenia.

So, with evaluability, today and then over the next couple of days, we will look at this in a number of ways. But you will see that we will be going disease by disease and looking for your help in helping us come to a common criteria that define the clinical disease, that define the microbiology, the endpoints, the clinical settings that are necessary for treatment because these are the things that, if we can agree on them in advance, we can avoid unnecessarily large studies, studies which are of no use for a regulatory purpose and we can make this process come to a conclusion about studies of new drugs in a more rapid and efficient manner.

[Slide.]

So, with that introduction, let me stop.

DR. CRAIG: Any questions for Dr. Feigal?

Thank you very much, David, for that introduction.

Next will be Renata Albrecht.

General Section on Evaluability Criteria Guidance Document

Introduction

DR. ALBRECHT: Thank you, Dr. Craig.

[Slide.]

It is my pleasure to begin the introduction of the document, Guidance to Industry: Evaluating Clinical Studies

at

of Antimicrobials in the Division of Antiinfective Drug Products. So it should come as no surprise to you that we have affectionately referred to this as the Evaluability Criteria Document for short.

[Slide.]

During the remainder of today and the next two days, what we plan on doing is presenting to you the contents of this document. After each of the presentations of the indications, we have committee members or invited consultants to start the discussion of those sections.

There will be some questions, general questions, that we would like to also pose for discussion. But I also want to comment that this document is open to the public for comment and we would like to invite anyone and everyone who would like to make comments to write them to us.

Any changes, additions or deletions, or suggestions about those, would be welcome. At this point, we only have an address. We are in the process of arranging an E-mail address so that you may send your comments electronically as well.

[Slide.]

I am just giving a brief introduction right now. During this introduction, what I would like to do is give you a brief background on how this document came to be, tell

at

you the current status of the document and our future goals for it, and then provide to you an overview of the presentations that you will be hearing over the next two days.

[Slide.]

Evaluability criteria have existed from the beginning of time or the beginning of drug regulation and this is probably one of our first sponsors submitting NDA 01 on stone tablets. Guidelines were important always. The first time they were formally written down was in 1977 and I actually went through my old records and found this document which it is probably difficult for those in the back to see, but it is called the Guidelines for Clinical Evaluation of Antiinfective Drugs.

The document is nine pages long. But that was the beginning.

As you know, in 1992, the IDSA, under contract with FDA, published the IDSA FDA Guidelines. In that same year, the Division of Antiinfective Drugs published the Points to Consider Document. The evaluability criteria weren't, per se, addressed in either of those explicitly. This omission was sort of recognized and, therefore, it was agreed that it would be important to update the guidelines, circa 1990s.

at

Therefore, a core committee on evaluability criteria was formed.

[Slide.]

The Division of Antiinfective Drug Product Committee on Evaluability Criteria was formed about a year ago. It is chaired by Dr. Lillian Gavrilovich from our division and, on the committee, is representation from medical, microbiology, pharmacokinetic, toxicity, chemistry and statistical disciplines.

[Slide.]

The charge of the committee was to write the document. It was done by individuals. Different people wrote different sections. The sections, after they were written, were brought to committee meetings which occurred weekly and were discussed by members of the committee.

After many meetings, and many comments, and lots of hard work and lots of revisions, we collated this into the one document. Again, it is probably hard to see, but, at this juncture, it is about 100 pages long when printed hard copy.

[Slide.]

The first draft document became publicly available in February of 1997, this year. As many of you have already discovered, it is posted on the Web. I have written the

at

address here. For anybody who hasn't already located it, I would be happy to give you address later.

For those without access to the Web, it is also available from the Drug Information Branch in the Center for Drug Evaluation and Research.

I also want to take this opportunity to acknowledge and thank all the people that were responsible for generating this draft document that we have at the moment.

[Slide.]

The list is very, very long and I am hoping the font is small enough so if I have omitted somebody, nobody is going to recognize who I forgot to mention. There were many people from the division involved on this team project.

[Slide.]

There were also individuals outside the division who were involved in clearing the document and who were also involved in presenting this document and making it public during the next several days.

[Slide.]

The disclaimer is that any errors are the duck's fault. We are not responsible.

[Slide.]

Just to reiterate what Dr. Feigal talked about.

at

This is a guidance document. That means it is not a rule. It is not a law. It is not a regulation. It doesn't go through notice and comment or rulemaking, et cetera. It became public knowledge through the Federal Register Notice that was issued regarding this advisory committee meeting.

As a guidance, this document does not mean to bind anyone. It is the Agency's current thinking or at least proposal of which direction we would like to go.

Let me also add that this document, at present, is a draft. Quite prominently on each of the pages, if you print it out or if you read it, it says, "draft guidance; not for implementation;" that is to say, it is still a working document. We are asking for comments from everyone and, of course, as you have looked at it, you have noticed that some of the sections haven't yet been written.

So, clearly, we are in a draft stage. Really, quite seriously, we want everybody's comments on this.

[Slide.]

What is the purpose of this document? Certainly, it is meant to compliment the other existing guidance documents, as I mentioned; the IDSA Guidelines and the Points to Consider. The document, as it stands, describes general considerations that are important in designing and implementing clinical protocols.

at

The purpose is to provide recommended evaluability criteria that should be used by industry as the guidance to industry implies, but that also we would like to use within DAIDP for the review of clinical studies.

[Slide.]

The ultimate goal, of course, is to have the final document when all the sections have been written, when all the comments have been incorporated. This document could be used by both industry and the division to review clinical trials. We believe this would yield consistency of clinical-study analysis among companies and the division and that it would simplify the review process of applications.

This goal is also in keeping with the Good Review Practices Initiative within the Center.

[Slide.]

The document, as I mentioned, in its draft form, is 100 pages long. The first 25 pages consist of an introduction, a general consideration section dealing with both preclinical and clinical issues.

[Slide.]

You may wonder, well, if we are talking evaluability criteria, what are we doing back in the preclinical realm. Certainly, the success of any evaluability criteria depend on sound planning and

at

implementation that goes on from the earliest stages of drug development.

So we do need to start with the preclinical issues. That consideration and the planning needs to continue through the clinical protocol and analyses. Sort of as an obvious illustration, you can't ask somebody to analyze the coagulation studies if those coagulation studies weren't planned for in the protocol.

[Slide.]

The sequence of presentations that we proposed is for the remainder of the afternoon, we will talk about some of the general considerations. The chemistry section will be presented by Dr. David Katague. Pharmacology and toxicology will be summarized by Dr. Martins Adeyama. The microbiology, both preclinical aspects and clinical aspects, will be presented by Dr. Sousan Altaie. Pharmacokinetics will be discussed by Dr. Frank Pelsor, statistics by Dr. Ralph Harkins and, if we are still alert, I will do the clinical section at the end.

[Slide.]

Then, the remainder of the document, the remaining 75 pages which cover the individual indications, will be discussed tomorrow and Friday. As I have already mentioned, many of these sections have been written but some are still

at

pending. We have currently identified 28 indications. I believe about 12 are written in draft form.

[Slide.]

So, just to tell you what to expect, starting tomorrow morning, we will hear a presentation on evaluability criteria for pneumonias by Dr. Luigi Girardi with discussion by Dr. Craig. Bronchitis will be presented by Dr. Susan Thompson, again with discussion by Dr. Craig. The gonorrhoea indication will be summarized by Dr. John Alexander with comments by Dr. Roselyn Rice.

Sinusitis will be presented by Dr. Albrecht with discussion by Dr. Altaie and Dr. Jack Gwaltney who will be arriving tomorrow. The otitis indication will be presented by Dr. Brad Leissa with comments by Dr. Marian Melish and Dr. Richard Swartz.

Friday morning, Dr. Janice Soreth and Dr. Susan Altaie will present the UTI indication with comments by Dr. Barth Reller. We will conclude our presentations with Dr. Alex Rakowsky discussing skin and comments by Dr. Carmelita Tuazon.

[Slide.]

With that, I think we can go into the individual presentations.

DR. CRAIG: Thank you. I guess the first

at

presentation is Dr. David Katague.

Chemistry

DR. KATAGUE: Dr. Craig, members of the advisory committee, Dr. Feigal, Dr. Albrecht, colleagues, ladies and gentlemen, good afternoon.

About 25 years ago, I was told, in my first public-speaking class, that to attract attention from your audience, you must always open your talk with a joke. In addition, to get rid of your stage fright, you must imagine that all the audience are sitting in the john and you are looking at all of them having a bad time.

This is really to assure that at least you will have a captive audience the first 30 seconds. Anyway, ladies and gentlemen, I do not have a joke. However, I have captured your attention. Let me start with my first slide.

[Slide.]

The IND NDA CMC information; let me emphasize that most of this is information. They are recommendations, not regulations. They are needed in several stages of drug development, the pre-IND, IND Phase 1, 2 and 3, Pre-NDA and the actual NDA, post-NDA, manufacturing supplements, and SUPAC which is the Scale of Post-Approval Changes.

Completeness of the CMC information, chemistry, manufacturer control, for those of you who are not chemists.

at

By the way, if you are a chemist, you are allowed to sleep during this presentation but please don't snore.

[Slide.]

The preferred format could be divided into two headings; the drug substance, otherwise known as the bulk drug or bulk materials. There are other names that I just learned that sometimes a drug substance--they call them API which means active pharmaceutical ingredient. But, for the sake of this document, let's call it a drug substance.

The second item would be the drug product which is the formulated drug, sometimes just called a drug, sometimes called a drug product.

[Slide.]

My talk will center on eleven items under drug substance and eight under the drug product. You will notice that there are items that are duplicated. The manufacturer, for example, the regulatory specification and methods and container-closure system and, last but not least, stability studies.

[Slide.]

Let's talk about the drug substance. Normally, Item No. 1, we will need a characterization and proof of structure. I forget that first we have to have a description. A description should have the appearance, some

at

of the physical and chemical properties like the melting point.

However, in the case of proof of structure, we normally would require an elemental analysis, infrared, NMR, UV, mass spec, optical activity, X-ray defraction, single crystal data if available. For proteins, amino-acid sequence, peptide map and secondary and tertiary structure if known.

Normally, in the antiinfective drug products, we don't receive a lot of protein or peptide INDs but lately I have been observing that we are getting a few.

[Slide.]

The number 2 item is the manufacturer, a list of all firms associated with manufacturing and controls of the drug substance, contract lab for quality control and release and contractor for stability studies must be submitted. In general, most of the manufacturers of drug substances are from foreign countries, Europe, Japan and the Far East, for example, India.

[Slide.]

Item no 3, and we are still in drug substance, is synthesis and method of manufacturer. For example, the starting materials should be listed, the sources, the methods and the results of the analysis of the starting

at

materials, reagents, solvents and auxiliary materials. The grade, ID, minimum purity level and steps used in the manufacturer of the reagents.

[Slide.]

No. 4; we have the flow chart. We would require--not require. I don't want the word used, "require." It is a no, no. We would want the description of the synthetic manufacturing process; for example, a fermentation, extraction procedure, must be provided.

A general step-by-step description of the synthesis or manufacturing process should be provided including the final recrystallization of the drug substance. The reason why I mention the final recrystallization, the final solvent is important here because it will be needed later on in the specification of residual solvents.

For biotech or natural products, the validity of the stability of cells during growth and the capability of removing viruses and other impurities by extraction and purification should also be conducted.

[Slide.]

The flow chart containing information should provide chemical structures including stereo configuration, if applicable. The intermediates, either in situ or isolated, and significant side products should be listed.

at

Solvents, catalysts and reagents should also be provided.

In the case of biotech or natural products, fermenters, columns and other equipment reagents should also be listed.

[Slide.]

For Phase 3 IND, if there are any reprocessing procedures and controls, they have to be described.

[Slide.]

Item No. 5, and we are still on drug substance; controls at selected stages in the synthesis or manufacturer process to assure that a reaction completion has been achieved as well as purity or proper cell growth should be described for isolated intermediates that require control, the acceptance criteria and analytical methods may be described.

[Slide.]

No. 6, reference standard; the synthesis, purification of the reference standards, or working standards, used to support the IND should also be described if it is different from that of the drug substance. The analytical test results for the working standard against the regulatory acceptance criteria should also be provided.

[Slide.]

Item No. 7, regulatory specs and analytical

at

methods. Under analytical methods, I would like to mention some of the ICH document Q2A, test and validation of analytical procedures published in the Federal Register, March 1, 1995. Another ICH document, Q3A, impurities of drug substances, also published in the Federal Register, January 4, 1996. These two are good references and will describe in detail what is required submission.

We have acceptance criteria; purity/impurity profile should be identified.

[Slide.]

Microbiology; microbial limits should be considered if appropriate. In most cases, it is not required.

[Slide.]

No. 9; batch results, summary of the test results, analytical data, chromatograms, certificate of analysis for relevant lots of drug products should be provided.

[Slide.]

No. 10, the container-closure system. A detailed description of the container-closure system, the use of transport and/or inventory the bulk materials should be described. It is important that this container-closure system was simulated and the drug-substance stability studies. Now, in the case of the drug substance, the

at

container closure is usually a methyl or fiber drum lined with polyethylene bags. That is the usual container-closer system.

[Slide.]

Stability studies; one of the important requirements. You should have stress or accelerated studies. Again, the requirements in detail on this is published in ACH Document Q1A, stability testing of new drug substance and products, published in the Federal Register, September 22, 1994.

The recommendation/implementation date for this document is 1-1-98. Again, stress studies should include inherent stability of the drug substance and the potential degradation products. The methods should be capable of detecting degradation products. This is sometimes known as stability-indicating method.

Studies may include various pH, temperature, relative humidity, presence of oxygen and/or light.

[Slide.]

No. II, the studies and protocol. Protocol should include study design, list of tests, sampling time, heat test and expected duration of the stability program. The study should include short and long-term storage condition. Again, methodology should be described in detail.

at

Stability data should include the lot of box numbers, manufacturing sites, the date of manufacture. It is recommended that each table of data contain data from only one storage condition. This would really help the reviewer review the data. Individual data points for each test should be reported.

For analysis of results, we could have statistical analysis. The discussion should be based on the parameters being investigated and the stability program. The discussion should demonstrate that adequate controls in stored condition are in place to ensure the quality of the product used in the clinical trials.

Again, stats may be provided using the FDA program and advertisement for the division. If you need more information, I think we can provide it for you.

That ends our discussion of the drug substance. Now we shift our attention to the drug product

[Slide.]

It is a formulated bulk drug. Sometimes it is just called the product or sometimes it is just called the drug. Number one, we need the component and the composition. Qualitative and quantitative composition unit of use should be provided; for example, milligram per tablet. The components should also be identified by

at

established names in compendial status if they exist. The batch formula should also be provided.

[Slide.]

Number two, we have specifications and methods for components. Again, they are either active or inactive ingredients. The active ingredient is the drug substance. This should be described by the product manufacturer. Inactive ingredients could either be compendial or non-compendial.

In the case of compendial ingredients, the methods and acceptance criteria that are in the official compendia should be only referenced. It doesn't have to be repeated in the application.

[Slide.]

However, for non-compendial ingredients, analytical methods should really be submitted, a description of the manufacturer and control of these non-compendial ingredients should be submitted or appropriate reference provided; for example, a drug master file in the approved IND, or an approved abbreviated NDAs.

The third item, manufacturers, the same listing as I did in drug substance.

[Slide.]

Method of packaging. Production operation is a

at

step-by-step procedure and the operation should be submitted. Packaging, labeling process should be submitted. In case of labeling, reconciliation procedures should be submitted. End-process controls, both reprocessing procedures should also be submitted.

[Slide.]

Regulatory methods specifications; again similar to the drug substance but, in this case, either the degradants-profile impurities--I put there a reference in the ICH document, Q3B, impurities and new-drug products, Federal Register, March 19, 1996, details are published in that document.

Again, microbiology if applicable and, again, batch results.

[Slide.]

6, container closure system; this is slightly different from the drug substance. A general description of the system, the DMF authorization, name of suppliers, manufacturer, should be provided. Additional information would be needed for novel delivery systems such as metered dose inhalers.

[Slide.]

7, stability; again the same requirements as drug substance.

at

[Slide.]

Labeling; for Phase 1 and 2 INDs, a mock-up or printed representation of the proposed labeling and labels that will be provided to investigators to be used and the drug container should be submitted. Investigational labels must carry the caution statement for 21 CFR 312.6 which states "for investigational use only."

[Slide.]

Last, but not least, my favorite environmental assessment. For IND, a claim for categorical exclusion will be submitted under 21 CFR 25.24. For NDA, the environmental assessment may be waived for most of the NDAs, hopefully after Gore's REGO initiative is finalized in the Federal Register.

Hopefully, it will be in June, 1997. I won't hold my breath until this is published. This will really save a lot of time and energy for my reviewers as well as money, I guess, from the sponsors, not to be required to submit and environmental assessment.

Additional information, which will be provided at NDA stage. You have your preclinical formulation, inspection GCMP and methods validation.

[Slide.]

My second-to-the-last slide is the summary of ICH

at

quality activities. There are two there that are at step 5. Step 5 means that they are almost ready for implementation. For those of you who are surfing the internet, this summary is covered on the internet at the Pharmweb site.

[Slide.]

For my last slide, I have a summary here of the ICH guidelines and implementation. Please note that the first document, Q1A and stability testing, is recommended for implementation in January 1, 1998. Q3A, impurities and new drug substances, is supposed to be implemented January, 1998. The rest are January 1, 1999.

Again, I thank you for your attention.

DR. CRAIG: Questions? Dr. Katague, how high is the temperature that one looks at in terms of stability? Is it just room temperature or do you go higher?

DR. KATAGUE: There are two conditions, stress and long-term. In long-term, you have 25 degrees and for stress or accelerated studies, it is usually 40 degrees at 75 percent relative humidity.

DR. CRAIG: How long are the exposures? The only reason I bring this up is there is much more of a tendency, or we are seeing increased use of antibiotics for home IV. Frequently, with pumps that are sometimes put under the shirt or in a way where one could see a higher temperature

at

than what one would see with just room temperature.

One wonders about whether, at that higher temperature, especially if one was using continuous infusion where the drug is going slowly over a 24-hour period, how stable the compound is. Is that kind of information generated with what is done now?

DR. KATAGUE: Usually, we have what they call cycle studies. Of course, in the ICH guideline, it provides for fluctuation and temperature, especially during the transport of the drug where the temperature in the warehouse--if the drug is in Africa or in the tropics, there would be temperature changes.

DR. CRAIG: But in solution, let's say.

DR. KATAGUE: In solution, normally you should have data to show that the drug is stable for certain hours in solution. They should have data the show that.

DR. CRAIG: Any other questions?

Thank you very much.

We will move on to the next one, Martins Adeyemo.

Pharmacology and Toxicology

DR. ADEYEMO: Members of the advisory committee, Dr. Feigal, Dr. Albrecht, ladies and gentlemen.

[Slide.]

During the course of my presentation this

at

afternoon, I hope to relate to you the roles of the pharmacologist and the toxicologist and the importance of preclinical animal toxicity data in drug development and review in the Department of Antiinfective Drug Products.

[Slide.]

The primary roles of the pharmacologist and the toxicologist in drug review actually are twofold. One is to review and analyze the pharmacology and toxicology data submitted in the IND and NDA applications with emphasis on protecting humans from the potential toxic effects of the test chemicals through clinical trials and drug approval.

[Slide.]

The other important role is to provide guidance to the industry on what types of data are needed for drug evaluation, the appropriate in vivo and in vitro studies to obtain the toxicity data and when to conduct such studies to save time and other resources.

[Slide.]

The data generated from whole animal and in vitro systems are used to evaluate how the drug affects the body, which we generally refer to as a pharmacodynamics. We use this data also to evaluate how the body affects the drug which we normally refer to as the pharmacokinetics. Also we use the data to evaluate the complete toxicity

at

profile of the test drug including drug-induced histopathological changes.

[Slide.]

The use of whole animal and in vitro systems are necessary to obtain the safety data in drug development because animals are used as surrogates for humans and, more importantly, for ethical reasons. There are certain studies that must be conducted in animals and not in humans. For example, testing for teratogenic effects of a compound. If a compound tests positive for teratogenicity, for example, as was true for Clarithromycin, it may require a bold warning against usage in pregnant women.

[Slide.]

We recognize that the role of the pharmacologist and the toxicologist is in the IND stage of drug development. It helps to make this process more efficient. We encourage pre-IND meetings with industry. Usually, industry will require a meeting for guidance on the overall drug-development plan, for chemistry, manufacture and control, pharmacology and toxicology, microbiology and clinical issues.

[Slide.]

At the meetings, the sponsor will present to us the drug type and the mechanism of action, if known at that

at

point. The sponsor will also discuss any available pharmacology and toxicology data available. Such data may be sponsor-generated as well as information from the literature will be acceptable for the pre-IND meetings.

We are also interested in knowing the intended route of administration and proposed clinical dose, if known, also. The sponsor will also tell us the intended indication and the target population.

[Slide.]

At the conclusion of such meetings, the toxicologist will offer advice on the type of data needed in the IND submission to support the safety of the compound in the clinical trials. If limited animal pharmacology and toxicology data and pharmacokinetics data are available, potential human toxicities could be identified and monitored in the clinical trials.

[Slide.]

After animal pharmacology and toxicology data have been received and have been reviewed by the pharmacologist, the data are used to determine if the proposed clinical protocol in man are reasonably safe to initiate as presented by the sponsor. We also use the data to inform clinical investigators about the animal toxicities associated with the compound.

at

The data also help the clinician in determining what basic and safety monitoring is needed to protect volunteers and patients such as the use of Holter monitors for cardiotoxicity with some macrolides.

[Slide.]

Other importance and uses of the animal pharmacology and toxicology study data include to identify the complete spectrum of toxicities attributable to the compound, and, hence, to be able to predict for man the target organs and tissues such as the kidney, the liver, bone marrow or the gastrointestinal tract.

We are to review this data to recognize the potential for the following types of target toxicities, such as the nervous system, the reproductive system, genetic toxicities, and carcinogenicity.

[Slide.]

We also use this pharmacology and toxicology data to aid in the selection of doses, relevant route of administration answering important questions such as is the proposed dose acceptable in terms of risk, margin of safety via the intended route. Does the route of administration in animals mimic the intended route in humans.

These data are also used to insure that the animal data support the duration of drug use in the clinical

at

trials. The duration of the relevant animal studies should be equal to or exceed the proposed duration in man.

These data are also used to characterize the toxicities in terms of permanence or reversibility; e.g., as in aminoglycosides and drugs used in sepsis. This is particularly important because sometimes some of the intended patient population may also have certain preexisting other function impairments.

[Slide.]

These data are also used to identify toxicities that cannot be tested for in humans, as I said earlier, for ethical reasons such as fertility impairment, teratology, genetic toxicity and carcinogenicity. This information will be included in the drug labeling.

[Slide.]

Last but not least, we use the pharmacology and toxicology data to aid in the risk-benefit assessment of whether to allow the use of higher doses with acceptance of higher risk to patients to be treated for indications for which there are no approved therapies. As we have been discussing all day, for example, febrile neutropenia, vancomycin-resistant enterococcal infections or sepsis.

[Slide.]

Now we are talking about the types of animal

at

pharmacology and toxicology study data that we like to see in the IND and NDA submissions. In a typical IND or NDA submission, we would expect to see the following; special pharmacology study section. These studies primarily examine organ functions. They may be conducted according to the non-good laboratory practice.

Such functions that they monitor include cardiovascular and nervous systems, liver, kidney and gastrointestinal tract. In the toxicology section, all studies which are submitted into the IND or NDA applications should be conducted according to the good laboratory practice regulations. These studies include single-arm repeat-dose studies, genetic toxicology, reproductive toxicology studies and special toxicity studies.

[Slide.]

The special toxicity studies include immunotoxicity studies, investigating the possibility of allergenicity as has been shown with beta lactams; inhalation toxicity studies, if a compound is indicated, for example, for cystic fibrosis; phototoxicity or photo core carcinogenicity studies as in the fluoroquinolones.

We may also require, as a special study, dermal toxicity studies and carcinogenicity studies.

[Slide.]

at

With respect to carcinogenicity studies, they are usually not needed as antiinfective drugs are used mostly for short-term duration therapies. However, they may be needed, based on the weight of evidence, of course, if, for example, the compound is positive in mutagenicity assays, if the compound has structural similarities to known classes of carcinogens and if the compound, from the repeat-dose toxicity studies showed evidence of hyperplasia and preneoplastic lesions.

Carcinogenicity studies are required, however, for drugs indicated for chronic usage; that is, continuous or intermittent drug usage for more than six months.

[Slide.]

Prior to phase 3 and new drug application submissions, we do expect that most toxicology studies should have been received and reviewed by the agency, especially in the division. This is because the data generated from animal toxicity studies related to dose, duration of use, route of administration and relevant monitoring of possible adverse events are used to support the extensive phase 3 clinical trials.

[Slide.]

When the NDA is submitted, we expect to see the following in the NDA. All data from completed toxicity

at

studies used to support all the clinical trials from phase 1 through phase 3, all requested special toxicology studies. If there are any phase 4 commitments, they may be related to any chronic animal toxicology studies, as the carcinogenicity of photo core carcinogenicity, we would like to see confirmation of the existence of such evidence spread out in the NDA.

Also, a draft product label containing information generated for the pharmacology and toxicology sections should be in the NDA.

[Slide.]

Product labeling in the NDA; in the product labeling, the following preclinical animal toxicology sections may be addressed. They include carcinogenesis, mutagenesis, and impairment of fertility. In the section of pregnancy, this will address teratogenicity and pregnancy categories.

In the section on nursing mothers, the information that goes here has to do with if the drug is present in the dam's milk and if there are no comparable human data to state otherwise.

[Slide.]

In the section for overdosage, we have discontinued the use of LD50. By the way, LD50 is the

at

littlest dose of a compound that produces 50 percent mortality in the tested animal population. However, now, we use statements describing signs and symptoms of toxicities and significant mortalities seen at and above an identified toxic dose. This is important because the toxic dose need not be to the maximum tolerated dose. It could be a dose higher than the MTD.

Furthermore, the animal toxicology section is optional. It contains well characterized toxicities seen in animal studies but they were never seen in clinical trials. Such toxicities could include neurotoxicities, cardiotoxicities, and arthropathies as was seen for fluoroquinolones.

[Slide.]

45-day fileability meeting; usually, on the 45-day NDA submission, a fileability meeting is convened by the division essentially to identify any missing information. This is not a meeting to talk about the quality of the datasets because a review of the NDA has not even started yet. This is essentially to identify if there is any missing information in the NDA to make it fileable.

With respect to pharmacology and toxicology, the following are considered essential for an NDA to be fileable. All required and requested toxicity studies

at

should be completed and submitted in the NDA.

Such studies include teratogenicity, reproductive toxicity, acute and subchronic toxicity, phototoxicity, dermal irritation and carcinogenicity studies.

The proposed labeling sections relating to human doses should be expressed in multiples of the no-observable-effect doses in animal studies either as a ratio of the drug dose to the total body-surface area or comparative serum-plasma levels used in the AUCs.

Lastly, there should be a statement in the animal-study section that shows us that the studies were conducted according to acceptable and state-of-the-art protocols reflecting FDA's animal-welfare concerns.

That concludes my presentation.

DR. CRAIG: Thank you.

Any questions? In regards to your last question there, where you look at the doses in relationship to the no-observed-effect. How high are they usually, in general, for most of the drugs? Are they one-tenth of the no-observed-effect or sometimes much closer?

DR. ADEYEMO: Sometimes it could be closer but, in general, it is about one-tenth.

Any questions?

Thank you very much.

at

Next, I think we will have microbiology by Dr. Altaie.

Microbiology

DR. ALTAIE: Good afternoon.

[Slide.]

I am Sousan Altaie, a member of the Microbiology Group in the Division of Antiinfective Drug Products. I am struggling with a cold and if I start violently coughing, don't be alarmed. I have a glass of water that can take care of me.

[Slide.]

Our discipline of clinical microbiology expands over the clinical and preclinical issues. You heard my colleagues addressing the pharmacology and chemistry issues. I will be talking about microbiological aspects of preclinical studies.

[Slide.]

As far as the clinical issues are concerned, there is an area of issues and I will be only addressing the microbiology issues in study designs.

[Slide.]

For preclinical issues, before an antiinfective is tested in humans, we, of course, need to test it in vitro and in animals.

[Slide.]

In general, preclinical microbiology programs should be designed to learn about the drugs antiinfective activity in vitro and in animals including the following parameters. I will be discussing each parameter separately; mechanism of action, antimicrobial spectrum.

[Slide.]

Emergency and mechanisms of resistance, antiinfective interactions, and intracellular and subcellular concentrations, evaluations of antiinfectives in animals.

[Slide.]

For mechanism of actions, measures should be made to determine mechanism of action of the new antiinfective in order to provide an insight regarding the development of resistance through alterations of the drug's target size or other mechanisms if they exist.

[Slide.]

When one wants to study an antimicrobial spectrum of an antiinfective, in vitro study activities against a panel of pathogenic bacteria should include the aerobes, facultative anaerobes, anaerobes, fungi and also American tissue-culture strains. CDC has a defined set of organisms called challenge sets and they have a known mechanism of

at

resistance.

One also needs to test isolates from a variety of clinical settings, outpatient, inpatient, community and teaching institutions.

[Slide.]

In vitro activity against a panel of pathogens can include Rickettsia, mycoplasma, Chlamydia, spirochetes and mycobacteria. Similar patterns of microorganisms should be studied for assessment of the activity of antifungals and antiprotozoals as well.

[Slide.]

Susceptibility testing should be standardized with respect to medium and inoculation procedures. Growth and susceptibility test results are affected in vitro by inoculum-size, pH, temperature, osmolarity, ionic strength, the medium's composition, the medium's physical state--is it solid or is it a broth--cationic strength and growth factors and, finally, the partial pressures of gas and moisture when the test plate is incubated.

[Slide.]

Tentative breakpoints are set to largely differentiate subpopulations of isolates according to factors such as pharmacokinetics properties, serum-protein binding properties of the antiinfective and, based on

at

agreement with alternate susceptibility testing methods.

[Slide.]

When tentative breakpoints are set, they might be adjusted or defined for fastidious organisms such as *Hemophilus* and *Streptococcus pneumoniae*.

[Slide.]

We also should have quality control along with susceptibility testing and tentative quality-control limits are based on central tendencies of replicated measurements using well-characterized microorganisms. These tentative QC limits after they are set may be adjusted to move away clinical susceptibility testing results from false susceptible readings.

[Slide.]

To address the emergence of mechanisms of resistance, one should have methods that are widely accepted and should be used to detect the emergence of antimicrobial resistance. Cross resistance to the same class or other classes should be evaluated and development of resistance by organisms other than ones targeted by the antiinfective should be evaluated because, in a human body, you have an area of microorganisms and microflora and they could pass the mechanism's resistance to each other.

[Slide.]

at

Mechanism of resistance and methods by which this resistance is transferred to other microorganisms should be determined. After the mechanism is determined, it should be verified by testing organisms that possess or lack the resistance determinants.

[Slide.]

For antiinfective-antiinfective interactions, a checkerboard titration is appropriate to look for synergy antagonism and so on in the in vitro setting. Intracellular and subcellular concentration are important in certain antiinfectives especially when a pathogen is phagocytized but not killed by the host and when an antiinfective has the ability to enhance or diminish the activity of phagocytic cells.

[Slide.]

During the animal studies, these studies are designed to estimate dosage schedules for humans. They also are designed to determine potential efficacy in specific infections. And they also are designed to evaluate potential efficacy that cannot be evaluated by in vitro methods.

[Slide.]

So, in consequence, animal models may be used to explore the advantage or disadvantage of a combination

at

therapy. Penetration of drug into infected sites, timing of prophylaxis, reticuloendothelial clearance of the organisms and intracellular killing.

[Slide.]

To make the transition to clinical issues, when clinical trials are conducted, one needs to use laboratories that are pretty expert in what they do. These laboratories should be College of American Pathologist certified and Healthcare Finance Administration licensed as high-complexity facilities.

The microbiology staff should be experienced in routine microbiology procedures as well as in recovering anaerobic and fastidious organisms. They should be expert in doing susceptibility testing and specimen handling in storage and retrieval.

[Slide.]

When one wants to design a clinical study, protocols should outline specific clinical and microbiological procedures and criteria for diagnosis and follow up in as much detail as possible.

[Slide.]

The following criteria to be considered for optimal biological diagnosis; you need to know the timing of the specimen collection, specimen collection and transport,

at

by what method the specimen was collected and how it was transported and how long, especially, it took to get to the laboratory before it was tested.

Quality of the specimen, itself; there are methods to determine, for example, in sputums, to do a gram stain to see if you have an appropriate sample; do you have sputum or do you have spit, instead.

Identification to the species level is important because the trend in the division is to label specific organisms for specific indications. Knowing the organism to the species level become important.

Appropriate use of serological and immunological and molecular diagnostic casts are encouraged if the culture is not feasible. We would rather have an isolate but, if we don't have an isolate and technology is limited, we do accept the other methodologies.

[Slide.]

When one does antimicrobial susceptibility testing, one should use standardized methods that routinely include quality control and isolates should be saved by the investigator in order to verify the species of the organism, the antimicrobial susceptibility testing results and mechanism of resistance in case a patient fails the therapy.

Antimicrobial susceptibility testing should

at

include both dilution and disk-diffusion methods.

[Slide.]

When one reports that this diffusion results to us, we would like to see the zone reported in millimeters instead of just the interpretation.

[Slide.]

When one does the dilution methods, we would like to see the full range of two-fold dilutions with the following scheme of one below and above and to see the results reported and analyzed as far as the MIC50 and 90 are considered.

Commercial systems using limited screening dilutions or breakpoints are not acceptable. When you look at the antimicrobial susceptibility testing for anaerobes, the broth-disk dilution technique is not acceptable.

[Slide.]

Evaluate microbiology results and clinical efficacy by grouping of pathogenic species and special subsets. We don't want the sponsor to lump all the organisms together. We would like to see subset analysis of methicillin-resistant Staph aureus being separate from a methicillin-susceptible Staph aureus.

We would like to see vancomycin-resistant enterococcus being analyzed separately from

at

vancomycin-susceptible enterococci.

[Slide.]

We like to see the analysis of Hemophilus influenzae, Staph aureus, Neisseria gonorrhoeae and Moraxella catarrhalis on the basis of beta-lactamase production and we like to see penicillin-resistant Streptococcus pneumoniae separately analyzed from penicillin-susceptible Streptococcus pneumoniae.

Last but not least, we like to have analysis of extended spectrum beta-lactamase production of the organisms.

[Slide.]

Emergence of resistance should be monitored by full-species identification, antimicrobial susceptibility testing and characterization of resistant mechanisms. When I say "to be monitored," a simple criteria of increase in MIC of greater than four-fold or increasing zone diameter of greater than 3 to 6 millimeter suggests changes in antimicrobial susceptibility patterns.

[Slide.]

When these changes in antimicrobial susceptibility are detected, one needs to retest the original isolate in parallel with the new isolate and one needs to identify the original isolate in parallel with the new isolate. Typing

at

techniques may be necessary to differentiate the original from the new superinfective strains.

[Slide.]

With this, I would like to conclude the issues of microbiology and thank my colleagues in the group of clinical microbiologists in the division; Peter Dionne, Harold Silver, James King, Mendra Utrup, Fred Marsik, Robert Widdon and our team leader, Dr. Sheldon.

Thank you. I will entertain any questions if there are any.

DR. CRAIG: Questions? I guess I am always the only one asking them here. I guess one of the questions I have is how consistent are you in terms of what you look at when one is setting up tentative breakpoints. I think another committee that I serve on, the NCCLS, actually has a document where they list the various items that they specifically look at.

Are you always fairly consistent, always looking at, as far as population analysis, pharmacokinetics, animal models, all those things with all the different--to help in making that decision?

DR. ALTAIE: Right. Pharmacokinetics did not used to be an issue that we looked at very carefully. But, currently, we are including the pharmacokinetics as a

at

parameter in setting up those breakpoints.

DR. CRAIG: At least my general feeling is once we start on the tentative breakpoints, the way trials are done, since we toss out the people that don't fit in those things, we essentially confirm that those are the breakpoints. So the initial decision, I think, is a very, very important one, it eventually ends up.

DR. ALTAIE: Yes.

DR. CRAIG: Anything else?

Thank you very much.

Let's move on to the next one, Dr. Pelsor.

Clinical Pharmacology and Biopharmaceutics

DR. PELSOR: Good afternoon.

[Slide.]

I am Frank Pelsor and I am the team leader for the Clinical Pharmacology and Biopharmaceutics reviewers that support the Division of Antiinfective Drug Products.

[Slide.]

For my presentation this afternoon, I would like to present an objective of drug therapy that we see as really driving the kinds of information that we ought to collect. I will talk about some factors that determine a dosing regimen, some approaches to determining the dosage regimen and I want to focus on the kinetic approach.

at

Then we will outline some of the types of studies that we can use to collect the kind of information that we need. Lastly, I would like to outline a bit of a time line for what we believe this information is useful.

[Slide.]

The objective that I see that really will drive the kind of information we want to collect is that, for drug therapy, we want to produce and maintain a therapeutic response while minimizing undesirable and toxic effects.

[Slide.]

The dosage regimen that we use in order to accomplish the objective really is based on a number of factors. Pharmacokinetics is only one of those, but other factors which we will get into in a moment, do affect the pharmacokinetics and so there is a relationship between some of these factors. They don't really stand alone.

For the next few slides, I will go into these various factors in a bit more detail.

[Slide.]

These kinds of factors don't have so much to do with the kind of pharmacokinetics information, the basic parameters that we want to collect, but they do provide sort of a macrodirection for us. In terms of activity and toxicity, we would be interested in the toxic dose, the

at

minimum therapeutic dose, the relationship between effective and lethal dosing in terms of the therapeutic index, the kinds of doses that produce side effects and the dose-response relationship between these various levels of effect.

[Slide.]

The clinical state of the patient is very important in determining the dosing regimen. We know that age, weight and gender affect various pharmacokinetic parameters. As well, we would be interested in the condition being treated. For example, if we are looking at a middle-ear infection versus a skin infection, the pharmacokinetics and how that drug is distributed in the body will be an important consideration.

Also, the existence of other disease states. We know that hepatic insufficiency and renal-impairment affect the pharmacokinetics of the drug. And there are environmental factors, also, that need to be considered such as smoking.

[Slide.]

In the overall planning of a dosage regimen, certainly the convenience of the regimen to the patient is important. Multiple drug therapy in terms of potential drug interactions is a consideration and, also, coupled with

at

convenience, how compliant will the patient be in taking the dosage regimen once it is designed.

[Slide.]

There are other factors such as resistance and pharmacogenetics that we really are becoming much more aware of, of their importance in developing dose and regimes. Drug interactions, as I said before, due to multiple therapy are an important consideration.

[Slide.]

But, really, the focus, now, for us will be to look at the pharmacokinetics of the drug under review or under development. Specifically, we are interested in fully describing the absorption, distribution, metabolism and excretion and, of course, how all of these factors play with the other factors that we have listed so far makes this a very complex sort of problem to collect all of this information.

[Slide.]

As far as approaches to determine a dosing regimen, there really are three of them. The empirical approach is one where you have familiarity with the drug. You may start out with a regimen. You may make some alterations depending upon what you see. But it probably won't involve any kind of kinetic analysis from our

at

standpoint.

The second approach is the one that we will focus on because we believe that this information can really be quite useful in really optimizing the dosing regimen. Lastly, there is probably a mixed kinetic and empirical approach, a little bit of both. It is probably more often used.

[Slide.]

I want to focus in on the kinds of key pharmacokinetics parameters that one really needs to collect to develop an optimal dosing regimen. There are two areas of regimen design. There is the dose rate and there is the dose interval. In terms of the dose rate, at steady state, you are looking at the amount going in versus the amount coming out.

In terms of developing the amount going in, a critical factor is knowing the fraction of dose that is available. Certainly, for IV administration, this is one. But for oral administration, it can be 0.2 up to 1.0. So there is a broad range. And this is one of the critical parameters called bioavailability that we will want to determine.

As far as measuring the amount going out, it is the relationship between the clearance of the drug and the

at

concentrations that you achieve. You are interested here in determining some kind of target concentration in relationship to toxic concentrations.

So, as I have outlined in white, we have really four critical parameters here. The half-life drives the dose interval that we are going to select. There are these four criteria parameters, but these parameters don't stand alone. There are both non-critical and additional critical parameters that we need to determine. I have a slide coming later that will show some interrelationship between them.

[Slide.]

This is a plot of some hypothetical dosing schemes just to give an appreciation for how some of this information is useful. You can't see very well, I don't think, the largest dose which is twice the baseline dose, which is a dose that is given every three hours.

Then I doubled the dose and am giving it every six hours. We are able to see the effect of half-life during the interval because it drives the decay. If we couldn't tolerate concentrations from the double dose, then we are limited, perhaps, to working in this range.

So it is important that we understand the rate of decay that is the half-life and its relationship with dosing interval. The half-life also tells us how long it is going

at

to take to get to steady state. Believe it or not, these three dosing regimens all have the same average concentration.

It will take, on average, 6.6 hours here for a half-life of one hour to reach 99 percent of the steady state. So this is the utility of these parameters.

[Slide.]

As I mentioned, there are additional parameters. The fraction of available dose excreted unchanged. We like to know something about the metabolism or we would also like to know whether or not renal excretion is the only or primary route of elimination. The blood-to-plasma concentration ratio is going to give us information that will help us determine the maximal bioavailability for extravascular administration of the drug.

The extent of protein binding will give us a feel for the distribution of the drug and, as well, the volume of distribution will give us an appreciation for how the drug kinetics are changing in different clinical states that the patient may experience.

Lastly, the rate of bioavailability or rate of availability is an important parameter for oral drug products.

[Slide.]

at

As I mentioned, this slide is a sampling of some of the parameters like clearance, half-life, volume and protein binding and the relationship, either direct or inverse, that there is between the parameters. Although I mentioned only ten parameters, there are additional ones that affect the criteria parameters.

And so, as we said, the number of studies and the amount of information balloons very quickly.

[Slide.]

The types of human drug concentration studies that we would carry out to determine the useful kinetic or critical kinetic parameters are biopharmaceutics-type studies, pharmacokinetic studies, pharmacodynamic studies and then, lastly, population-style or type pharmacokinetics and pharmacodynamic studies.

I will go into a bit of detail now about the various kinds of studies breaking them down further.

[Slide.]

As far as biopharmaceutics-type studies that deal with the dosage form, we will be interested in bioavailability, particularly for oral dosage forms where we are concerned about products that have bioavailability problems where, for example, maybe only 30 or 40 percent of the dose is getting into systemic circulation.

at

Bioequivalence deals primarily with comparison of a formulation due to, for example, process changes, reformulating, site change, those kinds of issues where the basic tablet or capsule is still the tablet or capsule but some changes.

In our area, however, we do see bioequivalence-type criteria being used to compare, say, a formulation of a suspension, now, for children to an available tablet. Another area of biopharmaceutics kinds of studies is the effect of food. We do see food effects frequently. They are not always clinically significant but it is something that we have come to recognize needs to be evaluated during the course of formulation and drug formulation development.

[Slide.]

This now is getting into the basic kind of pharmacokinetics studies where we are looking at the absorption, distribution, metabolism and excretion. In this area, we will be looking at both single and multiple-dose studies.

We will want to know the time course of the concentration profile at the doses that are going to be used, either in the clinical studies or later proposed for usage of the marketed product. There are

at

dose-proportionality studies where we will be looking at a range of dosing and changes in subsequent plasma concentrations because of the change in dose.

I want to add here, also, that for racemic mixtures, we would expect, at this point in time, that a sponsor would also look at the individual isomers and determine this kind of information as well.

[Slide.]

There are, in addition to the basic kinds of pharmacokinetics, as we mentioned earlier, there are changes due to a variety of factors. So it is usual that we would see studies in elderly patients, pharmacokinetic studies to evaluate the change in parameters due to age, and pediatric patients, and then in various disease states, whether it is renal impairment, hepatic insufficiency or potential for drug/drug interactions because of the condition of the patient and other drugs they may be taking.

[Slide.]

In terms of the pharmacodynamics where the information is important, and where sponsors may be thinking about potentially adjusting dosing regimens, it would be important that they provide or evaluate the kind of information like time about MIC for organisms where time-dependent killing is an important property or where, in

at

the case where concentration-dependent killing may be a property, parameters like peak concentrations over MIC or area under the curve over MIC.

This information would be very helpful to have evaluated in the submissions that we see.

[Slide.]

Population pharmacokinetics and pharmacodynamics is a relatively new area. It is where one uses very sparse kinds of sample collection but over a large number of subjects to determine parameters. You can have basically two kinds of studies in this area. You can have design studies or you can use this methodology to do a post-hoc exploratory kind of analysis.

We have seen, not so much in the antiinfective area, but we have seen, in other areas like in cardiorenal, this kind of planned study being used to discover the population variation in parameters like clearance and volume.

In our area, we have seen the post-hoc kind of exploratory analysis being used to look at, for example, drug-drug interactions and whether or not one would need to do a definitive study later on to nail down the interaction.

[Slide.]

As far as when this information is most useful, we

at

believe that these studies should be conducted to provide the clinical investigators with the necessary information to plan and carry out efficient clinical studies. So, with this information, this battery of pharmacokinetic information really ought to be available, for the most part, by the time we are going into phase 3 clinical studies.

[Slide.]

Certainly, by the time that the application for the drug product comes to NDA, we ought to have this information so that we can include it in the label to allow physicians and other practitioners, clinical pharmacists, for example, to really plan and optimize individual patient drug therapy.

Thank you.

DR. CRAIG: Thank you.

Questions? By the way, I should acknowledge that Susan Cohen, who is normally the consumer representative for Dermatology, is sort of sitting in and acting as consumer representative for this meeting. Did you have a question?

MS. COHEN: I have several questions. One of the things I haven't heard discussed is what is the population going to be? Who are you going to use on your trial? Are you going to use children and can this medication be used on children? There are a lot of questions I don't seem to find

at

here. Who is your population?

DR. PELSOR: Well, the populations are going to vary from healthy, normal male volunteers to healthy volunteers of both gender to elderly patients to pediatric patients. There will be a broad range of populations included.

MS. COHEN: What about cross-cultural?

DR. PELSOR: Cross-cultural, ethnic kinds of variables are being explored more and more, especially as we gather more information via pharmacogenetics where we learn about the variation in drug metabolism. Coming from the laboratory bench, we are able to be directed to those specific kinds of populations, ethnic populations, that we ought to explore further.

MS. COHEN: So you sound like you are not sure yet what you are going to do.

DR. PELSOR: Oh, I think we have a fair amount of assurance of where we are going. I think this is a continually evolving area. I think that is the point I am trying to make, too. Science is still being developed.

MS. COHEN: What about the drug casing? Anything to do with what the drug is going to be--how it is going to be encapsulated?

DR. PELSOR: Yes. That is the area of

at

biopharmaceutics and that is a significant part of the investigation during drug development.

MS. COHEN: What if someone, during the trial, becomes ill with some other kind of disease other than what you were trying to look for? How do you determine how you keep the control or drop the control?

DR. CRAIG: Remember, we are talking preclinical here. These are the studies before we actually get into the clinical trial.

MS. COHEN: I understand that. But don't you have to set up your parameters before you start?

DR. PELSOR: I think that the protocols--for example, the phase 1 study where we are collecting a lot of this information very early on--do describe the scenarios and what we will do should a patient become ill with this problem or that or should they have an adverse effect, experience side effects, there are procedures for handling those subjects and the kind of treatment and follow up that they will get; yes.

DR. CRAIG: Extensive laboratory testing is done on virtually all these patients and pharmacokinetic studies.

DR. MELISH: I am coming at from, perhaps, a slightly opposite point of view. When you put pediatrics as a special population, or children as a special population,

at

in the past, they have often not been studied. Is there going to be an obligation that for any drug in which use in young people is expected that early studies will be done?

I think we harm children by protecting them from research risks. That means it takes years before drugs are tested or they may never be tested in children. That has been a bigger problem than protecting them.

So I would like to know that children will not be protected and that they will be tested specifically, and early.

DR. PELSOR: I think that with the new rules on the pediatric labeling supplements, we are taking some different approaches to this. But I would certainly let some of my clinical colleagues there address this question further.

DR. FEIGAL: I would just make some comments. This has been an area that has been evolving for a long time, particularly the issue of children. I think, actually, the use of antiinfective problems, because there are many infections such as otitis media that occur predominantly in children. It is actually easier to do the studies in children than in adults.

So if there is any area where children are fairly well studied, it probably is for these agents.

at

I think the considerations early on, when you are looking at how early to get children involved, depends on how much you know about the product already. With the kind of detailed information that Dr. Pelsor is presenting, you need to design a study where you often need to hospitalize the volunteer in a metabolic type ward and draw blood from them at very frequent intervals in order to determine the kinds of parameters that you have there.

Or you may do a very specific food-effects study. Some people seem to actually make their living doing these kinds of studies for companies in the test units that are around some of the big companies. I think of them as sort of drug test pilots. I am grateful people are willing to do that.

But children, I think, usually end up getting their pharmacokinetic studies done as a byproduct of the clinical studies when it is time to begin studying the dosing in children. You often have to do a little bit but it is hard to find children who can really volunteer to take a drug when they won't have a benefit from it in the same way that you can in an adult.

An even more problematic issue is determining pharmacokinetic properties when a neonate or a premature infant needs antibiotics. There are resources. The

at

National Institutes of Health has a neonatal pharmacokinetic group that actually is interested in doing drug-level studies in very small infants so that we can make progress in this area.

There is a process of interacting with the pediatric societies including those involved with pediatric infectious disease to identify the important drugs that we need to learn information about.

One of the real ethical questions that has been debated for a long time is whether it is ethical to test a drug in children before you know whether it is effective in adults. I think, like many conditions, there isn't an easy answer to that.

If it is for a condition for which there are not good therapies, then I think it is appropriate to test children early in that development. If, on the other hand, it is a "me-too" product that is designed to replace some other product for commercial or other reasons, then even the professional societies have been conservative and have said it is not appropriate to be testing children in that setting until you know that it is going to have the pediatric use.

So I think there is not a single answer to this. I think, from the division standpoint, we have a fair amount of experience with drug testing in children and we hope that

at

we can be a resource to companies that are not quite sure how to do this or even need introduction to some of the resources in the research community that can help them approach these kinds of things.

Frank, if you have other comments that you would like to make about this?

DR. PELSOR: No; I don't.

DR. CRAIG: Anything else?

MS. COHEN: Will there be any follow up on the people--when you get to the clinical trials, do you intend to, then, follow people after they have been in the trial to see what has happened?

DR. PELSOR: There are extensive descriptions in the protocols of how long and what kinds of follow up the patients are going to have. Yes.

DR. CRAIG: Let's move on to the next speaker.
Thank you. Dr. Harkins?

Biometrics

DR. HARKINS: Good afternoon. I am glad to see you are still all here with us. I think we have got one more after me and we can go to the barn.

[Slide.]

I am Ralph Harkins. I am a farm boy. I am also Director of Biometrics Division IV. I have six

at

statisticians supporting this division. Dr. Daphne Lin is the team leader and the others, Aloka Chakravarty, Nancy Silliman, Li Ming Dong. Joel Jiang isn't here. Sue Bell isn't here. They are back at the house working--barn.

[Slide.]

Our purpose today is not to present specific design and analytic method. I want to present issues relating to controlling potential sources of bias and evaluation problems. If we can control these, the design issues and analytical issues pretty much take care of themselves.

We have more statisticians working in the clinical-trials area today than ever before in history. It has increased about tenfold in the last ten years. They are developing a lot of new methodologies. It has increased about ten-fold in the last ten years. And they are developing a lot of new methodologies.

These guidance documents we are working on will be put in the Federal Register. It takes a phenomenally long time to change something once it gets in the Federal Register. So I don't want to lock us into an analytical methodology that would preclude us using new methodology that is being developed.

[Slide.]

at

The federal law that we operate under requires that we have adequate and well-controlled trials. But, in addition to that, we require that, if two trials are required, that they be independent. These are corroborative trials. They should not include the same investigators in both trials.

Also, we should have some measure of the quality assurance that the sponsor practices on the data as it is generated at the site and as it makes its way through the pipeline eventually to the computer and to us as well as the quality-control methods that they are going to use.

[Slide.]

I have covered this. The research activities going on today indicate that I ought not give specific statistical methodologies for doing analyses.

[Slide.]

Study-design considerations. Randomization. All of our statistical procedures are based on randomization methodologies. There are various methods arising today for assigning or allocating subjects to therapy that are not strictly applicable to our randomization procedures; the dynamic assignment of patient, the minimization procedure.

These are not amenable to our normal statistical procedures and we have got a number of academics working on

at

coming up with methodologies to analyze these properly. In the meantime, we have these data rolling in assigned to patients through these methodologies.

Quite frankly, I am not sure exactly what we are getting. The level and degree of blinding. Again, even if--we have had trials that have been put on clinical hold because the sponsor convinced the investigators they had the newest silver bullet. The investigators are sharp cookies. They recognize the old therapy and they recognize the new.

They took the people who looked a little bit worse off and gave them the new test drug. There were increased deaths. We put them on clinical hold while they explained what happened.

Choice of controls. We were talking about this earlier with the material this morning. Dr. Feigal mentioned that we have two different types of trials. The first is the superiority trial. We are comparing a drug against a vehicle or placebo. The level of the test in a superiority trial is the regulatory agency's risk.

In active controlled trials, the shoe is on the other foot. The power of the test, or one minus that, is the regulatory agency's risk. So, if we design a trial with X number of people and you come in with half that, you have increased the regulatory risk because you have reduced the

at

power to rule out differences large as or large as than we are wanting to accept.

Screening and selection criteria. In the antiinfective area, we have a lot of patients come in. We require they have a positive culture. They come back with a negative culture so, three, four days later we rule them out of the trial. I would like to know what happened to those patients because we are not only interested in writing a label for patients who had a pathogen, there is also the usual use of the drug, empiric therapy. We need to know what happened to the people you put out.

If there are strata or covariates that need to be considered, they need to be included. There is a later transparency that covers the need to include patients, elderly patients and patients of both genders. There are federal regs that require that we evaluate people 65 and over. In addition to doing the broad-base analysis, we also need to look at the males versus females on the test drug.

Those are the two strata that are necessary to be involved. Are there other special considerations such as immunocompromised patients.

[Slide.]

This doesn't happen as often today as it did five, six, seven, eight years ago, but the claims that the sponsor

at

wants to make that they state in their proposed label, in the past failed to be met by the protocol that they came up with. This is getting to be less and less of a problem. However, I did have this happen just about three months ago in another area that I handle.

Is it going to be an equivalency or a superiority trial? I just mentioned the difference between the two. The sample sizes required; how you calculate it based on whether you are doing an equivalency or superiority trial and you need to make sure, when you do the sample-size calculation, that you also include the elderly and sufficient males and females to do some kind of test at the end of the day to make sure your test product, or new product, is working as well in males as it is in females and vice versa, and also in the elderly.

Special populations; I mentioned a while ago the immunocompromised. There are other special populations that you may want to include in the trial. You need to make sure all people that you are going to make inferences to are represented in the sample that you submit to us.

[Slide.]

Analysis considerations; if your primary endpoint, your primary measure of efficacy. is time-to-event, then the statistical analysis plan needs to be one that uses that

at

approach. If it is a hard endpoint in time, such as number of cures after, or 28 days after therapy or 14 days after therapy, then you need to use the right type analysis to cover that.

We have integrated safety. This is getting to be more and more of an issue with us. But we need the data, and I will cover this in a moment in more detail, such that we can combine the data across trials and across indications to get a better handle on the safety of the product.

I mentioned the subset analyses; gender, age, racial, ethnic groups and any other subsets that we are interested in. On gender, I have recommended--gender and age are covered by the law. We have to do that. But I have recommended that gender be broken--I was recommending 45; now it is 50--so that we have women in the close-to-childbearing age tested against women who are out of the childbearing age plus we test them against the women greater than 65. Then we can also test women against men in those same three age categories.

Another issue if we find that there might be a problem, we need the weight of these patients because frequently the problem is not an age problem or an gender problem; it is simply a dosage problem, that the lightweight people are getting too much or that the elderly are not

at

clearing it rapidly.

Intent-to-treat and modified intent-to-treat analyses; in the statistical arena, the intent-to-treat, or the classical intent-to-treat analysis is all subjects randomized to therapy who have got one dose, at least one dose of the product.

In the antiinfective area, one of the requirements for inclusion is that the patient have a pathogen. It takes about three days for the results to come back whether or not they have a pathogen. So we have coined the phrase, "modified intent-to-treat analysis," the modification being that those patients who received three days of therapy but came back with a negative culture are dropped from the fully evaluable population.

I do like for those people to show up later on in the day, though, because, as I mentioned a while ago, we also have the right, or whatever, to write a label that would include empiric therapy, all patients who received this product.

Interim analysis; in the equivalency-type trial, interim analysis for determining efficacy has very little merit. As I mentioned a while ago, the power of the test is directly related by the number of patients we have. If you do an interim analysis about halfway through, you probably

at

do not have sufficient patients to rule out a difference of the magnitude that we are interested in ruling out.

By ruling it out, we end up with a confidence interval that keeps everybody in. It is a byproduct of ruling out.

Interim analysis for safety monitoring; interim analysis where you do not break the blind but you are looking to determine what the efficacy rate is overall in order to increase your sample size, possibly. These are acceptable interim analyses in the equivalency trial.

Multiple endpoints; in the antiinfective area, again, we do have two endpoints that we are interested in. We are interested in the clinical and the microbiological. They are joined by "and," so we do not make any adjustment for multiple comparisons. The adjustment is made by the "and."

There are other multiple endpoints of interest. If they are of interest to you, you need to specify how you are going to make adjustments and what you are going to do with those endpoints. I don't rule out the use of multiple endpoints. They are important in writing labels, as we mentioned this morning in the neutropenic studies.

Dr. Ross had a number of categories, moving from strict to more liberal. These are multiple endpoints but

at

they are also a sequential-type multiple endpoint and the sequential nature of the analysis would take care of the adjustment for that type multiple endpoint.

Losses and competing risks; frequently, there are early losses on these drugs that are just called lost-to-follow-up. When we examine the data, really they were failures. They were switched to some other therapy. These are not losses. They are failures.

Competing risk. If you are studying pneumonia and you have patients who have heart problems and they withdraw due to a heart problem that is not probably related to the drug or failure of the drug, that is a competing risk and you still need to take some account of that in your analysis.

[Slide.]

This is, and is not, statistics but it certainly impacts the quality of the data that we get and that we make our conclusions from. Quality control; data validation. There should be standard, easy-to-follow procedures for validating your data and quality controlling your data. You need to specify who is responsible, when are the activities done.

We have had, in the past, trials that the sponsor was going back to the individual study sites three or four

at

years after the data was collected to check the hospital records and the case-report forms to make sure all the data was there. That is too late. You need to do it right along with collecting the data.

How are the various pieces of the data tracked? If you make a change, do you have some kind of a record as to why that record was changed? Who all is informed? If you have a data manager and you are telling that data manager to change all this data, you need to tell that data manager why, under what auspices, you are changing that data.

Otherwise, they may think that you are trying to make a silk purse out of a sow's ear, so to speak.

How are questions and/or problems resolved with the database? Who all is brought into the ring to determine whether a particular patient or a number assigned to a patient is a success or a failure or they met the various evaluability criteria.

[Slide.]

This requires early planning. You need to make sure that you have compatibility among your CROs, if you use CROs, that they are using the same nomenclature, that they are using the same field length, that they are putting the same piece of information in the same field.

at

A few months ago, I had a CRO call me a little bit hot under the collar. He had gotten a piece of the action. When he started combining data across centers, he found that one center was coding males as a 1. The other center was coding males as a 0. He called the company up and complained and they said, "Hey; that is why we hired you."

He called me up to say, "Don't you guys have some standards that they have to meet?" We don't. We have recommendations. But, clearly, if you are coding your data backwards from one another, it creates some really serious problems especially if we are going to do gender analysis.

Standard formats. I mentioned that a moment ago, but if you are putting age in a field, that field should be used across all studies.

Nomenclature; the nomenclature for your laboratory data needs to be the same across all studies and we are now getting more and more foreign trials. The data needs to be converted to the same nomenclature, the same measurement scales, and so forth.

We need to be able to merge files across studies. In doing safety analysis and in doing some of our gender analyses, we are merging data across indications also. So these data files need to be such that they can be easily and quickly and accurately merged.

at

I'm through. Questions?

DR. PARKER: Ralph, you were mentioning the stratifications. But, for example, the 65 and over group, this is something that is being regulated by law that you are anticipating.

DR. HARKINS: Right.

DR. PARKER: Is this regulation merely that they have to be represented or does it mean, say, in a superiority study that you have to show a difference within that stratum.

DR. HARKINS: What the Federal Register says is that the population 65 and older, if you are going to make inferences to that population, then they have to be included in the trial in sufficient numbers that you can show there is no difference in the way the drug is operating, acting in the younger group versus the older group.

We are interpreting that as both safety and efficacy.

DR. PARKER: So you check for interaction, in effect, and, if you don't have it, then you use the main effect? Is that it?

DR. HARKINS: The problem with interaction is that the sample size has to be so huge to do interaction that I have ruled that out. That is why, in antiinfective, I have

at

the ability to combine across a whole bunch of studies to get age. In dermatology, I can't. I only have two trials. In cardiorenal, we only have two trials.

So it is difficult to get this age factor out in the open in these two-trial studies. But we are working on combining data across several indications. As long as the dosage is the same, the duration is the same, and so forth to get a handle on what is happening in the elderly population as well as looking at females at three different age groups and--they say we men go crazy at 40 or 50, anyhow, so I broke them up at 50, also, to look at them.

Any other questions?

DR. CRAIG: Thank you.

The next speaker is Renata Albrecht.

Clinical Studies

DR. ALBRECHT: I feel guilty because the rest of you have been sitting quietly and patiently for the last two hours listening to, actually, some excellent summary presentations. But I have now gotten to get up and stretch and so, even though we used up our coffee break, I am feeling great.

So if you guys need an excuse to stand up and stretch, just pretend you can't see the bottom of my slides and feel free to get up and move around and do all those

at

things and we will get through the last of these presentations.

[Slide.]

What I hope to do in about the next 20 minutes is summarize for you the general consideration section of clinical studies from protocol to results part of our guidance document.

[Slide.]

Issues is normally spelled with an "e," but we used so many "e's" in evaluability criteria we ran out, so I am sorry about the typo. But the sections that I am briefly going to summarize, in the general considerations section, are the study design and implementation.

The microbiology issues have been covered by Dr. Sousan Altaie. I will briefly talk about efficacy, evaluation and outcome. I would mention some of the terms that we use frequently and try to propose, perhaps, some standards for them.

I will talk very briefly about safety issues and, of course, the statistical considerations have been summarized just now by Dr. Harkins.

[Slide.]

That does say study design and implementation is the title. Just a review of some of the things that have

at

already been said. A protocol should be based on scientific sound rationale. Studies should be adequate and well controlled. Dr. Harkins has talked about blinding and randomization.

[Slide.]

Issues that are important in all clinical studies are patient selection and patient enrollment, what are the bases on which we select patients and how do we determine whom to enroll. Issues that go into that decision process are what are the inclusion processes we are going to use, what is the disease under study and how do we determine that.

What are the diagnostic criteria we use, the clinical criteria, radiographic criteria, if applicable, the microbiological criteria.

[Slide.]

A little bit about the type of studies. You are all familiar with the adequate and well-controlled studies as defined in the Code of Federal Regulations, but the Points to Consider actually identifies two types of studies in a somewhat different fashion as they apply to the antiinfective drug development area.

These are the clinical-only studies. By that, we mean that the diagnosis and evaluation is based on clinical

at

parameters. In many of these studies there is no pretreatment culture. For example in otitis media or sinusitis, one of the studies could be clinical only.

In some, no pathogen is isolated in all cases; by way of example, in the skin studies, although a culture is taken, sometimes the pathogen is not successfully isolated. The other type of study is the clinical and microbiological study in which it is necessary to identify a pathogen. Some of the obvious examples are urinary-tract infectious studies and uncomplicated gonorrhoea studies.

[Slide.]

Another element important in study design and implementation is the exclusion criteria. Exclusion criteria are intended to one, either protect patients and, therefore, exclude certain patients from studies, or to assure that the risk-benefit is appropriate so that the results aren't confounded by patient underlying disease states.

So some of the recurring exclusion criteria found in most studies are a patient with known hypersensitivity reaction to a drug or a class of drug, a patient who has recently received antimicrobial therapy, although there are exceptions and we will hear about those in the next couple of days; patients who have been on other investigational

at

therapy recently.

In many studies, pregnant and nursing women are excluded. Patients are usually not included in a clinical trial more than once with the exception that we heard this morning. Patients with underlying diseases, for example, renal failure or hepatic disease may be excluded for various reasons.

It is useful to have an exclusion log kept by the investigator to identify which patients were excluded and which ones were included.

[Slide.]

Other important considerations center around the drug selection. Issues about the test drug involve some of the points that have been discussed by the presenters before me; pharmacokinetic issues, microbiology issues and the results of phase 1 studies.

For the phase 2-3 protocols, a justification for dosage regimen, selection and duration is important.

A couple of points about the control regimen. Whenever possible, or when it exists, an FDA-approved control. If an active control is going to be used, it should be FDA-approved for the indication under study. The control regimen should show continued efficacy in the indication and in the organisms that are going to be

at

studied. A basis for this may be the literature or other studies.

Certainly, if at all possible, the control regimen should enable the study to be blinded.

[Slide.]

Other issues are the evaluation visits, which ones, how many. Some of the ones that we typically have are an entry visit. An on-therapy visit is often part of a protocol, an end-of-therapy visit and one or more post-treatment visits. I will define the term "test of cure" a little bit later.

[Slide.]

The protocol is implemented. The study is finished. The results are analyzed. The NDA is submitted to the Agency and then the Agency reviewers start the review process. Basically, that process involves checking, auditing, validating and analyzing the information that was presented by the sponsor. These include data. They may include case-report forms.

They typically include case-report tabulations. The reviewers read and evaluate the study reports and the integrated summary of efficacy that the applicant submits and then make a decision about the effectiveness of the drug for the intended use.

at

[Slide.]

One of the issues that was brought up and that I would like to address is if you start out with so many patients, how do we end up with fewer at the end and where are the "patient losses?" So I tend to always start with a denominator of 100.

So, on the Y axis, the 100 refers to 100 patients enrolled to begin with and then what happens as you are looking at the study results and the patient attrition is being accounted for.

What happens is sometimes patients are excluded simply because of age or lab-value abnormalities or the diagnosis. By that, I mean if you are studying bacterial otitis media, you did a tympanocentesis, you identified a virus. That patient does not have bacterial otitis media, so that patient would be excluded from a study. That is the same for a culture or pathogen being negative.

Dosing problems. If you are studying a BID regimen but the patient has got twice that dose, they certainly shouldn't be included in the analysis of the dose that was supposed to be taken during the protocol.

When you look at all these protocol violations and account for how many patients are, therefore, excluded, you end up with the bottom number which is the evaluable

at

population and, depending on the study and so forth, that number can be substantially lower than the entry numbers.

[Slide.]

Another element that causes difficulty with patient attrition is the evaluation visits and how many of them are planned and how many patients come and how many are not able to make it at the scheduled times.

In this graphic, the x axis represents the time frame. Going from left to right, if we assume that there were, let's say, five visits planned, an entry visit, an on-therapy visit, end-of-therapy visit, test-of-cure visit and then, perhaps, even a later one, the purple columns represent sort of the ideal. Ideally, all 100 patients that were planned would show up at each of these visits.

In reality, because people are people and they may have competing priorities and so forth, what tends to happen is we don't see the patients come back at all these visits and, in fact, what I am trying to show here is sometimes the patients will return but at different time frames than called for in the protocol.

Then the challenge becomes, with this starting number of 100, what percentage of these patients should be considered evaluable for having met all the entry requirements of the protocol. Sometimes, it may simply be

at

about 60 percent.

[Slide.]

Those are some of the study issues. Let me briefly touch on some of the definitions that we have included in the guidance document. This list is not all-inclusive. We would certainly welcome comments on additional terms that should be included or comments on definitions that you believe we should modify within this subsection.

By the term "documentation," we mean compliance with 314.50 as far as data available in the form of case-report forms or case-report tabulations.

[Slide.]

By clinical outcome, we are referring to the judgment that is made regarding the patient's response to therapy, based on a comparison of the patient's signs and symptoms at baseline, compared to the test-of-cure visit. Several possible categories have been defined including cure, improvement, failure and relapse.

Instead of reading the literal definitions, let me go ahead and try to sort of present a graphic interpretation.

[Slide.]

What I am trying to introduce is the concept that

at

the time line actually has a role in how we define this. The x axis, again, is time, entry all the way to the end of the study. And the y axis is the number of patients. The grey field, and it is sort of for simplicity of illustration, is patients who have symptoms present. The orange field is patients who are feeling better.

The purple field is the patients who are feeling well. The blue arrow refers to the test-of-cure time line or the final analysis visit.

[Slide.]

Now, what I have done is put some words to go with these graphic images to say that if, at the test-of-cure, we take a cross-section, we will see how many patients we would classify as being well or cured, and how many we would classify as not being well or having failed.

The other thing I would like to propose is that, perhaps, at the time when we are making the final decision on the patient's outcome, perhaps we ought to be able to use a two-tier system, either cure or failure, that anyone who has been classified as improved, perhaps we ought to be able to say yea or nay.

The other is the use of the term "relapse." I think we would like some comments on that. Is relapse something that happens before the test-of-cure or is that

at

something we think of as happening after the test-of-cure visit.

[Slide.]

So I guess the question under clinical outcome; what are the appropriate categories and how many of the categories should we use in classifying outcome?

[Slide.]

The microbiology outcome? By definition, we would propose that is the results based on the pretreatment and follow-up culture. Probably the main question or the primary question of interest is did this drug eradicate the causative pathogen. Some categories that have been provided are eradication, whether documented, meaning a follow-up culture was taken or presumed, meaning we are extrapolating the microbiological outcome based on the clinical outcome.

Persistence; again documented versus presumed. And other categories including superinfection which was discussed earlier this morning.

[Slide.]

Another term that we use in various indications is the term of "therapeutic outcome," which has also been referred to as global outcome or overall outcome. This is an evaluation that takes into consideration both the clinical and the microbiological outcome. Therapeutic cure,

at

generally, means all those are classified as cured. A therapeutic failure means an either/or type of failure.

[Slide.]

The test-of-cure visit. For purposes of evaluating antimicrobials, we believe the test-of-cure visit is the time point when the final clinical and microbiological assessment is made, whether the drug had the effect it is supposed to have according to the proposed labeling.

[Slide.]

This is just a graphic representation of the same thing, to say we have got patients coming back during the entry on-therapy, end-of-therapy, visit and then we expect to see those patients at that visit where we can make the final assessment. If they come back before, that is too early. If they come back later, what do we do with them?

[Slide.]

Another concept I would like to define is the concept of carrying forward failures. That is also illustrated graphically here. Let me walk through this diagram. In this case, again, 100 patients. If we say an assessment was made of these patients either on therapy or at the end of therapy and we say that 80 patients had an outcome of either cure or improved and 20 were failures,

at

then, at that specific time point, 80 percent were showing a favorable response.

What, unfortunately, sometimes happens is these 20 patients are dropped for all intents and purposes and only that were doing well are, again, reexamined at the test-of-cure visit. Then, if 70 are doing well and ten are not, it is reported that there is an 88 percent favorable response.

However, that response does not take into consideration the 20 patients who have previously failed. So if we take into consideration these 20 and these 10, then, in fact, the true test-of-cure response, carrying forward the failures from previous visits would show that we have got 70 patients doing well, 30 patients failing for an overall rate of 70 percent.

This is when you hear reviewers talk about carrying failures forward, what they refer to.

[Slide.]

Just a brief word about safety evaluation. Patients who have received at least a single dose of the drug and are seen at follow up are considered evaluable for safety and should be assessed. It is very useful to try to determine whether an adverse event or adverse reaction is related to a drug.

at

There should be a recognition when related events are seen. Various analyses are performed to see if there are any age, race, dose or other predictive associations. And there is as lot of good information available in these two documents, the Guideline for the Content and Format of Clinical and Statistical Sections from 1988 as well as a newly released document called the Good Review Practices Safety Guidelines that came out last December that have a lot more information on how to do safety evaluations.

[Slide.]

So that is basically a summary of the general-considerations sections. Now just let me take two minutes to sort of start the introduction for the presentations tomorrow and Friday.

We have about a total of 11 indications that have been written by members of the division. In trying to put some formatting consistency within each of them, we have basically identified seven or six areas. In each indication, there is a brief summary of the regulatory history and regulatory synonyms under which the indications have previously been known or approved.

There may be issues relative to study considerations that are discussed. There are proposed inclusion criteria, exclusion criteria, information on drug

at

dosing, proposed evaluation visits and proposed outcome categories.

[Slide.]

I have already mentioned previously the indications and the individuals who will be presenting them. I would like to say something questions at this point. I think many of you are used to, during advisory committees, having the FDA come up with a list of specific questions and then asking our committee to take a vote on those questions.

However, because this is a draft guidance document which is being presented for discussion and for comment, we believe that it was not the time to put those kinds of questions forward. Instead, I think what I would like to do is propose three areas for discussion or potential questions for people to address.

[Slide.]

These three general areas for consideration may be the following. As you listen to individual indication presentations tomorrow, consider what diagnostic criteria are appropriate. Which ones should we suggest be looked for, how many of the different criteria. Consider areas such as disease severity, symptom scores, perhaps, in defining disease signs and symptoms, issues relative to acute versus chronic or acute versus recurrent diseases.

at

So one category would be are the diagnostic criteria proposed reasonable. If not, what kinds of comments are there.

[Slide.]

The second very general area would be the evaluation visit. Which ones are relevant. Certainly an entry and a test-of-cure visit should be provided at a minimum, but how many others are relevant. How about the timing? Timing is important when you consider the pharmacokinetic properties of the drug.

Should a drug with a half-life of one hour have the same kind of follow-up visit as a drug with a half life of 48 hours? The answer is probably no but then how do you decide what the right follow up is.

What about the range of days? For UTIs, we have typically said five to nine days post-treatment. How broad a range would be reasonable to accept. So the second category of questions could center around evaluation visits.

[Slide.]

Lastly, what are the appropriate outcome categories for clinical, cure, failure. Which others? For microbiological, eradication, persistence? Which others? As we read the IDSA guidelines, in some indications there are five, six categories proposed. In others, two or three.

at

So the third general area could be what are the appropriate outcome categories for the individual indications.

[Slide.]

With that, that is not all. We are going to, I think, have a wonderful two days listening to presentations on individual indications by the FDA staff and we look forward to comments by the committee and the consultants on these individual indications.

DR. CRAIG: Any questions for Dr. Albrecht? Again, I just want to emphasize that we are in a data-mode collection and so, even though we are going to be discussing these by the members on the committee, we are going to be looking for input from the audience as well.

Our major limitation, though, is we have got to keep on a schedule so that we can get through all of them so that we may need to stop sometimes before we may have completely had all of the discussion that may be needed. But, at least we can then still send in materials that will be looked at to address some of those areas.

Open Public Hearing

Before closing today, I want to get in the two open public hearing speakers. We have two requests, one of them from John Roschafer who, I think, is representing the

at

infectious-disease pharmacists.

Do you want to come on up, John?

DR. ROSCHAFER: Mr. Chairman, members of the Antiinfective Advisory Committee, members of the Division of Antiinfective Agents and Ladies and gentlemen.

[Slide.]

My name is John Roschafer. Dr. Kenneth Lamp and I are here representing the Society of Infectious Disease Pharmacists. Our organization represents approximately 250 academic and hospital-based pharmacists who practice in the area of infectious-diseases pharmacotherapy. We have not had a chance to disseminate disclosure statements, but we are the recipients of research grants from the pharmaceutical industry and benefit as members of hospital advisory boards and through honoraria for scientific presentations directly or indirectly sponsored by the pharmaceutical industry. But neither Dr. Lamp nor I have made calls from the White House recently soliciting contributions.

I am a professor in the Department of Pharmacology at the University of Minnesota and past president of the society. Dr. Lamp is an assistant professor in the School of Pharmacy at the University of Missouri, Kansas City.

[Slide.]

at

The Society of Infectious-Diseases Pharmacists is asking the committee as they consider the development of evaluability criteria for the addition to the Guidelines for Infectious Agents or the Points to Consider Document, to formally incorporate specific terminology that would probe, identify and quantitate specific pharmacodynamic outcome predictors in phase 1, phase 2 and phase 3 trials.

During the course of our presentation, we would like to address three areas that we would ask the committee to consider. First, we would like to define for the committee the science of pharmacodynamics and how it pertains to antiinfective agents.

Second, we would like to identify how pharmacodynamics can be applied to antibiotic therapy to optimize clinical outcome and minimize drug exposure, adverse drug reactions and potentially limit the development of resistant bacteria.

Third, we would like to address how the introduction of pharmacodynamics into the new drug development process could optimize antibiotic dosage selection by validating objective and quantifiable outcome predictors for antimicrobial performance.

[Slide.]

Despite our scientific sophistication, patients

at

are often treated with unnecessarily high doses of antibiotic or a combination of antibiotics when a single agent would do. In reality, these practices reflect our inability to make objective, data-driven decisions as to when one antibiotic or a particular quantity of antibiotic is sufficient or when another antibiotic or a higher dose is needed.

At this time, the only routinely performed laboratory tests that predict antibiotic outcome is the minimum inhibitory concentration or MIC. While a useful indicator, the MIC has several drawbacks. First, the test is performed in vitro with a fixed or static concentration of antibiotic.

In patients, the antibiotic concentration is in a dynamic state of flux, forever changing. Second, MIC testing is performed using a fixed inoculum of exponentially growing bacteria whereas in patients, the bacterial burden may be substantially higher and the bacteria may be primarily in a stationary growth phase and more resilient to antibiotic therapy.

Also, the optimal environment to the laboratory may not emulate the clinical situation confronting the prescriber.

Approximately three decades ago, we were

at

introduced into the science of pharmacokinetics. This science attempted to mathematically model drug behavior by focussing on the drug concentration, time relationship. As a result of this discipline, the processes of drug absorption, distribution, metabolism and excretion were quantitated and mathematically modeled.

Eventually, these data became part of the new drug development application. Pharmacokinetics measures and mathematically quantitates the relationship between drug concentration and pharmacologic effect. As it pertains to antibiotics, the desired pharmacologic effect is bacterial death.

Over the past several years, we have been able to characterize antibiotic performance as concentration-dependent or time-dependent. Simply defined, the performance of concentration-dependent antibiotics correlates with increasing concentration to the antibody.

With increasing concentrations, the rate of bacterial killing, the extent of bacterial killing and post-antibiotic effect, or the PAE, all increase whereas with time-dependent antibiotics, the rate of bacterial killing and the extent of bacterial killing are maximized once an antibiotic threshold concentration is achieved, whereafter further increases in antibiotic concentration

at

will not increase the rate nor the extent of bacterial killing.

These observations have a profound effect on antibiotic dosing strategies and the optimization of antibiotic effect. With concentration-dependent antibiotics, the strategy may be to give larger doses less frequently whereas with time-dependent antibiotics, maybe to give less drug more frequently.

Hybrid outcome parameters which combine pharmacokinetic parameters with the bacterial MIC have been developed, quantitated and tested in in vitro chemostats, in animal models and in patients for both concentration-dependent and time-dependent antibiotics.

These outcome parameters offer the first insights into moving antibiotic prescribing from a subjective to an objective model and from a retrospective to a prospective view.

These data offer the opportunity to establish minimally effective criteria which would define the required antibiotic time or concentration exposure for optimal effect. These data would also establish maximally effective doses which would prevent unnecessary antibiotic exposure and help limit adverse drug reactions.

Threshold outcome parameters could also define the

at

required amount of antibiotic to prevent the proliferation of subvariant bacterial populations resistant to antibiotic.

[Slide.]

The first of these parameters is a time unbound antibiotic concentration remains above MIC. This parameter seems best applied to time-dependent antibiotics and investigators have actually determined the minimum amount of time above MIC required to achieve bacteriostatic and bacteriocidal effects.

The second of these parameters is the peak to MIC or peak concentration to MIC ratio. This parameter is probably best applied to aminoglycosides or other concentration-dependent antibiotics.

Peak concentration to MIC ratios of 10 to 1 for aminoglycosides have been described in the literature as necessary for optimizing the performance of aminoglycoside antibiotics. Currently, one of the most widely used methods for aminoglycoside dosing incorporates this concept into their derivation of dose and dosage interval.

The last pharmacodynamic outcome parameter is the area under the serum concentration time curve to MIC ratio or the AUC to MIC ratio. This parameter has been widely discussed as a valuable indicator for fluoroquinolones and other concentration-dependent antibiotics.

at

To have a reasonable chance at a successful clinical outcome, an area under the curve to MIC ratio of at least 100 to 1 has been suggested. Many investigators believe that a higher value of 250 to 1 or more will all but assure a favorable clinical outcome. A ratio of this magnitude has also been reported to limit the development of resistant bacterial subpopulations.

These data would suggest that objective outcome parameters can be identified, quantitated and incorporated into the drug evaluation or clinical decision-making process to objectively determine the appropriate antibiotic dosing interval.

Furthermore, evidence to date would suggest that investigators working with in vitro, animal or even human data are validating the pharmacodynamic outcome parameters being derived.

For obvious medical and ethical reasons, pharmaceutical companies involved in the antibiotic discovery and development process must focus on identifying the antibiotic dose that assures a favorable outcome for the largest number of patients. While this approach may be ultimately successful, many patients may be exposed to an unnecessary amount of antibiotic which could result in a higher incidence of adverse events.

at

[Slide.]

If, during the phase 1 and phase 2 evaluations, an appropriate pharmacodynamic outcome predictor or predictors were identified and quantified, these data, along with the pharmacokinetic profile of the antibiotic would provide valuable insight into selecting the appropriate dose and dosage interval to be used in phase 3 testing.

Phase 3 studies could then serve to validate these pharmacodynamic outcome predictors using direct or surrogate markers of clinical and microbiologic outcome.

On behalf of the Society of Infectious-Diseases Pharmacists, we would like to thank the committee for the opportunity to present our views this afternoon. We hope that the information presented will be useful to the committee as you attempt to revise the guidelines for the antiinfective agents Points to Consider document.

Thank you very much.

DR. CRAIG: Thank you, John.

Any questions or comments? I think, obviously, as a believer, it is one of the things that I think, in the long run, is a place to go. I think, right now, for the pharmaceutical companies to do some of these things is an increased cost.

I think the area that we have to work on is being

at

able to show also how, although it is an increased cost, in the long run, it can facilitate clinical trials, maybe reduce the number of patients that need to be looked at so that there is some incentive just to do extra data without getting some benefit out of it discourages the pharmaceutical company from looking at some of these aspects.

Let's go on to the next one. It is from Bayer. This is Dr. Jungerwirth who is Director of Medical Research, the Antiinfective Department.

DR. JUNGERWIRTH: Thank you Dr. Craig, Dr. Feigal and members of the advisory committee. First, I can tell you that I have often wondered what it would feel like to speak at ICAC on Wednesday afternoon, but this is probably what it is like. Thank you for your patience and thank you for your attention.

DR. CRAIG: But they haven't left. They are still here.

[Slide.]

DR. JUNGERWIRTH: We appreciate the opportunity to comment on the guidance document at this point. There is one issue that we wanted to raise for consideration by committee now and I will try to do so briefly. That pertains to the sinus culture technique which has been

at

proposed in the draft guidance document and, in fact, represents a change from prior recommendations in the Points to Consider document and also in the IDSA recommendation.

The specific proposal which we would make is that quantitative culture of sinus material should not be required for documentation of the three organisms which have been identified as critical in this indication, Hemophilus, Streptococcus and Moraxella, specifically, from a purulent sample obtained by a sinus puncture in an acutely symptomatic individual.

I think all of those definitions are important.

[Slide.]

I am sorry that Dr. Gwaltney is not here. I guess he will join us tomorrow, but the sinus is generally considered a sterile site. In many ways, it is similar to the middle ear which communicates with non-sterile sites but, under normal conditions, is considered a sterile site.

Pathogen regulatory and sinusitis remains an important priority for us in that the procedures required to obtain a sample by a sinus puncture are invasive to the patient and not normally a part of routine care of the patient. So we want to do whatever we can to increase the likelihood of acquiring every pathogen we can from patients who are tapped.

at

Quantitative methods for determining bacterial density and sinus aspirate material either aren't recommended or aren't standardized. They have been done by many different groups in different ways. If you look at the sort of combined literature, there are recommendations regarding breakpoints for significance that range from 10^3 all the way to 10^5 .

We don't believe that there are adequate criteria right now to determine what an appropriate breakpoint would be for this material acquired by a sinus puncture.

[Slide.]

I also would like to qualify my statements in saying that a different situation may exist in patients that have samples obtained endoscopically where an endoscope was taken through the nares and attempts were made to aspirate at the orifice, or if other organisms are isolated, organisms not typically associated with sinusitis or also mixed cultures.

In those situations, a very different situation may exist and there may be a requirement, in fact, to use quantitative culture techniques as a means to distinguish pathogens from non-pathogens.

[Slide.]

Just, in conclusion, what we would like to suggest

at

is that, as a clinician and just thinking about the clinical setting and speaking with our investigators who are largely in key positions doing this sort of work, if you have a patient that is acutely symptomatic with signs and symptoms of sinusitis, that has radiologic evidence of an abnormal sinus as suggested in the draft guidance document, and if one of the three key organisms is isolated from a sinus puncture through bone, properly done, that organism should be considered a valid pathogen without reference to bacterial density or CFU per ml data.

That is the end of my comments.

DR. CRAIG: Any comments on that or discussion now? I am sure this will be one of the items that we will make sure is addressed tomorrow. Diagnostic criteria was one of the areas that Dr. Albrecht said that she wanted us to address so that we could make sure that this is discussed tomorrow.

DR. LEISSA: Brad Leissa, medical team leader, Antiinfectives. Just for clarification on your point about not requiring quantitative cultures, is that also in the situation where you have mixed culture result or only when it is a single organism isolated?

DR. JUNGERWIRTH: I think that the situation is cleanest if you have a single organism isolated. That is, I

at

guess, where we would make the strongest argument. If you had multiple different organisms isolated, I think that I would be interested in looking at things like gram stain, purulence, other characteristics of the sinus aspirate.

Some of the articles that have been published, the amount of white cells has been an even better predictor of pathogens being present than actual colony count in the sample, itself. So we feel most strongly about the pure isolation of a single organism.

These three organisms, also; if it is viridans strep or some other organism which is more likely to be a contaminant, we would feel different.

DR. CRAIG: Thank you very much. As I say, we will make sure that that is discussed tomorrow.

We will end today. You can all go back and have a good night's rest so that you will be all set for tomorrow so that you can contribute so good ideas. We need your brain power tomorrow. So good night.

[Whereupon, at 5:43 p.m., the proceedings were recessed to be resumed at 8:30 a.m., Thursday, March 6, 1997.]

at

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666