DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

IDSA/PhRMA/FDA WORKSHOP

Tuesday, November 19, 2002

9:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

John Edwards, M.D., IDSA, Moderator

FDA:

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John Powers, M.D.
Renata Albrecht,M.D.
Janice Soreth, M.D.
Ed Cox, M.D., M.P.H.
Phil Colangelo, Ph.D., Pharm.D.
Daphne Lin, Ph.D.
Erica Brittain, Ph.D.
Karen Higgins, Sc.D.
John Lazor, Ph.D.

IDSA:

Richard Wenzel, M.D.
William Craig, M.D.
George Talbot, M.D.
John Bradley, M.D.
Jan Hirschmann, M.D.
Don Craven, M.D.
Stanley Deresinski, M.D.
Michael Scheld, M.D.
David Gilbert, M.D.
Louis Saravolatz, M.D.

PhRMA:

Alan Goldhammer, M.D.
Will Bushnell
Frank Tally, M.D.
James Poupard, Ph.D.
David Cochetto, Ph.D.
Christy Chuang-Stein, Ph.D.
Roger Echols, M.D.
Richard Gesser, M.D.
Lianng Yuh, Ph.D.
Donald Jaffe, Ph.D.
Tim Hinkle, M.D.
Clarence Young, M.D.
George Miller, M.D.

OTHERS:

Todd Weber, M.D. (CDC)

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. EDWARDS: I hope this is a good sign in that we are actually going to start the meeting a minute early. My name is Jack Edwards. I am the Chairman of the Public Policy Committee of the IDSA and I work at Harbor UCLA Medical Center, and I will be moderating this conference.

What I would like to do in the next few moments is just give a bit of a perspective on this conference from the IDSA notion, and then we will introduce the people at the front table, and then I have a few announcements to make before we actually start.

I think it is quite clear that the members of the IDSA, as they go about their encounters with the public and with patients, have become concerned about the availability of antimicrobial agents and concerned about the future of the availability of the antimicrobial agents. That concern really comes at a time that is sort of mismatched with the history of infectious diseases in that we are in a time now where infectious diseases are still the third leading cause of death in the United States. We have a tremendous problem with resistant

organisms developing. We have emerging and reemerging infections, and we have the threat of bioterrorism at the present time. These four points really match with a need that is critical for the development of antimicrobial agents and, at the same time, we are perceiving a real decline in the availability of agents that are coming along, and perceive that there is a decline in research and development of the agents.

So, today we have a unique opportunity in that we are able to bring PhRMA, FDA and IDSA together outside of the context of an advisory board meeting. This meeting really is intended to be a science meeting where we discuss issues that may lead to a solution to this mismatch in our situation at the present time.

The meeting will not be product oriented. It is not an advisory board meeting and everyone concerned is hoping that there will be a free-flowing scientific discussion where we discuss in some detail or in extensive detail some of the nuances that are important for the development of antimicrobial agents.

The IDSA is very concerned with what the patients need. PhRMA is concerned with issues of

developing antimicrobials in a very intensely competitive environment. The FDA has the job of determining what the efficacy and safety is of new agents coming along. But, actually, all three groups are aimed towards the same goal, and that is trying to provide the best possible situation for the public. I think in reality, although we are three different groups, we are all focused on the exact same issues here, and probably a word that is going to emerge over and over again through these discussions is balance and how development can occur within the confines of the needs for safety, the needs of PhRMA, and result in the best possible situation for the public in this country at this time.

So, I am hoping to set a tone of free-flowing discussion, a more relaxed tone than might be present at a usual advisory board meeting, which this is not, and am looking forward to a very interesting day.

At this point, I would like to go around the table and have each of the members at the table introduce themselves and I will start with Alan, to my right.

DR. GOLDHAMMER: Alan Goldhammer,

associate vice president for regulatory affairs at PhRMA.

DR. EDWARDS: We need to push the button to turn the microphone on and you need to push the button to turn it off. I have a wonderful gadget here that I am not familiar with but it is the electronic gavel, and I can silence all microphones any time I want.

[Laughter]

DR. TALLY: Frank Tally, chief scientific officer at Cubist Pharmaceuticals.

DR. CHUANG-STEIN: Christy Chuang-Stein, statistics, Pharmacia. I am here representing PhRMA.

DR. ALBRECHT: Renata Albrecht, director, Division of Special Pathogen and Immunologic Drug Products, FDA.

DR. SORETH: Good morning. I am Janice Soreth. I am the division director for anti-infectives.

DR. GOLDBERGER: Mark Goldberger, from the Office of Drug Evaluation, IV, FDA.

DR. POWERS: John Powers, lead medical officer for antimicrobial drug development in ODE IV.

DR. COX: Ed Cox, medical team leader, Division of Special Pathogens and Immunologic Drug Products, FDA.

DR. LIN: Good morning. I am Daphne Lin, statistical team leader for the Division of Biometrics, III, FDA.

DR. BRITTAIN: Erica Brittain, senior statistical reviewer, FDA.

DR. HIGGINS: Karen Higgins, statistical team leader, Division of Biometrics, III, FDA.

DR. WEBER: Todd Weber, senior medical officer, National Center for Infectious Diseases, CDC.

DR. SCHELD: I am Michael Scheld. I am from the University of Virginia and currently president of the IDSA.

DR. GILBERT: Dave Gilbert. I am from Portland, Oregon and I work in a community teaching hospital and I am the past president of the IDSA.

DR. SARAVOLATZ: I am Lou Saravolatz, from St. John Hospital in Detroit, Michigan. I am chairing the Infectious Disease Society's Committee on Antimicrobial Usage in Clinical Trials.

DR. WENZEL: I am Dick Wenzel. I am chair of the Department of Medicine at the Medical

College of Virginia, representing IDA.

DR. CRAIG: Bill Craig, University of Wisconsin, representing IDSA.

DR. TALBOT: George Talbot, previously an ID clinician by training and experience, more recently working with the pharmaceutical industry, and I am here representing IDSA.

DR. BRADLEY: John Bradley. I am a pediatric infectious disease specialist at Children's Hospital, San Diego UCSD and I am here representing the IDSA.

DR. HIRSCHMANN: I am Jan Hirschmann. I am an ID specialist as well, from the VA hospital in Seattle and representing IDSA.

DR. DERESINSKI: Stan Deresinski, Stanford University St. Clara Valley Medical Center in San Jose and vice chair of the antimicrobial use in clinical trials committee of the IDSA.

DR. JAFFE: Donald Jaffe, regulatory affairs, Pfizer, representing PhRMA.

DR. MILLER: George Miller, VP of R&D at Essential Therapeutics in California, representing Biotech.

DR. HINKLE: I am Tim Hinkle, chief medical officer of Versicore.

DR. YOUNG: I am Clarence Young. I am vice president for clinical development and medical affairs in anti-infectives at GlaxoSmithKline, representing PhRMA.

DR. POUPARD: Jim Poupard, director of strategic microbiology at GlaxoSmithKline, representing PhRMA.

DR. COCHETTO: I am David Cochetto. I am in regulatory affairs at GlaxoSmithKline, here representing PhRMA.

DR. GESSER: Richard Gesser, with clinical research in infectious diseases at Merck Research Laboratories, representing the PhRMA group.

DR. ECHOLS: Roger Echols, vice president of infectious disease clinical development at Bristol-Myers Squibb, working with PhRMA.

DR. EDWARDS: Thank you very much. Two quick announcements. We need to keep our visitor tags for both days so you will need to hang onto the tags for both days. At noon today, the people at this table will be escorted to the cafeteria for lunch, if you so desire. If so, could you please stay as the room empties out.

One other comment I wanted to make is that again, unlike an advisory board meeting, depending

on how our discussions go and time goes we will be able to have questions from the audience and discussion from the audience.

At this time I would like to thank all the people from the FDA for a great deal of time and effort that has gone forth in getting this meeting together. There really has been a lot of homework done. I would like to now turn to Mark Goldberger who will make a few introductory comments.

Opening Remarks

DR. GOLDBERGER: Thank you. I would like to welcome everybody to this meeting. I would like to give special thanks also to our colleagues from PhRMA and IDSA for their enormous effort to pull this meeting together, as well as to my many colleagues from the FDA, most notably John Powers and Li Chang for their hard work and all the planning that has led up to today. I would also like to particularly thank Dr. Edwards for his willingness to undertake what will undoubtedly be the difficult task of keeping the discussion going and keeping everybody on time during the next two days.

There is a lot of history to how we came to be here today, some of which I was personally

involved with and some not. There is a long history of guidance activity for antimicrobial drugs, certainly going back many years at FDA. Some of the notable features include the FDA/IDSA activities in the early 1990's with guidances; some big FDA advisory committees around 1997 to talk more about guidance development. In the fall of 1998 we had a two and a half day advisory committee with regards to the problems of antimicrobial resistance.

Then basically we had an issue that came up I guess about a year, year and a half ago with regards to what the standards should be for clinical trials, i.e., the so-called, infamous now, delta issue. That was to go to the advisory committee on September 13, 2001. My own personal opinion is the only good thing to come out of September 11 is that it got that advisory committee postponed till February of the following year, by which time we had the opportunity to have a more detailed look at some of the issues with regards to antimicrobial development.

I think there were some things we recognized. I mean, there certainly has been a lot of activity going on with guidance development.

Whether there had been genuinely new thinking about how to approach problems in antimicrobial drug development is perhaps a little less clear. Although we have had meetings with regards to the issue of antimicrobial resistance, I don't think we had yet gotten to the point of having clear-cut steps on how we were going to proceed to really get to the point of being able to provide advice to companies who were interested in this area.

Therefore, we took advantage of the opportunity in February to have a two-day advisory committee, to spend a day talking about issues related to delta and clinical trial design and spending a day talking about the issue of development of drugs for resistant indications, recognizing that these two are ultimately really not that distinct. I think that as a result of the discussions in February there was a desire to have some additional interaction between FDA, IDSA and PhRMA. The feeling was that a format such as this, a more open public meeting that would allow free flow of discussion, would be extremely useful in terms of developing a little more detail on some of the important scientific issues, and perhaps providing us with a little clearer road map as to

how to best fomd an approach to proceed.

I think that we all recognize that there is a growing need for new antimicrobials, especially those intended to treat serious illness due to resistant organisms. One thing we certainly want to do is to try to define the package of information that will most effectively allow us to obtain safe and effective therapy for such situations.

There is also a need to reexamine our approach more broadly to the development of antimicrobials for well-established indications, including the need to reconsider both the actual benefit of therapy in some of these situations and our approaches to demonstrating such benefit. I think, finally, there is a clear need to consider whether our paradigm for clinical development of new antimicrobials for multiple indications really takes full advantage of the kind of inferential thinking an experienced clinician might use in deciding how to choose therapy, that is to say how information from one indication can most effectively support others. I think that is an area where there is an opportunity to make some additional progress.

To meet these objectives we must address some significant scientific issues as well as regulatory issues. So, I hope that we can make substantial progress in this direction over the next two days. We also expect to have additional discussion on standards for approval of new products, a continuation of the dialogue that began last February. We recognize that this remains a concern of our colleagues from industry and basically we all look forward to a productive next two days, and I want to thank everybody again.

DR. EDWARDS: Thank you very much. We are going to start now with the topic of resistant pathogens and I would like to call on Dick Wenzel, from the IDSA, to begin the presentation.

Drug Development for Resistant Pathogens

IDSA Presentation

DR. WENZEL: In introducing this topic, what I hope to leave you with is that this is, first of all, a very important problem.

[Slide]

If we look at mortality as an endpoint, it is a life-threatening problem, one that is complex and one that, as an optimist, I think we can resolve.

[Slide]

Let me begin by showing you these data from Hughes and Datta, published in Nature. The title of the slide is "conjugated plasmids in the pre-antibiotic era." A microbiologist by the name of Murray was a strain saver. He collected enterobacteriaceae from 1917 on. These organisms came from North America, Europe, India, Mid East, Russia. They were mostly GI pathogens--Salmonella, Shigella, E. coli.

What Hughes and Datta did is take these strains from 1917 to 1941 in the pre-antibiotic era and examine them for genetic transfer function or plasmids, and found plasmids in 24 percent, again in the pre-antibiotic era. Not surprisingly, there was low level resistance: ampicillin resistance in two percent; tetracycline resistance in nine percent. However, no plasmids had resistant genes. The low level resistance in the pre-antibiotic era was located almost exclusively on the chromosome.

[Slide]

Things changed in the antibiotic era. An example of this is O'Brien's study in Science. I have labeled it "intercontinental spread of a new antibiotic resistance gene on epidemic plasmid."

Recall that in the next study the gene for gentamicin resistance was coded by virtue of two nucleotidyl transferases and all the organisms had identical Eco R1 fragment size and produced the same beta-lactamases.

The point of this slide is that within months now there was a spread of the epidemic gene on the plasmid, from the East Coast--Philadelphia, Boston, Syracuse, Chicago--to the West Coast--Gainseville and even down to Caracas, Venezuela. So, in the post-antibiotic era there was now rapid transfer of antibiotic resistance by virtue of the resistance gene on an epidemic plasmic.

[Slide]

How do they do this, if you will? Well, imagine two adult enterococci that actually contain sex pheromones and they induce plasmid transfer. So, if you look on the right, the plasmid-free recipient actually secretes a family of heat-stable protease susceptible pheromones, five or six pheromones seven or eight amino acids in length. If you will, the plasmid containing donor responds by synthesizing a protein adhesin facilitating mating. As a result, there is increased transfer

frequency of 105 to 106 fold. After transfer the specific plasmid pheromone shuts down.

[Slide]

As background let's look at just this year in the summer. The first case of full vancomycin resistance to Staph. aureus, with an MIC of greater than 128 mcg/ml, a woman 40 years old from Detroit, with a background of diabetes, peripheral vascular disease, chronic renal insufficiency, on dialysis, with a three-month history of a chronic foot ulcer. In April she had a methicillin resistance to Staph. aureus blood stream infection, and in June exit site infection with resistant Staph. aureus.

If you look here, on the left, you can see it was resistant not only to vanc but also to oxacillin. Curiously, susceptible to chloro, linezolid, Synercid and minocycline, trimethylene and sulfamethoxazole. But the point I want to come back to and relate to an earlier slide is that the mechanism for resistance was a VanA gene taken from the enterococcus by the Enterococcus faecalis so, if you will, a transposon. So, the possibility of epidemic plasmid transfer widely exists.

[Slide]

While we were getting over this, a second

case showed up in the middle of Pennsylvania, this time with an MIC of 32, fully vanc resistant, a 70-year old obese man weighing 500 lbs. He had had a history of a left lower extremity amputation secondary to osteo, in 1995. For two years he had a right lower extremity ulcer that had contained both VRE and methicillin resistant staph. In September of '02 he had osteomyelitis. He had vanc resistant Staph. aureus; as you can see, S. maltophilia, group B strep. and again the VanA gene was the mechanism. So, two different cities, probably two different organisms with the potential for widespread transmission.

[Slide]

If we were setting up a clinical trial for vanc. resistant Staph. aureus therapy there are immediately a number of questions. What is the gold standard? You can't use vanc. or meth. because the organism is resistant. Probably we would use trimethylene and sulfamethoxazole, based in part on Lou Saravolatz' study a number of years ago. What comparators would we use? Synercid, linezolid, or some combination? And, what scientific base do we have to choose the comparators?

[Slide]

Why did I focus in part on Staph.? Well, if you look back to this classic study from 1941, Sinner and Keefer, significance of bacteremia caused by Staph. aureus, 122 consecutive cases in the pre-antibiotic era, the case fatality was 82 percent. If you look at the total cases, on the top bar, of those who recovered, at the bottom, only one patient over age 50 survived Staph. aureus bacteremia. One might argue that we have better ICU support; we might have a drug that we could use, but this is a very virulent organism with high cases of fatality.

[Slide]

We know that we have to choose the correct antibiotics. This study in 2000 by Ibrahim and colleagues looked at ICU bloodstream infection and increased mortality with inadequate antimicrobial therapy. Here it is not only if we don't have an organism but also physician behavior because inadequate meant that the physician did not prescribe an antibiotic on day one to the patient to which the organism was susceptible in vitro. The accrued mortality in those who received an adequate antibiotic was 29 percent; inadequate, 62

percent.

When the authors modeled death, the risk factors for death, inadequate antibiotic therapy, wrong antibiotic, no antibiotic had an adjusted odds ratio of 6.9 compared to those who had adequate therapy even after you correct for other predictors of death. We need to choose the right antibiotic and have one available.

[Slide]

A little closer to home, if I look at some data that we have collected with Mike Edmund, and we have a national surveillance program called SCOPE with 50 hospitals around the country prospectively identifying patients with hospital acquired bloodstream infections. We now have data on 25,000 prospectively collected bloodstream infections acquired in the hospital.

But if you look at our first paper, crude mortality, if you will, is on the right axis in red, and the proportion of all nosocomial bloodstream infections on the left axis in grey, the top four organisms are left to right. So, coagulase-negative Staph., the number one cause in nosocomial bloodstream infections, of 32 percent of bloodstream infections acquired in the hospital 21

percent of patients will die in a month after that. Number two, Staph. aureus, 16 percent of blood stream infections acquired in the hospital, 25 percent crude mortality. Enterococcus is number three, 11 percent of blood stream infections and 32 percent of patients die. Number four is Candida, 8 percent of blood stream infections, 40 percent of patients die.

Left to right, coagulase-negative staph., 80 percent resistant to methicillin; Staph. aureus, 50 percent resistant to methicillin; enterococcus, 25 percent to 30 percent resistant to vancomycin. Candida today, only half are albicans, known to be susceptible to the first generation triazoles. So, we have a huge problem.

When you look at crude mortality, we know that that is a combination of the mortality directly due to the infection plus the mortality due to the underlying disease. This is an area of interest of mine. We have done a number of historical cohort studies to dissect out the contribution. The mortality directly attributable to the infection is at least half of the total of crude mortality.

[Slide]

Imagine this situation, if you look at attributable mortality the reason that is important is because that is the promise of better antimicrobial therapy. Key point, an antibiotic can only affect attributable mortality due to the infection; it cannot affect the mortality due to the underlying disease. So, imagine quintuplets coming into the hospital. They all have the same mortality from the underlying disease, in red--or a series of quintuplets. So, quintuplet one comes in and their mortality is 10 percent due to the underlying disease. Quintuplet two gets an infection and no therapy, a blood stream infection. Here the total or crude mortality is 50 percent but, in blue, is the attributable mortality, the best that an antibiotic can affect plus the 10 percent mortality due to the underlying disease. An effective antibiotic can knock the attributable mortality from 40 to 30, which moves the crude mortality from 50 to 40. A resistant gene could, in theory, be linked to a toxin which could then make things worse and add even more mortality or less. The key point is that antibiotics affect only attributable mortality.

[Slide]

Let me make a hypothetical argument about something in the ID community. This hypothetical argument relates to the recombinant human-activated protein C for severe sepsis and septic shock. I have no stock in Lilly. I am concerned about this but I want to make the argument anyway.

In their pivotal study the crude mortality in the control group was 30.8 percent and in the group that received human-activated protein C was 24.7. So, the absolute difference in mortality, 30.8 minus 24.7, is 6.1 percent. Many of us would say that is not a huge difference. The authors of the original study argued correctly that that did represent a 28 percent reduction in crude mortality, from 30.8 to 24.7. One could argue that, in fact, if half is due to attributable mortality and half is mortality due to underlying disease then, in fact, it was a 40 percent reduction in attributable mortality, from 15.4 to 9.3, to make the hypothetical argument.

[Slide]

In summary, I think clinical trials of anti-infectives for highly resistant organisms are clearly an important problem, and I have focused on life-threatening problems related to infections of

the blood stream. It is urgent. We just have to look in the last couple of months with highly resistant vancomycin-resistant Staph. aureus. It is a complex problem because it involves not only appropriate therapy but appropriate decision-making.

Importantly, I think mortality is a good endpoint. It has real meaning. But we need to do power estimates, cognizant of attributable mortality not just crude mortality. The gold standard and comparative drugs are very challenging decisions for us today but I think with creativity and the working relationship that this meeting embodies we can actually do this. Thank you very much.

DR. EDWARDS: Thank you very much, Dick. We are going to do all three presentations first and then open for discussion afterwards. So, at this time I want to call on Frank Tally for the second presentation. Frank?

PhRMA Presentation

[Slide]

DR. TALLY: I am here representing pharmaceutical manufacturers to talk about drug development for resistant pathogens.

[Slide]

I think the first thing you have to do is to look at the list of pathogens that fall into this category. Dick Wenzel just concentrated on Staph. aureus but there is a whole list of both gram-positive and gram-negative. I borrowed this slide from David Ross' talk this past February. It was in the advisory document that came from the FDA and this is a list I have put together with the resistance rates. But I think this is the type of list that has to be updated frequently. This is a list of nosocomial pathogens that present a problem. We are dealing a lot now with the gram-positive pathogens but the resistant gram-negative in the seriously ill patients is presenting a large problem and I think it will be the next wave of resistance that we have to deal with in the seriously ill patients in intensive care units.

[Slide]

On the community side there are a number of different pathogens. I put a star beside the vancomycin-resistant Staph. aureus because this is what everybody has been fearing. Dick Wenzel just covered it. With the two cases appearing in widely

diverse areas you know that there are a lot more of these isolates out there now, probably on a plasmid that is more epidemic.

We have the problem of resistance in Strep. pneumoniae. Methicillin-resistant Staph. aureus is growing to be a major problem in the community, and I think what we are seeing is the same that we saw 25 years ago when the emergence of penicillinase producing Staph. aureus spread out of the hospitals to communities and in a matter of ten years greater than 90 percent of the strains were resistant to penicillin requiring the development of new drugs.

We also have resistance in gram-negative organisms, particularly in salmonella and in N. gonorrhea, and we are seeing new resistance in N. gonorrhea. Finally, we have only seen macrolide resistance in Strep. pyogenes. I think everybody around this table is fearing the day when we get a penicillinase producing Streptococcus pyogenes because of the virulence of that particular pathogen.

These lists need to be reviewed periodically through some forum and be published. I think the inter-agency task force on resistance

is looking at this but I think this group has to periodically look at this and update these lists every two or three years to make sure we are on top of the current health need in our sick patients.

[Slide]

What about the development of drugs to treat these resistant pathogens? When you look at the antibiotic resistance it is really a complex issue without really simple solutions. We have talked about reserving antimicrobial agents to just treat resistant organisms. I have talked at these meetings previously and I think reserving agents really won't solve the problem. What it does result in is decreased research in both big PhRMA and the biotech section. In the biotech section you cannot generate funds from the public sector if they perceive that a drug would be restricted just solely for resistant organisms because of the tremendous cost it takes to develop these agents. We have already seen in big PhRMA a number of the big pharmaceutical companies closing down their antimicrobial discovery units because they can't match up with the other drugs that are in CNS and cardiovascular diseases, and the so-called return on investment isn't there for them. That is why

you are hearing even today about units being closed down in the pharmaceutical industry.

So, I think one of the things I would like to see out of this meeting is constructing a strategy to continue to discover and develop multiple new chemical entities so we will have drugs to treat these resistant pathogens.

[Slide]

Those agents can fall into a number of different categories. Right now there are a number of agents, which I won't go into, that are focused on gram-positive organisms. They are usually IV drugs but there has been one just recently approved. Linezolid is both IV and oral, which is an advantage in development. With IV drugs you have very few indications that you can go after and it requires patients being in the hospital.

We have the broad spectrum agents with multiple indications. Usually they are IV and oral. This is an area where people are still looking to have these broad spectrum agents.

We are looking for new agents, particularly many of the biotech companies are looking for new agents, but old agents can be reworked to get approval for these resistant

pathogens. Old agents will work when resistant pathogens emerge and that was the lesson with vancomycin. In the '70's and early '80's vancomycin was almost taken off the market because of little use.

[Slide]

But as you can see on this slide, with the spread of methicillin-resistant Staph. aureus you can actually measure the tonnage of vancomycin sold, and it tracks right along with the incidence of MRSA. So, the emergence of resistant organisms will drive certain drugs and certain drug use to very high levels. In the United States last year there were 15 million days of therapy with vancomycin. Unfortunately, we are starting to see vancomycin resistance so we need other agents.

[Slide]

But what is the problem in the drug development of agents for resistant organisms? There are very limited drugs in the pipeline. The promise ten years ago that genomics and combinatory chemistry was going to solve all of our problems, in retrospect it has failed to date. Many of us feel it will have the potential to come up with new targets with new drugs, but it is going to take

tremendous funding for these new approaches and these new targets to be developed. I daresay they are five to ten years away.

[Slide]

What are the problems with an IV only drug? You limit it to serious infections and so you have a limited patient database in different indications that you can go after, such as complicated skin, community-acquired pneumonia or hospitalization or nosocomial pneumonia or intra-abdominal infections.

We have talked about the selection of the optimum comparative agent. I think this has to be selected for the standard of care at that time, and that is why it is important I think with this group, having the ID society recommending what is the standard of care in 2002.

Also, IV drugs only require hospitalization, full treatment, and in this day and age patients don't stay in hospital very long. It has prompted home IV therapy but that is very cumbersome and very difficult to do, although in some cities you can do it well.

Finally, with an IV only drug you have a problem with criteria for oral switch. What you

would like to do is use the IV drug to bring the infection under control and then switch to oral therapy. There are several drugs being developed that don't have oral forms and the problem we have, regulatory-wise, is that if you switch to another class of drugs it is classified as a failure. I think one of the problems we want to address is can new guidelines be brought out to look at oral switch, and I will come back to that.

[Slide]

What about developing new chemical entities? You have to do two things. You have to show that it is effective, and it will depend on how easy it is to do these studies whether they are mild, serious or severe infections that you are looking at. Right now we are required to do two well-controlled trials with an appropriate delta. I don't want to get into the delta. I think we dealt with that in February. You need over a thousand patients with a new chemical entity. That means that you are going to have a study of between 2,500 and 3,000 total patients. If you take our cost rate now which, it is very expensive and it is getting more expensive to do these studies. That is one of the reasons that a number of companies

are looking at this very carefully and pulling out of this area.

[Slide]

It is particularly a problem when you are going after resistant organisms which are very difficult to locate in clinical trials. We have had a clinical trial now going for about 15 months, looking at comparative studies to find treatment for VRE. To date we have spent over five million dollars. We estimate it is going to take almost 23 million to complete a 360-patient study.

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If I look at this and start to look at my return on investment, my chief financial officer will start shuddering when he sees the cost. We have screened almost 2000 patients; only 42 were eligible for enrollment; only 22 of them had VRE. So, to date it has cost us $250,000 a patient. This is a staggering cost and one that many companies will not undertake. One has to look at the way we have constructed our studies now and see if there is an alternative way where we could bring these studies in more cost effectively and quicker.

[Slide]

We have looked at some of the action items

that we discussed, that David Ross discussed at the February meetings, and there is a Subpart E to accelerate enrollment using surrogate endpoints. We have looked at this but I think it is very hard to have a surrogate endpoint with a bacterial infection, and the endpoint is to eradicate the resistant pathogen. Animal models are not appropriate surrogates. Bill Craig will get into this later in the day; it is a guide to the clinical trials that you can do.

Using susceptible pathogens if the virulence of the susceptible pathogen is the same as the resistant pathogen would be an appropriate guideline. In the development of pipercillin tazobactam, when I was with Lederle, those were the criteria that were used. We studied 3000 patients with pip-tazo and only 256 fit the criteria but we were still able to get indications using the surrogate markers in specific small numbers of bacteria in each of the indications that were actually pipercillin resistant and pip-tazo susceptible.

I think the second potential surrogate that we could look at is the time to oral switch for IV only drugs. This is an area I think we

should look at in the future. You switch to oral therapy because you have had a successful outcome with the IV drug and the patient no longer needs that and you go home. But right now if you switch from an IV drug to a different class of oral drug it has to be classified as non-evaluable and a failure.

[Slide]

There are other action items to promote development of drugs for resistant organisms. When you look at MRSA the incidence is so high that it is easy. You can get MRSA in a number of different indications, including complicated skin infections, bacteremia and nosocomial pneumonia. However, for VRE the incidence is low and trying to locate the patients is very difficult, and it drives the need for a microbiological claim which gets to be very cumbersome because you are collecting the VRE from a number of different areas and it puts you into a quandary.

[Slide]

Again, you want to promote appropriate use of the drugs. I think that is something that we all agree to around the table. But restricting it just to resistant organisms--it would be okay for

MRSA because there is a large market and you could probably have a positive return on investment, but you won't for VRE because it is more of a niche product and people won't invest the money to get compounds in this particular area. I think products with safety issues that are active against resistant pathogens will be restricted because of the safety issue and IV only drugs will be restricted to hospital use. So, I think there are some built-in mechanisms in the molecules themselves that will restrict the agents some and actually delay the emergence of resistance.

[Slide]

Thinking about this, I was thinking there are three actual points that I would like to look at. One is with serious infections, following up on George McCracken's talk on meningitis in February, and looking at endocarditis. These are diseases where a microbiological endpoint is the key, and I think clearing of the cerebrospinal fluid or the blood of the pathogens, and no relapse after you stop therapy is really a clear endpoint. It is something that Dick Wenzel was just talking about.

What about surrogate endpoints? I think

we have to reevaluate and look and use susceptible and resistant isolates, gather the data on both, and some of the susceptible can be the surrogate for the resistance. In this way, with low frequency isolation of resistant organisms you can get an idea if this new chemical entity works in this disease. The microbiological claim is what number of resistant isolates do you need in the overall population. Currently, our VRE study is only for VRE. So, it is going to take us a long time to complete that particular study.

Finally, I think the requirement for two well-controlled studies for each indication has to be revisited and be carefully evaluated. Can you use the two well-controlled studies in two different systems? I think that is going to depend upon looking at the pharmacokinetics of the particular agent that you are developing.

[Slide]

Finally, to justify the high investment in the development of these drugs the drug's activity should really be based on its safety pattern and its effectiveness in well-designed clinical trials. I think what industry and regulatory agencies have to do is really to join together in dialogue so we

can design studies to get these new agents rapidly evaluated as to whether or not they are effective against resistant pathogens. Thank you.

DR. EDWARDS: Thank you very much, Frank. Next I will call on Ed Cox, from the FDA. Ed?

FDA Presentation

DR. COX: Good morning.

[Slide]

Following the talks of Dr. Wenzel and Dr. Tally, what I will try and do is try and focus on some of the issues that we would like to have discussed today, and try and highlight those in the slides that follow. Dr. Wenzel and Dr. Tally have already talked about a number of the issues that are important with regards to drug development for resistant pathogens.

[Slide]

The first issue that we would like some input on and discussion from the workshop group is how do we identify resistant pathogens of public health importance? This goes to the issue of which resistant pathogens rise to the level of posing a significant public health problem and a specific indication such that a claim would be reasonable to consider. Given that antimicrobial resistance is a

dynamic process that evolves over time, this raises the question of how would we identify these resistant pathogens.

[Slide]

One approach to this question might be to use a characteristics-based approach to the identification of resistant pathogens that pose significant public health problems within a particular indication. On the next slide I will actually show some of the characteristics that might be considered in identifying these types of pathogens. It is important to notice that a resistant pathogen might meet some but not necessarily all the characteristics that I will show on the next slide.

[Slide]

Some of the characteristics that might be considered in identifying a resistant pathogen of public health importance would include that the organism is one of sufficient prevalence in the disease under study; that the organism is one of sufficient virulence in the disease under study; that there are data to show that resistance affects outcomes; and the presence of resistance in the pathogen that is being studied.

Another question is, is the drug that is the subject of the resistant pathogen claim one that is commonly used to treat infections due to the organism? Are there an insufficient number or lack of therapeutic alternatives to treat the resistant pathogen of interest?

Then there is the related issue of is the organism resistant to multiple drug classes, in essence, narrowing the choice of therapeutic options. Then, other characteristics might include does the presence of resistance in the organism affect therapeutic decision-making? Then, another issue is, is the drug an essential treatment to prevent spread of disease within a population? An example would be a disease like tuberculosis where resistance to an essential therapeutic agent might lead to ineffective therapy which could result in spread of TB throughout a population.

[Slide]

There have been resistant pathogens for which we have previously awarded claims, for example, penicillin-resistant Streptococcus pneumonia; vancomycin-resistant enterococcus. Undoubtedly, some of the characteristics that I discussed on the preceding slide were considered in

these claims.

For resistant pathogens which have not been previously the subject of prior claims, the sponsor might submit data to address the characteristics of the particular resistant pathogen claim that is being sought to address the question of whether the resistant pathogen is one that causes a significant public health problem in the indications under study. This is an area too where we would like some discussion from the group here today, and other proposals as to how we might identify or address the question of how do we identify resistant pathogens of public health importance.

[Slide]

We have had several prior FDA meetings that have talked to the issue of antimicrobial resistance in drug development. Some of the meetings have been general meetings that have discussed antimicrobial resistance. Then, we have also had product-specific meetings with products seeking claims for particular resistant pathogens in specific indications. It is on this framework that we wish to further build with regards to the development of drugs for resistant pathogens and

the approaches that might be taken in a development program.

[Slide]

For a drug that is actually, as part of its clinical development program, seeking a claim for a resistant pathogen, a key portion of the data is the clinical data that provides evidence of the safety and efficacy of the drug based upon clinical outcomes and microbiologic outcomes within the target indication.

Not shown on the slide, but something I will come to in subsequent slides, is the issue of what role can data from other indications play in supporting the agent's safety and efficacy?

While there are still unresolved issues with regards to the use of in vitro data, data from animal models of infection and PK/PD data, we are also interested in discussion that talks to the weight of evidence that these other types of data might be able to provide, an issue that I will comment on in subsequent slides.

[Slide]

Then, with regards to assessing the data from a drug development program for an agent that is seeking a particular resistant pathogen claim,

certainly one way to look at the data that helps to address the issue of how the agent fares in treating the particular body site of infection is to look at how the agent fares in treating the particular indication. For example, is the drug a good drug for the treatment of community-acquired pneumonia? Then, moving down to a finer focus would be to see how the drug fares in treating the pathogen of interest, and this would be including susceptible strains of the pathogen, and then to the question of how does the drug work in treating more serious infections in the indication of interest. For example, how does the drug work in treating bacteremic cases of pneumonia? Then moving down to the issue of how do the clinical data shake out with regards to how the drug works in treating the resistant pathogen of interest?

[Slide]

Coming back to the issue of to what degree can we rely on data other than clinical outcomes data, here I am referring to PK/PD data, in vitro data and animal model data for the subject resistant pathogen in the target indication to provide support for a resistant pathogen claim. Then, also asking this question again with regards

to what level of evidence these types of data can provide for out-of-class resistance claims, for example, a fluoroquinolone seeking a claim for penicillin-resistant Streptococcus pneumonia, versus in-class resistance claim such as a glycopeptide seeking a claim for vancomycin-resistant enterococcus. This is an issue that we hope to have some discussion on here today.

[Slide]

Then, the question of how might we use data from other indications, and what role can these efficacy data from other indications for the same resistant organism play in supporting efficacy for the drug seeking a resistant pathogen claim? Just some examples, can data from a hospital-acquired pneumonia study support a community-acquired pneumonia indication? Can meningitis data support community pneumonia? Can CAP data support meningitis? Could, for instance, data from complicated skin structure infections support hospital-acquired pneumonia?

[Slide]

Across these different types of indications there are factors to consider when

weighing what the data from one indication might portend for the data from another indication. I think the thought processes that we are going through in looking at some of those examples are, you know, are there similarities of the disease process across the disease sites?

This relates to the organs and tissues involved, the similarities and the types of infections that the conditions involve; the drug levels achieved in these tissues; the spectrum of disease severity in the different indications. Then, host differences that might exist because of differences in the types of host that may have infections manifested in different body sites. Then, a last issue to mention is the certainty of diagnosis across these differing sites. For example, a blood stream infection as compared to an infection diagnosed from a non-sterile body site, such as sputum, and how the differences in the certainty of diagnosis across different sites might influence the weight of evidence from data from other indications.

[Slide]

With that, I want to turn it back to Dr. Edwards and he will take us through the points for

discussions which will mirror the points that I have gone through in the preceding slides. Thank you.

Discussion

DR. EDWARDS: Thank you very much, Ed.

[Slide]

The major points for discussion are listed on this slide. We are going to work through this list during our hour-long discussion period as thoroughly as we can. Let me open by asking Dick to comment further on the first issue here regarding identification of an organism a public health importance.

DR. WENZEL: Well, there are a number of people who have been interested in surveillance activities. Obviously, CDC has a number of surveillance operations going on. I mentioned the SCOPE study. There are a number of privately funded, that is through PhRMA, surveillance systems. I think it seems like an essential component of any public health program that we know what is going on, that we don't just know prevalence but I think the prevalence of the disease or the organism, the prevalence of resistance should be included, and other

epidemiologic features such as outcome because I think you can then link the organism, the infection, the resistance and life, death and quality of life issues in the same way.

So, I think we have to continue to encourage effective surveillance, effective meaning that it is validated somewhere along the line and we don't just call up people and say tell me what's in your lab, but somehow we have validation steps in there. The danger is with computer error and we can just have someone send the databases but if in some way they are not valid, that is, we have duplicate organisms or improper testing, all the issues that people around the table know very well. So, again, I would emphasize whatever we can do to encourage active surveillance that has been validated. Jack, I am not sure if I addressed everything you wanted but we can come back if people have issues.

DR. EDWARDS: Todd, would you have any comments about what Dick just said?

DR. WEBER: Well, I think he stated it quite well. As he said, there are a lot of different surveillance systems, some of which are quite robust and that can collect the kind of

information down to outcomes and other details. There are others that skim the surface somewhat in the sense of collecting strictly microbiologic data or just a few other data points.

Clearly, the more robust you get the more labor-intensive and expensive such a surveillance system is. None of these things really happens automatically. There is no magic system in place where these data can be automatically downloaded or collected, especially when you get out of the microbiology laboratory where at least there are some automated systems. But even there, there is a wide variety of systems that don't necessarily communicate with each other and certainly don't necessarily communicate with state or federal groups that want to collect those data.

You know, I can't say much more but certainly we would like to know better the prevalence or incidence of drug resistant organisms, more than we do today. There are few organisms for which I think we have very good data but it is certainly not nationwide, not in all populations that might be of interest. Health departments and also, of course, the funds available to set up those systems--CDC has a number

of projects under way to try to create common data elements and reporting from microbiology laboratories, etc., and state health departments, but that is really not completely in place yet and is not going to be a panacea even when it is finished.

DR. ECHOLS: Jack, are you looking for a threshold, not just systems in place to identify prevalent or resistant pathogens but what is the magic threshold that then qualifies a bug for public health importance that then might allow a different track in terms of drug development?

I am struck by Dick's presentation. I mean, he has two cases of Staph. aureus in patients and I think by anybody's calculations that is not a very high prevalence but it still has I think significance given what we know about the transfer of resistance. And, if we wait until it becomes a ten percent prevalence the animals are out of the barn and we are way behind the eight ball.

So, is the question here is there a prevalence, or do we need some other way of determining and integrating the clinical importance of a particular pathogen that then might have it be on a different track in terms of drug development?

DR. DERESINSKI: Can I say the example is important because I think what it points out is that it isn't just the crude numbers, it also involves the virulence of the organism, that is for instance, the mortality it causes, and also perhaps the mechanism by which resistance can be passed from one organism to another. We saw that very rapid spread of plasmid resistance in entero-bacteriaceae because of the ability to spread across species. These two cases of resistant Staph. aureus are an excellent example of why just crude numbers aren't sufficient.

DR. EDWARDS: Yes, George?

DR. TALBOT: Yes, further to those points, thinking along exactly the same lines, I think that focusing on prevalence alone, although it is extremely important for the reasons that Dr. Wenzel mentioned, can lead to some pitfalls. First of all, it does not necessarily reflect the patient and public health impact of a particular organism in a specific area. I think of, for example, acinetobacter in New York where the burden on the healthcare system and on the patients is huge. So, relying on prevalence alone in that instance can be very misleading.

Second of all, as Roger mentioned, if you rely on prevalence as the trigger for decision-making you are inevitably going to be in a reactive situation. Frank mentioned the point about the emerging gram-negatives and I think that that is closely linked there. If we wait until the prevalence of a certain gram-negative resistant pathogen reaches a "critical" level, given the time it takes industry to respond in a reactive fashion, it is going to be a problem.

DR. GILBERT: I wanted to mention another CDC-funded endeavor which I think has the potential of helping answer this question and bring some clinical relevance to the issues that are being discussed. We have these clinical microbiology survey surveillance mechanisms in place. They have already been mentioned. In addition, there is what is called the emerging infection network, which is a contract between CDC and about a thousand ID consultants around the country that are perfectly strategically situated to answer some of the questions that are being asked here. How many of these resistant pathogens are you seeing? How virulent are they? How many documented failures have you seen, etc., etc.? In my view, it is an

under-utilized resource that could help address many of the questions that have so far been raised.

Then slightly on a different subject, I think the question of when does it become important, and there are many factors obviously but one is when it begins to influence how we handle the drugs as, for example, the methicillin-resistant staph. In many hospitals around the country now for prophylaxis, for example for open heart surgery or artificial joint surgery, for 15 years, 20 years we have relied on cefazolin. In many institutions now where the prevalence of MRSA is in the 20 percent range the physicians, feeling responsible for their patients, are using vanco., which increases the metric tonnage which has already been mentioned. So, it does have an impact. Whether that number is 10 percent or 20 percent, I don't know but it has an impact on clinical practice.

DR. ECHOLS: In preparation for this meeting there was a list of organisms that was being generated. I don't know, John, if you want to comment on where that list is and if the agency is looking to perhaps use the clinical evidence from the experts to create a list of target

organisms that might be managed differently in terms of development.

DR. POWERS: Roger, we thought that perhaps it would be best--rather than come up with that particular list today because changing resistance is such a dynamic thing, perhaps it would be good to talk about the characteristics that would get an organism onto such a list, as a starting point today, given the limited amount of time that we have.

There are two ways to look at this. One is that there are organisms for which we have already granted indications, which is probably not that debatable and, in fact, beta-lactamase producing Haemophilus influenzae has been around for 30 years and we still grant indications for that all the time versus looking at newer things, emerging pathogens with resistance and how does one get onto that list.

When we came up with these seven things we didn't mean that an organism would have to meet all of these. We are talking about these as some pieces of the puzzle. For instance, when we were thinking about this VRSA came up clearly and it doesn't meet the prevalence issue but certainly

meets the virulence one. So, we thought today, in the time that we have, we could talk about it and if you want to cite specific examples of organisms that would go on such a list it would be more than helpful to approach it that way today.

DR. ECHOLS: Again, I am not so interested in the list of organisms but more the concept of whether the agency would be willing to commit to creating such a list that then could provide direction for drug development. I mean, certainly to get a bug on the list might require a certain threshold of evidence but then, you know, if someone starts development you wouldn't want to see that list change six months later and all of a sudden have the bug off the list for some other reason.

DR. POWERS: I think that is the danger of the list. It is so dynamic and the drug development process lasts for such a period of time that, for instance, if somebody started developing a drug for Staph. aureus by the time they finish it, you know, it is not a problem anymore. Penicillin producing Staph. aureus became a problem rather quickly. That could certainly happen again for another organism. By the time you finish a

development program or somebody else develops a couple more drugs then the issue is moot at that point.

DR. GILBERT: Roger, are you talking about having the list to somehow incentivize development?

DR. ECHOLS: Both incentivize but it is more having a clear target. I am not trying to sort of keep on this subject but once we identify what is an important target to go after, the question is do we come up with novel ways, in other words other than our traditional drug development? Do we come up with some innovative ways that can facilitate development of those drugs rather than going through what now is a very cumbersome process and, as Frank pointed out, almost an impossible task when you have a low prevalence of an organism to really study that within the context of randomized controlled trials? So, I am not looking just for a list but for a way of identifying a different track for drug development utilizing other tools rather than the randomized controlled trial.

DR. WEBER: I am sure that there are enough people in this room to come up with such a list. Agencies have the experts too to come up

with such a list. But I don't think any list is going to be useful without the addition of common sense. You know, listening to what you are saying, there are a couple of examples that I could imagine would cause trouble for you. Suppose a company decided that drug resistance to Streptococcus pneumoniae in infants was clearly a prevalent problem needing a new drug and they start work on it and put millions of dollars into it, well, now they have the conjugate pneumococcal vaccine and it is starting to have an impact and it may well wipe it out after some number of years. I don't know.

You know, is that the fault of the list makers? No. Is that something that should take that bug off the list? Eventually perhaps. But it is not something that is entirely predictable and I think it is also something where I am sure any company could sort of see the writing on the wall for something like that. So, I think there are going to be instances where other events change the importance of these bugs. Another example might be opportunistic infections in HIV patients. The extent of those problems and drug resistance in those problems may have been, at least for the time being, obviated by improved retroviral therapy and

all of a sudden those infections are gone.

So, I don't think the companies are naive about those other events so any list is going to be fluid because things are going to happen that may or may not be related to drug development itself.

DR. WENZEL: To come back to thinking more about Roger's question, I mean, if we agree that some type of valid surveillance is the starting point, I think from there we ask the question do we have a public health threat, and public health threat can be defined several ways. One is impact, that is outcome, mortality and morbidity. The second, as we have heard already, is transmission probability. The third is available options for therapy. I think we could come up with some or all of these sort of measures that this is a public health threat. It may not be realized yet.

At that point, to come back to Roger's question, if this is a public health threat then a public health response might be reasonable, that there be incentives for PhRMA to then come up with protocols to begin work on agents that might be used effectively for that. Just as we all go to the NIH for grants to study issues, there might be some mechanism that we could come up with that

would encourage competition, if you will, for protocols for developing a response to identifying a public health threat that the government might be willing to step in and help support.

DR. EDWARDS: Let me add to that, and then I want to ask Roger and Frank a question. NIH does have a list of entities that they encourage competition for research on which is acually derived through a very elaborate mechanism.

I am going to make a presumption here and, hopefully, you two will react to it. My guess is that you would be very much in favor of seeing some sort of a list that FDA valued and adhered to of important pathogens and encouraged competition for and were then able to focus development on that specific list with the presumption that that list would be relatively stable within a realistic developmental time.

Is that a fair assumption? What I am asking is not to explore the mechanism but just, let's say, the existence of such a list that would be desirable to focus on. Is that a fair assumption, Roger?

DR. ECHOLS: I think there are lots of things that help pharmaceutical companies develop

drugs and clarity is one of them. I mean ultimately we talk about return on investment but before you can get there, or even think about that you have to have some clarity around what it is you are trying to achieve and really the intermediary step is what you can get in the label. That is really the short-term objective. If by chance disease changes so the prevalence and the return on investment isn't there, so be it. I mean that is good for patients presumably.

But if we don't have clarity to begin with we our organizations are almost paralyzed because at a certain level we, sort of in the infectious disease development, understand the issues and the needs. When you try to translate that up to upper management who don't have a sense of infectious disease or the need they say, "well, show me. Show me where it can get us something in the label. Show me where it's something that can be developed," and, again, I keep coming back to if there are special pathogens that we want to go after, is there a different track to get there? That kind of clarity has to begin with identifying what the pathogens are.

DR. COCHETTO: Dr. Edwards, I will try to

add to that. I think the speakers this morning brought good information to bear on this. The roster of characteristics that we are looking at I think is very helpful and the characteristics are, in my mind, likely to be durable and I think that is quite useful. I think in the discussion we have heard good supplements to that roster of characteristics. Certainly common sense is a good supplement for any such roster and I would be in favor of adding that one. Attention to the mechanism of passing resistance is obviously important. Data to show the relationship between in vitro resistance and clinical outcome would be helpful information and, you know, the bottom line, the actual point that resistance is impacting practice patterns would be informative.

So, I think those expansions to the roster of characteristics are quite helpful. In terms of a list of specific pathogens, I don't know whether that is FDA's responsibility or other agencies' but the inter-agency task force does exist and Dr. Tally showed a couple of slides that, I suspect, most folks around the table this morning would agree are pretty good contemporary targets. That is not to say every single one of those pathogens

would be an important target five years from now but probably today I suspect we could agree that that is a pretty accurate contemporary list.

DR. TALLY: Yes, about trying to convince upper management in big pharmaceutical companies, and having done that before, it is a difficult task. The constituencies that the biotech companies have to satisfy are actually the public market, the people that are giving money to try and invest in that particular company.

Again, they want the same thing that Roger just talked about, clarity. If there is clarity, you can then build a story around the development to be able to raise the amount of money to be able to spend 200-300 million dollars that it takes to bring a drug to the marketplace. I think that is one of the things that you are headed for.

Possibly I think one of the things that Roger didn't say was are compounds being developed for this "list" of pathogens and when it goes to the agency is it going to get an expedited review or is it going to go into the regular review system? That may be a criterion that if the bug goes on that list, then there is a high probability because now you only know after you submit your

application and request it whether that is going to happen. Nothing has to be absolute in this life but if it has a very high probability that it will be an expedited review if you have the proper material to support that review, I think having that clarity does help get the resources to be able to develop these new agents.

DR. EDWARDS: Yes, John?

DR. POWERS: I think the issue of clarity is what we are looking for as well. As, Frank, you showed on your slide, there seem to be organisms that would appear to clearly go on anyone's list, multi-drug resistant gram-negative rods; methicillin-resistant Staph. aureus. Where we struggle and where we try to use these seven things is an example like macrolide resistant Streptococcus pneumoniae where one could argue that certainly it is of sufficient prevalence, but we get to that last bullet on the slide and that is, is there data demonstrating that there is actually a correlation with in vitro resistance with clinical outcomes?

Again, this becomes an issue as well when Dr. Wenzel showed something like the MICs for VRSA, which are clearly well above what you could achieve

in a human being, versus the story we saw with penicillin-resistant Streptococcus pneumoniae and some data showing that the original breakpoints specifically for cephalosporins, which the NCCLS has now changed, didn't correlate with clinical outcomes at all. So, we struggle with some things and I would like to hear what the group says about this, like macrolide resistant Streptococcus pneumoniae. There are case reports of people failing, but certainly there are people who fail with cephalosporin-resistant Strep. pneumo. and who die anyway, given host effects etc.

So, to answer your question, Roger, I think there are some clear no-brainers that go on the list but then why we want to use these seven criteria is because what do we do with the cases that aren't so clear, with macrolide resistant Streptococcus pneumoniae really being the example that we are struggling with currently?

DR. GILBERT: I couldn't agree more and that is why you have to have a link to the clinical world, however you want to establish that.

DR. DERESINSKI: I think you also have to look at this, as we have, as a dynamic event, with the assumption that whatever level of resistance

you have now will be worse in the future. As was pointed out, it is important to anticipate the future in this circumstance because of the long lead time in developing products. So, where we are now is not where we are going to be ten years from now with these organisms.

DR. GESSER: I just want to support that concept in a very strong way. We are where we are today because of decisions we have made in the past, and the question is should we use that same process to move forward or should we use a different thought process to move ahead from here.

Regarding the list, I think clarity is a concept that all of us are striving for. Certainly, it is the purpose of this meeting I guess. The value of that can't be overemphasized. I am sure for reviewers to have a clear structure as a basis for review for regulatory decisions is important. For developers that is essentially in the early phase of development. You heard that to get resources, not just money but people on board, a development program established or supported to pursue a particular area, that takes time. Then, it takes a substantial period of time to carry through the development process and ultimately,

hopefully, successful filing.

So, there is a kinetic process here. I am concerned when we say that, you know, we don't have a validated surveillance system yet. We all accept the limitations of the current surveillance system but that shouldn't stymie us from moving forward. I think it is a problem that needs to be addressed but I think, again, we need to apply the knowledge that we have at this moment to moving forward possibly along a different paradigm than we have in the past.

DR. EDWARDS: John?

DR. BRADLEY: I would just like to make a comment pulling together a couple of different concepts, the return on investment is something that has been brought up repeatedly, and the concept of resistant organisms in the United States, which certainly is the problem we have to deal with but I want to bring a global perspective into this. Even though we have universal use of the Haemophilus type B vaccines and are having increased use of pneumococcal vaccines, the last two large meningitis trials that we participated in were multinational and most of the patients actually came from outside of the U.S. So, the

concept of return on investment I think can be looked at on a global scale. I am not an accountant and I am not versed in these sorts of concepts, but it seems as though to track approval of a drug for a return on investment that may not only come from the U.S. but from the rest of the world could be a consideration in all of this.

DR. EDWARDS: Would anyone from PhRMA like to comment on that notion?

DR. POUPARD: I would also like to comment on the question that was raised about clinical outcomes. I guess I am concerned because the impact of a lot of this surveillance data would be are the MICs increasing because, from a public health standpoint, these are the things that we have to plan ahead for in drug development. The comment was you are impressed with the MICs of 128 because they are, without a doubt, resistant. But you have the issue of, you know, they predicted at one stage that penicillin would level off at MICs of 2 and maybe 4 and now we see 8's and 16's.

So, I am a little concerned. I think surveillance can give you a lot of that data. We are talking about surveillance as susceptible percent resistant, but it can also tell you the

trend and that this is increasing and that, for drug development, is really the key. To wait to say, well, yes, now it has reached the point where it is affecting the clinical outcome--again, to get back to reinforcing it, it is too late at that stage.

DR. EDWARDS: Comments on global stimulating, incentivizing?

DR. ECHOLS: I will just make a general comment. Global development is difficult to put in perspective for small companies unless they have partners, but even for big companies the marketplace outside the U.S. is a whole lot less free in terms of pricing, and reimbursement, and patent protection and everything else. As much as there is certainly equal, if not greater, need in infectious diseases, I would say that the companies, when they are making their return on investment calculations, don't place too much emphasis on sales outside the U.S. I say that knowing that someone will say just the opposite. Certainly, in our company antibiotics in sales globally are very important products and relatively even more important than they are in the U.S., but when you still look at all the uncertainties of

monetary, of patents, of laws, of pirates you don't plan on big-time return on investment just from outside the U.S. sales. If it can't do well in the U.S. it is probably not going to get developed. That is my opinion.

DR. EDWARDS: Other comments?

DR. YOUNG: I just wanted to pick up on a comment that you had made, John, and that is that I do think we also need to just look at this from two different perspectives when we consider the characteristics of a particular organism in terms of its public health significance. That is, there is both a population-based perspective in terms of understanding what the impact is on a large population, but I think there is also the perspective of the individual patient. I think that is sort of the quandary that we find ourselves in. You know, from an individual patient's perspective that particular isolate or macrolide resistant Strep. pneumoniae may in fact be very important and may trigger changes to the management of that particular patient. So, again, that is sort of something that we think about as well as we wrestle with these issues.

DR. EDWARDS: Yes, Mike?

DR. SCHELD: I was just going to react to something that you said, John, with regard to the macrolide resistant pneumococci because even though it may be difficult, I think what you will find is that it does change physician behavior. The problem I have is what is the most valid database, robust database to get that information on how it changes physician behavior.

Another example might be quinolone-resistant pneumococci which, if one database is to be believed, more than doubled, even though it is small, in the last year, from 1.4 to around 3.2 percent of pneumococci, and we view that in our community as a major public health threat even though we are not using quinolones as first-line treatment for pneumococcal infection. If we allow quinolones to be used in pediatric disease, in otitis media will that be the driver that makes that go right through the roof? I think those are things that we need to be concerned about as a community, but also it is going to drive decisions on whether they develop a new drug for a pediatric indication.

DR. EDWARDS: Frank?

DR. TALLY: Coming back to what John said,

I think there are no-brainers and you put them on the list. I think one of the questions I heard you ask is what type of data do you need brought to you for these marginal ones, and how can we best get that. I think this is why it was important to have IDSA at this meeting to try to give some feedback. There have to be systems out there to bring data on the importance of these marginal types of resistances.

DR. ECHOLS: By systems you mean ways to recognize the in vivo activity of the drug which, again, may be somewhat different from our normal drug development process?

DR. TALLY: If you look at that last bullet point, we will have tons of in vitro data. You will know the prevalence of a particular resistance. What you don't have is the clinical data currently. A lot of times you won't have a study really getting it for you and I think this is the problem you are pointing out with it.

DR. EDWARDS: Yes, John?

DR. POWERS: I guess, Mike, to get back to your point, with a lot of the issues that we come up with sometimes we wonder if the changes in physician prescribing patterns are really because

of a perceived clinical problem or because of an actual one. For instance, the idea would come up do people really use macrolides in severely ill people with Streptococcus pneumoniae disease? And, would an oral macrolide actually be used in that? So, in other words, somebody wants to use an oral macrolide or new macrolide that is actually good for macrolide-resistant Strep. pneumo. but the oral macrolide is use in the outpatient setting where the level of resistance might actually be lower in those patients, however, the clinicians might change their prescribing patterns anyway just based on the prevalence issue without the clinical data showing that there actually is a change in clinical outcome.

So, I wonder if sometimes we get into circular reasoning where we are just looking at the prescribing patterns. Just to sort of give you an idea though, we are trying to look at this and the FDA recently put out a contract where we are trying to look at both the prevalence of resistance and what are the organisms with these emerging resistance patterns and trying to link that to physician prescribing patterns as well.

DR. EDWARDS: Bill?

DR. CRAIG: Yes, I think you also have to look at the patient population. I think if you look at macrolide resistance where failures have occurred, the great majority of them have been in somewhat immunocompromised patients. That is a situation in which the drug has to do all the work. I also look at the MICs in the failures and they tend to be relatively high. If it was just an occasional failure that would be occurring I would expect to see also some lower MICs occurring there as well, which is not the case.

So, I think HIV patients are oftentimes excluded from these clinical trials and right away that patient population that may be at greatest risk for macrolide resistance is actually being excluded, and one is not collecting that kind of data in a clinical trial.

DR. POWERS: I guess that is the point we are trying to get at. We are not likely to see this in clinical trials so we are trying to look elsewhere to get that information. At the inter-agency task force that was held at ICAAC we had a global meeting. Todd, I believe you were there. One of the issues that came up was we may be able to get this information from other

countries, and one of the folks from Brazil actually said they commonly use macrolides in severe disease. Would it be helpful for us maybe to get this information from somewhere else because, Dr. Craig, I think you are right, we are not going to see it in a clinical trial.

DR. CRAIG: Yes, and it also depends on the mechanism. If it is MLSB and the MICs are exceedingly high it is going to be a different story than the efflux mechanism that we tend to see in the United States.

DR. EDWARDS: I suspect that you are constantly making a list of the no-brainers and then grappling with the ones that aren't such no-brainers where the real complexity comes. So, there sort of is a list only it is not an official list. That is creating some problems for someone like Frank who likes clarity.

[Laughter]

I don't think we are answering a lot of the questions that you want us to answer from these bullets at this point in this discussion. Maybe I am wrong but I don't think we are really getting into the nitty-gritty. But in the best of all possible worlds, would you like to have a list, and

how would you like to see it created, through what mechanism?

DR. POWERS: I think our issue too is that this list wouldn't just come from us. I think one of the things that Todd and I have talked about is that this would include some other partners besides just the FDA to say what is an organism of public health importance, keeping in mind the differences between the surveillance issues versus the drug development issues. But I think that is the idea there. Maybe I had not thought about the inter-agency task force as one way to maybe actually tackle this.

DR. WEBER: The task force is obviously large and all the agencies wouldn't have so much to do with this but it depends on the arena. I guess there are a couple of points I want to make based on the recent discussion. One is that we are talking about a list that has a column of numbers too, are we not? That hasn't been said explicitly but I am assuming that there can be a bug out there that is highly resistant but of such low prevalence, not that I can come up with an example, but of low risk for transmission etc., that can be on that list but that is really not of interest to

pharmaceutical companies. I mean, you want numbers that give you some prevalence data with this, I am assuming, but everyone just keeps talking about the list and the names of the bugs and I am just wondering if tacitly we are also talking about the numbers, as good as we have them, for prevalence and incidence.

I would like to just raise a point of caution about outcomes, in that proof that outcomes are severely worse with drug resistant infections are few and far between, and I think the reason for that is because there are still, for almost everything, alternative drugs available. While those alternative drugs still function, you may not have data that show very bad outcomes in resistant infections. That doesn't mean that we are not going to reach an end-game at some point when we run out of those available drugs and all of a sudden outcomes, of course, are going to be quite bad. But I think this speaks to a number of people's points about anticipation in terms of rising MICs, increasing multiple drug resistance, etc. I think those things are quite important to look at even in the absence of very good outcome data that is going to show that there are worse

outcomes given someone's infection with a resistant bug.

One other thing, again speaking in terms of lists, we were talking about bugs with specific patterns of resistance and I wonder if there isn't either a second list or a sublist on mechanisms of resistance that may really be what we would like to know about, which is if there are certain mechanisms of resistance that are becoming prevalent in one or more organisms maybe that is really what we are more interested in because that is going to signal what the prevalence of resistance to a certain drug or class is going to be, not whether it is Strep. pneumoniae etc.

DR. GILBERT: Jack, can I address that?

DR. EDWARDS: Please.

DR. GILBERT: I have been waiting for an opportunity to bring up a point that isn't quite on this list. The point that John made about global issues I think is relevant, number one. Not only from a financial perspective but in terms of the resistance issue. I mean we could wave a magic wand and solve resistance in the U.S. by one or a combination of mechanisms and yet resistance continues to evolve in underdeveloped countries

which invariably would impact on our population as well.

Using that a springboard, I am struck by, and part of this is naive I admit, the lack of apparent R&D at the basic level by industry. I mean we have gotten increasingly sophisticated in our understanding of the mechanisms by which bacteria, fungi or viruses become resistant. Back years ago when Staph. aureus--we came up with beta-lactamase and we responded as a global group interested in this. Now we know about efflux pump inhibitors. We know about bacterial hypermutation and I just learned about sex between enterococci and thank you for keeping me sexually informed here; I didn't know about the pheromones. But is industry interested or incentivized to start at this very grass roots level which ultimately will or will not lead to products that come into development? But it seems like there is a disconnect here between major scientific advance and then commercial application. Again, I may be naive in that regard.

DR. GESSER: I would like to just make a few comments. First of all, I am a "half-full" guy and I think there is a lot of activity identifying

novel targets. Certainly the genome project and the accessibility of those data have identified a number of potentially interesting targets.

DR. GILBERT: Let me clarify the point of my comment. There are novel targets, okay, a new cell wall target and so forth. I am looking for a magic drug that not only kills bugs but decreases the risk of emergence of resistance. If you turn off sex between bacteria you not only kill the bug but you get rid of this global spread at the same time.

DR. GESSER: Those are potential outcomes that could be examined in the course of a clinical trial. These are new concepts that people need to investigate. But the potential to have new chemical entities against novel targets I think is there. The question is, is there a mechanism, and are the resources available, and are the incentives there to encourage that type of development? So, I think that is an important issue and certainly looking at things in a different way in terms of selection for resistance or the incidence of super-infection or new infections during clinical trials is something that can be explored; something that could be explored also with existing agents

outside of the pharmaceutical clinical trial.

I just wanted to touch on two other points that I thought were important that were made. Todd made both of them. The first one is that the defined mechanism of resistance is important. I think that, hopefully, that will come up in the course of our discussion when we talk about in-class versus out-of-class agents and clinical development strategies and acceptable programs for drugs in-class or out-of-class. To define that I think you need to have a specific mechanism of resistance that is pertinent to a particular class.

The other comment I wanted to make I guess comes also from some of the comments that John Bradley made as well. I think the example was resistant Strep. pneumo. and will that change when we have vaccine that is widely taken and the epidemiology of the disease changes. It is still important for the kid who has PRP meningitis, who is looking for a drug that penetrates the CNS and has great activity against that pathogen, who hasn't yet received the vaccine.

So, you know, there are a number of issues and I don't think the anticipation of widespread vaccine use should restrict the way we think of

making this list and moving ahead. Certainly it is a factor one would consider if one had to prioritize one's resources, acknowledging that there would be a major impact with a new intervention coming down the road. But certainly for that kid who had the infection I think there is clear benefit of more potent and safe drugs.

DR. MILLER: I would like to add a little bit to that. I think we have been talking mostly today about factors which influence the development of drugs, and I think we need to talk a little bit about factors which influence the discovery of drugs, which is an even earlier stage, as Dave brought up. I think some of the same factors work but I think there are additional things involved, like for example, Dave, if you inhibit the sex between organisms you don't actually kill them; you make life a little less pleasant but it won't kill them. It is a little more complex basically.

One of the things that Frank brought up I think is a very special problem in the area of discovering drugs for antibiotic resistant organisms. That is, I think there is an unusual disconnect between one of the things that one of my old supervisors told me was really the most

important thing before you embarked on discovery of a new class of agent or new agent basically, you need two things. You need a scientific opportunity and I think resistance mechanisms is one scientific opportunity, and genomics is one approach to looking for new targets that would be active against resistant organisms. But the other thing that you need is a medical need. The reason for the medical need was if there was a medical need there would be a financial opportunity.

I think in antibiotic resistant organisms there is a bit of a disconnect between the medical need and the financial opportunity available to us basically, and I think it is probably an approach that we hold new antibiotics active against resistant organisms in reserve but we ought to recognize that this has a terrible impact on discovery of new antibiotic agents. I think the idea of macrolide-resistant Streptococcus pneumoniae not being very important perhaps has already had a tremendous impact on several drug discovery programs that I am aware of because it was thought that this would be an appropriate target. Perhaps the list was not very clear and we used our own list basically but we thought that

that was an appropriate target, and if that is not an appropriate target then those programs stopped. In some cases that may have been the only program within a given discovery research organization basically, and that means the end of antibiotic discovery in that organization.

I think we are going to have to take some kind of recognition of this fact and provide some kind of incentives for discovery programs to be focused around resistance mechanisms and so forth. I think the opportunity is not always great. One of the speakers talked about acinetobacter and I can remember that two or three years ago we had a wonderful structural lead for antibiotics active against acinetobacter and we talked about it, and if that were the only advantage they had, then that was clearly not big enough for a small company like ourselves who maybe would be happy with a 25 or 50 million dollar drug, but it just wasn't going to be enough if that was the only advantage we could have.

DR. EDWARDS: Yes, Bill?

DR. CRAIG: Again, the interesting thing would be what would happen if we had an oral penicillin that we were trying to develop now.

Would we consider penicillin-resistant pneumococci much of a significant problem? If you go back to some of the early trials that were done with placebo versus serum, back in the '30's and '40's, and look at the outcomes even in patients that were hospitalized, only 20 percent had mortality. What would it be if you started looking at those that weren't sick enough to go to the hospital and were treated in the community? There is a huge response that one is going to see just from our own immune system. So, as I was trying to emphasize, maybe you need to look at certain populations.

The other thing is maybe look at microbiologic effects instead of looking at clinical outcome, where you might find that if you don't eliminate the organism in that population there is a greater failure risk than in those where the organism is completely eradicated. I think such data exist for otitis media where the data suggests that if the organism is not eliminated only 67 percent respond while, if it is eliminated, 97 percent respond. So, maybe things like that can also be developed in pneumonia to let you focus then on a smaller number of patients looking at the relative risk that not eliminating the organism has

on the overall outcome of the infection.

DR. EDWARDS: Yes, George?

DR. TALBOT: To follow-up on that point and to come back to the point of clarity, I would like to make a couple of comments. First of all, I think it is an excellent idea to have a list of criteria for deciding when an organism would be of public health importance. Second of all, I think it is clear to me that having a list of target organisms would also increase clarity.

But then to get to Roger's point, what happens after that? Could we get clarity on the specific options for developing drugs solely for resistant pathogens? This is where I guess I admit to being a little unclear myself because I thought at the February meeting there was at least an emerging consensus that in the case of resistant pathogens there would be the possibility for a streamlined, focused drug development program that would be easier for companies to achieve. I think I recall numbers of patients mentioned as being 400 or 500. But somehow that seems to have been lost.

So, I wonder if we could talk a little bit about that point because it seems to me that if there could be clarity there it would answer some

of the questions about return on investment and incentives.

DR. EDWARDS: George, let me address those comments with a few of my own comments. I believe in the next session we are going to come back to those specific issues you just mentioned, but before we leave I am going to make a series of presumptive statements that may or may not be correct. I am just trying to understand the discussion so feel free to go right after them. Then I will ask another question that I think we need to ask before we leave.

My guess is, and as I say, please correct me if I am off base here, that Frank Tally would love to have a list of important resistant organisms, probably with a certain number of stars next to each organism that would be related to the likelihood of an expedited review, sort of like the movie rating system maybe on the possibility for expedited review. FDA would like also to have that list. It would make their job much easier in many ways, but like any of us, would find it a daunting challenge to create that list themselves and I think any of us would need to rely on lots of input from a variety of sources to create such a list.

The points on this slide represent grappling with individual issues that I am sure you all have done extensively because you do have to kind of make this list each time you are faced with a new application in this area.

So, the question I would like to come back to before we stop this discussion is what would be a structure that would be appropriate for the creation of such a list? I am not sure the answer is CDC. I am not sure the answer is inter-agency task force. That might have some logistical problems. Can the IDSA participate in the creation of such a list? So, on that point, I would like to turn that question over to the IDSA and, please, feel free to let me know if I haven't quite read the way the discussion is going. Yes, Mark?

DR. GOLDBERGER: I just want to make a couple of comments on that. One is that for issues that are complex, for instance macrolide-resistant Strep. pneumoniae as an example, we do already have a means available to address that question. The means available would be if necessary to bring it to one of the meetings of the anti-infective advisory committee which has a great deal of expertise, including substantial representation by

members of the IDSA, to address that very point. We do have a mechanism. It doesn't mean that another flexible mechanism that could also work outside of an advisory committee setting to identify for instance candida organisms for discussion at an advisory committee couldn't be quite useful, but we do have a means, for instance, in particular when there might be a difference of opinion between, say, a company and ourselves. So, that does already exist.

The other point I thought was worth making is, you know, I understand Dr. Talbot's concerns as well as Dr. Echols' because they do need to have some type of certainty in terms of their business plan. I would however say that, and I know they are both well aware of this, if they had a candidate compound for a given organism they are well aware of the fact that regardless of whether a list has been published they are more than welcome to consult with us via informal telecon, pre-IND submission, IND, etc., as to whether a compound against a certain organism would be suitable for the kind of development that we are talking about. That option, you know, is quite clearly open and has been open and remains open. So, I do want to

point out that advice is always available that represents the best thinking, for instance, that we have at the current time and is open to information that they may want to bring us which they may have, in fact, put together as part of their due diligence to decide whether this is something they want to go forward with.

I will also say with regards to something like MRSP, our problem there is if someone were to come forward today we are not sure what we would tell them, and that is the kind of situation that perhaps is best decided at in an advisory committee setting where we can give our perspective and the company in question, group of companies, PhRMA, etc. is free to give their perspective about the public health importance. Those are some of the observations I would make about how one can deal potentially with some of these issues.

DR. EDWARDS: Mike, would you comment about the idea?

DR. SCHELD: Well, I will speak on behalf of the Society and say that I think there are many and multiple ways in which we could assist you in the development of such a list. We have the requisite expertise and the clinical background.

We would, again, be pleased to do so. My prediction would be that our list would probably be a more inclusive one than might be generated internally but we would still be happy to do that.

Another thing that David has brought up is that through the emerging infections network I think you could get at this last bullet to some degree because even if you have clinical failures, say, in macrolide-resistant pneumococcus you may not report it in the Archives of Internal Medicine but you may well be able to discuss it in your chat room on your network and we can collect a series of cases for you.

DR. EDWARDS: Mike, just to clarify a bit, do you see the idea, say, as rendering their assistance mainly through the national antimicrobial advisory committee structure that is being formulated at the present time?

DR. SCHELD: I think I would have to think more about that, but that would make good sense. That is one mechanism for achieving the goal.

DR. EDWARDS: Yes, Stan?

DR. DERESINSKI: Yes, one question is in addition to these items, and let's say there were a list, it seems to me that there would be greater

interest in expediting the review of a drug that worked by a novel mechanism than, say, a beta-lactam that had greater affinity for the same penicillin binding proteins because you would predict that that wouldn't last long. Would that be the case, and how would you integrate that into this clear list and decision-making about expedited review?

DR. EDWARDS: John?

DR. POWERS: Could I just make an observation about that? Obviously, the thought process here would be that you need to make a list but before you make the list you have to decide what are the characteristics of what goes on the list, rather than us presenting you with some list internally by fiat. That is what we were trying to get at.

The second step is once one decides on what organisms go on that list, then we talk about how to develop drugs for that, and all the questions we have after this relate to that development process. But we were trying to take this in a step-wise way of getting at what would go on the list because I don't think it serves anyone's purposes for us just to throw organisms on

there and say this is what we think. We are trying to present you with why we think something should or should not go on the list, and the places where we are having our own internal discussions.

Mark brought up things where we might disagree and bring them to an advisory committee. We tried to put up the reasons for why we might disagree and to get at those but, clearly, we have a bunch of questions coming up after this that relate to the actual development process itself.

DR. EDWARDS: Yes, George?

DR. TALBOT: I would like to propose one criterion to add to the list. It relates to the issue of being proactive as opposed to reactive. If you think about the bioterrorism analogy, one is not waiting for a bioterrorism attack to decide that a potential agent of bioterrorism is an important subject for research, development and prevention. I think the same thing is true for resistant pathogens in the public health arena in the United States and elsewhere. So, I think the effort here should be less on waiting for a company to have a potential drug and then see if it could be developed against a possible resistant organism of potential public health importance, and more on

proactively identifying what the emerging threats are and facilitating and encouraging development, starting at the most basic level of antimicrobials against those pathogens. In summary, a criterion should be thinking ahead as opposed to reacting to what has already been seen.

DR. EDWARDS: Excellent point. If there are no other comments at this point, then we are going to take a 15-minute break before this discussion gets to a higher level of intensity. So, if you could please be back right at 11:15 we will continue then.

[Brief recess]

DR. EDWARDS: The second half of this morning's discussion will begin now. The second half of this morning's discussion is entitled use of exposure response relationship to facilitate development of drugs for treatment of resistant pathogens. We will have the same format with three speakers and then expand our discussion until noon. I would like to call on Bill Craig, from IDSA, to begin the three presentations.

Use of Exposure Response Relationship to Facilitate Development of Drugs for Treatment of Resistant Pathogens - IDSA Presentation

DR. CRAIG: Well, I was at that meeting that Mark referred to when the infectious disease advisory committee sort of had their two-day discussion on resistance, and pharmacodynamics came up at that session and was talked about. But I think over the four years since that time it has markedly matured.

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Clearly, where PK/PD analysis is being used, even as we speak, is to decide which drugs are going to go on even to start clinical trials and beginning Phase I studies. They are clearly used for selection of doses for Phase II and Phase III studies. They are clearly being used for susceptibility breakpoints for a variety of pathogens. The NCCLS makes it one of the four factors that is used for setting breakpoints. It is also being provided for dosing guidelines for pathogens where it is difficult to collect sufficient clinical data and where do we always have that, the subject we are talking about today, emerging infections.

[Slide]

I think it is quite clear, and industry has really bought into this, that PK/PD analysis

needs to be included in all phases of evaluation, from preclinical all the way up even including Phase IV. As I say, it needs to be included in the human studies that are evaluating efficacy. I think there are some potential problems--not necessarily problems but maybe limitations with PK/PD analysis in humans that people need to be aware of.

[Slide]

It is very difficult to reduce the inter-relationships among the various PK/PD parameters when one is using a single dosing regimen. Even if you use two different doses but use a single dosing regimen it is virtually impossible to separate the parameters. If you increase the time above MIC you increase the area under the curve, you increase the peak level--all of them tend to go up. That has clearly been demonstrated with the fluoroquinolones and the beta-lactams. There are articles out in the literature showing from human trials that each one of the various parameters can be correlated with efficacy.

I think in the past people thought that that was confusing, how could the animals say one

thing and human trials say something else? But whenever you only use one dosing regimen one can use any of the parameters. Jerry Schentag is sitting behind me and he can still use his area under the curve for MIC when it comes to beta-lactam antibiotics when he is using a single dosing regimen.

The other thing that I wanted to comment on there is that it may also be difficult to actually establish what the PK/PD target is unless one has a sufficient number of susceptible strains included in the clinical trial. We do need some failures in order to do this. This is one of the reasons why many of us in PK/PD have tended to focus more on microbiologic data than on clinical data because oftentimes we can find microbiologic failures more readily in some of the diseases than we can actually find clinical failures.

[Slide]

What about PK/PD relationships in in vitro models and also in animal infection models? I think the primary advantage that these have is that we can reduce the inter-relationships in time above MIC, area under the curve, and peak MIC and, as a result, actually determine which parameter is most

important in determining efficacy.

It also enables us to determine the target. By the target I mean the magnitude of that parameter that is required in order to develop efficacy. But, more importantly, we can also identify the factors that alter the target, such as how does a resistant pathogen affect the target? How does protein binding affect the target? How does the site of infection affect the target? There are all kinds of questions that at least can be taken into animal models and some into in vitro models to try and provide some information.

Just to sort of summarize what I think a lot of data has pointed out that has been accumulated over the last few years, there is increasing consensus that PK/PD targets from in vitro and animal models are predictive of efficacy in humans. Clearly, I think we have also been able to identify some of the factors that are important in target assessment. For example, the class of drug. You just can't look at beta-lactams and apply one number. We find that carbapenems are different from penicillins and even penicillins are a little different from cephalosporins.

We have clearly, I think, decided that

free drug levels is what one needs to focus on. Every time a pharmaceutical company comes up with a new drug, I am told this is the first drug that is going to show that protein binding isn't important. I think once we get it and study it in the animal models we come back again to saying that free drug levels is what one should be using when one is calculating out these parameters.

Frequently we need to make animals neutropenic in order to get the organisms to grow. For those that grow readily in both normal and neutropenic animals we find that the white cells can have a significant impact on the target, sometimes reducing it only slightly; other times having relatively major effects.

Most of the studies have not shown a big effect on site of infection, although I am a little concerned now about epithelial lining fluid and the impact on pneumonia and I think that is an area that clearly needs a lot more investigation.

We do see some differences with pathogens, however, if you look at all the data that has been reported in the literature looking at targets for resistant organisms, they have been similar or less than the targets for susceptible strains. So, we

are now finding that the MIC is not a good parameter for estimating what the potency of the drug is going to be against resistant organisms in in vivo models.

[Slide]

Just to bring this up, most of the studies that have been done so far looking at resistant strains have primarily been limited to pneumococci, to staphylococci, pseudomonas, a few gram-negative organisms but, clearly, one of the areas where I think this now needs to be extended even further is for organisms that are producing or have an ESBL phenotype.

Again, when we were talking about surveillance before, I think we also have to look at surveillance of our neighbors because those are the kind of organisms that eventually come here. If we look at klebsiella in Latin America, 45 percent of them have an ESBL phenotype. So, in some places this kind of problem can be significant.

[Slide]

How can we sort of apply some of this knowledge then to facilitate development of drugs for treatment of resistant pathogens? Let's take

the first scenario where we have MICs of resistant organisms but they are similar to susceptible strains. This is essentially a drug that is out-of-class for the resistance. An example might be fluoroquinolone as compared to penicillin and macrolide resistance. Here, what we would expect is that one would see that PK/PD analysis in in vitro and animal models and both susceptible and resistant pathogens would come up with very similar targets.

Secondly, one would then also do PK/PD analysis in humans with susceptible strains. Remember, they have the same MICs as the resistant strains and, again, we would expect that we should find data that would support the target that was developed in the animal models. Then hopefully, lastly, one would have a few cases of resistant infections to prove efficacy. This is the levofloxicin model that was essentially used in order to get the drug approved.

[Slide]

A second scenario would be where one has MICs to the resistant organisms but here the MICs are higher than the susceptible strains, and here we are usually talking about a drug in-class where

we may have a new macrolide that is active against organisms that are macrolide-resistant. Here again one would be doing the PK/PD analysis with susceptible and resistant pathogens and again one would expect that the targets would be similar.

But here I think one has to do something more since there is going to be a limit on the MICs. What is commonly done now and is at least accepted by the NCCLS is to do PK analysis with Monte Carlo simulations. Monte Carlo simulations is a statistical tool that enables one to take the variation that is seen in pharmacokinetics in a small population of people and extend it to a very large population, and then from that one can then, based on different MICs, see how often the actual target is attained with the drug in question. That gets one up then to being able to set a susceptibility breakpoint below which the organisms could be called susceptible. Then one still does the PK/PD analysis with susceptible strains and, again, one would like a few cases of resistant infections to prove efficacy.

[Slide]

There is, however, wording in the FDA Modernization Act that also talks about expediting

study where one can have a clinical endpoint or "surrogate endpoint" that is reasonably likely to predict clinical benefit.

[Slide]

Another section, under clinical investigations where they talk about a single clinical trial, talks about having one investigation and confirmatory evidence that is sufficient to establish efficacy.

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One then brings up the question could a well done PK/PD analysis in human infections, including both susceptible and resistant pathogens with the frequency that we have now--what we are really talking about here I think, at least from the start point, is RMSA, and would that provide the surrogate endpoint and the confirmatory evidence that would allow fewer patients to be actually enrolled in efficacy trials? Obviously, this would have no impact on the number of patients required for the toxicity assessment, but at least it may possibly be able to reduce the number of patients included in efficacy trials.

[Slide]

Where else could PK/PD analysis be used?

Well, I think it is already being used by the NCCLS. They have already published guidelines on what PK/PD information is needed. To my mind, it would be useful for industry if they actually knew precisely how PK/PD might be used for breakpoints or at least how breakpoints would be determined. This is clearly a place where I think this type of analysis has a role.

It has raised some breakpoints for some drugs that have expanded the susceptible population and cover some organisms that were previously considered resistant. Right now the analysis that NCCLS is doing I think will likely lower breakpoints for some drugs because of changes in the doses that are used now compared to when the drug was approved; new resistance mechanisms like the ESBLs; and I think enhanced knowledge about PK/PD.

[Slide]

Lastly, just a couple of comments about labeling. PK/PD analysis predicts efficacy with support listing of some organisms plus MICs in the package insert. Most practicing physicians, however, do not understand PK/PD targets. I think they understand time above MIC but when you start

talking about area under the curve in relationship to the MICs, that is a little different story.

So, I would clearly include the general target for the drug class in the label, but I would not think that it would be good to put in specific values for each drug. I think that starts to get people talking about minor differences that might not have any clinical significance whatsoever. What physicians do understand, and they get this information from their micro lab, is the percent susceptible for different drugs. So, I think it could be useful in presenting target attainment rates with particular pathogens, especially some with resistant organisms. Again, I would tend to give this as a greater than an upper limit for a maximum number, or give ranges without necessarily giving the specific numbers so we don't have people saying our drug has 99 percent; your drug only has 97 percent which, as I said, I think are probably numbers that are too small to actually result in any clinical significance.

[Slide]

In conclusion, I think the PK/PD analysis is a powerful tool for predicting antimicrobial efficacy in many common human infections and for

setting susceptibility breakpoints, and I think it should be used more for facilitating drug development for resistant pathogens through modified clinical trial design, through susceptibility breakpoints, and then also through some different ways of labeling. Thank you very much.

DR. EDWARDS: Thank you very much, Bill. We will just move right along to James Poupard, from PhRMA.

PhRMA Presentation

DR. POUPARD: It is good to be here to give a talk related to PK/PD when you are at a 90 degree angle between Bill Craig and Jerry Schentag. So, if I am a little nervous, you may know why.

[Slide]

My topic is the use of PK/PD to facilitate the development of drugs for the treatment of resistant pathogens.

[Slide]

I am going on the assumption and the premise that resistance is a current and future public health problem. I think my address today deals with it on a broader basis than some of the things we were talking about--just a list. Looking

at this broad background, it is this resistance that really I think has pushed the whole concept of PK/PD more into the foreground in making decisions on breakpoints and efficacy.

There are two points here. Many professional organizations and government groups have all these committees that really, if they are 100 percent successful, will slow the rate of resistance. None of these have the goal that they will eliminate resistance. Therefore, it makes it absolutely necessary that there are agents to treat infections caused by these resistant organisms because even if the rates are one percent at this stage, they are going to be much higher in the future. And, it seems that there are only two alternatives, either develop new agents or find new formulations for the current agents.

[Slide]

So, I would like to talk about what are some of the issues on approval guidelines for resistant organisms. It has been discussed this morning and I won't go into it but, again, it is difficult or impossible to achieve standard target numbers of cases due to drug resistant pathogens in clinical trials. The high cost has been mentioned

earlier today, and the number of years to do the study actually makes it rather unrealistic, and all this in the environment that the pharmaceutical industry, particularly large pharmaceutical industry is in right now where for not only drug discovery but for drug development we are in competition for funds from cardiovascular--from all the drugs that people take for many more years, other than for five days or ten days.

So, while these factors alone may not be significant when you put them together and put them in the environment of competing for funds to even get started on the discovery of some of these drugs, then these issues I think become very much more important.

[Slide]

So, what are the needs? The needs are for realistic FDA guidelines to secure labeling claims for agents to treat infections caused by resistant pathogens, and there is a need for inclusion of that information in the label describing the benefit of the new agents, particularly how to differentiate those from existing agents, to provide incentives to the companies.

[Slide]

My use of PK/PD--I am using it in a broader sense. Because of time limitations I am not going to get into Monte Carlo simulations but just PK/PD in general. As we have already heard, it is a powerful tool to predict the efficacy of antimicrobial agents. There is agreement among experts globally I think for the first time, particularly people that are setting breakpoints throughout the world using maybe different methodologies but, still, there is agreement that PK/PD holds a valuable parameter. We have already talked about some of the parameters that are there and have agreement on them so that they can be applied to facilitate the development and registration of products to treat infections due to drug resistant bacteria.

[Slide]

What is the role for PK/PD? Again, I am not saying that it will replace clinical studies but it should play a significant role in labeling and approval of certain agents. Again, the labeling is important because without that labeling the cost-benefit to the drug company is not there.

For breakpoint decisions there have been lots of discussions using PK and PD for breakpoint

decisions but I would like to focus on breakpoint decisions for resistant organisms. The trend in both the NCCLS and FDA, particularly for some of the newer agents, in setting breakpoints where there are not enough resistant organisms to do anything significant is to take the susceptible population, maybe give one extra dilution and put the breakpoint there on the basis that there is not clinical data to justify putting the breakpoint higher. This has worked very nicely. Also, one of the rationales for doing that is that as the MICs increase they become resistant and they stand out, and it is a very good philosophy to follow, except that when you are talking about resistant organisms, again, you would need PK/PD parameters to say this should include those resistant organisms.

The other is using PK/PD as efficacy versus resistant pathogens. Again, this is assuming that there is efficacy for the susceptible population of that genus and species.

[Slide]

The proposed role of PK/PD in labeling--again, it has to be included in the label. Some of the argument against it, as was

already mentioned, is that prescribing physicians are not interested in the PK/PD information. But for prescription guidelines and for comparing drugs it really is the label that we use to really formulate a lot of these decisions. So, things like time above the MIC, AUC/MIC specifically for the breakpoint and MIC-90s would be extremely helpful information in this.

Again, PK/PD to support the breakpoint would be critical in the sense that we talked this morning about lists, but in some cases that we mentioned one percent, two percent resistance is a very significant amount of resistance because it is going to be nothing but increased. Therefore, without that population and with the clinical outcome PK/PD is going to be a valuable aspect. Efficacy versus resistant pathogens, as has already been noted by Dr. Craig--you can argue and split hairs but, you know, essentially the data can be there as long as the company has the incentive to generate the material.

[Slide]

I will just talk about two scenarios. In the slides the abbreviations would be for penicillin-resistant Strep. pneumo.,

methicillin-resistant Strep. pneumo. and quinolone-resistant Strep. pneumo. The two categories would be a new agent for in-class drug, which would be a drug that has the same resistance mechanism, and a new use or a new agent for out-of-class drug, which would be a different resistance mechanism.

You keep on coming back to the question when you look through some of these scenarios of us addressing if the isolates are so difficult to obtain, then why is there a need for approval for resistant isolates? Again, if we come back to the fact that this is a public health issue; if we come back to the fact that it takes so long to do these studies, where in some cases the increased percent resistance is slow it may not be that significant but, with some of the predictions of quinolone resistance right now at a rate of about one or two percent and, therefore, impossible to do the studies and, yet, some people are predicting very high rates in the very near future. So, if we wait until that increases, then we certainly would be able to do the studies but then all the financial incentive may be gone.

[Slide]

Scenario one and, again, Dr. Craig outlined a lot of the details of how you would get here and I am just sort of taking it to the next step, there could be consensus of opinions as to what PK/PD studies are necessary to fulfill an in-class requirement to get a resistant label for breakpoint and indication. This includes PK/PD data in the label. It would be up to the company to provide the appropriate data, and to get a consensus of what the appropriate PK/PD parameters to measure are.

The use of the PK/PD data to help determine breakpoint would be significant because of some of the things I mentioned before and also strong support of PK data should lower the number of clinical isolates required per indication to get approval of a breakpoint.

The third item there, since the mechanism of resistance is the same in the in-class category there will be a limit to the appropriate penicillin, macrolide or quinolone MIC for the agent. Again, this could be determined and there could be consensus that 90 percent of the population must be susceptible, or some such figure.

The last one is data that need to be provided on the correlation of the penicillin, macrolide, quinolone MIC to the new agent or to the new application of the old agent.

[Slide]

As far as out-of-class, using PK/PD to get out-of-class labeling, the first would be the same. Again, you would have to come up with a consensus of what studies are necessary. The use of this data should help determine the breakpoint. With strong support of PK/PD data, again, the number of isolates could be lowered and the data that would be required would be the percentage of penicillin, methicillin or quinolone resistant organisms that are also resistant to the novel agent, and again surveillance data would be important in that.

[Slide]

In summary, the role for PK/PD to support approval and labeling claims for agents versus resistant organisms is that, first, PK/PD parameters, such as time above the MIC, should be included in the labeling. Second, PK/PD data should have a major impact on breakpoint decisions. Third, combined with limited clinical information this data should be used to support a statement in

the indications section for usage to treat infections caused by resistant pathogens.

[Slide]

In conclusion, PK/PD data in labeling and the approval process would accomplish three things. One, it would increase the number of agents approved for treatment of infections caused by resistant organisms. Second, it would provide differentiation of benefit of new agents or formulations, thereby providing companies with the rationale for development and commercialization of these agents. And, it would provide one incentive for companies to invest more to pursue solutions to the resistant problems more aggressively. I will end there. Thank you.

DR. EDWARDS: Thank you very much. I am going to call now on Phil Colangelo, from FDA. Phil?

FDA Presentation

DR. COLANGELO: Well, thank you and good morning, whatever is left of it.

[Slide]

I am Phil Colangelo, from the Office of Clinical Pharmacology and Biopharmaceutics at the FDA. I am going to try to round out the discussion

and continue with exposure response and application to antimicrobial drug development. I am actually going to speak more in generalized terms, not specifically towards resistance but in general because I think a lot of the things that we talk about with respect to exposure response and application of it applies to both susceptible and resistant pathogens.

[Slide]

These are some of the guidances. This is not an attempt to be comprehensive here but these are some of the regulatory guidances that promote the use of exposure response in various situations. The most recent is a guidance that came out from our Office of Clinical Pharmacology and Biopharmaceutics.

The third one down on the list is the specific guidance, the draft guidance that was developed and actually discussed back in '98, "developing antimicrobial drugs: considerations for clinical trials and individual indications." In that guidance we have wording with respect to PK/PD and the use of PK/PD and how it can be used, and its attributes within an antimicrobial drug development program.

[Slide]

Notice also the ICH E-4 document which sort of is a predecessor for the latest draft guidance with respect to exposure response. I mention it because the title is "dose response" and I think just to clarify and for some definitions, what we mean by exposure when we speak of exposure response is a measure of drug input, such as the dose or dose rate, as well as any measure of plasma concentrations, for example the maximum concentrations or the area under the curve.

By response we mean desired drug effects, as well as undesired drug effects. Desired drug effects examples being, in the anti-infective world, of course clinical cure, micro cure. But even to add to the response definition, I think it would be the use of some surrogate endpoints as well, as Dr. Craig had elucidated.

[Slide]

There is an antimicrobial drug exposure response working group that we have just recently formed, over the summer in 2002. This is a multi-disciplinary group which consists of members from the clinical, statistical, microbiological and clinical pharmacology review divisions. It is a

fledgling group right now. It was just formed. I am going to try to present to you what some of our thoughts are with respect to this approach.

[Slide]

Our objectives, as we outlined them to be right now, are that we would like to critically evaluate antimicrobial exposure response information and develop an internal consensus. I think, as has been said already, there is some type of consensus but we need to internally come to grips with exposure response information and see how it can best be used within a given application. When I say critically evaluate this information, I also mean not only within the submissions that we get but also within the literature, and there is a lot of literature out there and I think it is going to be a challenge and a daunting task for us to really look at that information and see what really good information we can extract out of it and where there may be some holes or some flaws within that information.

The second is to determine the applicability of the exposure response data that we get in antimicrobial drug development and finally then determine where exposure response data can

actually be used to support regulatory decisions.

[Slide]

Our potential goals that we have outlined would be to develop an exposure response knowledge base, or an exposure response database, if you will, and that is to compile the information that we receive in submissions, and we would like to stratify it by antibiotic class, by indication, as well as the organism and that would include those that are considered to be susceptible as well as resistant strains, and also by outcome, namely clinical and microbiological.

Another goal is to try and correlate this human exposure response outcome data with the in vitro animal data and, in a way, to sort of work backwards, if you will, to take the clinical data and to see whether or not there is a good correlation with those data that have been generated in vitro as well as in animal models.

[Slide]

I guess the way we see it is that exposure response really should be integrated within--or even a better word, I guess, throughout the drug development program. I guess the way we see it is that at the preclinical stage the in vitro animal

studies can serve really as the foundation, sort of the building block upon which then your clinical development program can be developed. I put there those double directional arrows to say that it is really an integrated, sort of an iterative process for which PK/PD or exposure response information can serve as sort of the common thread between all phases of development and serve as the glue, if you will, to really solidify the information that we get from preclinical in vitro and animal studies up through the clinical development stages.

I am not really going to talk too much about Phase I studies or actually not at all because everybody knows this and it is pretty well described. I am going to talk a little bit more about issues that we have discussed as a group with respect to in vitro and animal studies, Phase II and Phase III studies as well.

[Slide]

The in vitro animal studies, well-designed studies, we feel, can provide very, very important information for the clinical trials. They can be viewed obviously as hypothesis generating type trials. We discussed this quite a bit as the working group, and we have identified some issues

of importance and these have been discussed as well with Dr. Craig's presentation, but we feel that dose fractionation to establish the appropriate exposure response, index or even indices is very important. Obviously, correcting for protein binding is also an important factor as well. Neutropenic versus non-neutropenic animals we feel is also a very important factor and probably both type of models should be used.

Other issues that we felt are important would be the inoculum size; the timing of the drug administration relative to the inoculum; the duration of the experiment; and then what micro endpoints are then used. I think all these things need to be clearly defined and clearly presented as we try to use this type of information because when it comes down to it, I think what we are trying to do is see what the applicability is to the clinical setting of these types of studies.

[Slide]

Phase II studies we see as really proof of concept or testing your hypotheses that have been generated with in vitro and with the animal models. We feel it is also a very critical component of the development program. We probably won't get this

opportunity in Phase III but Phase II allows an opportunity to explore the exposure response in the targeted populations and to facilitate in the selection of the right dosage regimen.

There are obvious limitations but some of them that we discussed were that in the packages that we get we often see that Phase II only includes some limited indications, perhaps not always as relevant. In other words, a sponsor may try to extrapolate from PK/PD information for UTI for a drug, say, that is 80 percent renally excreted, eliminated in the urine, to try to extrapolate that and to use that argument for the treatment of, say, community-acquired pneumonia. There are also limitations of limited dose range that we see. We realize that this can be for ethical reasons as well. Then, oftentimes we don't get plasma samples obtained in Phase II studies.

[Slide]

So, I think some of the perception may be that Phase II is seen as maybe an unnecessary and high hurdle to get over, but we feel that it can really benefit us as well as sponsors in terms of establishing the adequate dosage regimens to take into Phase III.

[Slide]

With respect to Phase III, I think we feel Phase III is viewed as a confirmatory phase where we are trying to confirm the right dose or doses, as well as duration of therapy, confirming as well the relationship between exposure response, the various indices and outcome in patients. Some of the limitations that we see though are that PK sampling is usually not performed or, when it is, it is oftentimes not adequate to allow reliable estimates for the PK parameters through a population PK approach.

[Slide]

Some of the issues that we have also discussed with respect to the exposure response indices themselves or PK indices themselves are that there may not be an absolute or ideal value that is associated with a given index, and it may be specific to a particular drug or class of drugs, organism as well as the site of infection. There may be other PK/PD indices, in addition to those that have been discussed, such as time above or Cmax, MIC or AUC to the MIC. So, there may be others that may better, I guess, predict or correlate with clinical or micro outcome.

Another issue is that plasma concentrations may not always be equal to the infected tissue concentration. In light of that, a question comes up in our minds about can the PK/PD index that is derived from plasma, i.e., Cmax to MIC or AUC to MIC or even time above, can that index that is derived from plasma predict outcome at the site of infection? If the answer is, indeed, yes then is the magnitude of the index also the same at the site of infection as it is in plasma?

Another issue is in general the predictability of the indices to outcome, and factors that we feel have an influence on the predictability would be things like clinical versus the microbiological endpoint. Those can be very different and can have an influence on the predictability, as well as timing of the endpoint measurement; whether we are looking at the end of therapy or the test of cure; whether or not we are looking at an indication where there is a true drug effect versus spontaneous resolution; as well as the true microbiological eradication versus presumed microbiological eradication.

[Slide]

Finally, I would like to just sum up and say where we would like to be and where we are now. Well, I think we would like to be at a stage where we are able to optimize the exposure response indices to ensure an adequate dosage regimen for all pathogens, including resistant strains, and balancing that with acceptable safety.

I think that where we are now is that we are in the process of evaluating exposure response indices to support the clinical trial outcome data for pathogens. I think we would also like to use exposure response not only in the treatment of resistant pathogens but to use these approaches to help to minimize or prevent, if we could, the emergence of resistant pathogens.

With that, I will stop and I guess we will offer up discussion of any issues with the panel. Thank you.

Discussion

DR. EDWARDS: Thank you very much. We actually have a rather large list of questions for this part of the discussion and I think we are going to project all of them at this point.

[Slide]

I think what I would like to do is to

briefly go through them. Ed, before you sit down, we are going to need to show the rest of these, if we could. It is the demonstration of the efficacy in the disease in which the resistant pathogen is most likely to be present. Efficacy in hospital-acquired pneumonia when studying MRSA or complicated intra-abdominal infections for VRE. Utility of demonstration of efficacy in susceptible isolates of the pathogen as it relates to efficacy against resistant pathogens.

[Slide]

Can one use efficacy in one disease to support efficacy in another disease? Included within these points are the severity of the disease and can microbial proven ABS support CAP? Relevance of the site of infection. Certainty of the diagnosis in question.

[Slide]

The certainty of diagnosis, that is, bacteremia versus other forms of disease. The severity of the disease, VRE, UTI versus intra-abdominal infection. Certainty of poor outcome in the absence of effective antimicrobial therapy such as in endocarditis or meningitis, and how cormorbid conditions impact on assessment of

outcome.

We are hoping to track through nearly all of these areas through this part of the discussion. John, would you like to start us off?

DR. POWERS: If I could frame all three of these questions and put it in a more general way, Roger, you got to this issue of after we get to a list the next question is how do we streamline the drug development process. I think all of these questions actually go to that and PK/PD is one part of the equation of trying to streamline the drug development process. But we have a number of other questions as well that would actually go into this, above and beyond the preclinical stuff, and that gets to the idea of, for instance, using data on susceptible isolates of a particular pathogen to support efficacy in resistant pathogens. PK/PD might be part of that equation, but also how much clinical data one would require.

One of the issues that we struggled with internally is, is this different for, as Ed termed it, the out-of-class resistance? For instance, a quinolone for penicillin-resistant Streptococcus pneumoniae where the mechanism of resistance has nothing to do with the drug, as opposed to, say, a

glycopeptide for vancomycin-resistant enterococci or even a fluoroquinolone for fluoroquinolone-resistant organisms, one drug versus another. That is what we would like to hear some discussion on.

DR. EDWARDS: Bill, let me ask you to begin.

DR. CRAIG: One of the things that many investigators have tried to do, including our laboratory, is to specifically look at those questions to see specifically is the MIC a good test for correcting for the differences in the amount of drug that may be required to kill the organism. For example, what we found with quinolones if we are looking at a quinolone-resistant strain is that it requires more drug and it does that no matter what the mutation is. Whether it is a gyrase or whether it is a PAR-C or PAR-E it requires more drug but the ratio of area under the curve to MIC does not significantly change from what one finds with susceptible organisms.

We have also found a few organisms where the values are even less, for example, efflux for gemifloxacin. A drug which is effluxed, didn't

appear to be as important in the animal model as it is in the test tube. Maybe the efflux pump is busy doing something else or it is down-regulated in vivo.

Looking at those kind of resistances, we have not yet found a situation where the MIC has not reflected what amount of drug is going to be required to take care of the organism. In other words, we haven't found where the area under the curve to MIC ratio goes markedly high, where the organism still looks like it is susceptible but it requires a huge amount of drug in order to do that. This is looking at probably somewhere in the range of about 25 different clinical isolates as well as standard strains to try and make these kinds of determinations.

I think one of the problems that we have with animal model work is that people frequently want to study one or two organisms and think that applies to everything. As you know, in a clinical trial we may have a hundred different organisms so what is very important in the animal work is that you have to look at a lot of strains to try and at least gain some confidence that you are not just looking at two particular strains and if you try to

apply it to a larger number things are going to fall apart.

So, for doing those kind of analyses so far, and I guess we are limited with really good data for quinolones, with quinolone resistance, macrolides, and beta-lactams with beta-lactam resistant strains. The pneumococcus I think has been pretty well studied. Staph. aureus with MRSA I think is another one where a lot of different strains have been looked at. Then, for most of the gram-negatives, most of them have been your common, everyday susceptible gram-negative organisms. It is only lately that we have been starting to evaluate a large number of strains with various resistance mechanisms. Again, from the preliminary data that we presented down at NCCLS this last year, so far we are finding that the magnitude for the resistant organisms in terms above MIC for beta-lactams is similar or less than what we find for susceptible strains. So far in the type of analyses that we have been doing we don't see a major difference, but there are clearly a lot more analyses that need to be done.

DR. EDWARDS: Yes, Dave?

DR. GILBERT: Several things come to mind

but first, just for clarification if Phil Colangelo wouldn't mind responding, I was struck by a list of documents that have addressed PK/PD in the past and it looked like the major document was in 1998 and it is still in draft four years later. I am a little lost there and I am asking this not as a criticism totally but out of naivety. Then, the thinking is if I have a new drug that I am developing I don't quite understand if PK/PD is still under consideration or if it is a requirement. It is not clear to me; maybe it is to everybody else.

DR. COLANGELO: With respect to the document itself, I will ask Dr. Albrecht, if she wouldn't mind--

[Laughter]

--providing some status of that.

DR. ALBRECHT: You are giving me a choice? The document, "general considerations for developing antimicrobial drug products," is a document that covers multiple disciplines. As we will hear this afternoon, there is one area that has been under discussion for a number of years, and also the discussion was started on February 19th regarding the statistical elements. It is

that section where the dialogue has been complex and ongoing. It is really the reason why the document has not been finalized, and I think we will hear a lot more discussion this afternoon on some of the challenges that have faced that section. The PK/PD section I think was not sort of the holdup. I think the issues that Dr. Colangelo covered are as they stand now.

DR. GILBERT: So, how does it stand?

DR. GOLDBERGER: I think it is also fair to say that an issue that the first two speakers certainly addressed in detail was addressed last February, probably addressed at previous meetings as well and certainly back in 1988, that is, how much or how far can you go with PK/PD in supporting basically, you know, what kind of labeling and particularly what kind of indication you can get; how much of the data, say, for a resistance claim can come from that as opposed to clinical trials. That, truthfully, we are not able to provide definitive advice on right now because, I guess, we regard those as still not entirely answered questions, which is the point of having some additional presentations and discussions.

I think it unfortunate perhaps that we

haven't been able to come to closure on it, and I am not sure if that is on our side that we haven't had a chance to think about it in detail or the fact that it still represents that there are some not sufficiently characterized issues, or at least not sufficiently characterized for how it will fit in with a more limited amount of clinical data. I would have to say at the moment I probably lean towards the latter in trying to understand how much less clinical data is reasonable to try to go with, in addition to some of the PK/PD data that could be collected from a smaller, well setup study to support a resistance indication. I think at this point I know our thinking is not yet characterized as to how much that would really be. That is one of the reasons you are not going to see any definitive guidance yet because, I guess, from our point of view we are not sure yet what we would write in such a guidance.

DR. GILBERT: But can PK/PD data be put in the package insert at the present time? As a clinician, I would like that.

DR. GOLDBERGER: I will make a couple of comments and then I will see if one of the PK/PD folks wants to do that. We had a period when we

were working on a rule that will add some information in product labeling with regards to resistance, just sort of advising people, physicians and practitioners in general, about usefulness of antimicrobials in certain situations, including viral infections, benefits of susceptibility testing when available, etc. Some of the comments we got when we put this resistance rule out for comment was the idea of including more detailed PK/PD information. I guess one of the issues we had at that point is how readily available such information would be, and what physicians would actually be able to do with it.

So, I think that that is one issue. The other issue that we have to keep in mind, which is something I was just going to touch on very briefly in the afternoon, is we certainly, as you are all well aware, provide a lot of clinical pharmacology information in labeling now. Certainly, it is possible to provide PK/PD information but one must keep in mind that at some point when one provides information in detail about an organism it can be perceived to be giving an implicit claim of activity against the organism, which is basically the same as granting the indication. We then need

to feel comfortable with regards to that because from a promotional perspective it is possible then for that product to essentially be advertised as effective in that setting. That is also an issue that, truthfully, comes up in the internal discussions we have and from time to time in negotiations with industry. I don't know if John or Phil want to comment on this now.

DR. POWERS: One of the big sticking points for this I think is sort of a focus from ICAAC. Dr. Craig, you were one of the people doing the presentations there. It was one of those interactive sessions and Steve Zinner got up and asked a bunch of questions about PK/PD issues. What is the main parameter for beta-lactams, and everybody presses the button--90 percent agreement.

He asked the real key question at the end, and that was is this useful in clinical decision-making? It was 33 percent yes; 33 percent no; and 33 percent maybe. To me, that summarized the problem that we were running into. That is, everybody is agreeing on the in vitro and the animal side. When it comes to the linkages to humans, even the people sitting in that room had questions about what the clinical implications of

this stuff were.

DR. GESSER: I guess the first question one would ask is why that is, and why 33 percent don't know what to do with that information. Is it because they don't understand it, or they don't believe it, or they don't trust it? I think if the answer to that question is they don't understand it, then I think it is the role of the 67 percent to inform the 33 percent as to why they believe a certain way.

DR. POWERS: Does "maybe" count as a "yes"? Is that what you are saying?

DR. GESSER: No, no, no. What I am saying is you would like to bring those people to a point where they could make a decision. I guess the point I want to make here is that probably the way not to do that is to have a lot of numbers and terms that are specific to a certain discipline but, rather, to have an easier to understand format, which would be perhaps a section that deals specifically with resistance. That could be both the negative aspects of resistance, for example, not to use the drug in cases of influenza and things like that, but also a message about activity, and that activity interpreted by a panel

of experts in regards to the treatment of a resistant pathogen, acknowledging situations where there are limited clinical data. So, part of that would be PK/PD data, again, phrased not to say that the value of 10 was achieved in 10 rodents but to interpret those data and to state them with a certain level of confidence as to the meaning of that.

Again, specifically I am thinking about in-class resistance. I think you could make a logical argument that based on preclinical information and a body of clinical information against a susceptible strain of the pathogen, you could make a cogent argument that people might want to go ahead and use this agent in circumstances in which the resistant pathogen is encountered. I guess what comes to mind is the Levaquin story and the time frame in which that labeling decision and that information was available to practitioners.

I guess one could ask, let's say, there was a provision for a resistance claim for PRSP for an out-of-class agent available at the time of the initial licensure of Levaquin, did we gain any more assurance with the 14 isolates over I don't know how many years in 3000 patients? I think that is

really an important question for the group to address. Certainly we have information on 14 more patients. That information came from many different sources. Could that information have been attained in a post-licensure environment, which it was and, therefore, have a drug readily available probably three years earlier for use with appropriate restrictive labeling in terms of not sanctioning for an indication but indicating the limited amount of information that is available?

DR. EDWARDS: Yes?

DR. LAZOR: I would just like to follow-up on the labeling issue, but before that I would like to provide one clarification. I think a comment was made that guidance documents are requirements, or the contents of guidance documents are requirements. As stated, they are guidances, they are not requirements.

Going further on with the PK/PD in the label, I think that where we are at today if it has meaning and if it helps practitioners, then we would propose that such information be included. However, it is hard to take AUC information into clinical practice. So, I would propose that we actually even go a step further and if we try to

identify characteristics of patients or characteristics of disease states we may have the potential to alter exposure and relate those characteristics to dose. We can then actually translate exposure into a dose metric, if you will so it would be more user friendly in the label.

DR. EDWARDS: Mike?

DR. SCHELD: I would like to get back to Dr. Powers' observation of the one-third, one-third, one-third. In some respects, I think it is too general a question even though you think it is very specific. That is, if you asked an audience like that at IDSA is PK/PD information useful in understanding the best parameter for a class of drugs you would get 90 percent. If you asked if you can use the time above MIC of one beta-lactam versus another in choosing one beta-lactam in the clinic, you would probably get an answer no. If you asked the question if you could use AUC to MIC of a quinolone against a pneumococcus in predicting efficacy, you would probably get above a third saying yes. So, I think it depends on how you phrase the question.

Another thing that we are totally ignoring here is that these parameters may actually have a

correlation with the development of resistance in vitro or in vivo and that may be a driving decision for hospital formularies. The AUC to MIC ratio for quinolones against pneumococcus actually may drive a hospital formulary to choose one drug over another because they believe not that they are going to have better efficacy but may have a longer time to development of resistance if you have one that has a higher number. So, I throw those out there.

Another thing is if we dose these drugs the way PK/PD would predict that they would be the most efficacious, then we should have a lot more information on more than one dose for each drug, which we almost never do, which gets back to Bill's point earlier, 24-hour infusion of a beta-lactam versus intermittent doses. I don't see PhRMA supporting such studies and if we believe PK/PD we should actually look into it.

DR. EDWARDS: Yes, George?

DR. TALBOT: I think we are speaking about the label as though it is a single entity. Perhaps it is my naivete but it is not clear to me that that is the case. For example, I would say that putting more PK/PD information in the label might

be of some incremental interest to practicing primary care clinicians, of more interest to academic ID clinicians, of still greater interest to formulary committees, and so forth. So, I think that, in fact, there are multiple constituencies within the audience. This information might not be equally relevant to all of them but it would be relevant enough, in my opinion, to warrant including it.

DR. EDWARDS: Dave?

DR. GILBERT: I think it is a patchwork quilt. I consider myself sort of a hybrid of a clinician and erstwhile investigator and formulary committee participant, and so forth, and I want to know everything I can. I mean, I want to know the classical MIC data. I want to know Bill Craig's data or others' on the PK/PD.

I am going to move on to another area here. I want to know the toughest challenges that this drug can face. So, I want to know about how effective it is in endocarditis. I want to know how effective it is in meningitis, both in animal and in human studies. Because if the drug, whether it is in-class or out-of-class, is able to eradicate the organism or if it can cure

meningitis, that drug is going to work for pneumonia. That drug is going to work for skin and soft tissue. I don't need a zillion dollar study to prove it to me.

DR. POWERS: Could I ask a question about that because that gets to one of the questions we asked up here about one disease supporting efficacy for another disease? You have made that assertion, and this is where we don't have a problem with it, taking the more severe disease and relating it to the less severe disease. The flip side becomes more problematic for us. That is, suppose you have something like acute exacerbations of chronic bronchitis or acute bacterial sinusitis, those are the kind of indications we see the majority of. How do we use that data to support the more severe diseases?

DR. GILBERT: Well, I don't know the etiology of acute exacerbations of chronic bronchitis. I don't think it is often bacterial. But for the sinusitis and otitis I believe the double tap studies because then you have a microbiologic endpoint and you are showing eradication of the organism. Those are very believable, very credible and carry a great deal of

weight for most clinicians I believe.

DR. SCHELD: I guess one of the questions that you are asking is if you had a double tap study and showed drug X was effective in acute bacterial sinusitis, can you extrapolate that that would be effective in pneumonia, and I have a problem with that personally.

DR. POWERS: Or the other question to ask, Mike, would be could then we use that to ask someone to do just one study in pneumonia instead of two?

DR. SCHELD: That is a good question.

DR. CRAIG: As a PK/PD person, I am obviously less concerned about combining the sites providing that the concentrations that reach that site are comparable. So, I have no trouble with a fluoroquinolone for pneumonia as I would for sinusitis and otitis media. But if there are differences, then I think clearly one of the things that are starting to show up now is that epithelial lining fluid may be important for pneumonia, and some drugs like vancomycin may not penetrate as well there and that might contribute to some of the failures. Then we may see something different in pneumonia that we are not going to see in the

tissue infections like skin and soft tissue infection with vancomycin if there is inability of the drug to penetrate to where the organism is.

So, I think we have to know a little bit about the pharmacokinetics of the drug, but if the kinetics are the same getting the drug there, then I am more than willing to combine the information from the different sites.

DR. EDWARDS: Let's continue to pursue that question. Do others feel the same way on that side of the table? I mean, this is a critically important question here, combining different sites from two studies at the same site. Yes, John?

DR. BRADLEY: The issue of drug exposure at sites was brought up earlier and I think the drug exposures at each site needs to be evaluated before one can make that extrapolation. Clearly, middle ear fluid exposures are different than serum. Clearly, CSF exposures are different than serum. So, given that caveat that you have nice PK/PD at the site, I am very happy to extrapolate.

DR. CRAIG: Yes, I think the places where there are clearly differences, potential differences, ELF, epithelial lining fluid, CSF, humerus of the eye and, of course, urine, those are

the primary sites that I think are different and there are a lot of microdialysis studies now looking at free drug concentrations in tissues and we are talking about extracellular pathogens. The other place where things are obviously different is intracellular pathogens. There, the extracellular concentrations of the drug can markedly differ. So, it would be very difficult to extrapolate when you are talking about maybe drugs that are active against intracellular pathogens.

DR. EDWARDS: John, do you want to pursue that in more detail?

DR. POWERS: I guess what we are getting to is that it sounds like some things are combinable but, Mike, from what I heard from you I guess it depends, the degree of what is combinable as to which diseases support other diseases.

DR. SCHELD: I think we are all saying the same thing. If you have good PK/PD data at the site that you can predict, it depends on drug and bug. But you can combine that information. I think that is probably okay. If you had an extracellular pathogen that was going to be in either pneumonia or a sinus infection and you had good PK/PD data but, based on a lot of work Bill

has done, you could extrapolate how the drug works in ELF you should be able to put that information together. But you wouldn't be able to predict how some drug is going to do in Legionella from a sinusitis infection. You just can't do that obviously.

DR. TALBOT: the only thing I would add to that--I agree, the premise is that one has to be sure to ask some of the questions at least about drug-disease and drug-patient interactions. If, for example, you are saying that the concentrations achieved in ELF are adequate you should be okay because you have the same ratio as has been demonstrated for sinus or whatever, but the question still has to be raised what is the nature of that ELF. Is that ELF in a normal subject, or is that ELF in a subject with cystic fibrosis or chronic bronchitis, or what-have-you?

In principle, I like the idea and I agree with it but I think you do have to be somewhat cautious because of the drug-disease and drug-patient interactions. It is not insurmountable but it has to be considered.

DR. EDWARDS: Yes, Mark?

DR. GOLDBERGER: I think the last few

minutes has highlighted to us one of the really potential values of PK/PD, and that is in really being able to enhance the ability to make a rational approach to combining data from different studies in different indications, i.e., different body sites. I think that we recognize that this is a significant concern to industry in terms of the amount of clinical data that has to be produced for a multi-indication development program. This is a way to probably reduce that amount of data, probably also help focus on how one can get a resistance claim by effectively combining a number of isolates from several different body sites and, yet, do it in a way that is rational so people actually feel comfortable making that extrapolation. So, I think that this is actually quite important and an area that is probably certainly worth pursuing to make sure we have an adequate understanding.

The other comment I would just like to make briefly is something in response to what Dr. Gesser and Dr. Talbot said. Dr. Gesser raised a very good point with regards to levofloxicin and PRSP, for instance. Some of our own internal discussions, you know, when we talked about how

many isolates of PRSP do you need to grant that indication for levofloxicin or how many cases, I mean, we came up with potentially doing it on the basis of zero patients since, in theory, based on what you knew, you wouldn't need any patients.

The reason we felt that you ought to have some goes back to sort of a slight modification of what Dr. Talbot just said talking about, for instance, drug-disease, drug-patient interactions. There is also the issue of who gets certain infections. Are the people who get infected with PRSP the same who get susceptible pneumococci? Our feeling was because there was the possibility that people with PRSP might be somewhat sicker patients, it would be useful to have a limited amount of clinical data. The reason, in fact, that a small number was sufficient for levofloxicin was, (a) in susceptible patients the performance of the drug was outstanding, close to 100 percent cure including every patient with bacteremia and, (b) the performance in the PRSP patients, although a small number, was also 100 percent. That was the underlying basis. It is certainly a topic worth discussing, but our own perspective was that those patients might be different and it seemed prudent

to get a limited amount of data in them.

DR. POWERS: Can I bring up another point? Dr. Gesser, what you said about levofloxicin--remember, that development program for looking for those 15 isolates started at a time when the organism wasn't as prevalent. And, I think there is a double-edged sword to this as well, and that is what Dr. Talbot said about being proactive. On the flip side then how difficult is it to obtain those cases?

The next question that comes up is can one design a study knowing now what some of the risk factors are for patients to have resistant organisms, and more focus your development program to those people so that you are not looking at 3000 people to get 15 isolates? You can sort of zero in on them a little better.

DR. EDWARDS: Dick, what comments do you have about that last point, identifying risk factors?

DR. WENZEL: Well, you could for certain organisms when you know them, obviously. I mean, if I wanted to find triazole-resistant candida I could probably go into a unit that has been using gluconozole for two years and use some other sort

of clinical measures for people who are at risk for getting infection. So, I think the approach is doable, and I think it is, John, probably a reasonable effort to try and be efficient. There is a lot we don't know yet, particularly related to resistance, and they change all the time, as you know, because just trying to predict VRE it turns out that we might say, you know, well, we will track everybody who has had vanc. before, cephalosporins or anti-anaerobic drugs. It turns out that we can also look at people who have methasone-resistant staph. and we are going to find a big chunk of them that way and vice versa as well. So, I think that approach is right and may be of some use to industry.

DR. CRAIG: In SID specifically looking at techniques, looking at clinical characteristics to try and identify where the resistant organisms are so that one might be able to enhance your yield but, unfortunately, what quite oftentimes comes out is length of stay and sometimes the patients that don't meet other qualifying factors are, therefore, eliminated. To me, the biggest group of adults for penicillin-resistant pneumococci and macrolide-resistant pneumococci are the HIV

patients but, unfortunately, that is a population that is usually excluded from most clinical trials. They are the group that I mentioned earlier. When you look at the failures, that is where you find the failures, they are all in patients who have some immunocompromise. So, that is the enriched population where you can also see whether the comparator agent is going to be successful.

DR. POWERS: So, the next question would be should those patients be excluded from clinical trials.

DR. CRAIG: Well, I am not sure they should.

DR. DERESINSKI: Can I take a shot at that? For the AIDS patients I think when you look at the failures, the failure rates are directly related to CD4 counts and the people that often fail are people with HIV disease that have CD4 counts less than 100 or less than 50. Where the frequency of the disease is very common across all CD4 counts and oftentimes it is the presenting complaint for a lot of these patients I would suggest that immunocompromised patients with HIV that get pneumonia that have CD4 counts above a certain level could be included in these trials to

enrich the population.

DR. ECHOLS: If I might comment from some recent experiences, we presented data from a Phase II program that involved over 1000 subjects with a variety of respiratory tract infections where we did population PK on I think probably 700 or 800 of them, trying to draw a correlation between drug exposure and susceptibility of the organism and response. It is a very enriched database but ultimately, since most of the organisms were highly susceptible and the drug exposures were so high, you really couldn't draw any meaningful endpoints from it, but the data was there. The data is there for people to chew on and, hopefully, the agency will find some utility in it.

Then going to Phase III and doing population PK studies, we also did it for a different reason in an entire Phase III program conducted globally. There are certain practical aspects that people need to be aware of. When you go out to 500 study sites around the world and you are talking about timed specimens, it is not a Phase I unit or even a Phase II program where you have things that are much more controlled. If someone comes in with pneumonia in the middle of

the night and gets a dose and then you expect to get a timed two-hour post-first dose PK sample, it often doesn't happen, or the labeling gets messed up and so someone has a level which is supposed to be a trough or vice versa. It is very difficult to do in a large Phase III program.

The other comment that I would like to make is that we have often talked today about surrogate markers. A surrogate marker, in the eyes of sort of a clinical scientist, is a very useful tool. In the minds of our regulatory colleagues, I think it often is a challenge to determine what the validation is, what the clinical validation is. It is one of the questions that keeps coming up, what is the data to support that this surrogate marker actually demonstrates clinical benefit?

Again, particularly in infectious diseases, whether it is antivirals or antibacterial infections or antifungals, it is a three-part process. It is the host; it is the organism; and it is the drug and its exposure and it is not simple. Every time I try to look at databases that we have generated with PK/PD, it is not easy to say that someone with a certain relationship between drug exposure has a bad outcome and someone else

has a good outcome.

I think if we can't somehow make a leap of faith based on enriched science at all levels, and if we keep coming back to saying, well, where is the data to validate a certain surrogate marker, we are really not going to progress anywhere. I would predict that, outside of very well-controlled probably animal models, once you get into the human, and particularly larger clinical trials, the correlation just doesn't hold up. So, we are left with this dilemma. If certain surrogate markers have reached a point where they are valuable, then I think at some point we have to make a leap of faith and say that is the best we have and that is what we can use.

But to keep coming back and trying to validate them--I mean, it took ten years to validate PCR in HIV and another three years to finalize the guidance--actually, five years, from 1997 to 2002; it just came out. But even that was a very difficult process. It couldn't be reproduced today because the clinical endpoints aren't there.

DR. EDWARDS: Dick, before we go on, I wonder if it is possible for you to comment on the

confounding variable of comorbid conditions which may negate a proper analysis of the PK/PD data?

DR. WENZEL: I am still reeling from Roger's point. I get anxious every time I hear surrogate markers so I have to at least explore that just a little bit. If you mean by a surrogate marker something that already has been correlated with outcomes, as Bill had said earlier, that is one thing. When I hear you say leap of faith, that gives me chills because I think we should not go in the direction of a leap of faith if we don't have that correlation or it is an in-line relationship of cause to effect.

Do you want me to go on to the second point or let Roger talk?

DR. ECHOLS: Leap of faith--I mean no one wants to make a leap of faith. It is like jumping off a cliff and saying, "gee, I hope I land on a nice, soft cushion," or something. But what I was trying to point out is that John tomorrow, or others, might say what is the role of the antibiotic in meningitis, and it is to sterilize the spinal fluid. But even that is a surrogate marker. If you tried to validate sterilization of CSF at 48 hours with clinical outcome based on the

last ten years of meningitis data, I would say you can't do it.

DR. WENZEL: But do you want to use it or not then?

DR. ECHOLS: Pardon?

DR. WENZEL: Do you want to use it or not?

DR. ECHOLS: I do want to use it, as we will see tomorrow. But if you basically say that sterilization of CSF is a surrogate marker for clinical outcome, to validate that based on empirical clinical trial evidence, I don't think you will be able to do it.

DR. WENZEL: If you can't predict an outcome from the sterilization, then you shouldn't use it.

DR. TALBOT: Could I just mention that my talk later this afternoon is going to address that example and this question and maybe how you can sidestep it a little bit. Those are exactly some of the issues that have been concerning to me. Also, as you correctly point out, the fact that I think the terminology that we use revolving around surrogate marker perhaps isn't conducive to mutual understanding yet. I think the three groups here probably have somewhat different ideas of what a

surrogate marker is.

DR. ECHOLS: That is a good point because we use that term somewhat loosely.

DR. TALBOT: Right.

DR. ECHOLS: And it can be a really difficult thing to nail down.

DR. TALBOT: Yes. So, a surrogate marker, as I think I mentioned in February, may be a fine endpoint for clinicians but, as you pointed out, for our regulatory colleagues that raises hackles whereas for PhRMA it sure would be nice. So, I will come back to some of those points in my presentation this afternoon.

DR. CRAIG: I think you can use the animal model data, as I mentioned, with kinetics and doing some Monte Carlo simulations to actually look at what in a Phase II clinical trial you might be able to come out with, with some resistant organisms. If you had done that with your compound looking for pneumococci the data would have told you don't bother looking; you are going to be so high with your values you are probably not going to stand a ghost of a chance of showing it and if it does come out, it is probably not real.

So, I think you can use PK/PD to help you

make your Phase II studies better so that you stand a chance of actually being able to come out and support it. I think that is one of the reasons why you only had a third that said it was clinically significant. The final tie of tying a lot of this data with the clinical data is still somewhat slow to come. It is that final tying the bow around everything that I think is what is required to really get overall acceptance.

DR. GILBERT: Mr. Chairman, I would just like to ask a procedural question. Does the group think it would be useful to have some consensus votes here. We are discussing a lot of key issues and perhaps, with the motivation of establishing some degree of clarity, if we had non-binding consensus votes on some general issues, would that be helpful or agreeable or not? I have two in mind if the group so wishes.

DR. EDWARDS: Well, let me open that up for discussion because it is a complicated question. Let's see if we can get a consensus on the answer.

DR. POWERS: I guess our idea when we initially started this was that this was supposed to be a scientific discussion and non-binding in

any way. On the other hand, if people want to voice their opinion by way of a vote, we would be happy to hear it.

DR. GILBERT: Well, let me throw two ideas out just so the discussion on whether we should do it or not is focused. What I have in mind, and some of this came from discussions during the coffee break, is a consensus that on the list of resistant pathogens of public health significance at the present time there is agreement that resistant staph., methicillin-resistant and glycopeptide-resistant staph., VRE, the resistant pneumococcus to a variety of pathogens and these multi-drug resistant non-fermentative gram-negative bacteria, pseudomonas, acinetobacter, would be on the list. There are obviously many other candidates that could come, not come, or whatever, but that we have a list.

Then, the second consensus for vote would be that we want to capture pertinent PK/PD data in package inserts, whatever constraints are eventually put on them but to not just lose that data for use by the professionals that would find that data of value in addition to everything else that is in a package insert.

DR. EDWARDS: In having a similar meeting at the end of the MSG meeting, we started our meeting saying we were not going to have a consensus. The leader of that meeting set that premise down for the structure of the meeting. I personally had a total aversion to that whole idea because I sort of think very concretely and I like lists and all sorts of things. As it turned out, I think that meeting was more productive than had we actually systematically tried to have a vote and arrive at a consensus.

I am feeling a little bit this way at this moment, Dave. I think the two situations you have just suggested we probably all pretty much agree on unless I am misinterpreting the progress of the meeting. I think that the list of pathogens that you suggest would be on the list of 90 percent of us here. The big issue, and I don't think we are able to do it, would be to make the next list and that could get very complex and very difficult, and I am not sure that is the purpose of our meeting. If the idea were that we were to put forward the notion that we felt very strongly that some sort of an organized, feasible mechanism existed to create the list and update the list and continually keep

the list current, that is the sort of consensus that I think I would be in favor of and I think such a structure would be something we really haven't talked about in much detail. I mean, there have been some suggestions made involving the FDA, the inter-agency task force, a group that is beginning under the auspices of the IDSA, so heading in that direction I think might be something that would be concrete and useful.

I am just not sure that we want to conduct this meeting voting regularly on a specific issue. How do others feel about that? And, is the discussion format useful? Let me ask that question to the FDA at this point.

DR. POWERS: I think we have gotten a lot of helpful information already today, and some of these things we are going to address--Roger, your point about microbiologic endpoints, we are going to get to when we talk about specific disease states in a lot more detail. George is going to talk about it this afternoon. I think this is very helpful to us.

I guess one of the issues I would have, Dr. Gilbert, is that you slipped macrolide-resistant strep. pneumo. on that list,

which is one of the things we were asking about, some guidance on whether that should be on a list or not. So, that is the kind of thing we want to hear some more about.

DR. TALBOT: Could I just mention that I would suggest, short of the alternative of voting on whether we want to vote--

[Laughter]

--I would support the chairman's proposal to keep it a bit more general. The other point about the list, to extrapolate from your point, Mr. Chairman, it seems to me that there could reasonably be an A list and a B list, and the B list would be the watch list, those that are emerging into the realm of potential public health risks but maybe aren't quite ready to get there because they don't meet the criteria. So, maybe macrolide-resistant strep. pneumo. is on that list. It might never make it to list A but it would show that the community of all of us here has to revisit that periodically. That would ensure a mechanism I think to keep the A list a living, changing list.

DR. HINKLE: May I comment?

DR. EDWARDS: Yes.

DR. HINKLE: I don't have any debate with

your list of pathogens of public health interest. I agree completely. But I struggle, as George mentioned earlier today, to understand what belongs on the B list or A list without understanding what we are going to do with the list. MRSA is clearly a pathogen of interest. I can recruit patients into clinical trials with MRSA. If you believe quinolone-resistant Strep. pneumoniae is a pathogen of public health interest, I can put a patient in a clinical trial for that. So, how we handle those is very different for me. So, the list is a fine concept but it seems to me we are putting the cart before the horse; what are we going to do with it? I don't understand that yet.

DR. GILBERT: We have a lot of constituencies here to respond to your query, but it seems to me it is multifaceted. Certainly, it has import in a public health significance for which ones we are going to track and which ones we aren't going to track. Which ones are we going to follow the trend for and, therefore, start discovery, development and so forth early to anticipate rather than to react. It has implications as far as funding from Congress. Should the Institute of Medicine do a study on

highly resistant organisms to make this visible to the public? Increased funding of agencies that would be involved in the public health aspects of it--I mean, it is multifaceted. I think it could be very useful to many constituencies.

DR. EDWARDS: To summarize the consensus discussion, let me say this: Dave, in spite of the fact that you brought this idea up to me at the break and I acted very enthusiastically about it--

[Laughter]

--and now I am about to say that I think maybe we ought to just hold off on a structured voting consensus sort of format as long as this discussion continues to be useful, and perhaps we will come back and revisit the idea as we go into other areas. Yes, Mike?

DR. SCHELD: I would like to get back to one thing that Mark said and hear from some of my colleagues because I think it would be of great use to the agency if we felt, as you probably do, that eradication of a resistant pathogen from one body site could be predictive in another body site, and if you knew PK/PD data at those two body sites could you use that data in aggregate. I would say, given some of the caveats that we have heard from

our colleagues, especially Bill, yes, you could do that under certain circumstances.

DR. POWERS: Tim sort of brought this up too, that is, where are we going with all this stuff? It sort of gets back to that initial point and this is something, George, that you brought up back in February, and that is sort of laying out an outline for how one would approach this.

The first question one could ask is suppose you had a drug that was active against vancomycin-resistant Staph. aureus and nothing else, are you ever going to develop that? Your market now is two patients so that is not going to get developed. So, as a practical matter, the drugs that are going to get developed have probably activity against susceptible pathogens, including the common ones in a particular disease and the resistant pathogens.

The thing that George brought up back in February was this idea we have up there right now, demonstrating that your drug is effective in a disease where that resistant pathogen is most likely to be found. For instance, MRSA is most likely found in skin infections and pneumonias. So, the first hurdle would be show that your drug

actually works in pneumonia, period. The second thing would then be to come in with some minimal amount of clinical data, supplemented by PK/PD, on eradication of organisms at various body sites and use that information to support the resistance information.

Then the question comes up of the magnitude of that in clinical information. The reason why you need any clinical information, to answer Dr. Gesser's question, is are there host differences for who gets susceptible pathogens versus who gets resistance?

The third question would be are there differences in the magnitude of how much clinical information you would want to see for the in-class type drugs versus the out-of-class type drugs where you are not as worried about, say, a quinolone for penicillin-resistant pneumococci because the mechanism is different?

We see that as a three-step outline and that is what we would like to hear some comment about. I can blame it on Dr. Talbot because he suggested this back in February.

DR. EDWARDS: Bill?

DR. CRAIG: I just wanted to add that one

of the other clear sites where we see MRSA, and we don't even have a guideline for, is primary bacteremia which is a significant pathogen, which was discussed at the advisory committee in the past and it was the recommendation of the advisory committee, and I think the only thing that came out so far was for catheter related, not for primary bacteremia which is clearly a significant problem that results in death with inappropriate use. So, I think that would be an area where it would increase the opportunity for PhRMA to develop drugs with a primary bacteremia guideline.

DR. GILBERT: I would just like to echo that because there is a heck of a lot more of primary staph. bacteremia than there is hospital-acquired pneumonia due to staph., which I think is a pretty rare entity if you use strict criteria.

DR. EDWARDS: I can't resist making a comment about the same principle applied to candidemia, as we have discussed on many occasions. Yes?

DR. CRAVEN: In answer to your question, is there a difference between risk factors for people who have resistant organisms compared to

sensitive organisms? Taking pencillin-resistant Staph. aureus as an example, I think there is a lot. In studies that have been done there has been a whole series of clinical studies looking at bacteremias with MSSA compared to MRSA. Usually they are in the hospital a little longer; they have had more antibiotics; they have more comorbidities; they are in the ICU; they have more devices. So, I think you have to be really careful about trying to extrapolate data from sensitive strains to resistant strains.

Likewise, I think you have to be very careful about trying to extrapolate data from one particular site to another site. What happens in these sites is very complex. It has to do with the organism, the host defenses, the underlying diseases, etc. Also, for staph. the point that was just brought up is really important because a lot of these patients have primary or secondary bacteremias so they seed not only one site but they are seeing five or six sites, like bone disease, osteomyelitis, epidural abscess, splenic abscess, etc. and I think it is very hard, particularly with Staph. aureus, to try and lump these into a category so that you could expedite your drug. The

worst thing to do I think is to expedite a drug and then have a lot of caveats that weren't really understood, and then you have a lot of problems afterwards.

So, I personally would be very reluctant, particularly just using staph. as an example. You would have to look at each organism, virulent factors, etc. because it varies by different pathogens. I would be reluctant for Staph. aureus to make those extrapolations.

DR. POWERS: Could I ask another question? I guess the issue you just hit upon is why we would like to see some clinical data for people with resistant organisms as opposed to none. So, the question we really have is how much. That is certainly what the folks from PhRMA are asking us. How much data would one want to see then for the resistant isolate? Say that it is a given that it works for susceptible ones?

DR. CRAVEN: I think that is a complex issue and we probably shouldn't digress, but we can discuss it separately. I think there are a lot of issues that have to go into it and then you have to sort of decide how you do your studies, design those studies measuring those parameters. There

are a lot of parameters, different surrogate parameters. I was going to talk about pneumonia tomorrow. There are some surrogate parameters that are starting to emerge. We generally look at outcomes like death or clinical cures but there are a lot of other markers that we should be using in clinical trials in trying to get this information and trying to get faster drug development. We look at a lot of variables besides our traditional outcome variables.

DR. TALBOT: I think with the extrapolation issue there is one thing that one would need to be careful about, and Dick alluded to it. It is the attributable benefit. Let's say you had confidence in your PK/PD driving factors and you knew you would accomplish them in patients with a susceptible pathogen and with a resistant pathogen, both groups similarly, and let's say you knew that the drug worked very well against susceptible pathogens, would you be justified in extrapolating that information to resistant pathogens, and how much data would you need?

Well, I think we have said you would like some data just to make sure that you haven't missed something big. But I guess what I caution against

is that because those patients with resistant pathogens are different you can't expect to see the same absolute response rates. So, let's say your drug worked 95 percent against vancomycin susceptible enterococci in the urine, it might only work 65 or 75 percent against those that vary because they are more likely to have confounding underlying factors. So, I think one needs to be aware about making a one-to-one conversion in terms of the expected absolute efficacy rates.

DR. EDWARDS: Yes, Mark?

DR. GOLDBERGER: You can imagine, of course, that our problem is, using the example you just gave, is that 30 percent or so difference simply due to confounding factors, or is it due to something else? You know, we have to try and make that judgment since it makes a big difference in how you ultimately describe a product, say, in labeling.

DR. EDWARDS: Yes, Richard?

DR. GESSER: I think we all agree that we would all prefer to have patient specific data in the specific situations that we are talking about, but there is a cost and a consequence and that generally is time. Again, I think Dr. Craig made a

number of points. Those patients who have resistant pathogens are different in many ways, such that to design a trial to get at the answer to the question of is the outcome in those 14 patients or 20 patients, or whatever, the same as that which you saw in the 300 patients you had in your community-acquired pneumonia program, you are not going to be able to answer that. So, there is a cost entailed and that cost is really waiting.

I guess the question again is how much greater assurance, having waited, do you gain, and is there another way to approach that accumulation of assurance, so to speak, and could that be done? Let's say there was a critical need or identified need for a specific agent in a specific circumstance, one of the ways we heard was that maybe we can get at this by enriching clinical trials to select for that population. We have all tried to do that to a certain degree to this point and we haven't been that successful. Maybe we can be more successful in the future and certainly that is going to be an issue that we will talk about as we go on. But could you stage this level of assurance? For example, make an agent available in a limited way with a commitment to supply patients

specific data as it rolls out, I mean, there are risks entailed in that.

DR. GOLDBERGER: Let me just say that sort of our thinking would be, you know, because of this concern that people with resistant organisms are sicker, you take a drug; you get some resistant organisms and you study it in patients with severe pneumonia, whether it is hospital- or community-acquired pneumonia depending on the organism in question. You study it, for instance, in patients who have severe complicated skin and soft tissue infections, including people with significant diabetic infections. You study it in people, for instance, with intra-abdominal infections if it is appropriate for the organism. As you are collecting organisms you are also doing something else, you are fundamentally beginning to show that across a broad range of seriously ill patients the drug can perform well.

That helps you with the idea that even though there may be some differences in the resistant organisms you have at least got a handle that this is a drug that you are comfortable using to treat severely ill patients. Then I think your overall comfort level goes up as opposed to simply

getting an indication that may be less challenging and then trying to do everything else with a small open-label study that has a mish-mash of patients. That would be, at least ideally, the kind of perspective that, you know, we would sort of have.

DR. EDWARDS: At this point, in keeping with the notion of staying on time, we are going to have to suspend the conversation right at the point where we have gotten a real intensity rolling. Perhaps we can come back to it after lunch.

Once again, I believe you have a map that describes some suggestions for lunch. For the people who want to have lunch in the cafeteria here, at this table, could you please stay until the room empties out and then we are going to be escorted as a group. Thank you very much, and we will start again at 2:15.

[Whereupon, at 12:05 p.m., the proceedings were recessed, to resume at 2:20 p.m.]

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

DR. EDWARDS: Mark, I had to kind of cut you off at the end.

DR. GOLDBERGER: No, I don't know whether people, either from IDSA or industry, wanted to have any further reaction to what I said. From our perspective, we could envision a development program that would help address this issue of the fact that there are important patient factors associated with having an infection due to resistant organisms by having some clinical trial data in indications in which patients are fairly ill, and ultimately, in addition to having the study that would support that indication, the hope would be that if you studied several indications the need to have multiple studies in any indications or, say, in more than one indication would be significantly reduced. You would be able to have some, you know, increased likelihood of getting resistant organisms and, perhaps utilizing some PK/PD data, would feel fairly comfortable in combining the data on those resistant organisms across these indications and you would come up with a package that was reasonable from the point of view of a pharmaceutical company actually being

able to implement. It would provide, you know, useful information from a business perspective; would provide useful data that, when it was put in product labeling, people would actually be comfortable that one could state fairly well how the drug was likely to perform; and perhaps address the issue in a simpler way to get some reasonable data in resistance, recognizing the problems with trying to do these large open-label trials as your major basis of getting data in resistance indications which, in the end, sometimes leaves you with hundreds, if not thousands, of patients and, yet, difficulty in actually drawing reasonable inferences as to the performance of the product.

The question is whether there needed to be more dialogue about that because that kind of was rather a lot right before lunch.

DR. EDWARDS: Yes, Bill?

DR. CRAIG: I would just say that I think it is very clear that you would still want to have PK/PD data in there because one of the things that we know is that disease states can alter the pharmacokinetics of a drug and change the protein binding. So, there are a variety of factors that you would want to be able to control for in that

kind of group. So, I think doing PK/PD analysis as well would be an important aspect.

DR. YOUNG: Mark, just for clarification, do you mean that you would be obligated to do one trial in each of those separate indications so that the information from those single trials would then be pooled to support statements regarding resistant organisms?

DR. GOLDBERGER: Yes, in other words, part of it depends on the product in question; part of it depends on the kind of indications you are going to study. If you are going to, for instance, study a product for community-acquired pneumonia, hospital-acquired pneumonia, intra-abdominal infection in, say, complicated skin, community-acquired pneumonia is probably the easiest or one of the easiest of those indications. You might, for instance, do two trials there and one trial in each of the other indications. If one were comfortable about the PK/PD across those different indications one might easily be able to synthesize those five studies into getting all four indications, and if you were able to capture, say, a significant number of resistant organisms, let's say resistant enterococcus out of the complicated

skin, a few out of the hospital-acquired pneumonia or out of the intra-abdominal, you might ultimately be able to glean that, perhaps supported by some small open-label study, as a more efficient way of doing a development program.

Now, the question is, is that scientifically reasonable, and is it potentially something that is desirable from the point of view of the pharmaceutical companies who have to implement such a program? Dr. Craig gave one point about the PK/PD, which I certainly agree with. The question is are there other comments about that.

DR. EDWARDS: George?

DR. TALBOT: I think that something like that is reasonable, extremely reasonable. Looking at efficacy against a resistant pathogen is to some extent a side question of a traditional development program when you are going to collect a lot of data in a number of different indications. I am still thinking though that there are going to be some situations where one has a really acute unmet medical need and it would still be highly desirable to have the option of a very focused and streamlined development program. As we discussed in February, one might envision maybe a total of

500 patients and extensive reliance on PK/PD data. So, I am reluctant to let go, if you will, considering that latter option, while agreeing with you that in the former case that makes perfect sense.

DR. GOLDBERGER: Just to follow-up on that, I mean we talked about that in February and the model for the resistant organism in question is looking at what infection it is. This was talked a little bit about this morning. Is it likely to be found? Let's assume this is a new compound. You would have to do, I think, a clinical trial in that indication, first of all to show that the drug was an effective antimicrobial in a serious illness. You would get some data about, hopefully, sensitive strains of that organism. If this was an out-of-class issue that would give you some additional information. You would supplement this by some study focused at trying to enroll either more organisms in question, whether sensitive or resistant, or just a small study to try to focus on getting some additional resistant isolates. That would get you, with your Phase I other studies, probably up to the minimum number for safety but then you would have to think, well, what are we

going to say about this drug in the labeling, and how ultimately should it be made available?

Now, if it is an IV only product with some toxicities or if it is a little difficult to administer, in fact, it is probably not that big an issue because the drug's use might be somewhat limited. So, I think that that is another option, but one has to look very carefully at the product labeling and very carefully about whether there needs to be any limitation at all on how the drug might be made available because we are then trying to do something on the barest amount of data possible in terms of understanding how well the drug performs as an antimicrobial and what we know in terms of the safety.

As you point out, if there is a clear unmet medical need, if it is a serious illness, we have no other alternative therapies, one therapy with a lot of resistance, etc., etc., you know, the trade-off for those patients in a drug that may not have safety fully characterized is probably reasonable. It doesn't mean you would want to use it, for instance, on every patient that came in with pneumonia. That is the kind of concern that would somehow need to be addressed.

DR. TALBOT: Right. Just to make that more concrete, I am speaking exactly about that situation you described and I think the example that maybe Dr. Miller gave about the drug for acinetobacter is what I am thinking of, which is that a drug like that was abandoned because, I assume, it wasn't viewed to be economically feasible to take that anywhere. So, that is the kind of candidate drug that I would be thinking about for this extremely focused program where there would be an acute unmet medical need. Even VRSA might not meet that criterion. For VRSA you might need to have a much more robust database across susceptible isolates, multiple indications, and then get a VRSA indication on top of that with a more focused or enriched population of VRSA cases. That is how I am thinking of it.

DR. EDWARDS: Any other comments? If not, we are going to move on to the first part of the agenda for this afternoon, which is entitled regulatory and other incentives in drug development. I will begin with Mark Goldberger, from FDA. Mark?

Regulatory and Other Incentives in Drug Development

FDA Presentation

DR. GOLDBERGER: I will talk about incentives sort of from the point of view of what we currently, at FDA, have to offer. I know we are going to hear folks from industry talk about perhaps other types of incentives. There may be some overlap, including incentives that probably require some type of legislation, you know, to achieve.

[Slide]

Realistically, we have obviously talked about the problem that antibiotic resistance is increasing. What I am going to cover here is some of our perspective about the issue of facilitating development of antimicrobial therapy for resistance and related claims. Obviously, there is a role, that we are not going to cover so much in this meeting, for preserving the usefulness of current and new drugs in terms of their activity, but we should not forget that this is really ultimately, to be successful, a two-pronged approach.

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There has been a lot of discussion about need for guidances, etc. One thing that actually surprised me a little bit at the meeting today is the idea that if we don't put out some type of

written guidance no one will come and ask about a specific situation, a specific new drug, a specific organism. I do want to take this opportunity to disabuse anyone who believes that they are not welcome to call up to arrange either a pre-IND meeting, a telecon, submit an IND depending on how much data they have, etc., to discuss whether a particular organism seems to be appropriate for development, etc. We do try to provide that advice. That advice has the benefit, remember, of being as current as it can be since it will be the thinking at the time that there is communication rather than something that may have been written a couple of years ago and not updated. But we do want to encourage people to recognize that that type of consultation is available in terms of dealing with these issues.

We also try, as appropriate, to use our advisory committee if particular questions come up related to certain types of study design in difficult areas. We have done that with otitis. We have done it at times with febrile neutropenia, and a broad range of things. That is something we intend to continue to use.

In terms of facilitating development, we

have some pretty well-established tools that exist and I will try to go through them in the next couple of minutes--our Subparts E and H fast track designation, and then I just wanted to say a bit about exclusivity.

[Slide]

Subpart E has been around for 14 years. I might say for those people who were concerned about a draft guidance, Subpart E is, I believe, 14 years old and it is still an interim regulation.

[Laughter]

In fact, it had its birthday on October 21 because it was issued on October 21, 1988. This is for life-threatening and severely debilitating illness. It utilizes a risk-benefit analysis in decision-making. I mean, one of the first places to really talk about the idea of early consultation and increased communication, even starting before Phase I--this is one of the places where pre-IND meetings first came from. It finally talks about the idea that approval is possible earlier in the drug development process basically by the use of what was then described as Phase II data.

I think this is very important in sort of setting the standard for applying regulatory

flexibility during the development and review of a new product for these types of illnesses. If you read through any of the information about Subpart E you will recognize that it was intended to be applied fairly broadly in terms of the possible illnesses.

[Slide]

That was followed a few years later by Subpart H, 21 CFR 314.500. That will be having its birthday I think next month. I think that is final. Serious or life-threatening diseases. The idea was a meaningful therapeutic benefit over existing therapy. This is where the idea of a surrogate endpoint that is reasonably likely to predict clinical benefit really came from in terms of the authority to actually use that approach.

I found the discussion today interesting about surrogate endpoints. On one hand, there was some discussion on is a microbiologic endpoint a surrogate for clinical response. There was some discussion, yes; some discussion, no. If it was, presumably then it would be okay. I suppose one of the alternate ways of thinking about it is not really a surrogate. Actually, the microbiologic response is all that we need. However, if that is,

in fact, true then it clearly must be a surrogate or a predictor because if it didn't predict satisfactory clinical benefit, then it wouldn't be all that we need.

I am not sure completely about the differences between those two but basically we do have the option to use microbiologic endpoints in terms of predicting clinical benefit. That is truthfully less of a major issue sometimes in short-term therapy where you are going to get the data fairly soon on both. It became, obviously, a very big issue with regards to HIV where studies have to be much longer. It does give us flexibility certainly in looking at the issue, for instance, in meningitis both microbiologic and clinical endpoints, but there it is really a matter not so much of using it as a surrogate but of understanding how best and most efficiently to combine the use of a microbiologic and clinical endpoint, rather than not having them together, just understanding how much data you really need from each. That is a really different issue.

The other things that are covered in this are the issues of confirmatory trials, expedited withdrawal, prior submission of promotional

material which I don't think we need to talk about in any detail today.

[Slide]

This was followed a few years later by fast track which combines parts of Subpart E and H. It talks about a new therapy addressing an unmet medical need. It is worth noting again that this is written quite flexibly. It is talking about an unmet medical need in terms of the drug working better than previous therapy. It works better in a particular population than previous therapy. It is safer than previous therapy. There is a population that can't take the current therapy because of intolerance, or whatever, and in that situation the drug offers a benefit.

So, it was designed to be extremely flexible. I think it is very important to realize that. If you read through the guidance about this, it makes it quite clear about that. It also includes a provision to accept for review a portion of a marketing application prior submission of the complete package.

It is also worth mentioning that there was talk about if a product came off the list, the infamous list that we talked about this morning,

whether it would get priority review. In general, the expectation is that a product that gets fast track designation, and we would be expecting that most of these products would be getting it, you know, the expectation is it will generally get a priority review. I say generally because technically you make the final decision after you look a little bit at the data when it comes in and see if basically the drug worked like it was supposed to. In other words, you can get a fast track designation literally based on not much more than an idea if it is submitted very early in drug development. That is, I have a compound that looks like it would be the first to do such-and-such, it is possible to get a fast track designation on not much more than that. The longer you wait the more information, not surprisingly, you are expected to show.

The decision about priority review is ultimately made not upon potential but actually upon results. If the product performed well and it did what was expected of it, you know, the likelihood is that it will, in fact, get a priority review. So, that is the issue. But we will obviously, work with you as much as possible in

order to get a satisfactory outcome.

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As far as other regulatory initiatives, there is exclusivity. There is the orphan drug exclusivity, seven years of marketing exclusivity for the compound first for the given indication. The compound could have been an old compound and doesn't have to have any exclusivity to add this on top. There is Waxman-Hatch exclusivity which attempts to give back some exclusivity that was in part, you know, used during the development of the product. It is now available for new antibiotics. I think antibiotics that were not the subject of regulatory or approval action as of sometime in 1997 I think.

Then there is pediatric exclusivity. The reason I mention that is that it is six additional months added on to existing exclusivity. Some people have wondered whether that type of approach for new antimicrobials or for another drug that a company had in return for developing a less profitable new antimicrobial would be useful.

That kind of brings us to the last, which people have had a lot of enthusiasm about, the wild card exclusivity. That is, you develop a drug that

doesn't have much of a market and you get some period of your exclusivity added on to a product of your choice which might be a much bigger seller. Basically, that is not currently available. That is something that would require legislative action, but I have heard at any number of meetings over the years a lot of enthusiasm for having something like that be available.

[Slide]

What are the other things that sort of naturally flow from these issues of increased communication, trying to take approval actions earlier on? A basic one, and we have talked about this already, is reducing the size of the clinical trial program. A lot of what we talked about this morning, and probably will continue to talk about, are ways that we can do that effectively, really focusing on situations where we are trying to meet unmet medical needs of different types.

We always have to keep in mind that we are having to address the trade-off between our ability to assess effectiveness and the resources required to perform a trial. Fundamentally what that means is the smaller the trial sometimes, the greater the uncertainty about the results. One of the ways to

deal with that is to look across a whole development program, and that can be quite an effective way of dealing with these degrees of uncertainty. When you only have a single clinical trial, as we spoke of a little while ago, even with PK/PD etc., there will always be greater uncertainty and one needs to accept that in terms of deciding whether to go forward and in thinking in terms of how a product ought to be labeled.

We talked a little bit, and certainly we talked in February, about the idea of substituting quality for quantity in at least some clinical studies. That is, the smaller numbers of the well characterized patients as opposed to huge open-label trials that enroll hundreds or thousands of patients and, yet, are difficult to draw any types of significant inferences from.

I think that we talked a little bit this morning about strengthening the length of clinical inference and, a few minutes ago, the idea of how studies and data fit together as a package. I do believe this may turn out to be one of the most effective ways to move forward, increasing the overall efficiency of the development program in terms of having to get away from the assumption

that all indications are going to require, for instance, two trials; having a better way of getting more useful data about resistant indications, etc.; allowing us perhaps as well to use susceptible organisms as well as resistant organisms for resistance claims.

I think all those are probably possible. They have the advantage that although there may be unresolved scientific issues, they do not require any kind of change in our formal regulations or certainly statute. These are the kinds of things that are all possible to do, and I think that is one of the reasons to probably really be thinking about them. These are things we can do now. These are things we don't have to wait for additional legislation. The consequences of the above, hopefully, will be a way to move products along faster. There will be some circumstances in which uncertainty may be greater than we are customarily used to, and that is something we have to learn how to deal with and it is something that at one level we are going to have to accept with regards to certain new products.

That is nothing new. Certainly, what we knew about products for HIV when they were approved

was much less than we are commonly used to, and we were able to live with that even though there were some significant toxicities associated with that because of the benefits. Again, if we are able to identify products that are offering genuine added value, the issues of unexpected or untoward safety events will be more easily dealt with than in situations where the product really represents little change from what is already available.

[Slide]

As far as some of the scientific issues, we have been through these in a lot of detail and there are still some issues, for instance, sometimes in definitions of resistance. When we were talking about the list this morning we touched upon the clinical importance of some resistant isolates. This is important because there will be times when a resistant isolate, although its clinical importance may be limited from a business point of view, may be very attractive for industry because a large number of patients may, in fact, have infections due to that, or the organism may occur in situations and indications that are attractive to develop and, truthfully, MRSP is a good example since it occurs in upper respiratory

infections which are attractive for many companies in terms of developing new products. So, it is important to think carefully about the implications of making decisions about the importance of such isolates.

Finally, you know, is the use of preclinical and early clinical trial data in combination, I think again we have touched on that a lot. We may need at some point need to really start thinking about the details of this but I think we have made a reasonable start in that direction. Again, these are all things that are possible to deal with. We certainly don't need any additional legislative authority to move ahead.

[Slide]

There are some limits to our authority that are worth mentioning. Remember, obviously FDA can't develop a drug. We obviously depend upon industry. That is one of the reasons for having meetings like this so we can have a dialogue and learn what the concerns are from industry; see what the issues are in terms of moving forward. That is why it is extremely valuable, for instance, that the Infectious Disease Society participate so we get a broader perspective.

As I said before, new types of exclusivity such as wild card exclusivity would require new legislation. Finally, in preparation for David Cochetto's comments, just a reminder that promotional claims are derived from statements in the labeling. So, we always try to be careful in terms of what is put in the labeling because if it is put in any section of the labeling it can still be promoted. That is not to say that companies are out there constantly advertising things that have no relationship to anything, but it is not to say that that has never occurred either. So, we are always very sensitive about that even though it is helpful for us to hear what types of changes and labeling approaches would be of most value.

DR. EDWARDS: Thank you very much. Next we will hear from David Cochetto, from PhRMA. David?

PhRMA Presentation

DR. COCHETTO: Thanks for the invitation to join you today. I appreciate everyone taking the time to come to this workshop. I think it has certainly been helpful so far and I look forward to the remainder of the discussion.

[Slide]

I am David Cochetto. I am in regulatory affairs at GlaxoSmithKline, and have been part of the antibiotic working group in PhRMA for several years.

I will try to condense a number of my remarks since I think we have touched on many of these things over the course of the morning session and certainly Dr. Goldberger just hit on many things that I can mention, which is good and healthy because it basically shows we really are largely on the same page in terms of the issues that we are facing with antibiotics development.

We all recognize, as has been said numerous times, that there are a number of no-brainer target pathogens of public health importance for which medical need clearly exists. I think within the industry, those of us who work in that sector, recognize and struggle with the fact that discovery and development of new antibiotics are at a competitive disadvantage in an R&D portfolio.

[Slide]

I will just say a couple of words about that. Why exactly are new antibiotics at a disadvantage in R&D portfolios? We have touched on

these already today as well. Certainly, most antibiotics are used for limited durations of treatment as opposed to a number of other pharmacologic classes. Prescribers are certainly increasingly trying to avoid non-essential use of antibiotics to decrease selection pressure for resistance and certainly decrease cost of care. From a commercial perspective, the growth of the antibiotics market value is considerably below the average growth of other classes of prescription drugs currently. And, there are declining prescription volumes for antibiotics.

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To the last point, I thought I would just show you some data that we track within our company. This is just one straightforward way to look at the last five years of the prescription antibiotic market in three major regions of the world, the U.S., Europe and Japan. Basically, if you index back to 1997 as a level of 100 in all three regions there is approximately a ten percent decline in prescription volumes for antibiotics. While that is healthy, in a number of respects it is discouraging to some of our companies from a commercial perspective and that creates some of the

tension that we struggle with.

[Slide]

What can be done to position antibiotics more favorably in R&D portfolios? A number of us have touched on incentives over the course of the morning, but basically you can consider incentives in two large pots, if you will. On the cost side of incentives, we have talked about looking for ways to try to increase the efficiency of development of antibiotics since ways to increase efficiency would obviously reduce cost of development. Certainly, ways of leveraging information to reduce numbers of trials, leveraging non-clinical and early clinical data, as Dr. Goldberger just said, can be helpful tools in increasing our efficiency.

The other side of the equation is the return side. I think several of us have used various terms for this over the course of the morning. Things that occur on the return side of the equation are things that from an industry perspective would reduce uncertainty in development and lead to solidification of the sense of return on R&D investment in various drugs. I think today's workshop is actually quite helpful in that

regard because it demonstrates to industry that there is a receptive environment for these products. Both the medical community and health regulatory authorities are here today, speaking about the degree of medical need for a variety of products in this area.

Dr. Goldberger has just walked folks through the application of a number of current regulatory incentives. Within our company we have experience using all of these. There are a number of companies here that have experience as well with Subpart E, Subpart H, fast track designations and priority reviews. There is actually fairly substantial regulatory literature on these things. Suffice it to say, they have been helpful in speeding development of drugs in a number of classes and providing useful incentives, particularly where you can put multiple programs together so that during the IND phase, for example, you have a fast track designation and you leverage Subpart E. Then, in the NDA phase you may be able to leverage both Subpart H and priority review. So, combining these programs can actually be quite powerful. We have touched on a number of aspects of clarifying achievable labeling, and I will say

some more about that.

[Slide]

Market exclusivity--I won't say much about this. Dr. Goldberger has already pointed out that clearly it would require legislation. That is not my forte or the forte of individuals in this room. In terms of extension of exclusivity, I would certainly agree. I think there is pretty clear industry consensus that so-called wild card exclusivity would be very appealing and that would be relatively easy to justify, frankly, compared with a number of other incentives.

[Slide]

Let's turn to the potential role of a guidance because I think development of a guidance is something that actually is within the purview of this particular group and, as has already been said, is something that the Division can work within FDA to move forward without the need for any new legislation or any new regulation. FDA's history on development of guidance, from my perspective, is actually very good.

[Slide]

There are dozens and dozens of guidances on many, many disease states, certainly not just in

infectious disease. Guidance is tricky in that guidance is guidance. Guidance is very clear in that it represents FDA's best thinking at that point in time, and certainly the burden is on the sponsor organization to check in with FDA on a real-time basis as drugs come forward, potential drugs come forward, to assure that any more contemporary thinking beyond draft guidance or current guidance is incorporated into the sponsor's thinking. As I said, there is a whole range of guidances and many of them I think have really been very, very valuable for development.

There is not a current guidance that explicitly addresses development of antibacterials for treatment of resistant pathogens. I know the Division is interested and, in fact, has probably started in this direction. The bottom line of the value of a guidance is that it would reduce uncertainty in the minds of sponsors. Clearly, it would not be a guarantee but would reduce uncertainty to some extent around things like regulatory expectations; the degree of investment needed to work in the area. It would be one gauge of the degree of interest in the medical scientific community in moving the area forward and,

hopefully, could provide a certain degree of transparency regarding labeling expectations and potentially Phase IV activities, particularly in a Subpart H kind of paradigm.

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I have touched on these points already. I think Dr. Goldberger as well has. I am basically just reiterating that a guidance can certainly be an incentive to sponsor organizations so I won't go further into that.

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Let me switch to my final series of points really around the potential to address in a labeling guidance a hierarchy of medical scientific evidence that could potentially be translated into a hierarchy of labeling looking across the microbiology section, clinical pharmacology section, indications, obviously adverse reactions and other components of labeling. Mark is absolutely right that labeling translates into the company's claims about the product that can be communicated in other forms of labeling and certainly product advertising as well. So, that clearly states why it is important to sponsor organizations. Labeling has been used historically

as a tool to provide incentives for other classes of drug development.

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I think the question for many of us to think about is what is our view about that. Would we support inclusion in FDA guidance of some hierarchy of labeling outcomes based on a hierarchy of evidence of activity and efficacy against resistant pathogens as outlined in some scenarios?

[Slide]

These three scenarios I have given you represent extremes of a spectrum in a sense. They are certainly not all-inclusive by any means, and actually they have all been discussed essentially already in the dialogue this morning.

The first scenario is on the limited evidence end of the spectrum where the sponsor organization has data on in vitro susceptible clinical isolates to the antibiotic, and performance of those clinical isolates with other antibiotics as well.

[Slide]

In fact, currently it is the case that such data are presented in the microbiology section of labeling, typically under the statement that I

am showing here in quotes, that the following in vitro data are available but their clinical significance is unknown. The effectiveness of drug X in treating clinical infections due to these organisms has not been established in adequate and well-controlled trials. So, there is some effort to put the in vitro data in perspective, that clearly there have not been substantial clinical trials conducted; the data are what they are with their limitations.

[Slide]

A step up from that, in a sense, could be to supplement in vitro data by various PK/PD information where the sponsor would present data demonstrating a PK/PD relationship in humans that is applicable to the resistant pathogen of interest, hopefully, thereby showing a reasonable likelihood of clinical benefit in patients with the infection due to the resistant pathogen. For example, the mean serum drug concentrations associated with benefit in an appropriate animal model are, in fact, achievable in humans with a particular dosage regimen.

[Slide]

One of the possibilities--essentially I

have mirrored the kind of language that was attained in the ciprofloxacin labeling for post-exposure treatment of inhalational anthrax, in the paragraph in the middle. Again, I think this is an extension of some discussions this morning where the key phrases would be that drug X has been shown to be active against pathogen Z both in vitro and by use of serum drug concentrations as a surrogate marker.

In the final, the yellow phrases, that serum concentrations of drug X over time in humans serve as a surrogate endpoint that is reasonably likely to predict clinical benefit and provide the basis for this indication. Direct evidence of clinical efficacy is not yet available.

So, I think part of the discussion we should have is are there situations where actually obtaining that direct evidence in clinical trials could reasonably be pursued following an initial approval for this limited indication.

[Slide]

The final scenario is, in part, one that has been done for a few compounds where clinical efficacy is demonstrated. We began a conversation in February, and Mark just alluded to the potential

to show clinical efficacy of a drug in a reasonably small number of well characterized cases with an infection due to a particular resistant pathogen, probably recruited into a catch-all type of protocol. We have had some discussion, and I suspect we will have more discussion about the appropriateness of pooling evidence across multiple relevant body sites, hopefully, with supporting PK/PD information. That type of scenario would probably lead to the broadest type of labeling statement where there is explicit language in labeling around the clinical indication that is sought due to that particular pathogen.

[Slide]

In summary, I think we have recognized that antibiotics are disadvantaged currently in an R&D portfolio. Regulatory incentives and other incentives are needed to stimulate continued investment in this area, particularly for drug resistant pathogens. Wild card exclusivity and new guidance would provide incentives to the extent that they are both marketing, commercial incentives, and a new guidance would be an incentive in terms of reducing uncertainty in the area.

Clearly, durable medical interest in this field in the development of new antibiotics is in itself, in my view, a very important incentive and to the extent that the agency, PhRMA, IDSA and other professional bodies continue to focus on this topic, I think that alone will foster increased discussion within pharmaceutical companies for taking harder looks at these targets.

Let me stop there, Dr. Edwards, and turn to Dr. Tally.

DR. EDWARDS: Thank you very much. Dr. Tally?

Biotech Presentation

DR. TALLY: Looking at incentives is kind of trying to think out of the box from a biotech point of view.

[Slide]

Big PhRMA already has adequate funding from large portfolios of marketed products and they are able to pick and choose and have the resources. We have heard that antibiotics have to fight for those resources but there are a lot of people sitting around the table that have been very successful in getting those funds. What we are hearing is that more of the antibacterial units are

actually being spun out. So, I think we are going to have a lot of company out in the biotech area in developing antimicrobial agents.

We have a different set of issues. We have to go out and raise money and we have to do it in very difficult times. So, there are a number of incentives that may be developed to allow companies in the biotech sector to access more funds. I think we have talked about expanded access in which you have a drug that you know is working in an area and you can have expanded access so there will be some money coming in to the company. We have already talked about the expedited review and patent-term extension has been talked about. You have the Waxman-Hatch Act and there are others.

But I think what we can do is also look at some funded consortiums. The model is in cancer and AIDS. There is a lot of government money put into these to establish investigators with different groups. In cancer there are a number of these groups which facilitate doing the clinical trials.

When we were looking to think out of the box I got the legal counsel involved and our CFO involved, and they came up with the idea of getting

loans. Right now, the biotech industry, if you go for a loan to a funding agency you are at very high risk. If the pharmaceutical company goes you are not a high risk. So, a biotech company has to pay a lot of money to get a loan from a private bank.

Well, there are government projects, loans or government guarantied loans out there, and there were two models that were brought forward. Probably one of the most successful models is the model to induce home ownership, which was determined a number of years ago to be a very good thing for the American economy. The government then formed a couple of companies called Fannie Mae and Freddie Mac. What this did was guarantee low loans, or actually loans to returning servicemen at no interest rates. That prompted tremendous home ownership, which in the United States runs upwards of 70 percent. That same thing was actually done in England to increase home ownership about 15 or 20 years ago through another loan process.

So, it worked. What did it do? It stimulated the economy, more home building. It increased people's pride in their homes and really is one of the engines that has driven our economy. Can this type of program be put together where

biotech companies can go and get a low interest loan to carry out their clinical programs?

There is actually another model out there. It is called small business loans. But most biotech companies that have a drug that they are bringing into development are much too big to qualify for that particular type of loan. But since the model is already out there I think it can be talked about. Both of these would take, obviously, legislative approval to do it, and the guarantied loan is, of course, repayable upon commercialization of the agent that you are going out for. So, that is one of the areas I think we could work on from a biotech view. I know the bio group is looking into legislation for some of these.

[Slide]

There are three other areas I think that the biotech can look at. One is tax credits or deductions. Right now in the United States it is only valuable to profitable companies. Most biotech companies have been losing money for years and having to go into the public market.

There are two things that can be done with tax credits. The first one is to extend the period

for tax loss carried forward. That would make a company that is about to bring a drug onto the marketplace be able to become profitable quicker by applying those types of carried forward tax losses. Right now the limit is seven years. It is about as long as it takes you to develop a drug so just when you have the drug your tax credits drop off the precipice and they are not worth anything. So, that could be one legislative thing.

The other is transferable tax losses. There are such laws in Europe and in Canada where a company that is not profitable can sell their tax losses to another profitable company at a discount rate to raise money that way. This would take a legislative move in the United States also but it is something that I think bio is working on right now with.

We know there are targeted grants out there. SBIRs, I am sure most biotech companies have them. We have talked about CRADAS at the inter-agency task force meeting about a year ago, but the problem with CRADAS is that the companies lose control and it takes forever to get them approved and you can't keep up with your time line. So, I think we looked at CRADAS for funding Phase I

and II studies. We need to streamline the process and not lose total control of how to conduct these.

Finally, my legal counsel threw out that maybe the government can give rebates on successfully completed studies, but if I get a successfully completed study I can go out and raise money and probably don't need the rebate with it.

These two slides are just trying to think out of the box on some of the different ways that the biotech industry would look at getting incentives to continue the drug development in times of short cash. Thank you.

Discussion

DR. EDWARDS: I want to thank all three speakers for thoughtful and very nice discussions in this area. We have a few minutes to open the issue up for discussion. Does anyone have a comment they would like to start with?

DR. POWERS: Can I ask a question, Jack?

DR. EDWARDS: Yes.

DR. POWERS: Dave, could I ask you a question about some of the proposals you put up on your slides? One of the things I think we heard a couple of times this morning was the idea that eventually clinicians would like to see how the

drug performs in people and get that clinical data, which was the third proposal of your three things. I am just asking this as a question, if a company were to get in their label that the drug has activity in vitro and it goes on the microbiologic list, is that a disincentive for the company then to pursue getting that clinical data down the line? In other words, one could imagine that a pharmaceutical representative walks into a doctor's office and says our drug has "activity" against this pathogen, which might then be perceived by the clinician as this drug works in clinical disease. So, is it a disincentive then to get that future clinical data from patients?

DR. COCHETTO: I will comment and with my two colleagues on the right we represent three companies and they may want to comment. I guess there are two things I can say about that. On the one hand, I suspect it is not a disincentive to have that in labeling because at the same time I am pursuing that, for example, on a GSK product Richard is pursuing it at Merck, in an ideal world, and Roger is pursuing it at BMS, and a number of other companies, and ultimately I think we are probably also all pursuing clinical evidence. So,

in that type of step-wise progression I don't think it is a disincentive in that I think we would want to be moving forward. Recognize that the ability to really impact practitioners based on in vitro data alone is going to be somewhat limited. Although it is helpful in an arena where probably there aren't very many therapeutic choices, ultimately the clinical data is what is going to be more impactful. That is one comment.

The second comment is that to some extent it depends on some of the regulatory mechanics. I mean, if that target pathogen were sufficiently important that the sponsor and the agency were willing to engage in trying to move that registration sooner in time, one of the ways that could be done is to look at the Subpart H provisions where delivery of a certain amount of clinical evidence would actually have to be presented as confirmatory data.

Those are two comments. I don't know if you, gentlemen, have others.

DR. ECHOLS: Actually, I think it can be controlled, I mean, either as a Phase IV commitment to provide clinically relevant data and failure to do that would result in removal of the information

from the in vitro section. I mean, there is an appropriate stick to go along with the carrot. If it is just in the microbiology label you can talk about it to physicians or point it out to physicians but you can't use print promotion or something like that.

I think your point is a very good one because initially when you said that I was thinking, boy, my marketing people, they could use that. They could say, you know, well, in vitro it is 100 percent effective and in the clinic it may only be 50 percent effective, and they say we don't want the clinical data in the label. But I think there are ways to control that.

DR. GESSER: I agree with everything that has been said and I think the issue is really what you are hoping to accomplish with that information and how you want to manage it. If there is value in having that information in a preliminary state, then you want to manage how that information is going to be disseminated and I think that is the responsibility that the sponsor and regulatory agencies work together on. Even though we sit at this table together, I think competition is a large component of what we do as well.

DR. EDWARDS: I would like to make a summary statement for the moment and then ask the IDSA people to comment. Dr. Goldberger very beautifully described what the mechanisms are for incentive development that exist currently. I will take the prerogative to say that much of what we are talking about this morning and will continue to talk about is a way to leverage those to the absolute maximum.

However, I believe they are failing for the most part, those that exist at the present time, as we are each day hearing of a new sort of withdrawal from activity in this area. Actually, today is where we are at a point where we have heard rumors, although nothing published, of another major pharmaceutical company leaving anti-infectives, and there was a very interesting address in "The Washington Post" yesterday about the critical nature of this issue that touches on anti-infectives as well.

It seems to me that the discussion that we are having now really is more focused towards a more sort of global approach to the incentive which involves legislation changes. Before actually asking the IDSA folks about this, I would like to

ask both David and Frank what would be the most powerful incentive, or if they can in some way rank order for us some incentives at this moment that would really make a difference and stop what we perceive as a very dangerous trend that is occurring at the present time. David, could you comment on that?

DR. COCHETTO: I am just huddling with my two colleagues here, to the right. We have a consensus of three companies anyway, and I suspect it would be a broader consensus that probably at the top of that list would be so-called wild card exclusivity which, obviously, would require legislation.

Beyond that, Roger's group and the group that I am part of work in the HIV area as well. My own perspective is that, as Frank mentioned, the idea of funded consortium has certainly been leveraged to the advantage of the HIV community. I can't speak from personal experience about the oncology area but certainly in the HIV area I would support that proposal.

I actually, personally, do not dismiss the things that are within the reach of this group. I do think talking further about the regulatory

approaches that Dr. Goldberger summarized does have merit. I don't think we have fully explored the limits of what could be achieved through those. To go back to some of his remarks, I think our experience has been that those programs are really quite flexible and, depending on the sponsor and the Division's creativity, I think there is more that could be achieved through those existing programs. I think a guidance could build further on that. I will stop there.

DR. EDWARDS: Frank?

DR. TALLY: The wild card exclusivity for a biotech company with one or two products would not be a major advantage for a biotech company, but I would say an exclusivity like that--you could apply it to that one drug if you could get it for that one drug. So, I put that at the top also. For biotech companies, and it sounds like we are going to be joined by more companies coming out of PhRMA--

DR. COCHETTO: Sorry, Frank, before you leave wild card exclusivity, one of the ideas floating around is that if you developed a product in this area you would obtain the wild card. So, part of your licensure agreement, if you were

partnering with another company for your product distribution, would be that you could trade that to another organization.

[Laughter]

DR. TALLY: That would be an incredible advantage for a biotech company. I wasn't even thinking along those lines. I would be. But for biotech companies it is the need to raise inexpensive money. So, I think the transfer of tax credits and the government guarantied loans may be the area where you can raise funds to carry out and be able to supplement the funds that you have.

We have just borrowed six million dollars from a bank and we have to leave three million in escrow, believe it or not, because we are a high risk company. If you had a Fannie Mae or Freddie Mac loan you would have the whole six million.

DR. GOLDBERGER: Can we write you a letter of recommendation?

[Laughter]

DR. TALLY: So, that is one of the problems with high risk companies but I think there are ways to build those in. But I think everything we have been talking about today goes right along with all the incentives that we have with

streamlining the development by this dialogue we are having over these two days.

DR. EDWARDS: Realizing how difficult a question this is for the IDSA current president and current past president, would you reflect on the incentive issues because really we have talked about all of them and they are going to require some sort of legislative activity?

DR. SCHELD: Well, I am not surprised that wild card exclusivity is appealing. I certainly would feel the same way if I was in the shoes of the individuals around you, Jack. I don't know, and I doubt that anybody over here, except perhaps George, knows enough about all of the regulatory provisions that we have gone over this afternoon to know how you would choose among all of them and prioritize them, but it seemed to me from the things that Frank brought up that the funding consortium, as we watch how ACTG works and others, as well as the Fannie Mae, Freddie Mac paradigm, have a lot of appeal. I think if they need the help and the backing of the ID community to try and put some of those things through, we would like to talk about it.

DR. GILBERT: Just to amplify, I agree

with what was just said and we have a public policy committee of the IDSA and we have an antimicrobial use committee. Advocacy is one of our prime strategic objectives. We feel that the impending shortage of crucial drugs is terribly important. That is why we are here. So, I think we just need to be educated in this prioritization. That is key. I mean, if we are going to help advocate if this comes to legislation, we need to have the colleagues who are members of IDSA but also work in the pharmaceutical industry help us with that advocacy.

DR. EDWARDS: I would just make a comment from the perspective of the public policy committee. I really think that we need to begin thinking about the issues regarding exclusivity as attainable goals in terms of changing the legislation. This meeting is very helpful to us in order to develop strategies to carry that notion forward, that is ultimately changing legislation, and we need every piece of background we can get because attaining those goals will not be easy. There is absolutely no question about that.

DR. GILBERT: Jack, I am sure you agree that we ought to maximize everything that Dr.

Goldberger outlined because the legislative process is going to take a while, even if one is going to be successful.

DR. EDWARDS: Absolutely. Obviously, there is a lot of room for maximization within that area. David, I was very happy to hear you comment positively regarding the room we still have available in the structure that does exist at the present time. Roger, you were going to make a comment?

DR. ECHOLS: When FDAMA went through the legislature and pediatric exclusivity became law, I can't think of anything that has had a greater impact on big PhRMA at least in terms of orienting people to do specific tasks. It was just incredibly powerful. It was as close to a no-brainer, no need for discussion decision-making process that I have ever seen. Again, I am just not sure that IDSA or even FDA is aware of how impactful that was.

It is a dangerous thing too because I think once the issue of patent exclusivity is out in the media there are also those who want to take shots at that and don't necessarily understand all the rhyme or reason. Even if IDSA and FDA

supported it, I am not sure how viable it would be in the legislation but I just want to make sure people know how powerful a tool that was to really make things happen.

DR. EDWARDS: Yes, Dave?

DR. GILBERT: Mike and I are sharing our angst, which is mostly out of ignorance. I guess I don't understand why we are pushing or why a lot of folks are attracted--you are not pushing but why you are attracted to the wild card exclusivity. You are saying the pediatric exclusivity was so successful so why not exclusivity for a new drug active against one of the resistant organisms on the hit list? It just seems like the political flack is going to be unbelievable. If I am swapping exclusivity, you know, for a hypertension drug versus an antimicrobial--

DR. ECHOLS: First of all, the pediatric exclusivity was sort of tacked on the big money makers. So, the drugs that we are talking about now for niche needs are not going to be big money makers in and of themselves, otherwise we wouldn't need incentives. The incentive for pediatric exclusivity was to do clinical trials and provide PK data in children where there was really no

return on investment necessary. There was a drug that got pediatric exclusivity I think for cholesterol lowering. I mean, that is not a big market in kids. But the incentive to do that was without a thought because the drug already was a block buster.

But we are not talking about block busters. But I could foresee, you know, to developing a drug for tuberculosis which, to my knowledge, no one in big PhRMA is really looking at actively, but if there was a wild card attached to developing a new drug for tuberculosis and you got six-month exclusivity on the drug of your choice, that would be a pretty big incentive.

DR. GESSER: It just allows for a redistribution of the focus of resources within a company. As I said, antibiotics are at a disadvantage relative to other products and that is why it was such a simple response, because the value of those other products is greater.

DR. DERESINSKI: My guess is that what David is concerned about is the potential PR aspect, and I think that the answer is that this requires an educational program for the public to understand that we have a looming disaster and that

this is a means of dealing with it.

DR. ECHOLS: If the impetus for this came from the IDSA and the FDA with really no lobbying on the part of industry, that could present a very different picture than if industry was trying to lobby for it, and I am not aware that anybody is. The first time I thought of wild card was an idea that Mark Goldberger gave me many years ago when we were talking about TB in a public forum.

DR. SCHELD: I don't think we should lose sight also of the possibility for funded consortia. That has a lot of appeal because fundamentally the members of the IDSA, many of them, work in groups of that nature and try to get new scientific information out there while, at the same time, addressing an important public health problem. I would be willing to say that antimicrobial resistance is in the same order of magnitude as HIV and some of the other diseases we have talked about today. We already brought up TB and we might as well think about antimalarials. There may be a way of addressing it that way through the membership of the IDSA which has considerable expertise in approaching NIH and other funding agencies about this type of issue.

DR. EDWARDS: We would have the same sort of potential with not only the funded consortium but also the SBIRs and the CRADAS perhaps in making those more user friendly to industry.

DR. SCHELD: I am very familiar actually personally with SBIR and STTR. I think probably most small biotechs have been very aggressive in approaching that mechanism for funding. I don't know much about CRADAS and I would like to know more, and maybe this will be a side bar conversation I will have with Frank.

DR. EDWARDS: Well, this was a very interesting discussion with some great ideas. There is I think a bit of a call for a challenge to some of us interested in this, particularly from the IDSA standpoint. Unfortunately, we are going to have to leave this part of the discussion at this time but I hope that outside of the meeting we will have a chance to pursue this much further. I am now going to turn to the issues regarding non-inferiority margins in clinical trials. We are a little bit behind time but I think we are going to catch up. We need to just start right off with George Talbot, who will begin this very interesting discussion.

Issues Regarding Non-Inferiority Margins in Clinical Trials - IDSA Presentation

DR. TALBOT: Thank you, Mr. Chairman and Dr. Goldberger. Thank you for the opportunity to speak today, and Dr. Gilbert who is now absent, thank you as well.

[Slide]

I agree with the chairman that the last session was extremely interesting but I have to say that even though I am an ex-clinician, my remaining clinical acumen detected a slight waning in the electric current throughout the room here, the onset of a certain lassitude, at least in some members of the audience. I wish Dr. Wenzel were here because he could have perhaps taught us something about the attributable lassitude in the room. I was trying to think this through and some of it certainly could be postprandial letdown and that is probably a fairly sizeable amount of the lassitude, but some of it probably is the thought why in the world do we have to talk about delta again. I think our chairman indicated that maybe we should talk about delta a little bit more quickly than we were planning to, to begin with. With that in mind, I will try to speed things

along.

[Slide]

I will start with describing for you the approach I will take in this discussion. First of all I am going to identify some questions on delta-related issues which are relevant to clinicians. By way of a Q&A type session, I am going to provide some answers and possible solutions to these questions including, in particular, information that clinicians would find useful with regard to this issue, and also how this information could be made available.

I want to warn you right off that what I am not going to tell you is what the delta should be for each indication. So, don't get too excited just yet because I think we will have a chance to talk about it. The other thing you may be wondering is why in the world I am talking about this, of what interest it is to clinicians. I happen to be able to blame Dr. Powers for this because when I spoke with him about what I should address in my topics today he said, well, tell us what clinicians think about these things and I did, in fact, make an attempt to validate some of these points with my current clinician colleagues at

IDSA.

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By way of background, since this is the first discussion of this session I thought I should mention a little bit about delta-1 and delta-2, and I would like to thank Dr. Powers again for clarifying some of these concepts in an excellent presentation at ICAAC. Others, including Drs. Temple and Ellenberg, have written about this eloquently.

A delta-1 is the estimate of the advantage of a standard therapy over placebo. Delta-2 is generally what we have been concerned about in the February meetings as well a little bit today, and that is the maximum acceptable loss of efficacy of a new therapy over the standard therapy. So, when we are talking about the delta we picked for HAP we are talking about what is the maximum acceptable loss of efficacy for the new drug over the standard.

For any given indication delta-1 is usually determined from historical data. I say usually because in anti-infectives there is not a placebo arm. Delta-2, which has been a somewhat more contentious area, is ideally set only by

clinical judgment. That is, what amount would we be willing to give up in terms of efficacy but there are substantial pragmatic considerations, specifically sample size.

[Slide]

Here is the first of my clinician queries. I sort of toned this down because what I really wanted to say is, you know, "what the hell are delta-1 and delta-2?" I thought about "what the heck are delta-1 and delta-2" but I trimmed it down to this for public consumption. I think it really is an important question. I mean clinicians don't necessarily understand these comments and they may think why do I even need to know about them? Why are these relevant? After all, FDA is approving a drug, therefore, it must be good enough for me to use for my patients.

I think the answers to these things are several-fold. First of all, informed clinicians, those here today and others, are aware that these two concepts dramatically affect both the availability and the risk-benefit of new antimicrobials. These are key concepts driving what drug companies study, how they study them and what regulators can or cannot give us. So, I would

submit to you that further user education about deltas is important. The goal there is to disseminate knowledge to these users to improve treatment decisions.

With regard to delta-1, it is a question of, well, how does this new therapy stack up relative to placebo? For delta-2 it is if I use this new drug, how much loss am I potentially having here over what I would have used otherwise.

[Slide]

Query two, in what infections is the efficacy of antimicrobial therapy no better than that of a placebo? Would that be true for ABECB? For acute bacterial sinusitis? I would like to know because I have been prescribing these drugs based on the premise that they have activity and they help. If they don't, I would like to know that.

So, I think that clinicians, if they thought about it, would want information from placebo-controlled studies of self-resolving infections. The goals here would be to better define delta-1 for a given indication such as those mentioned, and also specifically to improve patient care by defining when antimicrobials confer no

benefit.

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Of course, in taking such an approach one has to mention that placebo-controlled studies of antimicrobial therapy must include several aspects, first of all and foremost, patient safeguards so that in any of these indications that I mentioned certainly there would have to be no risk of serious sequelae if antimicrobial treatment was delayed or omitted.

Another important issue with respect to definition of delta-1 is what are your clinical endpoints going to be. I would submit that time to symptom resolution is a valid endpoint, as much as cure is. This is something that I discussed with John prior to today's meeting.

Finally, any studies to elucidate delta-1 or the advantage of a new therapy over placebo have to address relevant patient and disease subpopulations, really what clinicians are going to see in practice because if the studies don't look at those patient populations the results are going to be meaningless because the clinician is always going to be tempted to say, yes, I know about that study but my judgment and my experience for my

patient means I should give the antibiotic anyway.

[Slide]

Another important point, which Lou Rice actually made me think about, is reflected here. I would like to be confident that a new antibiotic for severe infections isn't meaningfully less effective than what I already prescribe. I am sort of assuming that FDA is taking care of that but how is "meaningfully" defined for approved drugs? Where would I find that information and how would I know?

That raises the question of whether the label should communicate to some extent the level of statistical confidence in the results of the studies leading to FDA approval. I looked through a few of the recent labels and I think there is one antifungal where there was a point estimate and confidence interval given, but for the antibacterials there were point estimates given of response rates but no confidence intervals and nothing about how the trial was sized and the type of benefit that could be assured. So, that is a question that I would pose to the group.

[Slide]

Ah, the delta! A clinician might ask

should the new antimicrobial always have to pass the delta hurdle to garner an FDA approval. It is my opinion, and not the IDSA membership's opinion necessarily but it is my opinion that this hurdle shouldn't necessarily have to be surmounted for the situation of the streamlined development program for an acute unmet medical need, for example, specific multi-drug resistant pathogens. I think the analogy there also might be the anthrax example mentioned previously. There may be some situations where the medical need is so great that you don't require that a formal hurdle be achieved.

On the other hand, I think most clinicians would like to have a fair amount of certainty that when a drug undergoes a traditional development program with multiple indications an appropriate delta is applied, or a process is applied, and that that should be feasible given that the goal will be to accrue a robust efficacy and safety database.

[Slide]

That is all fine you say but, as a clinician, what I see is that there is a severe drought of information on utility of new antimicrobials in many of the most clinically concerning indications. It is not clear to me, as

a clinician, why this is. I mean, it is clear that there is a medical need; why are there no data?

I think partly this is due to an indirect relationship between infection-related morbidity, on the one hand, which is what concerns clinicians, and the feasibility of subject recruitment into clinical trials.

[Slide]

I have tried in a totally non-scientific way to illustrate this on this slide. If you look across the top, I have illustrated recruitment in the non-quantitative terms of easy, moderate and difficult. On the left side I have mentioned patient morbidity as high, medium and low. You could try to attach mortality rates on the left side and say that low is less than 5 percent, medium is 6-15 and high is above that. I am sure you could also apply some metrics to the top row.

I sat down and I tried to fill this in and, if you look over here, I really couldn't come up with any indications which are easy to recruit and inexpensive to recruit but had a high morbidity. Similarly, there aren't too many that are difficult to recruit but have a low morbidity. Most of them fall into this axis right here,

ranging from something like uncomplicated skin and skin structure infection, on the lower left side, up to these problem indications, on the right.

[Slide]

So, what are the problem indications? I think, and my colleagues here today agree, these are really among the most clinically concerning infections and, yet, here exactly is where there is difficult recruitment but with the problem of high morbidity and mortality--endocarditis, meningitis, osteo, some types of invasive fungal infection, resistant pathogens, HAP to some extent, and a number of the pediatric problematic infectious diseases. So, here are indications where data are needed but it is not coming.

[Slide]

As a clinician, you might take a pragmatic approach that for these problem infections isn't it better to have some clinically meaningful information rather than none, and have it sooner rather than later. I mean, give me something that has been vetted by an independent scientific body like the FDA, and let me know about it in that context so I can have that information to help me guide treatment decisions when no other information

is available.

[Slide]

So, the question that arises is why not provide information on just bacteriologic endpoints for these problem infections? This data is useful--clearance of bacteremia, for example; clearance of bugs from CSF. There are some limitations but that would be useful. I think that is true but, indeed, the limitations should be highlighted. Specifically, as we mentioned, if you look at just microbiologic endpoints there will be limitations on what you can deduce from corresponding clinical endpoints. These may be insufficient for FDA to conclude effectiveness using what I understand to be the regulatory definitions thereof. This is because there will be low power to detect drug-disease and drug-patient interactions.

I want to highlight here one key assumption in talking about this, that is that bacterial eradication at this point is not a validated surrogate endpoint. I think we will hear more about that tomorrow in meningitis. Clearly, with clearance of bacteremia there are some questions about that. Clinicians think it is a

pretty good endpoint but maybe regulators would think that is not validated.

[Slide]

If that is true and we have this construct, how can FDA and industry increase the availability of clinically relevant information on those five or six problem indications that I described a moment ago? Let me take the example of acute bacterial meningitis. That has to be one of the most problematic indications for a clinician, and I think it is one where there is truly a dearth of relevant information for new drugs. What if we chose, instead of looking at clinical outcome which would require hundreds of patients with a small delta, to look at the effect of a new antimicrobial on CSF bacterial load?

[Slide]

The suggestion that we would come up with is to do just that, look at that endpoint and add the results of studies on this endpoint to the clinical study section of the label. Now, certainly maybe it should go somewhere else. Maybe it should go in the indications and usage, but I picked the clinical studies section for reasons we could go into if you want. Certainly, those data

should be supplemented with available data on clinical endpoints in the same subjects but the context and limitations of those clinical data should be explicitly stated. But the data on bacteriologic endpoints would be in the label and would be there for the customers to use.

I think there is an analogy, a precedent, and that is the in vitro pathogen listing. The relationship between susceptibility is determined by MIC90 and the potential utility of an antibiotic is accepted; it is put in the label. That is a surrogate endpoint, if you will, in a way. What is done though in the label is that it is mentioned that the clinical significance of these findings is unknown.

So, I would think that for an endpoint such as bacterial kill in acute meningitis you could put the data in but indicate the limitations thereof, and mention that the clinical significance is unknown because the delta-driven trials to reach a firm conclusion could not or have not been done.

[Slide]

This information should be added to the clinical studies section only if the results of those studies are consistent with what you know

about the drug otherwise, non-human and clinical PK/PD data. Certainly the effectiveness of the compound should have been demonstrated in other indications, as we talked about earlier. And, certainly there should be non-clinical or clinical data indicating potential safety concern.

[Slide]

Why would this lead to more information becoming available to clinicians? Why would this approach help? Well, my thesis, which my colleagues in industry will have to comment on, is that the ability to place even this amount of information in the label for these problematic indications would encourage the conduct of studies in these indications. There would be something in the label that was scientifically driven, that had been subjected to independent review, that could be discussed by reps, but the limitations of which were clearly defined.

[Slide]

If we try to bring this together into thinking about the delta hurdle, I asked the question when should the delta requirement be applied. I have mentioned already that I feel that there are some situations where it should not be

required, the streamline development program. For a traditional development program, if you have these non-problem indications, the readily studied ones, I would suggest that the delta requirement should be applied, and just what the delta is I know that John and Christy will get to in a few minutes.

For difficult to study indications, if you wanted formal approval of the whole indication then, yes, you have to come up with a delta that is meaningful. If you can use a validated surrogate endpoint, great; use that. If you can't and you have to use clinical endpoints, all right. The difference would be to provide the option of adding just the bacteriologic endpoint data to the clinical studies section, with appropriate caveats and, therefore, hopefully you would get studies in patients with endocarditis, in patients with meningitis and so forth.

[Slide]

In summary, clinicians need and want a variety of things. First is education on delta issues, as I mentioned; information in selected indications from placebo-controlled trials. Most acutely, they want resolution of the information

drought for the most clinically concerning indications. This may mean getting some information rather than none.

Points to consider are that data could be included in the label on bacteriologic endpoints, and the label could also include some information on the confidence of efficacy results for approved indications in a way that would be clinically meaningful. Finally, I think that it would be desirable to have some studies, or at least further discussion about when and if bacteriologic endpoints are valid surrogate markers.

[Slide]

With that, I would like to thank the following people and, hopefully, you will find this a useful contribution to the discussion. Thank you.

DR. EDWARDS: Thank you very much, George. Christy Chuang-Stein will now speak from PhRMA.

PhRMA Presentation

DR. CHUANG-STEIN: Right, I am not here representing IDSA as the slide indicated.

DR. EDWARDS: You are welcome to join us.

[Laughter]

[Slide]

DR. CHUANG-STEIN: I thought about dazzling everyone with very elaborate slides but then I thought I really need your attention during the next 15 minutes so I thought I do not need any distraction. Therefore, that is why we are using black and white slides here.

The antibiotic working group of PhRMA is grateful to have this opportunity to share with you implications and challenges of the non-inferiority margins. We would also like to share with you some thoughts the group has in our joint effort to search for relevant margins.

[Slide]

Consider a clinical trial where a new antibiotic is compared to an approved product. The non-inferiority margin has a dual role. First, through the choice of the use of the margin, we would like to show that the new antibiotic has efficacy better than the placebo, should a placebo be included in a trial. Next, we would like to demonstrate that a new antibiotic has efficacy within a range of the approved product, with the range determined primarily based on clinical considerations.

[Slide]

This non-inferiority margin has a profound impact on the sample size required for a clinical trial. On the next three slides I will show you the impact of the margin.

On this slide we assume that we would like to have a 90 percent probability to declare non-inferiority if the new antibiotic has an identical success rate as the comparator. For illustration purposes, I let the success rate range all the way from 50 percent to 90 percent. On this graph the yellow bar numbers represent the situation where we have five percent as the noon-inferiority margin. The number here represents the number of subjects required for each treatment group. The green bar numbers here represent a situation where the margin is set at 15 percent.

Let's look at a situation where the common identical success rate for the two groups is 80 percent. We will need about 1400 subjects per group if the margin is set at five percent. On the other hand, we will need about 150 subjects per group if the margin is set at 15 percent. You can tell that the sample size obviously varies dramatically as a function of this margin. Also,

as the success rate approaches 50 percent the sample size required goes up. This is because of the variability associated with the binary response getting a little higher as we approach this 50 percent mark.

I would like also to indicate here this sample size. This refers to the number of clinical evaluable subjects per treatment group if clinical outcome is the primary endpoint. So, for some of the situations, especially for five percent, there is no hope of conducting such a large study.

The choice of the power is very much a sponsor's decision. There is no regulatory requirement on whether the power should be 90 percent or 80 percent. But from a sponsor's perspective, we would like to minimize the probability of failing to accept non-inferiority if the new antibiotic actually has an identical success rate as the product that is on the market. On the other hand, if the sponsor is willing to accept a 20 percent risk of erroneously rejecting non-inferiority when the new antibiotic has the identical efficacy as the comparator, we can look at a sample size requirement when the power is dropped to 80 percent.

[Slide]

Notice that it compares to the previous slide. For the 80 percent success rate situation the sample size is getting smaller, roughly about 75 percent of what we had before. But realize this 25 percent saving in sample size is obtained at doubling the risk for the pharmaceutical sponsor. Therefore, as a pharmaceutical sponsor we need to kind of struggle to maintain the balance between sample size and power here. Because of our emphasis, our desire to minimize the risk of erroneously rejecting non-inferiority, 90 percent is not an uncommon choice for power in the pharmaceutical industry.

One question or one comment was raised during the February advisory committee meeting. That is, when a new antibiotic is being developed sometimes the sponsor would hope that a new antibiotic actually is slightly better than the comparator. If that is the case, won't we need a smaller sample size to conduct a study? That is, indeed, the case. If we know that a new antibiotic is slightly better than the comparator then, yes, we have more room to get to a lower bound of the confidence interval.

On the other hand, there are also a lot of situations where a new antibiotic is developed because of an anticipated better safety profile or a more convenient dosing schedule. If that is the case, you know, clinicians or the marketplace are willing to trade a little of the efficacy for a better safety profile, better tolerability or more convenient dosing and administration. If that is the case, what sample size will be required if we know beforehand that a new antibiotic is just slightly less efficacious than the comparator?

[Slide]

On this slide I show some of the sample sizes we will need. This is the case where we anticipate that the new treatment, the new antibiotic is five percent less effective compared to the control. In this particular case, obviously, we wouldn't set the margin at five percent because we are already at a five percent mark. The question is if I set the margin to be 10 or 15 or 20 percent how large a sample size will I need? Again, the sample size here reflects the sample size per group.

I look at the situation where the control success rate is around 80 percent. So, in this

particular case I would have the comparator success rate to be around 80 percent. The new antibiotic is expected or is anticipated to have a success rate around 75 percent. Here we are talking about true success rate. Nobody knows what a true success rate really is, but when we design the study we do all sorts of hypothetical situations trying to maximize our chance for success. So, if I have a scenario where the comparator has a success rate around 80 percent while the new antibiotic is expected to have a success rate around 75 percent I will need a very large sample size, about 1500 per group for a 10 percent margin. I need about 370 per group for a 15 percent margin.

For the 10 percent margin this number is 440 percent that we need should the new antibiotic have the identical success rate as the comparator. For the 15 percent margin, this blue bar, the number is about 240 percent of the anticipated sample size before. So, this is another situation where, if our new antibiotic is expected to be just five percent less than the comparator, it is almost impossible to conduct this study or finish this study in a timely fashion. So, that is something for all of us to chew on, the various scenarios

that the pharmaceutical sponsor needs to face when we are looking at sample size.

[Slide]

Obviously, the choice of the non-inferiority margin is a very difficult one, otherwise we wouldn't be here. As we mentioned earlier, the margin has a dual role because we are comparing the new antibiotic against a comparator, hoping that if we conclude that the new antibiotic is within a range of the comparator we will be able to make the leap of faith that the new antibiotic is also better than placebo. This requires critically the fact that the comparator is better than placebo by at least that amount, that range. Unfortunately, we really do not have much comparative data against placebo. Whatever we have came from the days of a different era. So, we are in this critical information drought in terms of comparative data of the current antibiotics over placebo.

The second challenge we face, as mentioned earlier, is that the margin selection really needs to address the seriousness of the infection as well as the feasibility of conducting the trial. This delta, non-inferiority margin here, is the minimum

of the delta-1 and delta-2 that George talked about. It is really a composite of those two considerations mentioned earlier.

However, we do have opportunities that we cannot ignore. The very fact that we have this forum where the three sides can sit down and address those issues will help us move a step closer to finalizing the draft guidance, including the recommendation on maybe a range of the delta or non-inferiority margin. In selecting or recommending that range of delta, I would like to reiterate the fact that an antibiotic trial has a special feature in the sense that we typically look at multiple endpoints of similar importance in one trial. More than that, we typically have more than one trial to support an indication, and even more than that, we typically study multiple indications for a particular antibiotic. In essence, we have a lot of information packaged together to submit the file to the regulatory agency. We cannot ignore the fact that the information is not coming just from one trial.

[Slide]

To give you one very simple illustration, we have some numbers here and I will go through the

numbers. Here is a situation where we assume the comparator has a cure rate of about 80 percent. We anticipate that the new antibiotic also has a cure rate or success rate of around 80 percent. We would like to have 90 percent power. We set the margin at 15 percent. Based on the sample size chart I showed earlier, we need roughly 150 evaluable subjects per treatment group.

On this line there are two sets of numbers. Underneath the line what I have is the difference in the success rate between the comparator and the new antibiotic. So, it is the comparator minus the new antibiotic. The next value here indicates that the new antibiotic is less efficacious than the comparator, while the positive number here indicates that the new antibiotic has better efficacy than the comparator. On top, here, is the probability that we will conclude non-inferiority when the difference is given by the number below. By design we will have a 90 percent chance to declare non-inferiority if the new antibiotic has identical efficacy as the control. That is the design specification. If the new antibiotic is five percent less in terms of the success rate than the comparator, the chance of

declaring non-inferiority is 58 percent.

Going further down, if the new antibiotic is 10 percent less efficacious than the comparator, that probability drops to 18 percent. Again, by design when we get down to minus 15 percent, here, we have about a 2.5 percent chance to declare non-inferiority. If I have an 18 percent chance to declare non-inferiority when the difference is 10 percent and if I do two studies, the chance that both studies will allow me to declare non-inferiority when the difference is, indeed, 10 percent is no more than 3.2 percent.

So, here we are combining information from two studies. I use the "less than" sign here because a lot of times the conclusion is not based on one single endpoint. We look at a clinically evaluable population. We look at the intent-to-treat population; we look at a modified intent-to-treat population; we look at clinical outcome; we look at micro-outcome; we look at multiple endpoints; we look at multiple analysis population. We want all different kind of analyses to give us a consistent picture before we accept a study as a positive study. So, that is why this "less than" sign is used here.

[Slide]

What are some other thoughts the group has in terms of moving forward? For the design aspect, we were wondering if we are facing serious infections with high mortality and if there is no approved antibiotic for that particular disease whether we can think about conducting another comparative trial, and what we would use as a criterion for when is the lower bound of the confidence interval for that success rate to be exceeding a particular prespecified clinically relevant threshold. Of course, this threshold will have to be decided upon beforehand based on how much we know about the mortality or the failure rate for this particular infection. For this we would basically borrow the paradigm from the oncology area where some of the accelerated approval is based on Phase II non-comparative study results.

The second bullet is related to our current need to conduct global drug development. We do know that in different geographic areas different comparators are being recommended and if we are truly conducting a global development program with different controls being used for

different regions, whether we can design a study where we are comparing the new drug against standard of care, basically we will be pooling data from different regions to come up with a new drug against a standard of care comparison.

The third bullet has been a long debated and heatedly debated issue, the one-sided against two-sided paradigm. The ICH E-9 statistical principle for clinical trials specifically said that a one-sided confidence interval or one-tail testing is consistent with the non-inferiority paradigm. We would like to submit this once more to the agency for consideration. We are talking about the possibility of reducing sample size. For the 80 percent success rate, doing one-sided confidence interval can reduce the sample size by 20 percent. We do think we have a scientific justification, scientific ground for bullet three that can help us reduce the sample size.

Finally, we realize that it is time that we build up our knowledge base regarding the comparative efficacy of our current antibiotics against placebo. How to get that information, how to move forward, I will leave that in the expert hands of our IDSA colleagues. Thank you.

DR. EDWARDS: Thank you very much. John, I am going to take the prerogative, if I may, even though we are not scheduled for a break we are in the seventh inning stretch here, and I would like to take about a five-minute break before we have the final presentation and then what is likely to be a very interesting discussion. I will tell you that we are going to finish at five o'clock within confidence intervals that encompass a very few number of minutes. So, if you would please return within five minutes, that would help us stay on time.

[Brief recess]

DR. EDWARDS: At this time, John Powers, from FDA, will continue on with the last segment of our discussion of the delta issue.

FDA Presentation

DR. POWERS: I was telling Dr. Schentag, behind me, that I blew it; that I put myself at the end of the day for the last talk. Somehow I messed up here.

[Slide]

I think Dr. Talbot brought up this issue of what does this all mean to clinicians, and I was dissuaded from titling this talk "delta: it's all

Greek to me"--

[Laughter]

--because some of this stuff is very important and sometimes we just don't realize it. We had a biostatistical conference with PhRMA about two weeks ago and I said to Christy when I tell a clinician this drug has 90 percent effectiveness and this one works 85 percent, they will say, "okay, I believe it." Now, I tell them there were 12 patients in each arm and they will say, "no, now I don't believe it." They did that statistical calculation in their head that included things about delta and they didn't even know it. So, the question, again, is one of educating people as to what this means.

[Slide]

What are two ways of looking at what delta is used for? There are two things. One is after completion of the trial it is helpful to look at the delta to determine is the drug effective or not. There are two ways of looking at this. One is direct determination of how the efficacy of the test drug relates to the control drug within that trial. The second thing is the indirect determination of the benefit of drug over placebo.

I thought it was interesting that Dr. Wenzel said he got nervous when we made "leaps of faith" and, yet, we do that every time in a non-inferiority trial. We make a leap of faith that that drug is better than placebo because we have indirectly measured that in that trial. That may be fine for some very serious diseases but then when we look at this in some more detail it may get trickier for some non-severe diseases.

What is the delta used for prior to initiation of the trial? That actually answers the question of can the trial be done practically and it is used to set the sample size. Christy talked to you a lot about this issue of sample size. But then the question comes up of what is the appropriate sample size. I guess the real key word there is appropriate. If one would look at, say, a study out here and then one looks at, say, bacteriologic efficacy where one can get cure rates that are up even in the 90 percent range, one can do a trial with very small numbers of patients per arm. But then the question that comes up is does a trial this small allow you to say anything about those drug-disease or drug-patient effects that Dr. Talbot referred to in his talk?

On the other hand, a trial with 3000 patients per arm, not even considering that you probably need 4000 patients because of the evaluable dropout rate, is not doable. So, can we come to some compromise in between?

[Slide]

The other issue that we can look at here is that the risks involved in erroneously concluding non-inferiority are different for different diseases. So, the question we are asking here is what is the risk of treatment failure? In severe diseases treatment failure could translate into greater morbidity or mortality for patients.

In non-severe, self-resolving diseases one could argue that the risk to the patient isn't as great directly from treatment failure, however, this could lead to inappropriate prescribing of the drug for patients who might not benefit and, in fact, there is a risk for patients there because relative to placebo every drug has increased adverse effects. The other issue here is spread of antimicrobial resistance when one has prescribed a drug for which one may need no antimicrobial at all.

[Slide]

So, we are really asking two separate but important questions in a drug development program. This goes to the idea of looking at the totality of the data across all the studies that are looked at for an antimicrobial. As Christy pointed out, we have the benefit here in anti-infective treatment that we look at a number of indications. If one study is an anti-cholesterol drug you look basically at one disease. However, with anti-infectives we have the opportunity to look across a spectrum of illness.

So, the overall drug development program answers that question of is it an effective antimicrobial but the second, implied question there is, is the drug effective in a specific infectious disease? There, we look at the individual studies in a given disease indication.

One of the things when Dr. Goldberger was presenting his information about looking at a clinical development program is that there is the implied fact in there that for each one of those studies the drug actually does what it is supposed to do. The individual studies in a given disease indication may vary depending upon the characteristics of that drug, things like Dr. Craig

brought up of whether it penetrates the site of infection, various host factors. As we heard this morning, immunocompromised patients are likely to do less well and, even more importantly, the natural history of the disease.

[Slide]

So, how did we get to where we are today and talking about this? We talked a lot about sample size in the last few minutes, and the 1991 "points to consider" document had this step function approach to selecting delta which was based completely on sample size. It was a recommendation and not a dictum, however, it sort of became such and even underneath that step function in "the points to consider" document it says that for severe diseases one may need to take into consideration other things.

So, in February of this year at an advisory committee meeting we agreed that we would look at the delta for each indication separately so that we could take into account those disease specific factors. Since February we have been trying internally to look at the placebo-controlled trials for each disease. What we have tried to do here is to look at all available studies, not just

those which showed a benefit of antimicrobials over placebo.

One of the things that came up in the PhRMA biostatistics conference two weeks ago was exactly this fact. One needs to look at the range of data for a given disease, not just the positive studies. What we have tried to do then is to get some estimate of what is the range of benefit over placebo in these trials for various diseases.

[Slide]

We have come to the conclusion that there are really three types of diseases in relation to delta. So, there is no one-size-fits-all. The first kind of disease is one where the magnitude of benefit of drug therapy over placebo is known. We can put a number on it and it is very big. Those would be diseases like acute bacterial meningitis and endocarditis where if one does not receive therapy, the likelihood that one will do well is very low.

The second kind of disease is actually in some ways more problematic, and that is where the magnitude of benefit of drug therapy over placebo is unknown and may, in fact, be modest or small. Those are diseases like acute bacterial sinusitis,

acute otitis media and acute exacerbations of chronic bronchitis. Some of the issues here may have to do with the way some of these trials are done. For instance, not getting bacteriology in acute otitis media and sinusitis studies makes them very problematic and the bacteriology, even if obtained, in acute exacerbations of chronic bronchitis trials is very difficult to interpret.

Finally, there is the third kind of study where the magnitude of the benefit of drug therapy is unknown as far as putting an exact number on it, but may be large enough not to be of concern when picking the delta, at least the delta-1. Dr. Wenzel showed a slide this morning with some data from Ibrahim, in Chest, in 2000, which showed that people who got inappropriate therapy had a mortality rate of 60 percent with hospital-acquired pneumonia whereas with appropriate therapy they had 24 percent. So, one would say that is a 40 percent benefit. We have never looked at a study with a 40 percent delta, therefore, the question that comes up there is not related to delta-1 but to delta-2 and the acceptable loss relative to control.

[Slide]

When one goes to look at these historical

placebo-controlled trials though, there are obviously a number of problems that come up. If we look at a trial that was done a number of years ago, there are differences in medical practice today and adjunctive therapies that we didn't use before. There are differences in the range of organisms and the resistance patterns of those organisms in the placebo-controlled trials from years ago. There are also differences in the enrollment criteria and endpoints compared to current trials. As Dr. Talbot pointed out, we may want to look at things like time to resolution of symptom endpoints in self-resolving disease but that is nearly impossible to do in a non-inferiority trial because you don't know what those endpoints would be in a placebo-controlled trial, and many of the older placebo-controlled trials don't look at things like that.

Finally, there are differences in cure rates across various patient populations. For instance, if one would just say community-acquired pneumonia, is there a one-size-fits-all delta for community-acquired pneumonia? Or, does that matter if you are studying an intravenous drug in severe hospitalized community-acquired pneumonia versus an

oral drug in less severe outpatient community-acquired pneumonia?

[Slide]

I think Christy touched on this and I just wanted to put this in a different graphic representation. That is, whether a drug falls within that non-inferiority margin, which we glibly refer to as making the delta, is not independent of how the drug actually performs in the clinical trial.

For instance, if you have a drug where the point estimate of efficacy is close to control, say just three percent worse--Tom Flemming brought this up at the advisory committee as well and probably had some more detailed slides than I have here, but if one has a drug that is close to the efficacy of the control agent, the likelihood that you are going to fail to come within the confidence interval of the lower point estimate of the delta is probably pretty small. On the other hand, when you have a point estimate that is further away from the control, such as in the bottom example of minus nine percent, that is where you run into trouble about whether you can make the delta or not.

That brings up the clinical question of if

a drug actually works very well or even if it is on the other side of zero, then you have less of a worry about making the delta or not and it is with the same exact sample size that you can actually do this.

[Slide]

What we have tried to do then is to come up with some idea of how we would approach this given the limitations on the data that we have of placebo-controlled trials. One suggestion that we would like to discuss today would be to look at these prior placebo-controlled trials, with all of their attendant issues, and determine a range of deltas for a given indication. Obviously, this has the issues that we have discussed.

One of the things to keep in mind is that the ICH-E-10 document actually cautions about performing non-inferiority trials at all if one doesn't have the data on delta-1. The other issue is if one would come up with a range of deltas for a given disease, so for instance, one would study one of these non-severe indications and we come up with a range of deltas somewhere between 4 percent and 12 percent, the natural tendency would be to pick the 12 percent because that allows you to get

the smaller sample size. However, ICH E-10 also cautions about being suitably conservative when selecting that delta.

One of the other things that our statisticians have asked me to talk about also is that those are the point estimates of the benefit over placebo. Some people have actually recommended that you use the confidence intervals around that point estimate which, again, would get you to a larger sample size but I think that is something we need to talk about today as well.

[Slide]

Then there are the considerations within an indication. In the example of community-acquired pneumonia that I used one could make the case that if you are looking at severe community-acquired pneumonia the delta for that disease might be different than outpatient less severe community-acquired pneumonia, but also take into account the size and scope of the development program and the characteristics of the current study. For instance, in acute otitis media studies that were done in the past without baseline tympanocentesis one had great questions about what the benefit over placebo actually was. Can we

select a delta that may be larger if now we are looking at studies with microbiologic underpinnings with actual baseline tympanocentesis? Then, the last thing one might want to take into account, as Christy mentioned, is the number of trials per indication which may give you some more confidence.

[Slide]

The other thing we can talk about is not non-inferiority trials as the only example here, but also can we look at some alternative trial designs? The other important thing to keep in mind is that for some of these alternative trial designs the sample size might actually be smaller than the non-inferiority trial. So, can we look at things like superiority of one agent over control? This may be helpful in some of the non-severe diseases. It may be a tall order to ask for a drug to be superior to a control in immunocompromised patients where the host effects may limit your ability to reach a cure rate.

The second thing to talk about is maybe doing placebo-controlled trials, as Dr. Talbot talked about, with maybe this option for early escape therapy. In other words, a patient remains on placebo for two days, three days, five days,

whatever people think is appropriate. If they are failing at that point, then they go on to a drug therapy so that the ethical issues of leaving them without therapy are addressed.

Finally, there are dose-ranging studies, and linezolid was approved for vancomycin-resistant enterococcal infections based on a dose-ranging study where one could look across those.

Finally, Christy brought up this issue of non-comparative data and how would that impact on the development program as a whole? In other words, there is a difference between looking at non-comparative data as part of the overall drug development program versus non-comparative data as the only thing upon which the development program hinges. Also, superiority and placebo-controlled trials would allow us to examine endpoints such as time to resolution of self-resolving diseases. This is not such a novel concept as for diseases such as influenza and traveler's diarrhea. We already look at time to resolution of symptoms in those kinds of diseases.

I am going to turn it over to Dr. Edwards at this point and leave these slides up here about the things we can discuss, and I think you have

these questions already printed out as well.

Discussion

DR. EDWARDS: Who would like to start? It is actually a lot of information we have been given in these three very nice discussions. Roger?

DR. ECHOLS: I have been around long enough to sort of tell old stories and I am reminded of the first time I heard a discussion about delta, and it was when the guidelines were first being designed back in the late '80's and I didn't really know what delta was. It was explained by statisticians and we got into the one-sided versus two-sided, which still now 12, 15 years later is unresolved, and it is one thing I think we could make progress on.

But the other thing I think comes down to something that Walt Wilson said. He was the sort of expert on endocarditis and we were talking about delta in terms of sample size feasibility and whether it was 15 or 20 percent, and he was aghast. He just said, do you mean to tell me that I have to explain to a patient that I can have a 95 percent cure rate if I use standard of care but if I use this experimental drug the study might show something that was 10 or 15 percent worse than

that? He said, I could never accept that. So, for something with a cure rate in the 90-some percent, the step-wise delta was very, very tight. In terms of endocarditis they talked about minus five percent as the lower boundary. Of course, no one has ever done an endocarditis study because it is not doable.

The key I think in solving some of this is something that has been mentioned many times today, you know, what is your endpoint. If your endpoint is microbiologic, I think you can achieve a tight confidence interval in certain situations, such as bacteremia, maybe endocarditis, meningitis. But if your primary endpoint is clinical where your success rate is not likely to be 95 percent, particularly in your life-threatening infections, or at least not 95 percent without sequelae like valve replacement or some neurologic deficit, then you will never be able to have that level of confidence. So, it still comes down to what is it that you want to be confident about. Is the patient, you know, walking out of the hospital under their own speed or have you eradicated the infection?

DR. POWERS: Can I make a comment? Since

we are going to get back to this clinical versus micro thing, I think a lot of this is going to come up tomorrow when we talk about the specific indications. But I just wanted to put this in perspective. The guidances as they are written now--there are certain diseases where microbiology is the primary endpoint--uncomplicated urinary tract infections; acute uncomplicated gonorrheal infections--the way the guidance is written now, that is what it says, microbiology is the primary endpoint.

What we have been talking about tacitly today is accepting microbiologic endpoints for severe diseases like meningitis. That is a different issue and I think we need to realize it when we talk about accepting microbiologic endpoints as the primary endpoint. We need to make that distinction between severe versus non-severe.

The other issue I wanted to bring up was something I tried to show on that sample size graph. At our July advisory committee on acute otitis media one of the speakers showed that one could do an otitis media study with double taps, showing eradication with 33 patients per arm. The question at the end of that trial is what do you

know about the safety of that drug in kids when you have those 60 patients with otitis media? So, I guess one of the questions I wanted to ask the group here is where does the sample size get too small?

The third point I wanted to ask is, Roger, you brought up this idea about surrogate endpoints in HIV. The time to measure a clinical endpoint in HIV may be years down the line. Some of the other places where we accept surrogate endpoints would be like cancer where we look at regression of tumors instead of the actual outcome. Those are things where the clinical outcome is years away. In infectious diseases we are actually talking about only weeks down the line.

So, the question that comes up is if one can measure the clinical outcomes, shouldn't one look at those? The issue then becomes but then they start driving the sample size. Therefore, the question is, is there a reasonable delta one could select around those lower clinical outcomes in something like meningitis that would give one a sample size that would allow one to look at the drug-disease and drug-patient interactions but not be so onerous that companies couldn't perform the

trials?

DR. ECHOLS: Actually, Walt, you and others have convinced me that for life-threatening infections, for severe infections, in a perfect world we want to have a tight confidence interval. We want to be confident. Since we can't do placebo-controlled trials we have to do non-inferiority trials. None of us wants to either work on a drug, approve a drug, develop a drug or treat a patient with a drug that is not as good as other drugs that are out there.

To me, backing up on what is an adequate confidence interval is one way to achieve what is feasible, but I still think that--we will talk about meningitis again but particularly in these life-threatening, multiple confounded situations, whether it is hospital-acquired pneumonia, sepsis or meningitis, the clinical outcome is not determined just by the antibiotic. The clinical outcome is determined by their underlying disease, how long they have been sick before they were treated, too many other things. So, the reliance on clinical endpoints as a primary is, to me, just too confounded and you will never be able to sort through it.

DR. TALBOT: Agreed that the outcome is dependent on the disease, but I think the concern is when the antibiotic is having an effect on outcome that is not efficacy, when there is a drug-disease or drug-patient interaction in terms of safety that is problematic. So, if it were always true that the antibiotic is taking care of the bug and then the rest of that has nothing to do with the antibiotic, I think you would be okay but that is the hesitancy for going for all clinical information.

To take further your point in some of the issues we have discussed, in endocarditis or acute bacterial meningitis I would have no problem. In fact, it is what I was trying to suggest, to have a tight delta in a comparative study with 20 or 25 patients per arm with a microbiologic endpoint. Where I have trouble taking the next step is to give full approval of effectiveness for that because you don't know about the drug-disease interactions and drug-patient interactions in those patients.

So, what I am suggesting is that there be an intermediate step in the label where you can say that you achieve this with these endpoints but that

you have some limitations in what you can conclude. To me, there is precedent for that. Please forgive me if I am stepping on regulatory toes, but I think there are some precedents in terms of the in vitro list and I think you might be able to get there pretty quickly while you are trying to validate some of these markers in terms of their clinical relevance as well as their micro relevance.

DR. EDWARDS: Yes, John?

DR. BRADLEY: Roger, John and I had a conversation last week so that we wouldn't duplicate our talks on meningitis and many of these points came up. With meningitis you can't afford to miss it. You need to get a microbiologic cure. We can talk more about microbiologic as a surrogate for cure in this particular situation, but you need a relatively few number of patients to show that you can sterilize CSF with new antimicrobials. I am very happy with that in terms of does the drug work.

The side effect profile is something else again, and with meningitis in particular the doses of the drugs are usually higher than they are with other systemic infections so the toxicity profile may well be different. It is something, as we all

discussed, that is very important to track. With two quinolones at least, there are some long-term follow-up data in which joint problems which may show up months or years later are currently being tracked, but that is sort of an extra study that will be looked at as time goes on, which is probably not going to slow down approval up front for the indications that these companies are applying for.

As you mentioned, Roger, with meningitis the clinical outcomes can have very little to do with the microbiologic efficacy of the drugs. You can get death when you sterilize the CSF. In one of the studies failure of the drug, when you looked into the case report form, the investigator changed the drugs from the antibiotic to INH rifampin and pyrazinamide. So, obviously, they were thinking this was TB meningitis and not bacterial, yet that was a failure of this antibiotic in the clinical trial.

So, I do need clinical information on toxicities and effectiveness and, again, we will discuss this more tomorrow. But the micro is the most important to me in showing that the drug does what it is requested to do.

DR. EDWARDS: Dr. Gilbert?

DR. GILBERT: Well, I am always dazzled by the statisticians so if I slip on the ice referring to statistics, you will forgive me. But it seems to me like there are three deltas, not two deltas. There is the first delta for the placebo-controlled trial and we have talked about that. The hang-up seems to be the second delta, and it seems like you could subdivide that. You could have a bacterial efficacy delta using microbiology endpoints. For those conditions where we can get microbiology endpoints you can enroll a small number of patients. I think we should do away with the word "surrogate" by the way because we all have different definitions of "surrogate" but that is another issue. But we have one delta for microbiology efficacy, and then another delta that we could call the adverse effect delta. So, you run your trial for these really tough infections, meningitis, otitis with double taps, even endocarditis, with small numbers of patients where you have clear-cut, crisp microbiologic endpoints. Then you run all the other trials, the whole powerful database for skin, soft tissue and whatever else you are studying, and that has an

adverse effect delta of whatever it is going to be. It can be much looser, ten percent or whatever is decided to be appropriate. Looking at it from the patient perspective, we want to have a delta for adverse effects and a delta for efficacy.

DR. POWERS: I think that is kind of a compromise position we are trying to get to, to say can we select two separate deltas for some of these trials, one for the microbiologic endpoint and one for the clinical endpoint, but make the one for the clinical endpoint reasonable so that the trial can get done? I think there is a problem with what Dr. Wilson said, and that is that going into the trial you don't expect that your drug is going to be 20 percent worse. That is way out on the margin. What you really hope is that you are X percent better but, at the very worst, you hope you are only this much worse. So, going into it, the margin is really the protection for the patient, the way I look at it, that the drug isn't going to be horrendously worse than what you have out there already.

The third point there is probably some place we don't want to go, and that is that some of these side effects are rather rare. If one were to

put a delta around it, it would be near impossible to do the trials. So, what I think you end up doing with safety is you end up looking for a signal but not putting numerical or statistical values around that.

To go back to Dr. Gilbert's assertion, I guess what we are trying to get to is can we get a clinical delta that is reasonable and a micro delta that might be tighter, and then look for a safety signal without putting any numerical or statistical values around it.

DR. GESSER: I suspect you are talking specifically about meningitis because I think the tightness of relative deltas will vary by the indication. It seems like we have strayed into a safety discussion and safety is of primary importance but I suspect our intent here was to discuss proof of efficacy. It goes without saying that safety is handled in a different way and these discussions of delta are not tied specifically to safety. I think, as Dr. Gilbert points out, the safety data often comes from other indications and for difficult to study indications like meningitis or endocarditis or some of the others that we have mentioned, the types of safety databases that we

often require are not going to come from that population alone. I think that is important.

DR. POWERS: I think it is important to realize that there are safety differences across those diseases. For instance, the duration of treatment in endocarditis may show you a safety issue with that drug that you wouldn't see in the other parts of your safety databases.

DR. GESSER: Right, and dosing, but that needs to be looked at in totality, not specifically when one is trying to assess what tests should be used to demonstrate the delta-2 issue that the investigational drug is no worse than the comparator that is chosen for that study.

DR. EDWARDS: Christy?

DR. CHUANG-STEIN: Yes, I hate to put on my statistician's hat and remind people about the sample size. That seems to be what statisticians are doing in their respective companies. Even if we use the micro, the eradication rate as the primary endpoint, the confidence interval can only do as much as it can. The width of the confidence interval is reciprocally proportional to the square root of sample size. So, even if we have the eradication rate as high as 95 percent but if we

only have a sample size of 20, that confidence interval is going to be pretty wide. It is not going to meet, you know, minus five or minus ten percent. So, the high eradication rate is not going to help. The sample size will have to be pretty high to meet a very tight margin there. We can go back to one of the slides where the cure rate or success rate was about 90 percent. If we push that even a little bit further to the right the sample size will go down a little bit but it is not going to get us to 20 or 25.

DR. TALBOT: I think the corollary to that is if, as John suggests, you would think about a second delta for a clinical endpoint, maybe wider one. Without looking at the numbers, I am still concerned that for some of these indications even a 20 percent delta would still translate into patient enrollment requirements that would be not feasible. For example, let's say in bacterial meningitis you decide that you want a 90 percent eradication rate for your control and a five percent margin for bacteriologic, you do your calculation and it is 40 patients, or whatever. If to that group you apply a 20 percent delta for getting clinical proof, you are still talking about a pretty big trial again.

So, I need to look at the numbers, but I am not sure how much you are really saving by adding that clinical delta. I still find it appealing to think that you just report the microbiologic endpoint as well as the data from safety across all the other populations, efficacy across all the other indications, etc. and just say here are the microbiologic data. We met this delta but we can't infer completely what the clinical safety profile is, and skip the delta.

DR. POWERS: I guess the issue that comes up there then is now you are talking about one of the most severe diseases you will ever treat and you are not going to give clinicians information on what the actual clinical cure rate is in that disease.

DR. TALBOT: Well, you would but you wouldn't power the study using a delta. You would report the clinical results observed in that population in which you had assessed your microbiologic endpoint but you would note the limitations of that.

DR. POWERS: I guess looking at it from our point of view, the question that might come up then is suppose one did a trial in meningitis where

one showed 95 percent bacterial cure rates in both arms of the trial, and then when you looked at the clinical success rates one is 80 percent and one is 70 percent. Now you have numbers so small that you can't decide whether that difference in the clinical cure rates is just because you didn't have enough patients or if there is a true difference in clinical cure rates between those two drugs.

Let me bring up this issue about why because, again, it goes back to whether one accepts that all the drug does is eradicate bacteria. Last week's New England Journal of Medicine had a paper on dexamethasone in bacterial meningitis. Mike, your and Alan's editorial about some of the trials done in the past didn't give the steroids before the antibiotic, and I thought why is that? Why would that be an issue? That is because, you know, you have talked a lot about how the antibiotics affect what happens to these inflammatory mediators. So, the idea here is that, yes, there is a host response but the antibiotics impact what that host response might be. It is not just that it eradicates the bacteria and that is it. So, if one didn't think that was important, then why would one need to give the steroids before the drug if

that wasn't an issue? So, the question that then comes up is are there host-drug interactions that one would not be able to measure in any other way, other than looking at the clinical outcome?

DR. TALBOT: Right, but the alternative is if you don't make it easy to study the drug you are going to have no information on the drug. You are not even going to have microbiologic. At least if you focus on microbiologic and note the limitations of the clinical, you will have those data in the label with the appropriate interpretations ensured by the agency pointing out, for example, what the limitations are; certainly pointing out the differences in the unsatisfactory outcomes. I would like to hear from my active clinician colleagues, but I think that is better than having nothing about it.

DR. SCHELD: I think it is better than having nothing. You raised a very good point, John, because of the inflammatory issues which are stimulated by bacteriolytic drugs, and all the issues of whether a drug that was not bacteriolytic but was bacteriocidal might actually be better in this disease. I don't want to get into that today, but I think having the information on the rate of

bacteriologic eradication in spinal fluid would be very meaningful to clinicians. It really doesn't help you set the trial size though for a clinical endpoint. If you pick an endpoint, like they did in the dexamethasone trial which is basically walking, talking, going to school, perfectly normal, no neurologic sequelae versus everybody else, it took 300 patients and nine years in five countries to get there, and that is the real issue, and they picked an endpoint where they might be able to pick up such a difference.

I don't know what the compromise situation would be but I think that we have to get somewhere with rates of bacteriologic eradication because, you know, all the work that is done in experimental meningitis in the literature looks at colony forming units per milliliter of spinal fluid per hour of treatment. If you actually look at those kind of experiments, adding a modern-day quinolone to a third generation cephalosporin is better than the standard regimen we are using today but we are never going to know whether that is better in humans right now. We just can't do that.

But there might be a better way to look at bacteriologic eradication with one caveat. That

is, back in the early days when Roche was studying ceftriaxone in meningitis in Senegal, it looked like the drug was working fantastically well because none of the kids with H. flu meningitis had positive spinal fluid 12 hours after the first dose of drug. Then they did a very clever thing, which we also did in the laboratory, which was you add beta-lactamase to the CSF and they are all positive. So, with those kind of caveats, you just have to be careful with a bacteriologic endpoint.

Another example with endocarditis, and I wish I could have been there to hear Walter talk about this because I can imagine what he would say--"oh, my God, you get a 95 percent cure rate with virulent streptococcal endocarditis; you can't accept anything less," and I agree. We shouldn't accept 15 percent less. It is unacceptable. But you do a clinical trial, as was done a number years ago and which is the only one we have, where you compare a beta-lactam versus beta-lactam plus immunoglycoside in Staph. aureus endocarditis. Even though at the end of the day the clinical outcome looked to be about the same, clinicians still use that data to use combined therapy for the first three to five days because that is where all

the benefit takes place.

DR. POWERS: Mike, you bring up the exact point that is the flip side of what we are talking about. That is, where you see a microbiologic benefit that doesn't pan out into a clinical benefit. John Rex' study on candidemia, presented at ICAAC last year, is the same thing, amphotericin plus fluconazole versus fluconazole alone cleared the candidemia faster; no benefit clinically. Again, it is the same situation as talking about adding a second potentially toxic drug and clinicians making a decision based on microbiology that didn't pan out to have a clinical benefit to patients. I guess that is the flip side of what we are talking about here when we say that things might be microbiologically equivalent and not turn out.

Just to get away from meningitis, you can bring up an example of E. coli 0157 treatment in diarrhea where one could show that you eradicate the organism and, yet, there are suggestive retrospective case control data that say that may actually adverse clinical outcomes as far as increased incidence of hemolytic uremic syndrome in kids. So, it is not just meningitis. I think this

issue of are there clinical outcomes that would be important to measure come up with other diseases as well.

DR. EDWARDS: Mark?

DR. GOLDBERGER: There is a potential regulatory solution to some of this, and that is that I think it would be difficult to just sort of put in the label in some way the results of a study for meningitis, you know, and just sort of leave it there and then people are sort of supposed to sort out what to do. However, if a study were done, in fact, of a limited size with a favorable microbiologic response and, you know, obviously at the end of the day less ability to understand how the two products compared clinically, there is no question in any case that something like this would go, you know, to the relevant--in this case, the anti-infective advisory committee for discussion. There would be a lot of looking at rates of culture negativity and whatever data there was. But at the end of the day what could very well happen is a decision that you get an indication that might say drug is indicated for treatment of whatever type of meningitis was studied in situations, you know, where alternative therapy is unavailable or

inappropriate. In other words, it might end up with a second-line indication based on the fact that there was insufficient information to really draw conclusions about how it compared to the established drug, which was the control but, therefore, leaving it as an option for a situation where, for some reason, the control therapy was felt by the treating physician to be inappropriate.

I suspect that that is a regulatory approach that would be more compatible with, in general, how we have approached other problems than simply leaving it in the label and kind of leaving it in the air for people to sort through the culture negativity rates, not really saying anything about how it is indicated and then just leave it completely up to the clinician.

DR. EDWARDS: With that comment, I think we are going to try to bring the meeting to a close unless--yes, Bill?

DR. CRAIG: A potential advantage of eliminating an organism faster is that it will allow for a shorter course of therapy. It may not translate into any benefit in overall outcome if one uses a long course, but since the organism is eliminated quicker and, again, nowadays with all

the concern with resistance a shorter courses result in less exposure and that could turn out to be a positive aspect.

Concluding Remarks

DR. EDWARDS: If I could have just about two minutes, I would like to make a couple of comments in terms of an extemporaneous summary of the day. Even though we have tracked through about 25 topics today so far, I will try to keep it down to just two minutes.

We started out understanding that we have a problem. We need to continue to attract the development of new antimicrobial agents at a time when we are at a critical crossroad regarding needs because of resistance, because of bioterrorism needs, and because our armamentarium is just diminishing in quantity.

We pointed out the fact, something we haven't really emphasized but I wanted to just make the point that I think we are really in a new paradigm of studying patients in many ways. We have patients whose clinical records are about this big for almost all of the infectious disease problems that we are studying. Unlike an era when we had lots of patients with simple, acute

bacterial meningitis or acute endocarditis who came in off the streets and were uncomplicated, we are now dealing with a large population of immunocompromised hosts who really compound the difficulties regarding analyzing the effectiveness of an agent, more so that than the toxicity, although the toxicity certainly comes in here. Dr. Wenzel made the point very clearly that comorbidity is a big factor that we have to take into consideration.

We clearly know we have a big resistance problem. We went through a fair number of solutions to the problem, which included the possibility that it is an acceptable strategy to incorporate PK/PD data with limited clinical data carefully in evaluating the efficacy of new agents.

We did not develop very fully the notion regarding whether efficacy in one infection applied to efficacy in another infection and, therefore, would reduce the number of trials per specific entity. We touched on that but we really didn't develop that notion very far.

We talked over and over again about the fact that it may be feasible to develop labels containing information that is informative but not

conclusive and we have actually come back to that notion over and over again throughout the day.

We had a very interesting discussion about incentives and some very creative ideas were put forward. We have been working all day today, and will all day tomorrow again, on developing the notion of maximizing the incentives that do not require legislation at this time and that already exist. The IDSA is going to definitely explore the idea of pursuing incentives that may require legislation, and I think that job is on our shoulders at the present time.

We have I think agreed that the delta will be determined for each specific indication and that there is no across the board delta. The real challenge is trying to figure out how to apply that, and that is what we are grappling with here, and will all day tomorrow as we will come back to the delta issue over and over again.

There were two things we didn't discuss today, and perhaps we will have a chance tomorrow, that are I think of importance and those were suggestions made by Christy regarding the one-tailed testing to reduce population evaluation size, and we really didn't explore in a lot of

detail the issue of non-comparative trials which would be something I think the folks from IDSA would be able to contribute to. Perhaps we can come back to that tomorrow.

So, we have really tracked through a tremendous amount of territory today. I would really like to thank you all, all the presenters who did a very beautiful job of not only being clear but also on time. I really thank everyone who has put effort into this meeting, and this half has been I think very informative and really a great warm-up for what will be coming tomorrow.

We will start again at nine o'clock tomorrow. Are there any other announcements we need to make at this time? Please hang onto that badge so you can get in easily again tomorrow morning, and I think we will adjourn for today and thank you very much.

[Whereupon, at 5:10 p.m., the proceedings were recessed, to resume at 9:00 a.m., Wednesday, November 20, 2002.]

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