DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC) MEETING

Wednesday, March 5, 2003

9:00 a.m.

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Mark Goldberger, M.D., M.P.H.
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LEGGETT: Good morning. I would like to welcome everyone for today's March 5th's meeting of the Anti-Infective Drugs Advisory Committee.

A little housekeeping since it is now 9 o'clock, committee members, you have a little green menu in front of you. That menu needs to be filled out and passed to Tara, so we can get it in by 9:30 if you want to have lunch. Lunch will be served next-door in Salon D today, but we will need your menus.

Can we begin the day by having everyone introduce themselves. I guess I will start down at that corner.

Introduction of Committee

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

DR. COX: Ed Cox, Deputy Director, Office of Drug Evaluation IV, FDA.

DR. SORETH: Good morning. I am Janice Soreth. I am the Division Director for Anti-Infectives.

DR. ALBRECHT: Hello. I am Renata Albrecht, Director of Division of Special Pathogen

and Immunologic Drug Products.

DR. PORETZ: I am Don Poretz in private practice of infectious disease in Fairfax, Virginia.

DR. PATTERSON: Jan Patterson, Medicine-Infectious Diseases, University of Texas Health Science Center, San Antonio.

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

DR. TURNER: Tara Turner, Executive Secretary for the committee.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Oregon Health Sciences University and Providence Portland Medical Center.

DR. WALD: Ellen Wald, Pediatric Infectious Diseases, University of Pittsburgh School of Medicine.

DR. GLODE: Mimi Glode, Pediatric Infectious Disease, Children's Hospital, University of Colorado.

DR. BRADLEY: John Bradley, Pediatric Infectious Diseases, Children's Hospital, San Diego.

DR. RELLER: Barth Reller, Infectious Diseases, Director of Clinical Microbiology, Duke

University.

DR. CROSS: Alan Cross, Infectious Diseases, Center for Vaccine Development at the University of Maryland.

DR. BELL: David Bell, National Center for Infectious Diseases at the CDC in Atlanta.

DR. JORGENSEN: Good morning. I am Jim Jorgensen from the University of Texas Health Science Center.

DR. PROSCHAN: I am Mike Proschan from the National Heart, Lung, and Blood Institute.

DR. BROWN: Ken Brown, Infectious Disease, University of Pennsylvania, representing industry.

DR. LEGGETT: Welcome, everyone.

Now, Dr. Turner, could you read the conflict of interest statement, please.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is

discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special Government employees and Federal participants have been screened for their financial interests as they may apply to the general topics at hand. The following participants have reported no current financial interests with regards to pharmaceutical companies: Drs. Mary Glode, David Bell, and Michael Proschan.

Dr. Donald Poretz has reported a financial interest in a pharmaceutical company covered under CFR 2640.202(b) deminimus exemption.

The following participants have reported interests in pharmaceutical companies and the Food and Drug Administration has granted general matters waivers to the following SGEs which permits them to participate in today's discussions: Drs. James Leggett, Ellen Wald, Alan Cross, Celia Maxwell, Jan Patterson, John Bradley, Donald Poretz, L. Barth Reller, Judith O'Fallon, James Jorgensen, and Keith Rodvold.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member and consultant.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited speakers, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Dr. Francis Tally is Chief, Scientific Officer, at Cubist Pharmaceuticals. Dr. Tally also owns stock in Cubist.

In addition, we would like to disclose that Dr. Kenneth Brown is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Brown owns stock in Merck and in his rollover retirement account he owns shares in Pfizer, Genentech, and Johnson & Johnson, as of December 31, 2002. Dr. Brown also serves as a consultant to Wyeth and Merck and works one to four days per month.

In the event that the discussions involve

any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants involvement and their exclusion will be noted for the record.

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

Thank you.

DR. LEGGETT: Thank you.

Dr. Goldberger, could you please provide us with some opening comments.

Opening Comments

DR. GOLDBERGER: Yes. I would like to welcome everybody to the second day of this advisory committee. Yesterday, we had a very interesting discussion focused around a product. Today, we are going to continue what has been an ongoing effort stretching over a few years at least and actually more intensively over the last year or so to look at issues related to the development of antimicrobial drugs including antimicrobial drugs for resistant indications.

We have had a major two-day advisory

committee in early February of 2002, another meeting in the summer, a meeting with IDSA, PhRMA, and ourselves this past fall, and now today's meeting to talk about a variety of issues that we hope will lead to encouraging the development of new antimicrobial drugs and to also thinking about ways that we can really facilitate that approach, encourage companies by perhaps reducing the overall amount of resources that are necessary, but at the same time, at the end of the day, get information that is at least is of high quality, if not higher quality, than what we have been accustomed to in the past.

Today's meeting is going to focus on two issues that have come up as part of some of these meetings. One issue could be summarized briefly by referring to it as the list, that is, the list of microbial organisms, and today really we are concentrating on bacterial organisms that are of public health interest for which we should really be encouraging the development of drugs.

Again, the organisms on this list generally tend, in fact, to be those that have demonstrated some level of resistance to therapies that have been commonly used to, for instance,

treat.

We have had some discussions about this. Industry has expressed a great interest in having a little more in the way of something defined as to what organisms we believe are important, so that they can look carefully to decide whether or not these things I think represent appropriate opportunities for them.

We are certainly in agreement that providing guidance to industry about these things is useful. On the other hand, a list per se, simply making up a lot of organisms does require one to then be thinking about updating it, you know, on a regular basis, and one of the things we want to talk about today is how one sort of decides the kind of things that ought to be on some list, what are the parameters that are appropriate, so that the list can be dynamic and yet not overly burdensome in terms of thinking about what ought to be on it, and more to the point, if we can define some parameters, then that gives industry a little more flexibility.

Should a new issue come up, industry will not be in the position of looking to see is this on the list, is this not on the list. They will be

able to use parameters that have been discussed and defined to make an argument about why such organisms are appropriate targets for antimicrobial drug development.

So, that is going to occupy discussion I think most of the morning, and we have several presenters who will be talking about this issue. We hope to have a fair amount of committee discussion.

In the afternoon, we are going to talk about another topic that we hope will lead to more expedited drug development, and that is sort of looking at the overall package that many companies submit as part of, you know, development of a new antimicrobial.

As most of you are probably aware, it is uncommon although not by any stretch unheard of for a new antibacterial drug to come in for a single indication. Generally speaking, drugs come in for a variety of indications.

To give you a good example, fluoroquinolones is one example, as well as some macrolides, often will come in for a variety of respiratory indications, in part because from a purely business point of view, it makes much more

sense to have this package when you are trying to get drugs on formulary, so when you can promote them of having related indications, and in some cases, the breadth of indications will be even broader.

There will be respiratory indications, sometimes intra-abdominal indications, skin, complicated skin, et cetera, so the packages can be fairly large.

In general, multiple studies have been submitted for each of these indications. There are--and we will be talking about this, this afternoon--clear exceptions to the idea that you need multiple studies for each indication.

One of the things we really want to talk about is can we advance the model as to how indications could support one another to a point where it will facilitate overall development by perhaps reducing the size of a development program, and at the same time will provide a rational approach both to the general issues of development over a broad range of indications and to the related and very important issue that companies have addressed with us in meetings on a one-on-one basis, et cetera, I think has come up at open

meetings like this, as well as, we want to get an indication for a resistant organism.

Sometimes it is difficult to acquire adequate numbers of those organisms from a study or studies in a single body site, what is the latitude, how much pooling across body sites can be done. As you can see, that is related to the overall issue of how indications support one another.

We think this is an important issue. We think from a practical point of view, and I go back to the years that I have spent in practice, that clinicians are prepared to make inferences as to how a drug is likely to perform based on how it performs in other settings, and I certainly think that a drug that one feels more comfortable--this is my own personal opinion--about how a drug will perform in a seriously ill patient if there is already data suggesting that in other serious illnesses or infections, the drug has performed well.

I think that at times, although as a clinician we are comfortable doing that, from a regulatory point of view, we don't clearly have that laid out as to how that might occur, and I

think that that is an area that is worth talking about in some detail, talking about the parameters that might help us in deciding what indications could support one another, so that we can put out some guidance that will be helpful to industry in thinking about what a package might look like.

So, in any case, we are going to have some discussion about this in the afternoon with the hope of again facilitating antimicrobial drug development, as well as development for resistant indications, and we hope that at the end of day, that we will have enough ideas here that will assist us in writing some guidance that will be helpful to industry.

There has been a great desire, not surprisingly, and this goes across many areas in FDA and far outside anti-infectives, for industry to get some type of guidance as to how to proceed since they are much more comfortable, they can sit and look at what is required or suggested as opposed to having to depend on individual interactions, et cetera, although there is always an issue about getting guidances done because of the amount of people you have available to sit and write them.

Here, we actually have a somewhat different issue, which is not always quite as common. I actually believe one of the obstacles to writing some of the guidances, particularly what I was speaking about for the afternoon, how indications support one another, is that there are unresolved scientific questions about how far one can really go.

The one thing you learn about, you know, when you are writing a guidance or when you are writing a letter to a company, et cetera, if you are not really clear what it is you can do, what it is you are trying to say, what you actually write will turn out to be, you know, really kind of semi-disastrous or at least not useful.

So, before we embark on trying to get some sort of draft guidance out for comment, we would like to see how far we can get in resolving some of the underlying issues, so that everybody at least understands those issues, and then it is simply a matter of taking that and trying to put it into some clear English.

That in and of itself is no small achievement, but at least you understand what it is you think you trying to say, so that's what our

goals are for today. Again, we don't expect this to be the end of this process.

We expect to continue to have meetings like this, hopefully, another meeting, as well, with IDSA, PhRMA, et cetera, just to continue talking about these issues and to work through the variety of scientific issues that we think we need to do, but we are hopeful at the end of today, we will be a little closer to being able to provide the advice we would like to.

Thank you.

DR. LEGGETT: Thank you.

John, could I ask you to introduce yourself.

DR. POWERS: John Powers, Lead Medical Officer for Antimicrobial Drug Development in 04.

DR. LEGGETT: Thank you.

The first speaker of the day will be Jim Jorgensen who is going to talk to us about linkages of resistance determinants in bacteria.

Linkages of Resistance Determinants in Bacteria

James H. Jorgensen, Ph.D.

DR. JORGENSEN: Good morning, everyone.

I seem to have failed the first test and that is how to run the laptop computer up here.

[Slide.]

What I would like to speak with you about this morning is about antibiotic resistance and the era that we find ourselves in, in emerging resistance among a number of very common hospital-acquired and also now community-acquired bacterial pathogens.

I think everybody recognizes that we are in this very unusual era that none of us have ever seen or lived through before, and that is the era of emerging or evolving antibiotic resistance.

As you can see on the upper part of my slide, some would argue that this is really the era of emerging acronyms as we find new names for all of these different resistant organisms.

I think what is clear as we talk about VRE, VISA, and VRSA is that these organisms are of clinical significance and are becoming more frequent, and we have relatively few therapeutic options today.

Certainly, these organisms compromise the utility of some of our most important compounds, such as the extended spectrum cephalosporins, the macrolides, as well as the fluoroquinolones.

Certainly, the obvious need that will be

discussed today is exactly which organisms are of greatest importance and where do we need help in developing new compounds.

Now, what I have been asked to talk about specifically is this concept that I would call "associated resistance." That is some of the resistance mechanisms possessed by these organisms affect multiple members of the same class or family or subclass.

That is, for example, beta-lactam resistance in staph affects not only the semisynthetic penicillins, but also the cephalosporins and the carbapenems. But the second thing is those resistance mechanisms that may be genetically linked, that may be on the same plasmid or on the same transposon and are therefore transferred in mass from one strain to another.

The latter part of that is the fact that there are some frequently associated resistance mechanisms that are not co-transferred in the sense of being truly linked in the same cassette, but simply are very frequently found in the same clones or same derivatives of clones.

[Slide.]

I think everybody has seen these data and

I wanted to start here because it illustrates our point that in the era of the '90s, we went from almost no VRE in the United States or essentially case reports of VRE to, by the end of the '90s, about 1 out of 4 enterococcal isolates were vancomycin resistant. I could have used other examples, but I thought VRE would be a very good place to begin.

[Slide.]

VRE also illustrates the problem, that in the United States, almost all of our VREs occur in Enterococcus faecium. Inherent in most strains of Enterococcus faecium is also penicillin, ampicillin, and, for that matter, carbapenem resistance.

Now, these are not genetically linked events, but they are present in the background of that species. Many of these isolates also produce inactivating enzymes that affect multiple aminoglycosides, so most of these have high-level aminoglycoside resistance.

Despite the fact that we do have some newer antibiotics that have proven very useful in therapy of VRE infections, we already have experienced resistance developing during therapy

with some of the newer agents including linezolid and quinupristin-dalfopristin. So, it also illustrates the point of not putting all of our eggs in one basket, I believe.

[Slide.]

Now, this is a partial list and a lot of these organisms are where I want to delve a little bit deeper in the next few minutes.

For example, the last organism, Enterococcus faecium, as I mentioned, most of the time, probably 90 percent of isolates produce a low-affinity, penicillin-binding protein that provides resistance, not only to penicillin, but to other relevant beta-lactams.

I am going to spend a few minutes talking about methicillin-resistant staph and then I think there are some new things that are worthy of consideration, but methicillin-resistant staph or resistant to multiple members of that same major class, the beta-lactams.

Then, I think extended spectrum beta-lactamases are a significant problem, and I believe they will become more frequent in the near future, and these enzymes have hydrolytic activity against all of the current penicillins, true

cephalosporins, and also aztreonam.

Then, I will say a few words about resistance in Strep pneumoniae including emerging fluoroquinolone resistance.

[Slide.]

To begin with, MRSA, I think there are some new things here. MRSA have been around for a long time, and I think it is noteworthy that within about a year or so of the introduction of methicillin for clinical use, the first strain was recognized in the United Kingdom that was resistant to methicillin.

In the 1960s, there were some hospital outbreaks in Europe and the UK and certainly in the 1970s in this country. From the 1970s until today, I think you are all aware MRSA have become a major problem of health care institutions.

Now, one point I would like to make at this point is that these conventional MRSA or healthcare-associated MRSA strains have been multidrug resistant. Here, I mean in addition to other beta-lactams, other drug classes.

[Slide.]

However, what is new and I believe rapidly emerging is community-acquired MRSA and that

probably most of us first heard about this in Detroit among the injection drug users in that city in 1980 and '81, in which MRSA was quite prevalent among that population.

But then in the early '90s, community-acquired MRSA was described in Western Australia and also in New Zealand, and what was different about these strains and what should have raised our awareness was that these were not multidrug resistant strains. For the most part, they were resistant only to penicillin and oxacillin.

Then, the CDC reported four children in the '90s in the upper Midwest who had very serious community-acquired MRSA infections, and once again, these were not conventional hospital-acquired MRSA isolates.

The CDC has also done a great deal of work along with several state health departments to characterize community onset MRSA in Native American populations in Alaska, Minnesota, and also the State of Washington.

Also, I think during this period, MRSA has become a very frequent cause of skin infections in incarcerated individuals, both in penitentiaries

and in jails. Then, in the San Francisco Bay area of California, workers there have described that among the homeless populations, skin infections due to these community-acquired strains of MRSA have become quite frequent.

[Slide.]

What this means I guess is we need a new definition of MRSA or a new subdefinition and what the CDC is currently using is healthcare-associated MRSA, and that means to many of us the hospital-acquired strains that we are most familiar with.

These are patients who have recently been in the hospital where they acquired their strain or perhaps they have been in a rehab center or they have undergone or continue to undergo hemodialysis, or perhaps it has been communicated to them directly by a home or other healthcare worker.

However, we need some new definitions for these community strains, and I have used the term "community-acquired now a few times. CDC prefers the term "community-onset" meaning that the infection originates in the community, and it may have been through some conventional risk factor, such as recent antibiotic use or perhaps a

hospitalization, not recently, but in the distant past, and prolonged colonization, but there is still a number of patients who do not have any of the conventional risk factors, illustrating that this organism now does appear to be a true community-acquired pathogen.

[Slide.]

Now, there are several differences between the healthcare-associated and community-onset isolates, and they include the fact that I have already stated, the healthcare-associated strains usually are resistant to multiple drug classes.

Usually, this includes macrolides and lincosamides, usually aminoglycosides and also fluoroquinolones. In contrast, the community-acquired strains usually are only resistant to penicillin and oxacillin although some strains now are resistant also to macrolides and some to fluoroquinolones, but this is not predictable, this is not in most cases the majority of strains.

As I will show you a second, they contain a different version of the mec element, a much smaller element and much more easily transmitted among the community-acquired isolates.

These strains in the hospital usually do not have this toxin called Panton-Valentine leukocidin, whereas, the community-acquired strains usually produce this. At least the currently feeling is that PVL explains why these strains are so prone to cause skin or subcutaneous infections and also severe necrotizing pneumonia.

Also, these strains often produce as many, well, I should say as many as 19 different toxins or superantigens including staphylococcal, enterotoxins, possibly toxic shock toxin I.

[Slide.]

So, these strains phenotypically look different and they have, as I said, a different staphylococcal chromosomal cassette of SCCmec variety. Now, there are four types and, in fact, Type IV is now being subdivided.

What I want to show you, and I use this slide very reluctantly, is that the Type I is now considered an archaic version, and that is, it is not found in most current MRSA isolates.

Type II and Type III, which are found in the healthcare-associated isolates, are really very large and often carry with them transposons that code for other antibiotic resistance including

macrolides, lincosamides, and also aminoglycoside-modifying enzymes.

So, that SCCmec Type II or III, I think helps explain the MDR phenotype of the healthcare-associated strains. What is different is the Type IV is a much smaller piece of DNA, in fact, some would argue small enough to fit in the head of a phage and perhaps be transmitted through transduction.

This Type IV mec cassette does not include any of those transposons for multidrug resistance, so it appears that that is a transferable element that is now finding its way into very fit community-acquired clones of Staph aureus and contains only the essential information for methicillin or oxacillin resistance.

[Slide.]

Now, one of the things that is sometimes challenged is this concept that we should view MRSA as resistant to all beta-lactams, and I am aware that there are some beta-lactams under development that have high affinity for this PBP-2A or altered special penicillin-binding protein of methicillin-resistant staphylococci.

However, I decided to go back to the

origin, and that is, one of the first studies that helped to illustrate that beta-lactams, even if they appear active in vitro, do not provide adequate therapy in vivo.

This was a paper by Jacques Acar in Paris, published in Antimicrobial Agents in Chemotherapy in the early '70s. Illustrated in that early experience with MRSA in France, physicians did try to use cephalosporins to treat patients who were bacteremic or who had endocarditis, and when used alone, and these were cephalothin or cephaloridine, both agents that I think have among the best activities against staphylococci of all of the cephalosporins, what you find is that very few patients were cleared of their bacteremia using a cephalosporin alone, and if you added to it an aminoglycoside, you did somewhat better, but it was not really very successful therapy.

Recall that these strains did have aminoglycoside resistance determinants. When you looked at endocarditis, even though the number of patients was very small, these patients' bacteremias could not be cleared using either a cephalosporin or an aminoglycoside alone.

Now, certainly there are more modern data

than this, but I thought it might be useful to go back to the beginning just for a moment.

[Slide.]

Now, other resistance mechanisms that are commonly found or co-transferred in these healthcare-associated strains, as I have alluded to, include the macrolide and lincosamide determinants. They may be ermA or more frequently ermC, and they may be either constitutively produced or they may be inducible.

This TN554, which is commonly found in the SCCmec Types II or III, codes for this kind of resistance, and is co-transferred with methicillin resistance.

Aminoglycoside-inactivating enzymes can be produced by these organisms including this important so-called bifunctional enzyme which has both an acetylating and phosphorylating end or activity, and is the same enzyme found in many enterococci that have high-level aminoglycoside resistance.

Then, most of these healthcare-associated strains today are resistant to fluoroquinolones either because of gyrase A mutations or because they have an active efflux pump that removes the

drugs from the cells.

Then, they may have the ribosomal protection mechanism of tetM for tetracycline resistance or they may have an efflux pump that removes most members of that class.

[Slide.]

The other problem, however, that I think is more urgent and of greater concern is the fact that in this background of MRSA, we have seen either diminished susceptibility to vancomycin in the form of VISA or vancomycin-intermediate Staph aureus, in which about 8 times as much vancomycin is required to inhibit these strains as a normal strain, or recently, in 2002, in the U.S., we have seen the first true VRSA isolates.

Both of those isolates contain the vanA gene sequences from Enterococcus, and in the first case, the patient in Michigan, it was fairly clear that that was transferred from vancomycin-resistant Enterococcus faecalis, not faecium.

[Slide.]

Now, let me shift gears and talk for a moment about gram-negatives and about extended spectrum beta-lactamases. Most of the ESBLs that we are familiar with in North America are

derivatives from either the TEM-1 or SHV-1 enzymes.

These are the beta-lactamases ordinarily found in E. coli and Klebsiella that generally just code for ampicillin resistance, but when mutations occur, they may then hydrolyze at least at high inoculum all of the currently available penicillins, cephalosporins, and aztreonam.

As you can see on this slide, as of last Friday, there were a huge number of different TEM and SHV enzymes that have a different molecular structure or a different spectrum of activity. In fact, some of these strains appear susceptible to some cephalosporins, but resistant to others.

[Slide.]

Now, the molecular basis for this are point mutations that probably occur spontaneously in the genes that encode either TEM-1 or SHV-1, and even a 1 or 2 amino acid sequence change can take a strain from being very susceptible to a drug like ceftazidime to being highly resistant, so these are fairly subtle point mutations that occur every day.

[Slide.]

Some of these enzymes provide very obvious resistance to a compound like ceftazidime as in the case of TEM-10, while retaining very low MICs to

cefotaxime, so the argument has been, well, this is a potential difference between these compounds that perhaps could be taken advantage of.

[Slide.]

However, at very high inoculum, that is, if you increase the number of cells, the amount of enzyme present, you can see even the latest generation cephalosporins are hydrolyzed by these enzymes.

On the other hand, the structure of the carbapenems tends to resist hydrolysis by the ESBL and they tend to remain susceptible to that class.

[Slide.]

Now, again, clinical significance is very important. David Paterson from Pittsburgh, I think has done some of the most important work to illustrate the clinical significance of these strains, and in a 2001 publication, he reported a multi-country, multi-continent study looking at Kleb pneumoniae bacteremias, and about 18 percent or so of these organisms were found to produce ESBLs.

Nine of those were treated with a cephalosporin that, by conventional testing and conventional breakpoints, were either intermediate

or susceptible to a cephalosporin, however, among those 9, 3 patients died and 5 required additional therapy.

Overall, there were 32 patients that were treated with a cephalosporin that we would, based on testing of that drug by itself, consider either susceptible or intermediate to a particular drug. Among those that were classified as intermediate, all 4 failed therapy and 15 of 28 of the strains considered susceptible, meaning they had fairly low MICs, also failed therapy.

Among those were 5 patients treated with cefepime, to illustrate the last point, and 4 of those also failed.

[Slide.]

Now, ESBL-producing strains carry their gene for beta-lactamase production on a plasmid, and that plasmid can be easily shared among different isolates of the same species or between species.

Located on the same plasmid in most of the ESBL are genes that also code for trimethoprim sulfa and for gentamicin resistance, so here is an example of co-transfer of genes that affect more than one class of drug.

Unrelated to that is the fact that many and I would guess maybe 40 or 50 percent of isolates also were fluoroquinolone-resistant, but that is not a plasmid-mediated event in these strains and it is not co-transferred.

[Slide.]

Then, there are many other gram-negative rods, too many to mention in my limited time, but I just want to make a brief pitch for the importance of Pseudomonas aeruginosa and the fact that Pseudomonas isolates may have a number of different beta-lactamases including the ability to hyperproduce the ampC or Bush group 1 beta-lactamase to code for resistance to a variety of beta-lactams, but they may also have plasmid-mediated enzymes, such as PSE-1, -3, or -4, and also the less common ESBLs, such as the OXA group of enzymes that are not yet very common in this country, but are in some other parts of the world.

Many of these strains produce enzymes that chemically inactivate in aminoglycosides or they may have outer membrane protein changes which essentially close the door to penetration by the aminoglycoside group of drugs.

Fluoroquinolone resistance is now relatively common among Pseudomonas isolates often due to mutations in the gyrA gene.

Very interesting I think is this class of efflux pumps, often the Mex B, D, or F pumps that can be found in Pseudomonas, that every effectively remove fluoroquinolones and cephalosporins from these strains before they can have any activity.

[Slide.]

Now, I will say a few words about pneumococci to wrap up my remarks. First of all, everyone is aware of penicillin resistance in pneumococci. The point of this slide, the upper portion at least, is that there are several different penicillin-binding proteins that can be modified through self-transformation, that is, taking in DNA from another pneumococcal strain or even from a viridan strep that might be an oropharyngeal colonizer.

Pneumococci can then build so-called mosaic genes that code for penicillin-binding proteins of lower affinity.

For high-level penicillin resistance, there may need to be as many as 3 of these penicillin-binding proteins modified, but for

cephalosporin resistance, that is, extended spectrum cephalosporins, it is really only necessary to have 2 of these PBPs altered.

So, there are now some strains that are more resistant to cephalosporins than to penicillin.

[Slide.]

Now, looking at CDC surveillance data from the active bacterial core surveillance program published by Cindy Whitney in 2000, I would like to simply illustrate the point that penicillin-susceptible pneumococci, in this column, are rarely resistant to other drug classes, that is, they rarely have genes that would affect the macrolides, tetracycline, or the fluoroquinolones.

As you move to strains that have diminished susceptibility to penicillin, you see it is more frequent that those isolates may carry genes for other drug classes, and as you move to the penicillin-resistant Strep pneumos, it is quite common to see macrolide resistance, trimethoprim sulfa resistance, and indeed there is a statistically significant association between penicillin and fluoroquinolone resistance in these strains.

Now, that is not because these genes are all co-transferred, but rather these are clones of pneumococci that have become repositories, if you will, for many different resistance genes, and the fittest of these clones have now circulated throughout the world.

[Slide.]

So, macrolide resistance in the United States is most often coded by a gene called mefA or mefE, which is an efflux pump. A smaller number, a small percentage of strains have the erm gene, which codes for clindamycin, as well as macrolide resistance.

What is interesting to me is it is the reverse in Europe. The erm strains are much more common than the efflux strains.

Many of these strains also have tetM or an efflux pump, and many of the strains now, particularly the pen-resistant ones, have altered enzymes needed in the folate pathway that affect trimethoprim or sulfa or both to code for trimeth sulfa resistance.

[Slide.]

Quinolone resistance in pneumococci has become a major concern. The study published in

2002 by Davies and colleagues looked at strains that had borderline susceptibility to levofloxacin, but found that about 4.5 percent of these strains actually contain a first-step mutation of the parC locus that would code for higher MICs to drugs like ciprofloxacin, but not so much so for levo.

The second step or double mutants, on the other hand, become quite obviously resistant to the currently used fluoroquinolones, and those are estimated between 0.2 and 0.5 percent of strains in the U.S., so a very small percentage as of today.

However, when those mutations occur, as we have showed in this earlier study, those mutations, particularly those that involve both the parC and gyrA loci, also are the same targets used by the later, more potent fluoroquinolones and raise the MICs of those compounds, as well.

So, the concern here is that despite the greater potency of the newer fluoroquinolones, they still affect the same drug targets.

[Slide.]

Now, I think the real concern and where we ought to look is the data that have emanated from Hong Kong and have been published by Ho and colleagues, in which they showed in 1995, a very

small percentage of their pneumococci were fluoroquinolone resistant, essentially, the same as we currently see in the United States.

However, a few years later, that percentage had increased and then by 2000, it was more than 13 percent of all of their isolates, and if they looked specifically at the more resistant clones, that is, the penicillin-resistant strains, it was more than one-fourth of those.

Now, what is unique here is that this is a single clone or, if you will, single strain of pneumococcus that has been shared throughout patients in Hong Kong, so it is not dissemination of genes in the sense of transmissible elements, but rather a single, very fit clone that originated originally from Spain and is a serotype 23F clone, has now become very common in that area of the world.

So, the concern I think is could we see this sort of thing in North America.

[Slide.]

Now, my final slide is maybe food for thought more than firm data. That is, Elaine Tuomanen and colleagues in Memphis have illustrated a few strains, one at least associated with a

meningitis treatment failure in a 10-month-old that they describe as being tolerant to the bacteriocidal effect of vancomycin and also the bacteriocidal effect of beta-lactam antibiotics.

This child had recurrent meningitis after a full course of both cefotaxime and vanc therapy. They have been working to identify a particular gene associated with this defect, but this is a totally different aspect of a failure of the autolytic system of this strain or these strains which is triggered by both the beta-lactams and vancomycin.

So, this is I think a point of concern, but it as yet a fully clarified area.

So, those are my feelings on this and I guess I would say the reasons for this are that there are mechanisms that we recognize that affect closely related compounds, such as the beta-lactams with MRSA.

Also, there are mechanisms, some of which I have described, that are co-transferred, that are genetically tied together and go with one gene into a different strain.

Lastly, as I attempted to illustrate with pneumococci, there may be multidrug resistant

strains due to the fact that there are clones that over time have collected these resistance genes and maintain them for fitness in an environment of antibiotic use.

So, with that, I think I will conclude and I appreciate your attention.

Mr. Chairman, do we have questions?

Questions from Committee

DR. LEGGETT: Yes. Why don't we open it up for questions.

I have a quick one, I may have missed it. The vanco tolerance, was it pneumococci?

DR. JORGENSEN: Yes.

DR. LEGGETT: Jan.

DR. PATTERSON: Jim, would you like to comment on the linkage of resistance in Acinetobacter, multidrug-resistant Acinetobacter?

DR. JORGENSEN: Acinetobacters certainly can be multidrug resistant including penicillin, cephalosporins, and can acquire resistance to carbapenems, and I think that has been the concern, is that some of those strains, because of resistance to other classes, have been treated with carbapenems only to later become carbapenem resistant.

DR. LEGGETT: Don.

DR. PORETZ: In our hospital, the tertiary care facility, MRSA continues, we still continue to be active with the sulfa trimethoprim, 80 percent of MRSA sensitive to sulfa trimethoprim, doxycycline, minacycline still very, very active yet. Those particular drugs are completely worthless against E. coli, Strep pyogenes.

Is it just because those drugs have not been used that often in the hospital in the past or why do we continue to have 80 percent sensitivity with sulfa and semisynthetic tetracyclines?

DR. JORGENSEN: I think that's a good question. The vancomycin intermediate and vancomycin-resistant Staph aureus strains have all been susceptible to trimeth sulfa and would seem even to be perhaps the drug of choice for those strains in terms of a good susceptibility profile.

Many MRSAs are susceptible to minacycline and perhaps the reason for that is minacycline is not so well pumped by the tetracycline efflux pump that many of those strains have.

I think you are right about the potential utility of those agents against those strains, but not against the gram-negatives, and I am not sure I

can explain why except that organisms like E. coli and other gram-negatives are part of our normal GI flora and are exposed every day to any antibiotic we would take for any reason and perhaps that is a partial explanation.

DR. LEGGETT: John.

DR. BRADLEY: I think the complicated nature of resistance, the multiple mechanisms of resistance, the ability of organisms to develop new resistances highlight something that we have been talking about on a number of occasions, about the difficulty in assigning a drug approval for an organism resistant to one particular drug, and that as your presentation really predicts for the future, that the situation is going to get far more complicated than simple and not only will we have to deal with Strep pneumo that is resistant to penicillin, cefuroxime, clarithromycin, et cetera, but we are going to have to deal with pseudomonads that have multiple drug resistances, acinetobacter, and are we going to be needing to deal with drug approvals for drugs that are active against each and every one of those antibiotics that are resistant on your list, requiring that the sponsor produce treatment successes for each of those sets

of resistances.

So, you have done a beautiful job of painting the future for us.

DR. JORGENSEN: I wish it were more optimistic.

DR. LEGGETT: Barth.

DR. RELLER: Jim, your presentation raises many questions that I have. I will restrict it, if I might, to two.

First, you mentioned the development unequivocally of resistance while on therapy with linezolid, quinupristin-dalfopristin where if one did PFGE, it is clearly the same organism.

Of these mechanisms of resistance, and time wouldn't permit all of them, which ones are recognized, of the more common ones, to develop on therapy and which ones has that not been observed? For example, my understanding is with penicillinase with Staph aureus, going way back, that on long-term observations that the development or acquisition of that plasmid in vivo doesn't occur.

But what about these other mechanisms, and the importance of it is where one might be on secure ground with a susceptible organism at the initiation of therapy, but see it change right

under your eyes.

DR. JORGENSEN: Enterobacter.

DR. RELLER: Well, Enterobacter, the D-repression with this is enough, but are any of the others, is there a pitfall, is it actually even more complicated than what you say having to do with you think you are okay, but then the ground shifts even in the course of therapy of an individual patient?

DR. JORGENSEN: I think you are right with penicillin-resistant or I should say penicillin-susceptible Staphylococci. In order to become penicillin-resistant, your organism would have to go out and find the plasmid and the beta-lactamase gene somewhere else, so it is not likely to change during therapy.

In the case of the Bush Group I or ampC beta-lactamase, you have an enzyme present in virtually every isolate of Enterobacter, Citrobacter freundii, Serratia marcescens, et cetera, that is just sitting there waiting to have a mutation in its represser sequences to a very high level of resistance. So, that can occur in maybe a couple of days during therapy.

VRSA represents acquisition of a gene

group again from outside, so it is not likely to happen commonly. It had to go and find that gene in the right environment of those two patients.

VISA, on the other hand, represents acclimatization to the presence of vancomycin over a long period of time, this thickened cell wall that is developed and been described in these strains, which seems to be an adaptation to the pounding away of that strain by vancomycin over a period.

So, I think in many cases, these are genes that are acquired, transferred, et cetera, or may be kept by a strain when spontaneous mutations occur, such as in the case of ESBL, that those spontaneous mutations do not have value in an environment that is not saturated with antibiotics, so we see those strains mostly in intensive care unit patients where there is value to maintaining those mutations for production of a very high potency beta-lactamase.

DR. RELLER: The second question that is related is with the different cassettes with Staphylococcus aureus MRSA, hospital-associated community-associated, is there a difference in the common detection mechanisms used in laboratories,

salt screen plate, latex agglutination, PCR for mecA, are there differences in the ability to detect accurately methicillin resistance among these strains?

The analogy is with the resistance and the use of cephalosporins, in other words, are there pitfalls in detection that are related to the different cassettes?

DR. JORGENSEN: Well, first of all, all of the variants of MRSA contain the mecA gene whether there is a big piece of DNA that goes along with it or a small piece, so genetic tests, such as PCR, that detect the presence of the mecA gene would pick all of those up very effectively.

All of those code for PBP-2a, so tests that would detect the protein product of mecA also would be positive with all of those.

I think some of the hospital-acquired strains are more likely to have the heterogeneous expression of oxacillin resistance that is more difficult to detect by phenotypic tests, such as distifusion or MIC.

The detection, however, is somewhat compromised I think in the community-acquired strains because microbiologists have been trained

to look for multidrug resistance as a secondary key that a strain might be an MRSA. Even some of our instrument systems have been programmed with expert systems to look for resistance to aminoglycosides, tetracycline, et cetera, as a marker for MRSA.

So, I guess I worry a little bit that the community-acquired strains might be underappreciated because they don't have that additional red flag that I'm an MRSA.

DR. LEGGETT: Celia.

DR. MAXWELL: Excellent summary, Dr. Jorgensen.

I have two questions on your next to the last slide with the 10-month-old and the meningitis. Was it Strep pneumo, the organism?

DR. JORGENSEN: Yes.

DR. MAXWELL: An earlier slide, looking at the differences between healthcare-associated and community-associated MRSA, was the outcome in those patients that were treated or what was the outcome?

DR. JORGENSEN: Well, in the community-associated or community-onset isolates, many of these patients had skin or subcutaneous infections, boils especially. Many of these were severe enough that they didn't improve without

surgical drainage. As long as they were drained surgically, the limited data, and the data are not extensive, seemed to suggest it didn't really make a lot of difference which antibiotic was used.

On the other hand, if you used an effective antibiotic without surgical drainage, they didn't do all that well. There are some groups, such as some of the physicians who manage jail and prison settings, that favor use of either trimeth sulfa or doxycycline or clindamycin to treat those strains, but the limited data suggest they make very bad subcutaneous infections that may require surgical drainage.

DR. LEGGETT: Dr. Jorgensen, could you comment upon the growing data about cross-linkage between detergents and antibiotic resistance?

DR. JORGENSEN: Well, I can tell you that in two of the mec cassettes, there are genes for resistance to heavy metals like mercury and things of that sort, and may also have to do with iodine and other disinfectants, but that is all I could comment on.

DR. LEGGETT: John.

DR. BRADLEY: Just a quick extra piece of information on that 10-month-old with Pneumococcal

meningitis because it created quite a stir in the pediatric community, and Dr. Tuomanen has done beautiful molecular diagnostic dissection of the resistance mechanisms. This is an autolysin-resistant, a deficient organism.

Normally, with pneumococcus, once you hit it with an antibiotic and cripple it, it kills itself. Well, this organism won't kill itself and there is no antibiotic, not vancomycin, not beta-lactams, not fluoroquinolones, nothing that will kill this organism. It can prevent it from growing, so antibiotics are static, but you need more than a static agent in the central nervous system.

So, the implication isn't just for vancomycin resistance, but it's for resistance across all antibiotic classes for this organism, and we are just thankful that it hasn't seemed to have spread outside of Memphis or continued to increase in its prevalence there. Is that correct?

DR. JORGENSEN: Yes.

DR. LEGGETT: Thank you, Dr. Jorgensen.

The next speaker will be Frank Tally, who is going to give us an industry perspective on a list of pathogens.

From the first speech, it looks like the list of pathogens is all our common pathogens is all I can say.

Industry Perspective on List of Pathogens

Francis P. Tally, M.D.

DR. TALLY: Mark Goldberger set the stage for today's meeting with the two major themes of what is the list and do we need, can one particular study in one system support studies in another system, but I think in the documentation that was sent out via the Internet, there was also a third issue I saw in there, is the problem of decreasing research in the area of developing new antimicrobial agents, and I would like to kind of wind that into the discussion today.

[Slide.]

Why develop drug for resistant pathogens? Well, as you have heard, resistant pathogens kill people, and I will delve into some of that data. It was nicely discussed by Dick Wenzel at the November workshop meeting that we have talked about.

For a pharmaceutical company or a biotech company, one has to justify the expenditure of a large amount of money to develop a drug for a

particular area, so that drug should have specific advantages which allow the drug to penetrate into the marketplace and return the investment that the company has made.

An alternative, which I spoke about at sessions a couple years ago, if we are not going to do that, then, one should possibly even think about developing another institute at the National Institutes of Health to actually look at drug discovery for some of these, what we would call orphan pathogens, and do the basic work to come up with targets and particular lead molecules, and then turn it over to industry to go off with the development.

That is something I think we possibly should consider down the pike.

The problem in industry right now is that anti-infectives are competing with CNS drugs, cardiovascular drugs, and GI drugs that people have to take for the rest of your life, so there are huge markets and huge sales, and the anti-infective drugs are being prioritized down, and not going into development pipelines.

Most companies need a potential market of $500 million to bring a drug forward into

development.

That shifted the burden actually out to the biotech industry and there are a lot of companies out there trying to develop antimicrobial agents, but I can tell you the cost of developing is a problem in raising funds, and if you have been in this particular area or even had any stock whatsoever, you will understand what I am saying because at times, like three years ago, it was easy to raise funds. It is nearly impossible to raise funds this year even to start-up companies with very good ideas, that two or three years ago you could start.

So, we are in what I would call almost a nuclear winter of funding for biotech companies at this point in time, and you are going to see a number of those companies go under.

So, I think what is happening in the November workshop and with what Mark said will happen in the future, I think is absolutely imperative, that is, regulatory bodies, academia, and the pharmaceutical industry have got to get together to streamline this process, so we can develop life-saving drugs coming now.

What you need is microbiological

superiority, you have to be active against the resistant organisms, and you would like to have a drug that is not going to develop resistance very fast. You would also develop something that had a distinct pharmacological advantage, and finally, something that had a safety advantage.

[Slide.]

We have a well worked out paradigm. There are some scientific holes in it, but we do have the paradigm that you work first in the test tube to see if the bug is active, how it works, what its mechanism of action is, is it a cidal drug, is there low induction resistance, and is it active against both susceptible and resistant pathogens because you can't determine a priori whether the patient has a resistant or a susceptible pathogen.

The next step is efficacy and appropriate animal models, and this is hotly debated, with the key pathogens, both the resistant and susceptible pathogens, and also bringing in the elements of pharmacodynamics in developing what levels of drugs that you need. I know Bill Craig and George Drusano have discussed that at many of these meetings.

The pharmacokinetic requirements can be

worked out ahead of time also. You need an I.V. drug for serious infections. Many times you can switch over to an oral drug if you have it once the infection comes under control.

We need to know if the drug penetrates into the site of infection. John was talking about that strain in the central nervous system. You need to be able to penetrate into the central nervous system.

You need to be able to penetrate into the alveolars to get aspiration pneumonia or aerosol pneumonia. These are topics I think will be discussed this afternoon.

Finally, there is the risk-benefit analysis with the safety database.

[Slide.]

I borrowed a slide that Ed Cox showed at the meeting on the 19th of November on how you get on the list, and I know this is going to be gone into in detail a little later by John Powers, but I think there are two or three themes here, is there sufficient prevalence, because if there isn't sufficient prevalence, you are not going to be able to study it.

Two, is the organism virulent, does it

really have the public health importance that we are talking about.

Then, you go down to look at other sufficient therapeutic alternatives to really justify going forward.

So, what I would like to do for the rest of the talk, is kind of set some of the themes on how you go forward.

[Slide.]

First, the list. This is what David Ross presented a couple of years ago in a briefing document. This list is notable in that some of the newer resistant bugs, the Acinetobacters don't appear here, and I think this is a class that probably should be added to these lists.

[Slide.]

We do have very potent pathogens here. When you look at the community-acquired, Jim just went over a number of them. We have some other areas outside the gram-positives and the salmonellas and N. gonorrhea areas, so this is a list that has to go forward.

We have talked about the vancomycin-resistant Staph aureus and the looming problem that may be coming.

[Slide.]

Jim has gone into the multidrug resistance. This is a study we actually had the Focus people do for us, to look at the incidence of multidrug resistance in common and gram-positive pathogens, and you can see it is significant when you sample 50 different centers around the United States, so it is a major problem coming and it's a problem that is changing over time, so a system has to be put in place to be able to track this in order to identify the problem bugs.

We see the case reports as we are hearing about some new resistances, but people have to pay attention now to make sure they don't become a dominant pathogen.

[Slide.]

I would like to use Staph aureus as a model on how you would get onto the list, and you go back to some work, Chip Chambers published this actually in Emerging Infectious Disease in 1999.

This is what happened with penicillinase-producing Staph aureus. It appeared almost after penicillin appeared. It became a real problem in the '50s in hospitals. When I was in training in the early '60s, penicillin resistance

was not a problem out in the community. Yes, you would see it occasionally, but you can see very rapidly over the next two decades it became a major problem, and now the penicillin resistance is out there.

[Slide.]

We saw the emergence of MRSA. It was low. Jim reviewed the history of it. It is up to almost 50 percent now in many hospitals, and this actually drove the use of vancomycin. You can see the tonnage of vancomycin used as the incidence of methicillin-resistant Staph aureus came about. So, it does have an impact on the way the physicians treat patients.

[Slide.]

In the community now, are we seeing again what was seen with penicillin resistance? We have high levels of methicillin resistance in hospitals in nosocomial infections. We are starting to see it, and by word of mouth, we are hearing from almost every city in the United States that a significant percentage of patients coming into emergency rooms now have MRSA, so I think this is one area that has to be monitored very closely, and it has been seen in many different countries.

These organisms are fully virulent, actually, they are probably a little virulent than some of the hospital strains, and they have caused fatal infections in children. It varies as high as 21 percent in Finland, and in some of the localized communities, Indian American communities, there was actually an incidence of 55 percent in the children.

As Jim pointed out, these community-acquired strains are much different and they are not the multidrug-resistant strains, but they have something else that is much scarier. There was a recent study presented at ICAAC with 32 community-acquired MRSA isolates, of those 32 isolates, 31 were producing the superantigens Enterotoxin B and C which causes toxic shock.

So, these are organisms that have high virulence factors that we may be seeing as a major problem coming forward.

[Slide.]

Finally, the VRSA that Jim has already talked about, the two strains, one from Detroit, the other one from Hershey, Pennsylvania. It turned out the Hershey patient also had a vancomycin-resistant enterococci in the wound, but

the strain was lost, so you really couldn't tell whether or not that's where the vanA gene came in the Staph aureus in Hershey, Pennsylvania, and the organisms are not related, which is another scary factor.

So, I think this is what is starting to dictate is that we are going to need some new classes of drugs to drive on for some of these resistances because, as Jim pointed out, they are resistant to a lot of different compounds.

[Slide.]

We just heard a little bit about the development of resistance, and this is a slide Bob Moellering showed at a meeting I was at, and he looked at the rate of resistance to vancomycin versus linezolid. It took a long time for vanco resistance to come about.

That is probably because it wasn't used much, because we had many other anti-staphylococcal drug in the '70s and '80s, but when that tonnage went up to treat MRSA, the bugs had to do something, and they did an architectural, an engineering feat of putting eight genes together to overcome vancomycin resistance, but once that genetic bridge was built, it can be traded around,

but it took 30 years for resistance to develop to vanco, but with linezolid, it developed actually while the clinical studies were being done.

[Slide.]

There was a paper in CID in January of this year of the compassionate use where they had 19 cases emerge while on therapy, so it is a problem, and this comes back to the question about the U.S., and those are point mutations giving the resistance to linezolid in the ribosome, so they can emerge during therapy.

[Slide.]

But, unfortunately, it has also emerged in Staph aureus, and I am aware of three different isolates now of Staph aureus. Well, what is the problem with the Staph aureus?

We just heard maybe if you just drain it, it's okay, but if you look at bacteremia, probably one of the worse infections you can get with Staph aureus, and you look at the mortality, it is in the second set of bars, it's 30 percent. This is bugs that they kill people in a high percentage.

Indeed, the mortality rate with MRSA is even higher than with MSSA, but it is not only true for Staph aureus, but coag-negative staph,

enterococci, and Candida also when it is in bacteremia, the mortality is high. This is studies coming out of Dick Wenzel's group published in 1999. So, these are organisms that cause a lot of mortality.

[Slide.]

What about the pre-antibiotic era? This is a paper by Skinner & Keefer back in 1941. Staph aureus bacteremia had an 82 percent mortality. This is a real killer organism, and as the patient population got older, as you can see on the graph, the mortality was 100 percent. So, with our aging population and Staph aureus, this is a major problem.

[Slide.]

How about if inadequate therapy is given? Another slide that Dick Wenzel presented on data from Ibrahim in Chest in 2000. If you look at patients with intensive care unit bloodstream infections, and the numbers of patients are fairly large here, if you get inadequate therapy, the mortality is great, it doubles more than 50 percent.

If you look at the patients, the organisms that were causing this mortality with inappropriate

therapy, it was two main pathogens, Staph aureus and Pseudomonas aeruginosa. So, given the appropriate therapy early on, it empirically, really changes the outcome overall.

So, I think these are the type that have to be put together for different pathogens to get them onto the list.

Dick has also written a prospective article in JID in '99, looking at the impact of therapy and attributed mortality, and as he says in that article, the resistance genes just add to that mortality, so if you have a drug that treats the resistant organisms, you can bring the mortality back down.

[Slide.]

Well, what are some of the problems? We talked about this a lot at the February meeting and at the meeting in November. I am just using some of my old slides there, but one of the problems that we have right in the development of drugs is there is very limited drugs in the pipeline.

The promise that genomic sequencing in combinatory chemistry was going to cure it has failed to date. We still think that those new targets will yield some compounds in the future,

but I think it is going to be another 5 to 10 years before you start seeing those compounds come down the pike, and we need substantial funding to continue that.

[Slide.]

I am not going to go into the detailed drugs on the next two slides. You have those that you can look at. There are two approved drugs here, and then there are five drugs being evaluated for gram-positive infections listed. They are in different phases of development.

[Slide.]

Following up on the ICAAC, and from data in the literature, there is another group of drugs. These are all analogs of beta-lactams with activity against Staphylococcus aureus. What it is, is these compounds were engineered to bind to PBP-2a.

They do it much better than most other cephalosporins and carbapenems, and there are a number of them now going into development both in the United States and in Japan. That is the cephalosporins. The carbapenems have not made it to development yet, there is major problems in synthesis of those compounds and whether or not

they are going to be brought forward, and I included these just for informational purposes.

What is missing from the list? There is no drugs for gram-negatives, and gram-negatives are a looming problem in the hospital, and there is nothing that I see in the pipeline that is really going to add to the armamentarium, and that's why we need to encourage the development of drugs in this particular area.

[Slide.]

So, what about development of drugs for resistant pathogens? You need to promote development and appropriate use of them and the appropriate labeling. If you get restricted labeling, it is okay for an MRSA, but for a more focused product like a VRE, it is going to really negatively impact people developing drugs for that particular area.

But basically, what you come down to is with enough safety database if there are safety issues, but there is activity against resistant pathogens. That will actually control the use of drugs, and I.V. drugs only are going to be controlled in hospital or in home I.V. use anyway.

[Slide.]

I.V. drugs are a problem to develop. You need serious infections because patients have to be in the hospital. Selection of comparative agents, I don't think is that much of a problem because there is a lot of drugs out there which are considered the drugs of choice.

One should select the best agent, though, and I think this is a part of the monitoring by the FDA and Human Studies Committees to ensure that the best therapy is given as a comparative agent.

I think the criteria for oral switch are being developed with different partners.

[Slide.]

With serious infections, there was a lot of talk about using surrogate markers with clearing of the cerebral spinal fluid in meningitis, clearing the blood with pathogens, but, of course, you need clinical outcome also, but the importance of clearing pathogens out of the CSF has been brought up before.

Another question on what is the number of pathogens that you need, and I think we are going to be discussing that this afternoon, and the requirement for two well-controlled studies, this is one of the major topics of this conference, but

there is another initiative that has been initiated at the FDA, which I think industry should use more, and that is use the target package insert initiative to really increase the communication and to clear up exactly what has to be done, and increasing the use of that particular initiative may actually help in the development of drugs.

[Slide.]

Finally, how do we incentivize drug development? This is really more a biotech field than a Big Pharma field. For expanded access, there is the possibility of charging fees just to cover your expenses or to augment what you are raising on the marketplace.

There was a lot of talk about patent term extension at the November 19th meeting, and this is the initiative talked about by Mark Goldberger, about extending and giving a wildcard patent extension, that for developing drugs for niche products, you would then put the patent extension onto another product, and that drew a tremendous amount of enthusiasm from the Pharmaceutical Manufacturers Association.

How about funded consortiums? I think that is a model, also cancer and AIDS has already

had it, and we should move forward.

One of the other areas that was brought up by one of my colleagues at Cubist is possibly the development of a loan system or government guaranteed loans. This would facilitate biotech companies being able to access different types of funds than just the stock market, and being able to develop funds.

There are small business loans, but most biotech companies are too big to really get into that particular area. That particular thing could be modified also.

You then repay the loans based upon once you have commercialized the product.

[Slide.]

The final incentives are tax credits or deductions. Right now it is only valuable for profitable companies, and there are things to extend tax losses to carry them forward, so you do become profitable, you can apply them.

But the biggest thing, they actually have this in Canada and some countries in Europe, you have a transferable tax loss. A nonprofitable biotech company can transfer that to another company that is profitable and some mechanism of

raising funds.

These are just some of the ideas that have to be developed in the future, and many of these ideas cannot be worked on by this committee, but really have to be worked on by Congress to pass some laws to get into this area for funding.

We do have drugs coming down the pike to treat some of the pathogens. There are areas of problems particularly with gram-negative where we need more research, and I think having the clear guidelines of how to develop these drugs and then encouraging companies to get into this area will help us in the future because of the emergence of these resistant pathogens.

Thank you.

DR. LEGGETT: Thank you.

I will open for questions at this point. Don.

Questions from Committee

DR. PORETZ: Frank, it is common for certain organisms to use combinations of drugs, like Pseudomonas, people have been using double agents for a long period of time, tuberculosis we always do, and in the antiviral world with HIV disease we do.

Should we be more commonly using combinations of drugs to hopefully prevent the emergence of resistance for other organisms than the classic ones that we have used?

DR. TALLY: I think that is something that is going to come, and you point to Pseudomonas for combination therapy, and studies that were done a long time ago at UCLA for gram-negative bacteremia combinations seem to work better also in the neutropenic patient.

So, yes, it is a point in the future where combination drugs will probably be employed. It is something that would come in a Phase IV type of procedure, because in registering a drug, you need to show that the drug, one, works, and, two, that it is safe in an adequate number of patients, and it is very hard to do that when you are doing combination studies initially.

So, you need to do the first steps to show that you have a drug that is safe and effective in treatment, and then for the resistant ones in the sicker patients, in Phase IV, you could do the combination therapy, so I think you are going to see a lot more of that.

DR. LEGGETT: Alan.

DR. CROSS: At our hospital, because of our resistance problem, we have been, in fact, using more colistin than I have ever seen used since I started training. In our last talks, someone asked about the status or feasibility of detergent type antibiotics, and I was just wondering given the resistance mechanisms we heard about in the last talk, are there any resistance mechanisms we know about for detergent drugs, number one, and, number two, these drugs have been developed a long time ago and since then we have acquired increased skill in understanding the structure-function relationships, and are there any efforts or do you think there is any utility in perhaps going back to a drug like colistin, making some modifications, and at least perhaps mining that area?

DR. TALLY: That is an area that I actually mined a while ago particularly to try and change the molecule, the colistin molecule of polymyxa B, to take off the part of the molecule that was binding LPS to see if I could use it in septic shock.

There has been a lot of work on polymyxins and colistin to try and come up with better

molecules, and I haven't seen any data that they have been able to do it.

The inherent problem with those drugs, as you know, is the nephrotoxicity and that they really stay in the vascular space and don't penetrate much. I think there are other efforts to look at those molecules.

Now, the detergent-like drugs, you get to a point where you can't give them because they are indiscriminate on all membranes, so it is a fine line. I know there are two or three efforts out there now that people are looking at those types of molecules.

DR. CROSS: Do we know anything about the resistance mechanisms that may develop with those type drugs?

DR. TALLY: No, not that I am aware of. Barth, do you know?

DR. RELLER: No.

DR. BELL: Frank, that was an excellent talk as usual. You have to some extent bridged the topics to be addressed in the morning session and the afternoon session, and I wonder if you could help me right now, in response to my question addressing the morning session, this concept of

criteria for pathogens or I might call it drug-resistant pathogens of public health importance.

What is the relative importance of the two topics this morning and this afternoon to the industry? In other words, I can well understand the afternoon's importance because it impacts on the way you would do studies and the materials you would have to submit for approval.

How useful is it to you to have a list of criteria for drug-resistant pathogens of public health importance stamped by some government agency, is that not something you could figure out anyway or you and your investors could surmise anyway, do you really need some sort of criteria like that or is it really only as it might relate to this afternoon's discussion that that is of interest of you?

DR. TALLY: I think I hear what you are saying, David. It is important for us. One, it is important for the discovery scientist to know what organisms we will be working on. That is at one level, that are going to result in a compound that would have a commercial potential.

The second part of the question is your

ability to raise money. It is easier to raise money from very skeptical investors, and they are all very skeptical, it is easier to convince them if there is some type of broad criteria that you can then fit your compound into or your organisms you are working into to increase the likelihood that you can get funding. So, it is important to the industry.

Now, for Big Pharma, it is important for the discovery scientists in Big Pharma to convince their upper management that they can develop a drug in this particular area, so I think it is important in both areas.

DR. LEGGETT: Frank, you made mention of you first have to prove your drug alone works. In that regard, could you mention some of the efflux pump attempts in terms of looking at inhibitors?

DR. TALLY: There has been a huge effort on trying to develop pump inhibitors. It is an area I personally have kept my research out of because when you look at the genomes of many of the bugs, the versatility of their pumps is such that when you turn one off, another one turns on, and so it has been very difficult.

You can show for select strains that you

can inhibit the pump and restore the activity of ampicillin or one of the quinolones or fluconazole back to what it was in fungi, but as soon as you start going out and do a survey, another pump turns on at about 10^{-7}, 10^{-8}, and you are right back to where you were with another pump pumping in molecule.

I was into this area also when I worked at Lederle with the pumps for pumping tetracycline. Again, there is a tremendous genetic ability of the organisms to manipulate these pumps to handle all the toxins because that is the way they make their living.

So, there have been very good pump inhibitors, but none of them has reached the stage of commercial development that I am aware of at this point.

DR. LEGGETT: Thank you.

If there is no further questions, we will take a break here and reconvene at 10:45.

[Break.]

DR. LEGGETT: The next speaker will be John Powers, who is going to talk to us about a list of pathogens of public health importance.

List of Pathogens of Public Health Importance

John H. Powers, M.D.

DR. POWERS: Thanks, Dr. Leggett.

This is a continuation of our discussion that we started yesterday when we talked about labeling for multidrug-resistant pathogens.

[Slide.]

What I would like to show you today is some background on the requests that we have had from folks in the industry to list resistant pathogens of public health importance and why we even want to engage in this endeavor.

The second thing I would like to go over is to elaborate on the criteria for listing pathogens of public health importance, and you saw that on one of the Dr. Tally's slides this morning, and then try to go into some information that we at the agency have been trying to obtain on looking at those criteria and how to obtain that data on looking at those things for each of the pathogens, and then finally, some future plans for populating that list.

[Slide.]

As I said, today is a continuation of previous discussions on development of drugs for pathogens resistant to antimicrobials. There were

several Advisory Committee meetings on this topic in the late 1990s, but most recently, there was a meeting of this committee about a year ago, in February of 2002, and then a workshop in November of last year co-sponsored by the Infectious Disease Society of America, the pharmaceutical industry, and the FDA.

It is very clear from these meetings that one of the main topics is that increasing in vitro resistance among many of these pathogens is becoming a public health problem. In some cases already, this in vitro resistance is translating into clinical failures, and even if we aren't seeing clinical failure at this point, it may signal a decrease in the future usefulness of that drug or drug class.

[Slide.]

In November, at the workshop, there were discussions on the shifting of resources within the pharmaceutical industry to the treatment of more chronic diseases, something Dr. Tally already brought up again today, and there was a recent Wall Street Journal article, and somebody sent this to me, and unfortunately, it didn't have the date at the top of the clipping, so I can't tell you which

issue it was, but it listed the top 10 selling antimicrobials in the United States.

I just sort of condensed them all together and looked at the drug classes. There was not a single antimicrobial on that list of top 10 selling drugs, and on those were antidepressants, anti-ulcer medications, cholesterol-lowering drugs, and two drugs for anemia, but none of them were antimicrobials.

So, as Dr. Tally elucidated for us this morning, antimicrobials are not the moneymakers for the pharmaceutical industry. So, why even put together this kind of a list?

[Slide.]

Well, at last year's meeting of this Advisory Committee, representatives of the pharmaceutical industry requested that the FDA develop a list of pathogens for which drug development was deemed of public health importance. Again, this same issue was brought up in November of 2002 by both representatives of the Infectious Disease Society of America and the pharmaceutical industry.

At that point, we discussed, well, what would the criteria be for developing such a list,

and we felt it was important to come up with the criteria before we just started putting names of pathogens on a long list, the reason being that obviously, as Dr. Tally brought up this morning, this list would probably change over time, therefore, it would be nice to have some uniform criteria, and one of the other things Dr. Tally brought up is when a company wants to go develop a drug, they want to be able to sort of plug this in for their particular drug and the particular organism that they are looking at.

We could take an example of this. For instance, in the 1950s, in hospital-acquired infections, penicillinase-producing Staphylococcus aureus was a scourge at that point.

One could argue that there are plenty of drugs available now to treat just penicillinase-producing Staphylococcus aureus, and one would not put just that drug on a list at this time. However, methicillin-resistant Staphylococcus aureus is a different story.

So, you can see that some of these pathogens will change over time as to what would be considered of public health importance.

[Slide.]

How would we use such a list? Well, there is a couple of points that are important to bring up, and that is to get on this kind of a list, a pathogen would not need to fulfill every one of the criteria to be on this list. We are just using this as a kind of template.

The other issues that we need to discuss would be the drug sponsors would still need clinical data on treatment of resistant pathogens, as we discussed yesterday in our discussion on multidrug-resistant Streptococcus pneumoniae, and the reason we feel this is important is that there may be differences in patient characteristics of those who harbor resistant organisms versus susceptible organisms, and we feel it is still important to actually see clinical information on the treatment of those patients.

One of the other reasons that this may be important to have a list for the pharmaceutical industry, that came up in November, was the idea that perhaps these drugs could be given priority review.

Now, it is almost impossible to designate priority review upfront in the development process because as Dr. Goldberger brought up in November,

whether a drug gets priority review or not depends upon the results of the clinical trials, but at least it would be designated that perhaps the drug might get designated as a priority review.

For instance, just recently--now, this is public knowledge--daptomycin has been designated for priority review, as well.

Also, drugs may still be approved, but not garner a resistance claim until there is sufficient clinical data, and this is addressed as another important point. The issue here is the drug will be on the market and available for clinicians to use in their patients, but until there is a sufficient clinical database, they don't necessarily need to have a resistance claim.

The example of this is levofloxacin, which was approved in late 1996, but didn't garner a claim for penicillin-resistant Streptococcus pneumoniae until 1999, when there was sufficient clinical data to support its efficacy in the treatment of those organisms.

The other important point here is that this is a list for prioritization, and Dr. Leggett already pointed out in our discussions so far, we have essentially talked about every bug you could

possibly think of, but since this is for prioritization, what we are trying to look at is what do we consider most important.

So, because an organism isn't on the list doesn't mean it is not important, but we are trying to prioritize these things.

[Slide.]

So, what we did, there were seven initial criteria that you saw on Dr. Tally's list, and we condensed them down to six because it appeared to us that two of them essentially were the same thing, and I will go through these.

The first is that the organism is of sufficient prevalence in the population with the disease under study, and I will talk about these in more detail through the talk.

The second is that the organism causes severe or serious disease. We changed this from virulence because we didn't want to get into the issue of virulence factors as much as that those virulence factors actually translate into high morbidity and mortality for patients.

The third is that the drug to which the organism is resistant is commonly used in the disease under study.

The fourth is that there is limited available therapies due to multidrug resistance, and we had separated these out into two separate criteria before, but then we figured, well, if it's multidrug resistant, that is why there is limited available therapies, and we condensed that into one criteria.

Finally, a drug is used to control spread of the disease in the population, and I will give some examples of that, and then lastly, that there is a clinical correlation of in vitro resistance with poor clinical outcomes.

[Slide.]

So, let's go through each one of these, and I will try to show you some of the information we have tried to put together for some organisms to put on this list.

The first is that the organism is of sufficient prevalence in the population with the disease under study. The first point here is that this speaks to the current burden of the public health problem. If an organism is really, really uncommon, not to say that it is still not important, but what is its relative importance compared to some to some of the other organisms

which may be more common for which we might desire drug development.

Dr. Tally also brought this up this morning. If an organism is very, very uncommon, then, it is almost impossible to get clinical information and to study it, as well.

As we said, less prevalent organisms may still be important or they may become more prevalent over time, and again this list should be a dynamic thing where we will update this as time goes on.

Also, this brings up an initial point here about linking the disease under study and the organism, and most resistance labeling claims are related to efficacy in a particular disease, so one could argue that perhaps an organism is important in treating hospital-acquired pneumonia, but that same organism may not be as big a deal when treating an uncomplicated urinary tract infection.

Also, this provides the most helpful information to clinicians to show where the drug actually works in which particular disease, and we will talk some more about this issue of difficult diseases supporting each other this afternoon.

[Slide.]

So, let's try to look at some information on how common are some of these organisms. I am going to show this again for some of the committee members that weren't here yesterday.

The FDA has tried to obtain surveillance data in several ways, and one of the things we have done is to obtain this information from Focus Technologies through a contract that we issued last year.

We got this contract for the purposes of identifying and tracking resistant organisms of public health importance really for the purposes of drug development. The Surveillance Network of Focus Technologies includes 317 U.S. laboratories, and this information is updated continuously. I will you some information today as Dr. Jorgensen showed, something about penicillin-resistant Strep pneumo and 14 percent of those organisms being multidrug resistant. That number is a lot higher now than when that was published in 2000.

This includes community, government, and university laboratories, and hospitals that range from bed size of below 99 to over 500 beds.

[Slide.]

This Surveillance Network also includes

greater than 65 million antimicrobial susceptibility testing results for various bug-drug combinations. It is not an active surveillance network, and it is based on cultures which clinicians order.

We looked at this in several ways. One way we could look at this is per isolate, one way we could look at it is per patient, and when we did it, essentially, the results come out the same. So, all the information that you will see today is on a per patient basis, and we also looked at only one isolate per patient.

When we looked at that isolate, we looked at it from a first isolate per patient, last isolate per patient, and it came out to be the same in most of the cases, which brings up I guess an important point that Dr. Reller raised this morning, about development of resistance on therapy, but for the vast majority of what we looked at, the first isolate and the last isolate, the susceptibilities were not different.

This database includes over 500 microbial taxa and greater than 100 individual drugs, and covers almost 3 million patients who are both inpatients and outpatients, which gives us access

to an estimated 2.6 percent of all isolates tested per year in the United States, and some of the other surveillance data is about less than 1 percent.

[Slide.]

Here is some of the information that we tried to get to address this idea of how common is an organism in the population. As you can see, interestingly, of these greater than 500 taxa that are in this database, only 27 of those taxa account for 95 percent of the clinically encountered bacterial species.

So, if you look at this, as Dr. Tally pointed out, Staph aureus seems to be a fairly important organism here, 16.1 percent of Staph aureus make up this 95 percent, and the interesting thing is that the inpatient-outpatient split is starting to get closer and closer, 9 percent of these are inpatients, 6.5 are outpatients.

Although we discussed Streptococcus pneumoniae at great length, you can see that Streptococcus pneumoniae only account for 1.3 percent of this, with 0.7 percent being inpatients and 0.6 percent outpatients.

There is an obvious bias in this, and that

is that the kinds of diseases in which Streptococcus pneumoniae is most common, things like sinusitis, are also the kinds of diseases where clinicians may not choose to culture patients, so again there are some limitations in this data.

[Slide.]

I apologize for this being very hard to read, but it is awful hard to squeeze 27 taxa onto one slide and to try to show you some of the quantitative information, as well.

What we have here are 27 taxa listed from most common to less common on this list, and here is a point that Dr. Tally brought up this morning. If we look at the overall burden of disease, the Enterobacteriaceae account for almost half of it, and yet we see very little drug development for these gram-negative organisms.

When we split them up by the top 10 Enterobacteriaceae, we have E. coli leading the list, Klebsiella pneumoniae, Proteus mirablis, Enterobacter cloacae, Serratia marcescens, Enterobacter aerogenes, Citrobacter freundii, Klebsiella oxytoca, Citrobacter, Morganella on here.

Then, we get down to some of the gram-positives with Staph aureus accounting for 16.4 percent, and as Dr. Tally pointed out in that Chest article, it was Staph aureus and Pseudomonas that were the ones that had the excess mortality.

The organisms that come up next are coagulase-negative Staphylococci, Pseudomonas aeruginosa, and Enterococcus faecalis. Enterococcus faecium again, although we have talked a lot about vancomycin-resistant E. faecium, is 0.9 percent down here. Again, this isn't saying that these organisms aren't important, we are just trying to put this on a relative scale compared to some of the other things that we are seeing.

So, the organisms for which we are seeing drug development, like Enterococcus faecium and Staph aureus really the question is how do they fit in compared to these gram-negatives where we are not seeing a whole lot of drug development.

Some of the other things we see down here, Acinetobacter, stenotrophomonas, and then we get to Streptococcus pneumoniae, viridan strep, group A and B streptococci, Haemophilus influenzae, and anaerobes at the bottom.

[Slide.]

There are some limitations to this data, as I said, as it is limited to what clinicians actually order tests for. One can make a case that penicillinase-producing and quinolone-resistant Neisseria gonorrhea is an organism of public health importance, and yet when we went to look for this, over this five-year span, we could only find 1,500 isolates of Neisseria gonorrhea in this database.

Again, I am not saying that this is unimportant, it just shows that unfortunately, that we can't obtain much information and there are other mechanisms and I believe the CDC has an active surveillance for looking for resistance in Neisseria gonorrhea.

[Slide.]

So, one of the other things that we can do with this database is to try to track the proportions of infections over time to try to see which are increasing, as well. So, what we have here is the percent of all patients with bacteremias, and this goes from 1998 to 2002.

You can see that there is a slight increase in all Staph aureus and plateaus out from 1999 to 2002, but what you can see, at least from the data that we have obtained, is that the number

of methicillin-resistant Staph aureus bacteremias is going up, and there has been a slight decline in methicillin-susceptible Staph aureus bacteremias, so again this is just one way of trying to look at the burden of disease.

[Slide.]

One of the other things that bears discussing here is something that we talked about yesterday, about trying to put into the label information on helping clinicians to make treatment decisions.

One of the things that still clinicians will need to look is what their individual patterns of susceptibility are in their particular institution or their particular community because when you look at the spread of methicillin-resistant Staph aureus across 111 institutions in this database, it is enormous, so if you practice over here on the far left, you have a less than 10 percent incidence of methicillin-resistant Staph aureus and perhaps you don't need to worry about that when you are making treatment decisions.

If you practice over here, you have got a big problem. You need to consider Staph aureus

probably every time you see a person who is infected with a gram-positive.

So, looking at this information on drug-resistant pathogens isn't going to obviate clinicians still needing to know what the resistance pattern is in their own community.

[Slide.]

So, let's move on to the second criteria. Do the organisms cause serious and severe disease? This is really information that we can just garner from the clinical literature and what we know about the natural history of disease caused by these pathogens.

Again, resistance claims are usually linked to the disease under study. For instance, we have up to date granted penicillin-resistant Streptococcus pneumoniae indications for community-acquired pneumonia, but not acute bacterial sinusitis or acute exacerbations of chronic bronchitis.

It is also important about the range of organisms that cause various disease. If one were to grant an indication that said for all resistant Streptococcus pneumoniae infections, that may not be very informative to clinicians, and it also

doesn't impact on things like Strep pneumo causes respiratory tract infections, but it's an uncommon cause of something like urinary tract infections.

Again, these diseases range from fatal to self-resolving diseases, and it may be that the impact of resistance is most likely to be important and relevant to public health in the diseases which are not as likely to resolve spontaneously.

This gets to an issue of making public health decisions versus decisions in individual patients, so when we are approving a drug, we are looking at is this drug going to be used in millions and millions of people to treat that particular infection. That doesn't mean we are telling a clinician that if they see a patient that has been treated over and over again and has failed numerous antibiotics that they can't make a treatment decision based on what they are seeing in front of them.

[Slide.]

So, when we look at some of the stuff of splitting it up by source, this database gives us the ability to actually try to look at where are these organisms most commonly occurring. In this graph, what you will see is splitting up the data

on Staph aureus infections by source.

In here, we will see the yellow bars are all Staph aureus, the pink bars are methicillin-susceptible, and the orange bars are methicillin-resistant Staph aureus. What you can see is that from all sources, that we still see that MSSA outnumbers MRSA, but you can see that there is big differences across these.

When you look at bloodstream infections, they are pretty much getting equal to each other. Upper respiratory tract infections, it seems that methicillin-susceptible outnumbers methicillin-resistant, and in UTI, actually, surprisingly, methicillin-resistant actually outnumbers methicillin-susceptible although the overall numbers are quite small.

[Slide.]

So, the third criteria is that the drug to which the organism is resistant is commonly used in the disease under study, and this really speaks to the clinical relevance of drug resistance. Again, I gave this example yesterday.

One could argue that trimethoprim sulfa resistance is a problem when one goes to treat an uncomplicated urinary tract infection because that

drug is very commonly used. On the other hand, if someone gave you the information that this young woman had an E. coli resistant to Streptomycin, causing her UTI, that information is not very clinically relevant since people don't use that drug to treat uncomplicated urinary tract infections.

We are attempting to gather information on drug usage for various diseases from a number of sources, and actually it is quite difficult to split this up when you try to look at what clinicians are using for a particular disease.

There are a number of databases, like the IMS database, which look at overall drug usage, but it is a lot more difficult when you want to piece it down to what people are actually using it for. So, we are trying to look at the IMS database, medical literature, and we are also trying to contract with some other folks to actually obtain sources of information from their practices about what folks are using for various diseases, and this is because variations in medical practice and resistance patterns in various geographic areas and patient populations may differ.

It is interesting, when I was listening to

the discussion yesterday, I think one of the committee members said I don't think cefuroxime should even be on here, it is not a problem, and the person sitting next to me said gee, that is the drug of choice we use at our hospital for community-acquired pneumonia. So, I think there is differences across the practices that may impact on this, as well.

[Slide.]

The fourth issue is limited available therapies due to multidrug resistance. This is what we have tried to get a lot of information on. So, we have tried to use surveillance data to examine the relationships of cross resistance within a given bacterial taxa.

I showed you this data yesterday for Streptococcus pneumoniae, that the way we are trying to look at this is if an organism is resistant to one drug class, is it resistant to the other and vice versa, looking at it in both directions.

We also plan to do similar analyses for other organisms, as well for fungi, and what I am going to show you is some preliminary analyses today that we have done for some of these organisms

that we are by no means complete yet.

We assume that organisms which are resistant to multiple drugs are more likely to have fewer available drugs for treatment, as well, which would seen to place them higher on the list.

[Slide.]

So, like I did yesterday, I want to show you a blank graph, so that we will have an idea of what we are looking at. What we have done is we have placed on the X axis the number of agents to which the isolates are resistant.

On the Y axis is the number of agents to which the isolates were susceptible, so if you are right here, it means that these particular isolates that you will see, and we put a number of dots across this here, each dot representing one isolate usually, and so if an organism falls right here, it means that it is resistant to nothing and susceptible to six different drugs.

If an organism falls right here, it means it is resistant to one drug and susceptible to five drugs, and then you will see these dots that kind of trail off down here. What that means is that an organism that falls right here is susceptible to four drugs, resistant to one, and intermediate to

one, just so you understand what you are looking at when we do this, and then we will trail down here to the point when you get to see these dots down here, these particular isolates are resistant to seven different antimicrobials and susceptible to nothing.

So, obviously, what we are really interested in is the organisms that are falling down on this end. If we see cross-resistance in these organisms, what we will then look for is clustering of organisms here and clustering of organisms somewhere down here, as well.

[Slide.]

Let me give you two examples of an organism that appears to be multidrug resistant with linked cross-resistance pattern and one that does not.

Here, we did the same analyses in almost 8,000 isolates of Acinetobacter baumannii. The antimicrobials tested across these seven things here are gentamicin, ceftazidime, imipenem, ciprofloxacin, cefepime, ampicillin- sulbactam, and piperacillin. So, that is the seven isolates that run across both of these isolates.

What you can see is that the organisms

either cluster right here where there are the darkest dots, and that means that the organism is either susceptible to all seven drugs and resistant to none, but right here is where we see the other clustering of the organisms.

So, if you have a resistant Acinetobacter, it is most likely to be resistant to five or six other drugs and susceptible to only one or two at that particular point. So, this way, we are looking at it in both directions of not just starting out with, say, gentamicin resistance and seeing how many are resistant to gentamicin, we are looking at it in two directions.

[Slide.]

Let's look at an organism that doesn't fit this pattern. This is Streptococcus pyogenes group A beta-hemolytic streptococci. Here, we looked at penicillin, vancomycin, erythromycin, clindamycin, ceftriaxone, and levofloxacin.

What you see here is that multidrug resistance is not a problem with group A strep. So, you will see that these organisms are, for the most part, susceptible to all six of these antimicrobials, and there is very few of them that are resistant. Again, this trailing down here is a

few of them will end up being intermediate, as well, but when you look out here, there is almost none that are multidrug resistant or very few when we get out to this point.

So, if we are looking at this criteria at least of multidrug resistant, Acinetobacter is clearly an issue here, but group A strep is not, and that there are a number of other drugs that may be effective.

[Slide.]

Then, we can actually take this information and do more detailed analysis on the resistance patterns by taking these particular cells and actually looking at the seven different drugs and trying to see whether they are resistant or not.

If you just take this group right here where we are talking about organisms that are resistant to six different drugs and only susceptible to one, that is across this line here. The beauty of this is you can actually look as we increase, you can see when you start to lose particular drugs. I will show you this for Streptococcus pneumoniae where it is a little easier because there are not so many drugs across

the bottom here.

But what you can see is that once you get to this point with an Acinetobacter, that you are talking about 98 percent resistance to aminoglycosides, 91 percent to ceftazidime, 99 percent to quinolones, 97 percent to cefepime, 86 percent to ampicillin-sulbactam, and 99 percent to piperacillin, and all you are left with is imipenem, and even there, a third of the organisms are resistant.

So, this is the kind of information we are trying to look at to say would an organism go on such a list of public health importance because of the lack of available therapies here.

If you did the same thing with group A streptococci, you would see that 100 percent are still susceptible to penicillin, and a few of them are macrolide resistant, but that most of them are still susceptible to all those other drug classes.

Let's do the same kind of analyses with Streptococcus pneumoniae, and I just want to show you this to complete the thought that we did yesterday because I didn't show you these when we were talking about multidrug resistance, but the question came up yesterday of, well, most of these

organisms probably aren't resistant to two or three things.

Well, at this point, it looks like they are, and you can see that if we split this up, and we split this up just because if you overlay these two graphs on top of each other, you can't see anything, so we split them up into penicillin-susceptible isolates on the left and penicillin-resistant on the right.

If you susceptible to penicillin, most of these organisms still cluster right here, meaning they are susceptible to erythromycin, third generation cephalosporins, clindamycin, levofloxacin, and trimethoprim- sulfamethoxazole.

On the other hand, if you start out with the penicillin-resistant isolate, you can see most of these organisms cluster out here meaning they are resistant to at least two other drugs in addition to penicillin, so it is not that if you are resistant to penicillin, well, some of them are macrolide resistant and some of them are just resistant to trimethoprim-sulfa, they are resistant to at least three things.

[Slide.]

So, again, we can do the same kind of

information where we take this and look down at this, and actually, we did it right here just to show the extreme case of what's out here, but if we took this right here, you can do this for any of the lines, so if you look at the two drug resistance line, you can see that 94 percent are resistant to erythromycin, 95 percent to trimethoprim-sulfa.

Again, if you look down this list, you can see when you start to lose things, and you can see that the first drug to go is trimethoprim-sulfa, the second class to go looks like macrolides, and then the third class to go looks like clindamycin here, but yet we maintain susceptibility of third generation cephalosporins until we get way out here, and then you see that even there is 100 percent resistance to this, as well.

The reason I am showing you this is that what we would like to do is get your input today on what kind of organisms we should run through this kind of analysis to try to look at.

We plan on doing this for the 27 different taxa that I showed you in the beginning, but are there some other organisms that the committee would consider important to try to do this analyses, as

well.

[Slide.]

The fifth criteria was that the drug is used to control the spread of the disease in the population, and this is important for things like sexually transmitted diseases like gonorrhea and tuberculosis where we don't have good vaccines available, and really the means of limiting that spread of the organism in the population is the drug therapy itself as opposed to, say, things like vaccines.

[Slide.]

The last criteria is perhaps the trickiest one, and that is trying to draw a clinical correlation between in vitro resistance with poor clinical outcomes, and this really raises the question of is resistance in the test tube clinically relevant.

The reason why we also feel this is important is there are recent examples where in vitro resistance does not correlate with poor outcomes in the majority of cases, and there are other methodological issues when we expand this beyond just bacteria, such as things with like tuberculosis where we know that clinical outcomes

don't correlate with some of the in vitro testing for some of the anti-TB drugs.

But, for instance, we know that some of the data we are seeing now on penicillin resistance in Streptococcus pneumoniae at least in community-acquired pneumonia shows that until we get up to MICs of at least four for Streptococcus pneumoniae against penicillin, that there doesn't appear to be an impact.

Again, this is the issue of the disease in question because for meningitis, there appears to be that this may be more of an issue than for community-acquired pneumonia.

On the other hand, there is also some information in macrolide resistance in Streptococcus pyogenes pharyngitis that perhaps that doesn't make a whole lot of difference either.

So, the clinical impact of resistance may be more important, as I said before, and more apparent in more serious diseases which are less likely to resolve spontaneously.

[Slide.]

It is difficult to get information on clinical treatment outcomes. First of all, as Dr. Tally said, the organism must be prevalent enough

to even study and it takes time to accumulate that data.

The Pallares study that was published in the New England Journal of Medicine was 10 years' worth of data from Spain. Also, some drugs are not used to treat a severe disease where the difference between susceptible and resistant isolates are more likely to occur, and Dr. Tally showed that slide about the attributable mortality between these things.

So, for instance, in hospital-acquired pneumonia, it may be more apparent that susceptible, and the data that Dr. Tally showed from the Ibrahim article in Chest is about hospital-acquired pneumonia where you this big difference between susceptible and resistant isolates.

On the flip side of that, though, the cure rate for hospital-acquired pneumonia is about 50 percent, so the overall cure rate is going to be lower although the difference between susceptible and resistant isolates may be bigger.

On the other hand, suppose you look at a study of community-acquired pneumonia in PORT Class 1 patients, who are the least severely ill

patients. The mortality in those people is about 0.1 percent. How are going to be able to show a difference between susceptible and resistant isolates when a number of the--now, obviously, that is treated patients, so we are not saying that everybody would get better if they didn't get treated--but it is difficult to show a difference in that.

We can extend this to even other diseases like acute bacterial sinusitis where the spontaneous cure rate is higher, it is a lot more difficult to show this.

The other issue is where is your drug used, and we had this discussion back in January about macrolide- resistant Streptococcus pneumoniae. Again, macrolides are usually used in these people for things like community-acquired pneumonia in the outpatient setting who are likely to do well anyway.

What is the impact of macrolide resistance on that disease, it may be very difficult to tell. The flip side of that is that macrolides are very rarely used as sole therapy in the treatment of someone with severe community-acquired pneumonia. They are usually part of a combination regimen, so

again it becomes very difficult to determine what the impact of macrolide resistance is in that organism.

[Slide.]

The other issue is when we see increasing case reports, can we really call this mounting clinical evidence, and there is a couple of issues that make that difficult to evaluate.

The first is that there is a publication bias, people are less like to publish the fact that they put the person on a macrolide and they got better.

The second thing is the natural history of the disease, such as community-acquired pneumonia, where severe disease carries a mortality of approximately 30 percent regardless of therapy. So, if you see somebody who has severe community-acquired pneumonia and they were given a macrolide and they didn't do well and they had a resistant organism, is it because they had the resistant organism or is it because they were going to die anyway from their underlying disease?

The third thing is there are some data showing no effect of antimicrobial therapy on mortality in the first five days of bacteremic

pneumococcal pneumonia, and this is data that Dr. Astrian did at Penn back in the 1960s, and there is no reason to believe that that would be different. In fact, that is the reason why the Feikin article in the American Journal of Public Health excluded patients in the first four days of treatment because they wanted to take this into account, as well.

The problem with all these case reports is they lack comparative data showing a higher rate of failure in resistant isolates versus susceptible isolates. So, for instance, when we looked at the data for tolithromycin, we showed at that advisory committee that three of the five patients who received clarithromycin, who had macrolide-resistant organisms, one of whom was bacteremic, got better.

So, when we look at this in a comparative way, the question is can we show that these resistant isolates have a worse outcome, and this data, like I said, is very hard to obtain.

[Slide.]

Some people have done it, though, and I would like to show you some examples. This committee is pretty familiar with the discussions

about Streptococcus pneumoniae, so I wanted to use a different example here of group A streptococcal pharyngitis.

This was a study that was done in Italy in a four-month span in 1997. In Italy, their macrolide resistance is actually quite high, it is almost about 50 percent of group A strep are resistant to macrolides.

So, they did throat swabs prior to treatment at the end of therapy in these children all under the age of 14, and they looked at both the clinical resolution and the bacteriologic eradication rate in these children.

Out of those 3,000 kids who got cultured, 1,048 or about a third of them had a positive test for group A beta-hemolytic streptococci. 934 of them were tested for susceptibility, and all of those kids got looked at for clinical cure.

Only 668 out of the 934 came back for follow-up and that were able to be assessed for bacteriologic cure by a second culture. The macrolide resistance in their isolates at baseline was 46.3 percent of the isolates, and one of the phenomenon I find very interesting is that penicillin resistant was zero percent.

So, I constantly ask myself this question - penicillin is used all the time for various infections, why hasn't this bug become resistant to penicillin, and I think that is a very interesting, if unanswered question.

[Slide.]

What they showed was that the macrolide-susceptible organisms, which comprised 57 percent of them, the bacteriologic cure rate which was done at the end of treatment, at 10 days, was about 80 percent of those people. Even though 42 percent of the organisms were macrolide-resistant, almost 60 percent of them had a bacteriologic cure anyway. So, there is a big discrepancy, 20 percent more kids who had a resistant isolate still eradicated the organism from their throat.

Now, this goes to two different points here. Is this because this is pharyngitis, which is a self-limited, self-resolving disease in a lot of people anyway, or does it say that we are defining these breakpoints in some wrong way and that the drug is still having efficacy?

If you look at the penicillin-susceptible isolates, 100 percent of these were susceptible, and yet the penicillin only eradicated the organism

in 84 percent of the cases, so it shows that even in all susceptible isolates, that the drug isn't completely effective all the time, and there is a whole body of literature on this, too, that some people argue that perhaps other organisms in the mouth secrete beta-lactamases which inactivate penicillin when you are trying to treat group A strep, et cetera.

When they looked at the clinical cure rates, it was low no matter which way you sliced it, and, in fact, the failure rate with all these drugs was less than 2 percent at day 3 to 5 no matter which drugs you looked at, and they looked at penicillins, cephalosporins, and macrolides in this disease.

[Slide.]

So, what are some of the organisms that we have previously granted resistance claims for that would seemingly be easy to put on this list? Well, we have talked at length today about methicillin-resistant Staph aureus, vancomycin-resistant Enterococcus faecium.

In the past, we have granted claims for penicillinase-producing staphylococci, but one could argue that at this point in time, that

doesn't really represent an organism of public health importance, and it is probably subsumed under MRSA anyway.

We have granted indications in the past for beta-lactamase-producing Haemophilus influenza and Maraxella, and most recently, for penicillin-resistant Streptococcus pneumoniae, and we had the discussions yesterday of should we now, knowing what we know, be calling this multidrug-resistant Streptococcus pneumoniae.

Just to reiterate some of the things we brought up yesterday, some of the committee members talked about why don't we just turn back the clock and remove this and just say community-acquired pneumonia due to susceptible pathogens and forget about putting these resistance things in there.

Two of the points I brought up yesterday I think we need reiterating today. The one is not everybody who reads this label is an infectious disease specialist, so we want to convey this information to clinicians, and what do we want to convey, because somebody else said yesterday, well, the label shouldn't be an educational tool.

It says in the Code of Federal Regulations

that the label is actually supposed to show how the drug is supposed to be used for its intended use. The intended use is not for a bacteria, it is for a disease, and those diseases for the most part are treated empirically especially when we talk about Streptococcus pneumoniae, so what we are writing this label for is not so just infectious disease physicians know how to use it, but so how general practitioners and family practitioners and other people also are aware of this cross resistance pattern between these organisms and what they should be doing when they are going to treat people especially in an empiric setting.

[Slide.]

So, our future plans then will be to try to look at some of this information we have gathered, examine the epidemiology of organisms and causing these various diseases, obtain data on drug usage for some of these various indications to see what folks are actually using for these, look at the cross-resistance patterns in various organisms, and as I said, we would like some guidance from the committee of--we will show that slide again of the 27 different taxa and are there things you think should be excluded from that, that aren't

important, are there things you think should be added to that list.

Finally, to try to obtain some data on clinical correlations with clinical outcomes and resistance wherever possible.

[Slide.]

So, what we would like to do is based on today's discussions, to at some point in the future, and today we are not expecting to come up with a list coming out of this meeting, what we are trying to do is to have the committee comment on these six criteria for us that would make up such a list and see if there is anything that we should add or subtract to that list, and then try to go back and populate the list based on those criteria.

This afternoon's discussions are actually going to talk about some other aspects of drug development for resistant pathogens, which actually dovetail into this. Then, we talked about yesterday this idea of multidrug-resistant organism claims, which I hope we can expound on again today, and finally, all of this in the end what we are trying to do is use it to formulate a guidance for drug development for resistant pathogens.

DR. LEGGETT: Thank you very much.

It is now a little bit later, but we still have at least an hour or so of discussion. So, go ahead. We have some questions first. Alan.

Questions from Committee

DR. CROSS: John, that was a very elegant presentation of the multi-resistance. I wonder if you actually wrote down any of those organisms, for example, the Acinetobacter, by site of isolation, and, if so, is there any difference in terms of the likelihood of resistance at a specific site for a specific organism.

DR. POWERS: We are going to try to do that. For some of the organisms, we are going to try to split it up by inpatient and outpatient basis. We are going to try to actually look at it by bed size of the hospitals. We are going to try to look at it by geographic area, by census tract within the United States to see if it varies across the country.

So, we have got all of these planned analyses, and I was just trying to sort of give you the tip of the iceberg today to see what it looks like.

DR. CROSS: Certainly, in terms of the organism by site, it may dictate the

pharmacokinetics of the desirable drug that you want.

DR. POWERS: Right, and the other thing is that when I put up some of those sites, like CNS, central nervous system includes shunts, cerebral spinal fluid, so I just sort of gave you the broadest brush approach today because some of those things may be more important than others.

You may complete ignore a coagulase-negative staph coming out of CSF, but not out of a shunt.

DR. LEGGETT: David.

DR. BELL: The FDA, I believe is to be commended for its continuing efforts to facilitate the process of new antimicrobial drug development.

I think I can understand the potential usefulness of developing a list of criteria for drug-resistant pathogens of public health importance. I have some comments, that I am going to defer until later, the most important of which is I think that the currently proposed criteria need to be amended to include trend information.

I, however, have serious reservations about the Federal Government actually developing a specific list of pathogens stamped with FDA or

Public Health Service approval, and I wonder if it might be acceptable just to list criteria that then could be evaluated as the drugs or brought forth.

Let me outline my reservations about the specific list. One of them is that, of course, the list is going to change over time or should change over time. Who would develop the list and how would it be changed in a timely manner?

What would be the impact on the industry and on efforts at new drug development if the list changes over time particularly if a pathogen were to come off the list because let's just say there were some wonderful new drugs developed or a new vaccine that eliminated transmission to zero, or something like that?

Would pathogens ever come off the list or would the list basically only grow and become so long as to become meaningless?

My biggest concern, however, is what about the pathogens not on the list? One issue is could work on these pathogens not yield insights to help contribute to pathogens that are on the list. But my biggest concern about pathogens not on the list is that the fact that they are not on the list might compromise essential control measures to deal

with drug resistance that, as we all know, require approaches in addition to new drug development.

Let me give you an example. Currently, the FDA Center for Veterinary Medicine is engaged in a legal proceeding to try to withdraw approval for fluoroquinolone use in poultry. We fortunately don't have much fluoroquinolone-resistant salmonella in this country, unlike other parts of the world, but we have considerable fluoroquinolone-resistant Campylobacter that is linked to fluoroquinolone use in poultry, and it is the Campylobacter that is serving as the basis for the FDA's legal proceeding to withdraw the fluoroquinolones.

Now, the FDA's legal proceeding is being fought tooth and nail by industry, tooth and nail, and my question is suppose Campylobacter didn't turn up on this list of priority pathogens for public health importance. I think it is virtually certain that the industry would use that in contesting efforts to withdrawn fluoroquinolones from poultry, and they would say, I think it likely, this is burdensome regulation, see, it is not even an important pathogen, it is not even, et cetera, et cetera, and I think has to be

considered.

There are other approaches to drug resistance in addition to new drug development, and what would be the implications of a pathogen not being on the list?

So, I wonder, in closing, if it's possible to develop criteria, perhaps even with some examples, but stopping short of actually enshrining some sort of specific list.

Thanks.

DR. LEGGETT: Ellen.

DR. WALD: Just to make two comments. One is that although antimicrobials may not be on the list of drugs that you generated for overall, certainly as you look at hospital formularies, they are usually right there on top. Now, I suspect that the hospital-based dollars is relatively small compared to all dollars, but nonetheless, I think important.

Secondly, I would just like us to not exaggerate the nonsignificance of drug resistance because I think that in reality, it is probably almost all significant and that the fact that some infections do okay on drugs to which they are reported to be resistant, really reflects the

relevance of the breakpoints for the particular sites of infection, and that, you know, when you get to central nervous system disease or you get to an empyema or you get to middle ear disease where you have a significant stepdown of antibiotic concentration from blood to site of infection, then, in fact, you see very clearly that these drug-resistant organisms are important and pathogenic.

DR. LEGGETT: Barth.

DR. RELLER: I like the criteria that John condensed for the developing list and I wonder a couple of things, whether the caveats that Dr. Bell has articulated could not be encompassed by a wording "including but not limited to" on this list, and with specific examples.

One could argue, for example, for Campylobacter, that it is important to clearly certain antimicrobials curtail resistance, issues of day care, public health interest in containing infection.

But in addition, I wonder, John, on the scattergrams that you did, and given the utility of the TSN database as being one of the better, perhaps the best currently available, that

monitors, is a good sampling because of the diversity of hospitals involved, so that one doesn't get biases of the high concentration of resistant organisms in tertiary care hospital, but doesn't ignore their importance because of the past trends of what appears first in these centers eventually wends its way to communities. It is just a matter of how quickly.

And the complexity of dissecting out all of those shadows and dots is to develop subset data, and I am thinking about Item No. 2 on the list, organisms that cause serious and severe disease, of using the bacteremia isolates in that database as a first cut for rank ordering of pathogens with multidrug resistance.

The utility of that I think is more than what is immediately obvious. In complicated urinary tract infections, resistance may not be important or uncomplicated or not as important, but if one has bacteremia, I mean by definition, one has upper tract disease and a complicated infection.

So, you pick up those pathogens that in different sites may be important, and you also deal with the issue of an organism means different

things in different places. Similarly, most coagulase-negative staphylococci that are isolated and in the database, many are rubbish, whereas, the ones out of blood, particularly if one follows the newer guidelines in hospital-acquired infections, catheter-associated infections where there is a reproducible isolate of coagulase-negative, given how frequent they are, even though 80 percent may be contaminants, the 20 percent that aren't can cause serious disease including the occasional community-acquired endocarditis with coagulase-negative staphylococci, so that you have a natural selecter, if you will, that everyone would accept as serious and severe disease.

There is also some additional regulatory support for that approach in that some of the surrogates, with the emergence of resistance, for example, in VRE, one of the things that was important in the consideration when quinupristin-dalfopristin came before the committee was the use of cessation of bacteremia, and I think of Dr. Jorgensen's portrayal of the persistence of bacteremia from the Acar publication with third generation cephalosporins and methicillin-resistant staphylococci of the early data of where despite

aberrant or inappropriate testing, that now doesn't happen in any good laboratory, one could have been misled by in vitro susceptibility, but clinical failure.

So, I think mining the data that gives a cross-section of the country would be perhaps much more valuable than all of those numbers and all of those points that may obscure the central issue of these or by definition important organisms associated with serious disease.

You can actually cover, not only one, but some components of more than one of the six points in doing that.

DR. LEGGETT: John, what do we do about the not prevalent pathogens that we can't study that are of immense public health interest? For instance, anthrax, or viruses.

DR. POWERS: Some of the things we have done with anthrax, there has also been a recent animal rule where we are trying to get information in things that cannot be studied at all, to try to get that information.

The original anthrax approval was based on a study done in Rhesus monkeys, that looked at the efficacy of ciprofloxacin, doxycycline, or

penicillin versus placebo.

DR. LEGGETT: Yes, Mark.

DR. GOLDBERGER: I think that brings up, you know, sort of the broader issue, which is related to some of the things we are going to also talk about this afternoon, but in terms of thinking about how to study organisms that are hard to study.

An example that came to mind, I was just looking, you know, at the Acinetobacter data, to actually do a study to really determine if a new antimicrobial worked against the Acinetobacter would be a major undertaking.

So, the question comes up how does one go about making inferences, what are the other components of information you can use to get a feeling of whether a new antimicrobial is going to perform.

As a starting point, obviously, that includes looking at in vitro data, perhaps commonality of resistance mechanisms, the use of animal data, the study of the drug in perhaps serious indications analogous to where you would find the pathogen you are concerned about with other serious gram-negative organisms including

those that have similar resistance mechanisms, but it may be worth, at some point, whether we do it now or in part in the afternoon or at a subsequent meeting, talking about this concept of how one draws inferences from a variety of types of data to allow one to be reasonably comfortable that even if the number of actual isolates is not that high of the organism in question, the totality of the data that you have collected makes it reasonable to presume that this drug is likely to perform.

I think that that is an important issue because even beyond the Acinetobacter, I mean we have had concerns about resistant gram-negatives in a variety of settings, to ask companies to come up with enough of each of the types of gram-negatives to get that clearly put in the label is no small undertaking, and the question is at what point, when you have looked at serious infections due to a couple of, say, major gram-negatives, say, a klebsiella, an anaerobacter, a pseudomonas, and you have shown the drug performs well, do you begin to get enough confidence to be able to say you will label this for, say, this type of a disease, due to gram-negative organisms more broadly.

But I think at some point we are going to

need to have a type of discussion about how one draws inferences because there will be many examples of these hard-to-study, very resistant organisms that we need to collect useful information in some organized fashion about.

DR. LEGGETT: John, one follow-up question, can I play devil's advocate for a second. Since we first saw penicillin resistance and sulfa resistance, hasn't all drug discovery been driven by resistance? In other words, criteria No. 4, isn't that self-evident?

That sort of gets a little bit back to David's question, but in a different way.

DR. POWERS: My answer would be sort of in that we are actually in the process now of working--one of the things that came out of that November workshop was this idea that some of this has to be changes in the law.

The IDSA is actually trying to go to Congress to actually lobby to do some of these changes, and we are working in cooperation with them to try to look at what are companies actually submitting to us, not by drug name, but just sort of broad categories.

What we are seeing, and this has not been

completed yet, though, is that the number of new molecular entities is actually quite small, yet, the number of changes in formulations, such as extended releases or increasing the dosage of a particular drug, is what we are seeing a lot of.

So, when you say isn't all drug development driven by resistance, partly, yet, it is changing your dosage formulation from the tid drug to a q.day drug, is that driven by resistance or something else?

DR. LEGGETT: Money.

Alan.

DR. CROSS: I was just going to re-emphasize Dr. Goldberger's point that we are not simply talking about organisms like Acinetobacter that are hard to study. Over the last 15 years, we have been involved in the preparation of hyperimmune globulins and vaccines for things like Pseudomonas and Klebsiella, which were high on John's list, and it is a major undertaking to find enough centers that have enough of this disease to actually do a study.

So, it is not just the Acinetobacters and stenotrophomonas, that is of concern, and perhaps looking at common resistance mechanisms and being

able to perhaps pool that data may be of some use.

DR. LEGGETT: Celia.

DR. MAXWELL: Yes. As I was looking at the six criteria for developing the list, I was a little bit concerned that I didn't know where I would fit an organism like falciparum malaria. That is not prevalent in this country, but certainly it is deadly, it is prevalent worldwide in areas of the world, and we have an increasing risk of, let's say, sending troops or something like that, that are going to have an immediate exposure.

Where would we fit something like that?

DR. POWERS: I don't think we put the moniker in this country on the end of prevalent, so certainly you could argue that might be the prevalence of the disease in study. Falciparum malaria within the disease malaria is very common and very prevalent. I don't think in any way we meant to say just in the United States.

DR. LEGGETT: Jan.

DR. PATTERSON: I think the idea of a list is helpful. I think that would be helpful to industry to have some specifics, and it could be reviewed periodically to keep it up to date.

I have a little bit of reservation about prioritizing just the bloodstream isolates because, for instance, a lot of the catheter-related infections, taking the catheter out is the major therapeutic maneuver particularly for things like coag-negative staph, and for an infection, say, like Pseudomonas pneumonia, I mean a lot of times that is a lot more severe infection, but you don't have a bacteremia from it.

One way we have kind of gotten around, you know, giving us an out for just certain organisms on a list per se, for instance, at our hospitals, for the use of contact precautions, we say it's for multidrug-resistant and epidemiologically significant organisms, so that kind of gives us an out.

Like, for instance, Clostridium difficile, which we don't really think of as multidrug resistant, it epidemiologically significant and has some of the same implications, and maybe some of the bioterrorism organisms could fit in the same way.

I don't know if Salmonella and Campylobacter were on your list, but I think that probably fluoroquinolone resistant, foodborne

pathogens like that should be included.

DR. LEGGETT: Did you want to say something, John?

DR. POWERS: I just wanted to answer Jan's question. That's the kind of thing we are actually looking for, because when you realize most people don't culture when they have foodborne disease, so that is not going to show up on our list, but clearly you can make a case that that should be on there, as well.

There is a list of bioterrorism things, and sort of get this idea of making a list and the Federal Government making a list, the Federal Government has made a list. This is a list for bioterrorism-related agents. So, it is not as if we are doing something that is completely out of the realm of possibility here.

DR. LEGGETT: Mike.

DR. PROSCHAN: I am taking a risk here because I am just a country statistician. I am from Heart, Lung, and Blood, but I am trying to understand why the drug resistance doesn't correspond to poor outcomes necessarily. Actually, I don't even know the exact definition of drug resistance, but I am assuming that that is entirely

in vitro. Is that right, the definition?

DR. LEGGETT: Yes.

DR. PROSCHAN: So, is it possible that the body, you know, is able to handle a certain amount of infection, so that even if the drug kills half the bacteria instead of all of it, now your own body is able to fight the rest. Is that a possible?

DR. LEGGETT: That has been the major problem of trying to compare antibiotics to other drugs, because there is three parts of the equation instead of just two, so, it is not drug and us, it's drug, us, and bug.

David.

DR. BELL: I had a few comments on Table 1, the criteria that I just wanted to mention. The title, I would suggest that the title encompass the concept of drug resistance as opposed to just saying criteria for pathogens of public health importance, because, you know, there is influenza and there is anthrax, there is all kinds of things, and this is really about drug resistance, something in the title to that effect.

Point No. 1, I wonder if it should be "or" in the disease under study rather than "and."

Point No. 4, a few alternatives to treat the pathogen, I wonder if there should be some concept of ease of treatment, oral therapy, empiric therapy--

DR. LEGGETT: Dave, could I interrupt a second?

DR. BELL: Yes.

DR. LEGGETT: Are there any more questions for John's talk before we jump over, because, John, were you going to lead the discussion? No? Okay. So, we can jump on over. Finish what you were going to say, and then we have this page here of Points of Discussion.

DR. BELL: Okay.

DR. LEGGETT: It's not that I want to shut you up.

DR. BELL: The agenda kind of looked like it all went together, and I apologize, I didn't see that.

DR. LEGGETT: I know. That's a trouble we are all having.

DR. BELL: Do you want me to just--

DR. LEGGETT: Go ahead, jump in.

DR. BELL: Well, I will just finish. I mean ease of treatment, oral, empiric. No. 5,

there is no vaccine for that pathogen. I would suggest delete that parenthetical phrase because even when there is a vaccine, there is still going to be people getting sick and they are going to need to be treated, and the vaccine won't be offered for everybody or efficacious for everybody.

But the most important thing, something about trend information. We have run into this situation a lot where criteria for regulatory action, preventive action, whatever, tend to focus on rates rather than the trend.

Thanks. Sorry.

DR. LEGGETT: No, no, if you look at the bottom the page, that is exactly where we want to start, so that was fine. I just thought John was going to lead.

DR. POWERS: The slide I showed about the Staph aureus bacteremias that we were intending to look at trend information over time, as well, but we could certainly add that in, be a part of criteria No. 1.

DR. LEGGETT: Go ahead, Jim.

DR. JORGENSEN: I would like to suggest adding to these criteria. So far, we have talked about resistant organisms and the need for new

agents, but I am also concerned about infections in which very effective agents may no longer be available or may cease to be available.

Specifically, I am thinking about gonorrhea in which the four recommended agents currently, two fluoroquinolones in which resistance is common in some parts of the world and becoming more so in this country, and where the only other oral agent is no longer going to be available, so it may leave only one injectable drug that is predictably active against gonorrhea.

DR. LEGGETT: You mean by the pharmaceutical agents.

DR. JORGENSEN: Yes.

DR. LEGGETT: John.

DR. BRADLEY: Just a concept that unfortunately adds to the problem, not solving it, and it's in response in part to Dr. Frank Tally's presentation earlier this morning.

It takes several years once you identify a problem to actually bring a drug to the clinicians, so that they can use it. So, in putting together these criteria, and I think you have done a really nice job, I suggest that we cast a wide net because you don't know which of these resistances 10 years

down the road is going to be giving us lots of problems, and if you restrict your criteria, then, someone will say 10 years from now, gee, you were shortsighted and only look at the most prevalent likely pathogens.

As our ability to determine molecular mechanisms of resistance improves, it complicates things further. When I was in my fellowship, there is resistant Pseudomonas to ceftazidime and now it can be beta-lactamase, PORN [ph] deficiency, efflux pumps, and God knows what else is going to come up, and now we know these mex pumps can pump out not only beta-lactams but fluoroquinolones and probably a lot of other agents.

So, it becomes more difficult predicting which of these mechanisms of resistance is actually going to be a problem, and the time to development of agents is huge.

Secondly, and in addressing one of the points for discussion regarding not having enough patients with a particular organism, I think with the animal models that have been developed, that you were involved with, with Dr. Craig, with neutropenic mouse, Rhesus monkey models where you can actually model drug exposure for a pathogen in

a particular issue and get an idea of the Cmax to MIC or AUC to MIC that is required in the animal model.

I believe a lot of that information can be extracted into the clinical situation, so you don't need nearly as many patients to prove that a drug at a certain dose will work if you have laid all your groundwork with the animal model and then just a very few patients to confirm that the animal model is predictive will net you more information on fewer patients for these very resistant organisms which may be very rare.

DR. LEGGETT: John.

DR. POWERS: Could I ask you a question about animal models because, Jim, you asked this now, and, John, you brought it up a second time.

I want to refer to something we saw yesterday. One of the thing Mark was talking about was sort of building this body of information to show that the drug may be effective for a resistant organism.

What we saw yesterday was a drug which claimed to be effective for quinolone-resistant organism, and Pete Dionne, our microbiologist, showed an animal study where even though the dose

was doubled, that it still did not eradicate the organism from the mouse's lungs.

I was interested to hear, then, as we went around and talked, several of the committee members said, well, this is a drug effective against quinolone-resistant organisms, so it gets to be the point of how does one interpret that animal data when you see it and extrapolate that to what might happen in people.

DR. LEGGETT: That is the point of contention that one of the speakers at the open session is probably going to address.

Mimi.

DR. GLODE: I have two comments. I just wanted to reinforce what Dr. Reller brought up and then comment on Dr. Patterson's comment on that. I do believe that some patients--and also referring to Dr. George McCracken at an earlier meeting--some patients are more informative than others, so bacteremic isolates, CNS isolates, and therapy for those patients is more informative to me than many sputum cultures with the resistant organism.

But then I certainly took your point that perhaps more in adults than pediatric patients, catheters are removed when there is a

catheter-associated bacteremia. In most of our oncology patients, the first issue, if one is not desperately ill, is to treat through.

So, the catheters are left in place, repeat cultures are obtained, and antibiotics are provided, and this is a real challenge at the neutropenic host, et cetera, but that would be the standard in our hospital for pediatric oncology patients, so one has the opportunity then to say can this drug eradicate this organism in this setting, which is a significant challenge. One could then argue that that is a pretty informative situation.

My second comment goes back to the Wall Street Journal and anti-ulcer medications, but I just have to say this. I haven't read the labeling for any of these anti-ulcer medications, but with regard to physician education and perhaps patient education if you can get your hands on the PDR, I mean I hope they all say that the patient should be evaluated for the infectious organism that causes ulcers and then treat it appropriately with the antibiotics to eradicate it and be cured.

DR. LEGGETT: They are all getting them anyway for their viral upper respiratory tract

infections.

Jan.

DR. PATTERSON: Well, I just wanted to clarify. I was thinking more about short-term catheters and ICU patients. We also treat through in adults for the long-term catheters.

DR. LEGGETT: Barth.

DR. RELLER: Fusing the amplification of this information about the catheters, to me, a critical issue here is separating out the ones that, by definitions that have come up at the FDA having to do with what documentation would be required for studies and indication for catheter-associated bacteremia, because if one had an agent that actually was effective in clearing the bacteremia with the catheter in place by whatever mechanism, the new agent, given the frequency and the increasing importance of this organism and the increasing importance of these catheters as lifelines for the kinds of patients that are growing exponentially in healthcare in this country, and with home I.V. therapy, et cetera, a really rigorous definition of catheter-associated bacteremia and something that would work with or without, and clearly the

discussions of guidelines for that include whether or not the catheter is removed would be very helpful.

I didn't mean in any way to imply that only bacteremia would be a way to get at this, but rather that it would be perhaps the most efficient first cut at what everyone would accept as important, plus recognition that in, for example, CNS infections, a very high proportion of those patients, if they were done, would have concurrent bacteremia, perhaps a higher association than with any other entity apart from infective endocarditis in terms of the proportion who would have a positive blood culture to deal with, Listeria or, in the old days, Haemophilus influenza type B or the pneumococcus.

DR. LEGGETT: What I would like to do is talk a little bit more these criteria until people have discussed it under 10 minutes, and then go on for 10 minutes and talk about sort of the second point about the 27 taxa and the other sort of analyses before 12:30.

Before we go off the criteria portion of this, I would like to ask, where do you fit in, say, in drug development, something that alters

things, so, for instance, we know P-glycoprotein, that we never even thought much about in terms of HIV is now probably more important than what we used to think of as the cytochrome p450 in terms of making drugs ineffective.

Where do you tie in, and then sort of the whole efflux pumps in bugs are sort of equivalent to the MDR in cancer sort of chemotherapy, and I am sure, I can envisage a new drug development not at a particular pathogen, but at something that would enable the drug to work much better in the body.

Where is that subsumed in this or is that just sort of in a parallel universe in terms of deciding that something is important, because theoretically, I could think of a process by which a drug that inhibits P-glycoprotein would be of immense importance for a bunch of drugs.

DR. POWERS: I think what you are getting at is the bigger issue that we always talk about, and that is what we are really trying to treat here is a disease. It just so happens that in anti-infectives, that that disease is associated with an infecting pathogen.

Since a lot of these diseases are treated empirically, we usually ask that that drug show

efficacy against the most common organisms that are likely to be encountered.

So, for instance, if you were developing a drug for meningitis and it had absolutely no activity against the pneumococcus, but was a great Neisseria drug, what do you do with that, because, you know, the people are going to apply it empirically.

I guess if somebody came in with a drug like that, that had some kind of effects, it would depend how the drug works, but I would assume it would have to have some effect on the bacteria, or if it doesn't, they would have to show that leaving the bacteria alone still somehow cures the disease.

DR. LEGGETT: Ellen.

DR. WALD: I just wanted to make one comment about group A strep and which I think is an organism in which looking at antibiotic resistance is particularly difficult especially, currently, you know, in part, because it is definitely a self-limited disease, so from the clinical perspective, you might never notice that there was antibiotic resistance, we are in an era now where almost no one is collecting isolates certainly from patients with pharyngitis because they are doing so

many rapid diagnostic tests.

Again, even the availability of organisms and testing them, you know, has diminished. So, I think that we might not notice that as a problem unless there was an increase either in invasive disease or acute rheumatic fever, so that might be something that we need to keep our eye on even though it might be harder to do and harder to interpret what's happening clinically.

DR. POWERS: I think what that gets at, though, what I was trying to draw there in that, was the link between resistance and a self-limiting disease, and how it is to show that resistance has an impact.

Again, getting back to this issue we talked about yesterday of the drug label actually trying to convey some important information to clinicians, I guess you could sort of use the other upper respiratory tract issues that we have, are the diseases like acute bacterial sinusitis and acute exacerbations of chronic bronchitis where we are dealing with again a self-resolving disease, and yet drug sponsors have asked us several times for resistance labeling claims for those diseases, but pharyngitis is the example of where there is

data available to show that, gee, perhaps the resistance doesn't impact on that disease.

That is not to say that for something like community-acquired pneumonia that it would.

DR. LEGGETT: Ken.

DR. BROWN: I have no idea what the topic under discussion is right now, so I thought I would raise a couple of points of my own.

I would like to focus on something Frank Tally said because I think it goes far beyond the scope of most of our comments, and that is, that several things which have occurred and the state of things as they are, there is little to no hope that the drug companies are going to be able to develop adequate answers to these problems.

I think if you look at the fact that most of the available antibiotics, and I think all of the antituberculous drugs were discovered by or before 1975, and since that time we have had almost no new classes of compounds discovered.

That is frightening if you knew the numbers, and I wish we would give them to the statisticians, the numbers of soil samples that have been screened in the last 45 or 50 years by the pharmaceutical companies.

I think it is fair to say that there is essentially no chance that the pharmaceutical industry by itself can come up with the answer to this problem. I wish I could say Frank were the first person to suggest this kind of a consortium, but actually, the president of the IDSA, in 1978 or so, in his closing remarks, suggested that the very formation of such an institute which would be responsible for the discovery and development of new anti-infectives.

I think all this is complicated by something you just mentioned, Jim, which a lot of us haven't come to fully appreciate, and that is the role of P-glycoprotein, and some of us don't even know what it is, and MDR, and the interesting problem that some of us want the protection of P-glycoprotein to keep drugs like ivermectin out of the CNS, and others of us who treat cancer want to get rid of P-glycoprotein, so we can get the drugs into the CNS.

When you then combine that with the multiple drug that the patients who are being treated for HIV and have an effect or are affected by p450 or have an effect on P-glycoprotein, this geometric increase in the need for knowledge is

horrendous, and I think that to say that we are going to have a productive result from this small part of the discussion is a little bit scary, especially when, as Mark points out, we can't expect to really get even a list today and the slow rate at which we function as organizations contributes to this, and I don't know that there is an adequate way to get around the speed of our ability to do things, but I don't think it is going to be within the purview of the industry to do this, period.

DR. LEGGETT: Barth. Didn't you have your hand raised? You are too depressed after that.

[Laughter.]

DR. RELLER: I was trying to digest it. Just a follow-up to Dr. Wald's comment, and I realize why virulence was taken out of this and embodied in the serious, and how one could minimize the importance possibly in those places where it is a self-limited disease, but if one had to pick among the common bacteria, one that intrinsically is virulent, I would choose a group A streptococcus because of how quickly and how devastating it can be in certain clinical pictures.

If we were to have resistance in group A

streptococcus, we would have a real pathogen on our hands, and I think that one should be on the list because of what Dr. Bradley mentioned earlier of this timeline of how long it takes. I think it is second to none in its intrinsic virulence.

DR. LEGGETT: I would like to expound a little on that if I can, bringing it back to the point of trying to get back to the Campylobacter issue and my sort of pet peeve is Neisseria gonorrhea.

I think if you are dealing with a pathogen that only has a human reservoir, that has immense potential pathogens we want to be preventive and that might have to be either another criteria or folded into the ones that are in that list, to talk about what if type things.

We have sort of done it with Staph aureus because we now we are all nervous about being in the pre-antibiotic era again, but what happens, the same thing could be applied to group A strep or to the Neisseria or bring those things into this discussion.

Alan.

DR. CROSS: I wanted to ask the FDA or perhaps John, what types of contacts do you have

with other organizations, not just here, but around the world, the globalization issue. Part of that is we have talked about not having enough glue-based strep, but in the military, they have really some serious outbreaks every few years even recently.

I don't know if there is any sharing of those isolates with the nonmilitary organizations. Similarly, we heard about the resistant pneumococci in Hong Kong. Is there any type of surveillance program for bacteria that we have for influenza in terms of sampling around the world and trying to find out what's on the horizon, perhaps getting access to those organisms?

Then, there is the other issue in terms of trends, what David talked about, is that MRSA actually started in Europe and was there for a number of years before it occurred here. It was rather benign there when it first started, and then once we had MRSA here, it was a more significant clinical problem.

My understanding is it is less of a problem in Europe now. So, the point is that there are some global trends associated with these organisms that may be instructive in terms of how

we deal with things.

Is there any actual sharing of either data or specimens, for example, comparing your data under contract with perhaps what is going on elsewhere?

DR. POWERS: We are also part of an interagency task force on drug resistance that had a meeting prior to ICAAC last October or September, and where this issue was discussed--David, you set that up--about trying to get--and there is a whole section on surveillance, in fact, David is probably better equipped to answer this than me because he was the chair of that section.

But we are trying to get that kind of information. Focus Technologies tells me that we have the ability to get some information from outside the United States, as well, although we haven't tapped into that as yet to try to see, but that is one thing we could do would be to try to compare.

DR. LEGGETT: To follow up on Alan's question, is this sort of a project that is also undergoing discussion in Europe and abroad, sort of like along with the harmonization sort of globalization and that sort of thing, or is this

just solely a U.S. initiative?

DR. POWERS: David Bell is probably better to answer this because we were talking about all of this stuff.

DR. BELL: Is what in particular under discussion?

DR. LEGGETT: This project to try to come up with a list, in other words, the fact the United States prioritizes it or somehow allows industry to do what they want.

DR. BELL: You know, this is a particularly opportune discussion because I am actually about to go for a three-month detail to WHO to help them identify ways to implement their global strategic plan on containment of antimicrobial resistance.

Of course, surveillance is a major issue. There are a lot of major obstacles to good surveillance. We have had discussions both a CDC and I know elsewhere, for example, the EU, their surveillance system.

They phrase it in terms of marker pathogens, and we have looked at this concept also to try and get away from this idea that some are more important than others for the reasons I

mentioned, but just marker pathogens, and it would be Staph aureus and pneumococci.

The EU has a very nice sentinel surveillance system in their countries, and they have I guess it's pneumococci, VRE, I believe it's Staph aureus, and I think they just added E. coli, something like that.

Again, they are not trying to say these are the targets for drug development, they are trying to harmonize surveillance efforts in different countries in their jurisdiction and use these as, quote "important," unquote, marker pathogens, and I suspect we will see more of that around the world, but this is actually a very interesting discussion to me because WHO is kind of looking for what to do next.

DR. LEGGETT: Ken, it sounds as it you are pretty pessimistic even if there was this production of a list and there were incentives, as Frank talked about, in terms of providing money or those sort of things, you are basically saying even if there were much more incentives to come up with drugs with new mechanisms rather than me-too's or extensions of patents by, you know, increasing the milligram dosage, you are pretty pessimistic that

that is even possible, is that the gist of what you were saying?

DR. BROWN: If you try to count the number of rational drugs which have been put together, trimethoprim sulfa, that makes one. That was really based on permesamine [ph] and sulfa, which preceded it. That is actually the only one I can think of--

DR. CROSS: Influenza drugs.

DR. BROWN: And then if I look at the number of isolates which people look at, it is not that people have stopped looking at isolates, but 25 years ago, in a screen of 3,000 soil samples a month, 99.9 percent of the compounds which were isolated were already known.

So, what I am saying is the discovery of perhaps ivermectin from a soil sample next to a sludge sewer in a Japanese golf course grew Streptomyces, but we haven't had a lot of additional new compounds since that class.

So, all I am saying is statistically, we need to do several things better, and I don't think that just depending on companies that have to try to make money to keep themselves in business is going to be an adequate situation knowing what we

know and the increasing demands of the scientific community, which are appropriate, and the additional information.

When I think about the use of the macrocyclic lactones in combination of HIV drugs in Africa, where the CYP450 is not the same for people who live in Ethiopia and the southern tip of the Arabian peninsula versus the rest of the world.

It seems to me the complexity is frightening, and we need an institution bigger than any pharmaceutical group that I know of to participate and probably to lead it.

DR. LEGGETT: John.

DR. BRADLEY: I think the pessimism about industry not developing new drugs is certainly in part based on the fact that the financial incentives, the disincentives to develop a drug and lose money are huge, and there are both pharmaceutical company funded and NIH funded studies in looking at mechanism of resistance, so on the one hand, we are moving forward quickly in developing information on why the drugs are resistant, but the other side of the coin, moving forward quickly in developing drugs to meet the resistance has been the problem.

I think there are several ways that were brought up in November, brought up again today on how to get rid of the financial disincentive. I am sure that PhRMA has incredible resources to be able to approach these problems if given the right incentives, so I don't share the pessimism of Dr. Brown that it can't be done, I just think that the equation of how progress is put together needs to change.

In addition, there as we get more involved in mechanisms of resistance, perhaps on this list somewhere, knowing that many of these mechanisms of resistance cross between organisms by cassettes or plasmids, that as a mechanism of resistance of public importance goes on this particular list, like efflux pumps, that that can be a target for facilitating pharmaceutical industry development of drugs, as well.

DR. LEGGETT: Barth.

DR. RELLER: Dr. Brown, the pessimism, I wonder, as a provocative question, the problem that the home runs of the past, what is found in sewage, that the problem is a repetition of a failed or nonproductive model as opposed to an entirely different approach, in other words, the success of

the past may be an inhibitor for the future.

In other areas, non-antimicrobials, I mean the advances have come by an understanding of receptors and blockers, et cetera, so that maybe the approach is not looking in sewage or natural compounds, but rather an investment, and it may require, as Dr. Tally pointed out, a leap forward in terms of an institute that looks at basic science, that these cassettes, for examples, that Dr. Jorgensen, to actually understand the components, what turns them on and off, et cetera, and that the model for new drugs would be at that level as opposed to finding the needle in the immense haystack that has been part of the past discovery approach.

What do you think?

DR. LEGGETT: And then can we then come from a firmament and then go right to the very concrete before we go to lunch.

DR. BROWN: I think it is important for me to reflect that I didn't believe that diesels would replace steam engines with which I grew up. I was working in Ethiopia at the time of the smallpox eradication program, and I didn't think it would work.

So, while I had great hopes for the new information we have about genetics, I have to look realistically and say we thought we would have great advances in sickle cell disease from what we have known about the genetics of that disease or those 29 changes, and not a whole lot has come out of that, so I don't have as great hope for the wonders that we were going to get from the knowledge of the human genome yet, and it may take a while and I may be hopefully shown to be very wrong.

The final example I would give, we were told maybe seven or eight years ago, boy, once we get combinatorial chemistry going, it is just going to revolutionize things and we will have so many new things that you don't know what to do with them.

Of course, there is always a bottleneck after that, so I hope that I am wrong, however, I would love to see better ideas, and I think Frank's is a great one, that we need to pull together and get our heads together, and I agree with Barth that we should probably stop looking at just sewage sludge.

DR. LEGGETT: David.

DR. BELL: I have one other question. It might still be in the firmament, but recently, there have become enormous amounts of new resources available for issues related to the bioterrorism agents, diagnosis, treatment, and so on, I mean really enormous, and I am wondering if somebody from the pharmaceutical industry might comment on how they see, if they do, attention to the bioterrorism agents, which are microorganisms, after all, how some of that research might be leveraged into antimicrobial drugs for more common pathogens, I think the mechanisms have to be, you know, if we are talking basic research in drug development.

DR. LEGGETT: Do you want to say something, Frank?

DR. TALLY: There are a couple of points. It is in the firmament, this could go on for four or five hours talking about it. What we have to do is think out of the box. What Ken is saying is the old methods have wringed all the water out, and that is you still wring the thing, you are just not going to get any more, so you have to think of a new way to do it, and I think that is what we have to do with the genetic information we have, and the

next round is the financing, and it is look not just for drugs, but for vaccines for stimulating the immune system, and that type of thought has to start going in.

For the bioterrorism, people are working on that area, and there is now being grants coming into companies to try and look at new targets, and you can use anthrax as one of the ways to do that, a lot of common genes between anthrax and other gram-positives, the same as with gram-negatives.

DR. LEGGETT: What I took away from your talk was one of the basic things is that the science of antimicrobial drug discovery has to go back in a sense and be validated by the NIH, which kept telling us for years, oh, there is already a way to do that, we are not going to fund it, so in terms of getting back to the government and pharmaceutical agencies.

DR. PORETZ: Could I just ask one quick question about the surveillance network? Your contract to Focus Technologies, what was it, 317 labs, are those all in-hospital labs?

DR. POWERS: They are in-hospital labs, but they are hospital labs that also function as central labs for communities, as well.

DR. PORETZ: So, you get outpatient cultures in addition?

DR. POWERS: Yes.

DR. PORETZ: And you have been doing that for a period of time? Is that recent or what?

DR. POWERS: Is our contract recent or has Focus been doing this for a while?

DR. PORETZ: I mean that information, who is getting the information, is it just going to the FDA or is it being disseminated to anyone else?

DR. POWERS: Well, if you want to go pay Focus to get it, I guess you can get it for anyone else.

DR. PORETZ: No, but you get it.

DR. POWERS: Yes, the information that we get from them, we contracted from them to obtain.

DR. PORETZ: And what do you do with that information, just keep it internally?

DR. POWERS: One of the things we are doing here is trying to use it to make this list. The other thing is once we get your input, we actually plan on publishing some of this information in cooperation with them, as well.

DR. GOLDBERGER: But it is important, just to mention, this is a contract that became

effective only this past October, so some of the data you have seen is data we have only just started to get within the last month or two.

DR. LEGGETT: Speaking to that point, has anybody been able to come up with other bugs they would like to have the sort of analyses we were shown done with in, for instance, group A strep was mentioned, and I see that is on the list of beta-hemolytic strep.

DR. POWERS: I heard Salmonella and Campylobacter as two other organisms.

DR. LEGGETT: Salmonella and Campylobacter, which I did not see there.

DR. POWERS: No, they are not on there. Neisseria gonorrhea is not on there, which was one of the questions, I wanted to see if people thought that that was important to put on there.

DR. LEGGETT: Go ahead, John.

DR. BRADLEY: That's a pretty long list. Did you want to prioritize them the way the government did with bioterrorism agents, like A, B, C?

DR. POWERS: If you would like to. I mean one of things I didn't want to come across is saying I didn't think group A strep was important,

that wasn't what I was trying to say. One of the points I tried to make about the list is what do we see in the pipeline for development for E. coli, which is way at the top of the list? Almost nothing.

So, I guess the idea would be prioritization. I look at group A strep and I think, gee, that's a really severe disease, but then I look at the cross-resistance pattern and I see six other drugs to which that organism is susceptible including penicillin and clindamycin, which are the recommended drugs for severe group A strep necrotizing fasciitis. So, not to minimize its importance, but how does that compare to a Pseudomonas that's resistant to seven drugs, and I guess, John, that's your question about prioritization.

DR. LEGGETT: The logical first step in going through that is to take your criteria number--whichever one is that there is few options available and go that way, so you work your way back from zero drugs to one drug, to two drugs.

DR. POWERS: I guess one of the things we might address then, rather than putting the bugs in first, is go back to the criteria and say which of

those criteria should we rank in such a way as to be more important.

DR. LEGGETT: Go ahead.

DR. GESSER: Richard Gesser from Merck Research.

I would like to suggest along the lines that John is thinking, ESBL, Klebsiella, E. Coli, to start the conversation perhaps.

DR. LEGGETT: Good.

Anybody have any other suggestions? Go ahead.

DR. PORETZ: I couldn't see that list very well. We Mycobacteria and tuberculosis on that list?

DR. LEGGETT: No, I think this is just typical bacteria.

DR. POWERS: That is actually a good point. This is all typical bacteria. We didn't try to branch out yet into those other things. Like I said, we are going to probably do this kind of analysis for fungi and other things, but this was our first pass. As Mark said, we just got a lot of this information.

DR. LEGGETT: Go ahead, Jan.

DR. PATTERSON: I guess with regard to

prioritizing the criteria, I might see No. 4 as one of the higher priority criteria, limited available therapies due to multidrug resistance, and that is kind of what has driven a lot of our concerns in recent years.

DR. LEGGETT: I think in terms of prioritizing the list, where you could get your most bang for your buck is similar to the ESBL thing, where you could take care of both klebs and E. coli sort of at the same time, you know, sort of a common resistance mechanism, and then go from there.

I think, in general, another of the reasons to have this is I think it is going to give us lots of information about the cross-reaction of resistance mechanisms that we don't appreciate. We may think we know them in the abstract, but we don't really see how interwoven they are.

Go ahead, John.

DR. BRADLEY: I think the fact that Jan pointed out that multidrug resistance is a priority amplifies the fact that if it's multidrug resistant, there are likely multiple mechanisms of drug resistance including PORN changes, ESBLs, other beta-lactamases, efflux pumps, the whole nine

yards.

DR. LEGGETT: Alan.

DR. CROSS: Just to re-emphasize the point that is made, we have had a whole series of, quote "new" antibiotics based on combining inhibitors of a resistance mechanism with existing drug, so perhaps something aimed at at least a few identified mechanisms mixed with the existing good agents we have, would also start a new class of drugs.

DR. BRADLEY: How do you exactly want us to do this right now?

DR. LEGGETT: I don't know. The first I saw what we were supposed to be doing--

DR. BRADLEY: Is someone supposed to be putting a list up here?

DR. LEGGETT: I don't know that this morning we want to come up necessarily with the dominant list unless you guys tell us, I mean I didn't think that was the purpose.

DR. POWERS: I think the things we would like to know are - we have six criteria up there, Dave Bell, you commented on some of the things we should add into this or subtract out, and that is the kind of comments we were looking for, are there

some changes that we should make to this criteria, and then one of the clear things I am hearing is No. 4 should be No. 1.

Is there any other way that we should prioritize those? What I thought I heard was it sounds like No. 2 ought to stay No. 2 from what I heard from Drs. Wald and Reller about group A strep. Any other ranking of those things, should we change that?

DR. LEGGETT: No. 1 should be No. 6.

DR. PATTERSON: I would probably put the clinical correlation, I would probably put that higher up, like 3 or 4.

DR. BRADLEY: I think we should assume for purposes of the discussion that if it's resistant in vitro, that you will have a poor clinical outcome. In terms of linking the two, I think that's a completely different discussion how closely they are linked, but I think as we prioritize, to make it simpler, if it's in vitro resistance, in making the list, we should assume that you can't treat them with standard doses of drugs in the clinical arena, and then this afternoon talk about that other issue perhaps.

I would take it off the list.

DR. LEGGETT: I think I sort of would, too, because whether it's not the case now, it may be. I am not sure how that really helps us cull out things that we are not going to look for even though you have got some of the examples.

DR. POWERS: Maybe I should clarify a little bit, and this has to do with the discussion we had yesterday. When we come down to it, what end up doing with this is putting a bug-drug combination in the label, and that ends up being for a specific disease.

The reason why No. 6 is really there is this idea about suppose somebody comes in with a new drug, say, for instance, for macrolide-resistant group A strep, and they say, look, we are great for pharyngitis, does that really help the public health?

So, I guess what is missing from this list or I didn't make clear enough was the idea that this resistance claim that we are going to the label is an organism linked to a specific disease, much like we were talking about yesterday, multidrug-resistant Streptococcus pneumoniae for community-acquired pneumonia.

So, that is why No. 6 is there, to try to

lean it towards the diseases where resistance is more likely to be apparent instead of telling a drug company to spend all their money studying pharyngitis.

DR. LEGGETT: Okay. Barth.

DR. RELLER: I would be interested in Dr. Jorgensen's comments on Item No. 6, but thinking about that, one could consider 6 an NCCLS issue and indeed the committee is constantly trying to make sure that the detection of resistance is clinically important.

I think as an excellent example, Dr. Bell's comment earlier about resistance to fluoroquinolones among Salmonella is not that big of an issue here in the United States. Actually, I wonder about that, by what criteria. Most of the resistance, if not all of the resistance to fluoroquinolones, which is a major problem in typhoid fever, at least as drugs are currently used in some parts of the world, and as reviewed by Dr. Perry in his New England Journal review a couple of weeks ago, and under discussion and a working group in NCCLS is that the organisms look susceptible, but relative to yesterday's discussion, when there is a single mutation, they are nalidixic acid

resistant, and the discussion of whether the criteria are appropriate or even the breakpoint criteria for Enterobacteriaceae with ESBLs, if we had the breakpoint criteria that the Europeans have, whether or not they are ESBLs in the phenotypic strict sense, organisms would look resistant based on dropping the MICs that constitute susceptibility.

The prevalence of single mutations in typhae strains in the United States, many of which are acquired abroad, about 80 percent, but also in foodborne salmonella, the single mutations that are nalidixic acid resistant as presented at the IDSA this autumn, are actually substantial.

What does that mean clinically? Well, perhaps the most important thing it means is that you have got one hit, and when you get that second hit, they are probably not going to work, and it's easier to get maybe the second hit if you have already got the first hit.

So, I think it is an event waiting to happen, and that may be where you can get the mileage on this whole business about the quinolones in poultry and the feeds is that first hit although it is silent by NCCLS criteria currently, and maybe

silent clinically with appropriate duration and dosage of fluoroquinolone in the therapy of typhoid fever.

It is a failure waiting to occur with an additional hit. So, I think the main importance of No. 6 in my mind is reinforcing the importance of keeping the clinical laboratory on which all surveillance is based, be it bioterrorism or hospital infection control practices, or therapy of the individual patients, or the database on which the targets for future drug development are prioritized, to keep the scientific integrity including being linked, not only with phenotypic characterization, but as Dr. Jorgensen so eloquently presented, keeping that matched with the basic science underlying the mechanism of resistance is a fusion that is critical to maintain and to recognize that in some infections with some organisms, you can get clinical success because of the nature of the disease itself despite resistant other organisms, but in some infections like meningitis, you get autolysis-deficient pneumococcus.

We want to make sure that the in vitro recognition of that keeps in sync with the clinical

reality of it. So, I think actually this is a very important issue to keep the clinical and laboratory things, getting the same answer, so to speak.

Jim, what do you think?

DR. JORGENSEN: Well, I think while it is very complicated to do so, it is important or we are finding it more important to index the interpretive breakpoints with the site of infection or the type of infection.

Clearly, that is the case with penicillin and the cephalosporins with pneumococcus. But I think there are other resistance mechanisms that we have debated. For example, it has been debated whether macrolide efflux-resistant Strep pneumos are really significant in community-acquired pneumonia.

The argument has been made that those drugs achieve very high levels in the epithelial lining fluid. The MICs for those strains are not unreasonably high, they are maybe in the range of 4 to 32.

So, the argument has been made that this is an in vitro phenomenon, it is not significant. I would cite to the contrary, the four patients that were reported from the University of North

Carolina, who were treated as outpatients for community-acquired pneumonia with oral macrolides and who came back to the hospital bacteremic and had failed that therapy, and all four of those had efflux-resistant strains.

Moreover, the CDC has had an ongoing study of persistent positive blood cultures in patients who have bacteremic pneumococcal pneumonia, and if you look at the agents they are treated with, most of them are macrolides, most of them have efflux mechanism.

So, I think one thing that is clear is not everybody that has a strain we would define as resistant is going to die or is even going to fail in a dramatic sense, but there will be a percentage of patients who do not do well, and I think that percentage is worth paying attention to.

DR. LEGGETT: Alan.

DR. CROSS: I think in Item 6, it is important, but there has to be a huge caveat there, and I would like to talk on behalf of the host. The point has been made about informative patients, and I think that is really critical, and I would like to just remind everyone that we were unable to show that antibiotics, that appropriate antibiotics

were effective in gram-negative bacteremia, which ought to be fairly straightforward, until the McCabe-Jackson criteria tossed out the uninformative patients who were destined to die anyway.

So, what happens is how we define the informative patient in Item 6 is really critical. It has to be done in a very careful way if Item 6 will have any futility at all.

DR. LEGGETT: Do you think focusing a study on neutropenic sepsis, getting back to the positive blood cultures, that is the only two things you have got, is the bug and the drug.

DR. CROSS: Well, I mean when Dr. McCracken was here last time talking about meningitis, I think that also is an idea situation. We have the experience which we discussed yesterday of levofloxacin in bacteremia with penicillin-resistant Strep pneumo. We had 15 cases of that. So, those were highly informative, good patients, and it does not have to be a huge study, but it is a lot easier to evaluate.

This becomes particularly relevant for the ESBLs because the patients that tend to have serious infections with those organisms are very

complicated patients, many of whom, even under the best of antimicrobial care, will not have a good clinical outcome, and those have to be really separated out carefully.

DR. LEGGETT: We can continue to talk over lunch, but those comments take us perfectly into the discussion we are going to have this afternoon about one study versus the other and the quality of the data.

Since we are running a little behind time, why don't we just break for lunch, and we are scheduled to be back here at 1:30 for the open public hearing. At 2 o'clock, John Bradley is going to talk to us about how clinicians use data for clinical decisionmaking.

[Whereupon, at 12:45 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

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

[1:40 p.m.]

Open Public Hearing

DR. LEGGETT: The first speaker is Jerry Schentag. I hope you can introduce yourself and give us your two cents worth.

DR. SCHENTAG: I will introduce myself. There may be someone in this committee I haven't spoke in front of yet.

Jerry Schentag from the University of Buffalo. I have working relationships with most of the pharmaceutical companies in the area of PK/PD and I will declare that upfront. If I missed anybody, you know where to find me.

But I think I would like to just make one or two small points, some of which is to answer things that are already talked about this morning and a couple of questions that have been asked that I think I have some information to help with.

Then, in another more central point, which perhaps I will state first, and that is, that with AUIC or any other index of pharmacokinetics and pharmacodynamics, we have had a pretty good run here working with clinical correlations and also explaining I think one of the most important things

which we have talked about today, which is bacterial killing rate and also bacterial resistance.

The point I want to make about that is that it is the same number that describes the threshold of killing and the prediction pretty reliably of resistance. So, whatever you think of the absolute value, whether you agree with me that it should be pretty much 100 for everything or whether you think it should be different by different drug class doesn't matter in this statement.

The point is, it is always a predictor of resistance if you set your drug dose against an MIC of an organism right where you see the threshold at the beginning of your good effect.

Now, why is that important? Well, it answers the most fundamental question of all, which is that PK/PD actually predicts the effect of the drug on the organism. It may not have much to do in some clinical scenarios with what happens to the patient, but it has a lot to do with the organism, so that is the territory that we wish to stay in, and your pathogen list can actually be resorted against the drug classes and predict which ones are

going to develop resistance based on their current therapies, because this is selection pressure you are talking about.

So, for instance, John earlier asked why group A strep is not a problem for pharyngitis while the macrolides do have a problem. It is very simple. You are always over 1,000 for your AUIC even with the lowest dose of Pen-V K against strep group A.

With the macrolides, you are never much above 20 or 30, numbers which we normally associate with resistance or at least a prediction of it fairly soon. Vancomycin, which Frank talked about, he talked about it in the context of why it took so long it develop resistance.

Well, there are actually two scenarios of vancomycin resistance that are worth talking about. One is, of course, VREF, which happened first, and then MRSA. Well, with staphylococcus, vanco always had values of 4- to 500 because the MICs were down around 0.5 or lower, and the blood levels were always high enough on the AUC side, so that 0.5 into 250 or so would give you 400 to 500.

Now, why did E. faecium go first? Very simple. Sensitive E. faecium run around with MICs

of 4. Well, if you divide that into 250, that is approximately 62, it drops below 100, and quite a few years ago already, we did a small analysis of our patient population and sure enough, all the E. faeciums that start out 4 and sensitive were selected to develop resistance by vancomycin treatment.

Then, if you do that in a hospital population with just about any drug, you should see the same thing, so it's predictable.

This is perhaps a bit more pertinent, and this is my last point today, because yesterday, we went after the question of the quinolones finally targeting Strep pneumo with a high number. That's the first time we have actually formally targeted a PK/PD value around 250 or higher for the pneumococcus.

Up until now, we have been working on a situation where the dosing gives us 40 most of the time against Streptococcus pneumonia, so I mean we will see whether that is soon enough to help, but my view is, is that all of this is predictable, and the pathogen list ought to be set with some thought in mind for the drug and the dose and how that interacts with the MIC of the organism population.

So, you sort your organism population in such a say that you see the easy-to-kill bacteria where you are over 1,000 like the quinolones against Haemophilus, for instance, and the hard-to-kill ones, like Streptococcus pneumonia and pseudomonas, and then is you set your dose in the range where you are always low or just at the threshold for animal models that suggest bacteria static activity, which is, what, 30 years for most quinolones against gram-negatives and gram-positives, your resistance can be predicted from there.

I mean technology is available I think to make these decisions from the perspective of both pharmacokinetics and pharmacodynamics integrated.

That is what I have to say.

DR. LEGGETT: Thank you very much.

Richard Gesser is here, who I believe was part of the PhRMA task force with the November meeting.

DR. GESSER: Thanks very much. Jim, I guess invited me to speak. I am not speaking for the PhRMA group per se, but I was part of the PhRMA group at the meeting in November, and IDSA, as well, participated in that meeting.

First, I just want to echo some of the points that Frank Tally made. I think the points that he made were really pertinent to Big Pharma, as well as to Little Pharma, and the main issues, what we face.

I am in the Division of Antibacterial Clinical Research at Merck Research Lab, and we are competing for resources within the company as Frank competes for resources in the outside world. Those resources are all used. They are used for one purpose or another as the company decides.

I just want to focus on the purpose of the meetings today, and the meeting in November, I think it was Dave Cachetto [ph] from the PhRMA group who brought up the issue of the list, and there was some debate back and forth of the value of a list and people weren't prepared to make a list, and the list was brought up really in the context of just sort of general guidance, acknowledging that we are competing for resources, that drug development takes a long time, and what we were asking for as pharmaceutical research group was more guidance and clarity earlier on as to what was considered important in the field of bacterial resistance.

I think that the members of the group, I think IDSA supported this, as well, but I don't want to speak for them here, but a lot of people felt that a targeted list of pathogens acknowledging all the caveats associated with that list, particularly the concept of trends over time, the limitations of the list, the meaning of the list of people outside the purview of this group, all things considered, that type of a list and the guidance around that list, and what could be achieved with that list, I think part of the discussions this afternoon, how you would, for lack of a better term, streamline or use information, such as Dr. Schentag mentioned, PK/PD information, in vitro testing information, to go after uncommon pathogens, and again a focused list that was never presumed to be comprehensive entirely and always was presumed to be a working document, something to reflect the current environment was perceived as something that was very important in allowing us to devise development resources, to use those development resources, and to really campaign for resources either within our company or outside of our company if the clear importance of developing new drugs for these pathogens was stated, I think

it would go a long way to moving this along.

One last point. At that meeting, it was expressed with some concern that less resources were being able to apply in this area, and so that we were facing situations of increasing bacterial resistance and concern in an environment where it takes a long time to develop new products, and resources, at least new resources weren't easily being relegated to that area of development.

DR. LEGGETT: Thank you very much.

Is there anyone else who would like to take advantage of the open portion?

[No response.]

DR. LEGGETT: Thank you.

I think we will move on and have John Bradley address us on how clinicians use data for clinical decisionmaking.

How Clinicians Use Data for Clinical Decision Making - John Bradley, M.D.

DR. BRADLEY: Thanks very much, Jim.

I received a call from Dr. Powers earlier this week that there was another clinician who was supposed to be giving this lecture about how clinicians use data for clinical decision making, and since I was one of the clinicians on the

and since I was one of the clinicians on the committee, he decided to ask me if I could perhaps put together my thoughts on clinical decision making.

It is certainly nothing unique that I do, and any clinician on this committee could certainly give exactly the same talk, but the purpose of what I am trying to do is to demonstrate publicly all the sources of information that we use in actually taking care of patients, and how we take all of this data and use the data in order to cure the patients, which is, of course, our most important goal.

[Slide.]

We certainly use clinical information about the patient being treated, what are the characteristics of the patient, what are the characteristics of the infection that we are treating. We get organism information from the cultures including identification and susceptibility data, so we depend on our hospitals' microbiology lab giving us an NCCLS guidelines approved ID and susceptibility piece of information, so that we can select from those antibiotics to which the organism is susceptible

which ones to choose for the patient.

Obviously, the list of antibiotics that are tested by the micro lab happen to be those that are FDA-approved and available to us. We can certainly go to some research labs and get unapproved investigational antibiotics tested against the organism, but the vast majority of what we do has to do with FDA-approved therapies.

We take into account information on pharmacokinetics and pharmacodynamics now, as Dr. Schentag had mentioned, the toxicity characteristics of these FDA-approved agents which are active in vitro.

[Slide.]

So, we do clearly use the information that the FDA reviews and publishes in the package insert and on their web site. They certainly look at data on safety and efficacy, but they have approvals only for the particular indications that are submitted by the sponsor, and they have gone on record as saying that if there is an indication for which they have not been given data, that they are not saying yes or no, they just haven't been given data on which to make a recommendation.

So, it is unlikely that we will get new

indications for ampicillin because it is unlikely that a group will put all the financial resources requires into a sort of package labeling submission to go to the FDA and have them actually review it and approve ampicillin for something, and this certainly goes for virtually any other drug that is generic.

We also use the medical literature for the preferred antibiotic therapy, and certainly when the FDA approves a drug, they approve it with all the information they have, the best information at the time of the approval, but then a year or two or three later, unless there is more information that comes back to them, they don't keep annually updating all of the package inserts for every drug that they have approved.

That is something that we find from the medical literature. We have guidelines that clinical societies put together, like the IDSA, which is very involved in trying to tell physicians which is the preferred therapy for which particular infections and organisms.

In pediatrics, the American Academy of Pediatric's Red Book Committee, the Infectious disease Committee comes out with recommendations on

preferred therapies. There is the Sanford Guide, which is put together by a number of very prominent infectious disease clinicians who are internists, published clinical trials, some of which are excellent, some of which are not so good, some of which are downright misleading, but we are taught to evaluates these clinical trials in the literature and take the information from these trials that is valuable and extrapolate it to each individual patient, each individual infection that we are treating.

[Slide.]

Back to the patient. This situation was raised a number of times earlier today. The immune competence of the patient is very important in whether that patient can clear the infection. The extremes of age, the newborn and the elderly don't have the same immunologic capabilities as people in the middle.

The are comorbidities, associated illnesses, sickle cell disease was raised earlier in childhood, chronic bronchitis from the smokers in adult life, diabetes, there is a whole host of comorbidities which impact the progression of the infection and the ability of the host to clear this

infection. These are just a few of the things. In the time allotted, there is no way we can go into all of them.

Of course, we like to have an examination of the patient. That sometimes gives you clues on to where the infection is and what other problems that you may have facing you. We look at the laboratory information from the patient which includes organ dysfunction information, which impact antibiotic toxicity decisions.

So, if I have two antibiotics that are equally effective, one has renal toxicity, and I have a patient who has got pre-existing renal toxicity, I am not going to want to use that, I will want to use the one with less renal toxicity. Then, of course, we use imaging studies, as well.

[Slide.]

Now, trying to put together how we take all of this information to make the decision, I have tried to put together this Ven diagram, which includes circles from the FDA, the NCCLS, the CDC, and the IDSA, and other clinical organizations.

The FDA is certainly expert at evaluating the safety and efficacy of submitted data. That is their job. They tell me where the drug will work

and where it will not work, where to be cautious in the group of patients for which data have been submitted to them. They also caution me on where to look out for safety considerations, and I take their advice very seriously.

The NCCLS looks at the organism identification, that is their job, and interpretations of susceptibility, and they use those interpretations based on both in vitro testing and, of three years ago, pharmacodynamic considerations.

Now, the FDA is also historically involved in looking at breakpoints and what is susceptible in vitro, and there are FDA microbiologists who are certainly present at the NCCLS meetings, and it is an open forum for discussion, but the NCCLS puts together the guidelines which virtually every hospital in the U.S. and many in the world use in order to determine what is susceptible and what is not.

Things can change. The fact that third generation cephalosporins are now considered a bit more active against pen-resistant pneumococci. Beta-lactam-resistant pneumococci is one example of that. Their guidelines keep getting updated, so if

there is new information on resistance that impacts my being able to use a drug, it shows up in their documents.

The CDC is involved in epidemiologic evaluation of pathogens, particularly resistant ones, ones which are of public health concern, and I know the FDA and the CDC have some interconnection. There is probably a dotted line that goes between these two, but the CDC certainly feeds information on organisms to the NCCLS and feeds information on epidemiology to the IDSA and other clinical organizations.

So, everyone is involved in this decision making process, no one can do it by themselves. The IDSA and the other clinical organizations that I mentioned are responsible for recommendations for clinicians for actually treating patients for all infections with all antibiotics, so if there is an organism that the FDA has approved for a certain drug and a certain indication, then, if there is another infection that that organism causes, and a clinician wants to know if there is any data to treat this other infection, then, they will go to these societies to get some advice on extrapolating information from what the FDA has, again hopefully

based on clinical studies which give us good, useful, evidence-based information.

[Slide.]

Just to give you a couple of examples briefly, if there is a 12-year-old with leukemia and neutropenia, who has x-ray defined pneumonia, and grows a Pseudomonas aeruginosa that is ceftazidime resistant, but meropenem and ciprofloxacin susceptible from the bronch wash, we are supposed to decide what is the appropriate therapy for this particular child.

So, based on the susceptibility data, I will treat with meropenem based on the safety and efficacy data of meropenem in pediatric meningitis. So, I take the data from just as serious an infection, although perhaps a more immune competent host, and extrapolate with a high dose of drug, tissue penetration, killing of organisms that I will hopefully get a success using this drug to treat pneumonia in an immune-compromised host.

So, again, the FDA hasn't approved of meropenem for Pseudomonas pneumonia in neutropenic children, I am sure, but that doesn't stop me from using the drug in that scenario.

Now, if it's meropenem resistant, then, I

would go to ciprofloxacin, and there are clearly even less data in pediatric populations on quinolone therapy of Pseudomonas pneumonia, but I also use data that is published in the adult literature to help guide me on efficacy in these certain populations, but in kids perhaps I have to worry more about safety rather than efficacy for fluoroquinolones, so all of these things are going around all at the same time, and hopefully I come up with a reasonable recommendation for therapy.

[Slide.]

Another example, and this is something that we talked about earlier with respect to serious infections versus non-serious infections. Dr. Reller brought up meningitis, Dr. Glode brought up meningitis where if you don't treat it with an effective antibiotic, you don't cure the infection, in contrast to otitis media where there is a fairly high spontaneous resolution rate even without antibiotic treatment.

This is a real case which occurred in the pre-Haemophilus type B vaccine era, an 18-month-old with periorbital cellulitis and bacteremia, who was being treated with ceftriaxone, and I am asked by the resident why I don't use I.V. trimethoprim

sulfa, which was available at the time, because he frequently used the drug PO for treatment of H. flu and otitis, and the susceptibilities of type B H. flu and non-typeable H. flu are very, very similar.

Because no published series existed on bacteremic infections with H. flu treated with I.V. trimethoprim sulfa, I felt very uncomfortable extrapolating from otitis efficacy to sepsis and cellulitis efficacy, so I would not use otitis data to convince me that I can treat bacteremic disease, whereas, I would probably go the other direction if there were previous data on I.V. therapy of Haemophilus in bacteremia and cellulitis, would I feel comfortable using that drug in otitis, probably more comfortable, but I would also like to see data in otitis.

[Slide.]

So, when can you extrapolate efficacy? If you can successfully treat a difficult infection, you should be able to treat a simple infection.

[Slide.]

Certainly some infections are harder to treat based on penetration of antibiotic to the site of infection, intra-abdominal abscesses is one case, meningitis is another, versus infections in

which there is excellent penetration like urinary tract infections, you have huge concentrations of antibiotic in the urine, or pneumonia where you have got excellent blood flow to the lung.

The seriousness of the infection and spontaneous resolution of the infection, as I just mentioned, meningitis, or a pneumonia Fine Class 5 versus acute exacerbation of chronic bronchitis or acute otitis media where there is controversy in the clinical community as to how important treatment is in the first place. And then comorbidities, I have already mentioned, healthy young adults versus neutropenia states or old age or neonates in which you need to ask the antibiotic to do more in curing the infection.

[Slide.]

When can you extrapolate safety? Well, If I have a tough infection in a patient who is not responding, and the in vitro susceptibilities are sort of borderline, I will push the dose, and most of my colleagues would, as well.

We watch for toxicity certainly because there may not be as much data in the literature on toxicity at a higher dose, but in pediatrics, where we have the luxury of having meningitis studies

where almost double the dose has been used for a number of infections, and we have plenty of safety data, I feel comfortable then increasing the dose in other non-CNS difficult-to-treat infections feeling that the safety data for meningitis can be extrapolated to the safety data in a bad pneumonia empyema or a bad pyelonephritis with a perinephric abscess.

So, that's one situation again where I can extrapolate safety from a severe serious infection to treating less severe infections.

[Slide.]

So, to summarize, we use published data from the FDA and clinical trials on safety and efficacy for infections caused by a certain pathogen, considering the host and location of the infection, the antibiotic toxicities, and the in vitro susceptibilities, as well as the risk of failure, to extrapolate efficacy in using an antibiotic which has not been previously studied for the type of infection or the patient population that we are treating. I should have broken that sentence up into two or three, I apologize, but all the stuff is in there.

So, that is basically a nutshell of

clinical approach that I take.

DR. LEGGETT: Thank you, John.

Moving right along, Ed, could you please tell us about relating clinical data from one disease state to another.

Relating Clinical Data from One Disease State to Another

Edward Cox, M.D.

DR. COX: Good afternoon. It is a pleasure to follow Dr. Bradley. A lot of the principles that he has been discussing will be parallel with some of the items that I will be discussing as I discuss data from studies in one indication supporting studies in a different indication.

[Slide.]

Just to start out, and I know a number of the folks that have been present at these meetings, but there have been a number of FDA meetings on resistance, both meetings discussing the general topic of drug development for antimicrobial-resistant pathogens, and then also we have had discussions with regards to resistant pathogens in the setting of product-specific meetings that have occurred over the last couple of

years.

[Slide.]

The topic that I am talking about today stems from one of these meetings, the February 20th meeting, where we discussed drug development for resistant pathogens. One of the suggestions that came out of that meeting was to consider the degree to which a study performed in one indication could be used to support safety and efficacy in another indication, so that multiple studies would not be required within a multi-indication new drug application.

[Slide.]

Just to mention the Public Health Service Action Plan and some of the items in there with regards to product development. This overall approach of streamlining the regulatory process and identifying ways to promote the development of antimicrobial-resistant drug products is consistent with some of the action items that are within the PHS Action Plan.

[Slide.]

I also turn and just give a brief excerpt from our labeling regulations as to what guidance or what information or requirements, I should

actually say that our regulations provide us with regards to the types of data that we need in order an indication in the label.

The regulations say that, "All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies," and then goes on to define these studies.

[Slide.]

You will notice that is adequate and well-controlled studies in the plural form, and I think the word choice here in part reflects some of the considerations with regards to clinical trials, the reproducibility of observations that are made in clinical trials, there are inherent variabilities that can occur in clinical trials. There is the potential for bias both recognized and unrecognized that may occur in clinical trials. Chance findings can also lead to results in clinical studies.

So, by performing more than one clinical study, essentially looking for reproducibility, you may be able to, with a greater degree of certainty, determine what it is that you are see in the clinical studies that you are conducting.

[Slide.]

Today, we have been talking mostly about bacterial infections, and we also recognize the importance of resistance in non-bacterial infections, but we will, in fact, focus on some of the indications here for bacterial infections.

You will notice there is essentially a number of different indications that I put up here. I won't go through the abbreviations, but there is a wide variety of indications that one can study.

In looking across these indications, you will notice that some are more related to each other than others, as are the microbes that cause these infections.

[Slide.]

I think really what we hope to do here today--and Dr. Bradley has helped us tremendously I think in already elucidating some of the criterion and principles that he uses in his practice--is really to explore the science behind the practice of considering data that comes from outside of a specific target indication within a multi-indication NDA.

We have heard from Dr. Bradley some of the principles and practices that he uses, and that serves as a very good starting point for

understanding how we might approach this problem, but we also have to recognize, too, that as we move from the individual patient to a broader public health decision, one that would have regulatory impact, there is certainly a higher degree of rigor that one would be inclined to use as opposed to what one would use with a single individual patient.

The issue of using data from related indications is not something that is brand new. It is actually something that is recognized and has been in some of the prior guidances and draft guidance documents with regards to developing antimicrobial agents.

Our goal here is if we can clearly describe the rationale for the use of the evidence from studies in other indications, that raises the question can we develop criteria as to how such information may be used to support clinical studies in other indications for the purpose of drug development.

[Slide.]

Just to review some of the guidance documents that have provided some information with regards to the issue of using data from other

indications. The 1992 Points to Consider guidance document discussed circumstances within a multi-indication NDA where one trial within an indication, that is part of an overall drug development program that includes multiple indications, might be used.

It describes relationships between uncomplicated UTI and complicated UTI, acute prostatitis relying upon complicated UTI, uncomplicated intra-abdominal infections, such as mild diverticulitis, relying upon data from a complicated intra-abdominal infection study, and then also an intra-relatedness between complicated intra-abdominal infections and also GYN infections.

[Slide.]

Around the same time, the IDSA/FDA guidelines that came out in 1992 and published in CID, have some further comment on this issue that I found quite informative, so I will just briefly mention that here.

That is, the IDSA/FDA guidelines state that whenever possible, there should be more than one comparative randomized study for a proposed indication. They do go on to note that, however, in certain circumstances, a single, well-controlled

study may suffice.

The single trial may be sufficient for additional indications when a new agent has been shown to be effective in more than one trial for a major indication existing within the same anatomic location or organ system and caused by similar microorganisms.

So, I think these are, in part, some of the principles that John has been talking about and that also are part of the criteria that I will get to.

They do also provide some examples that are informative as to their thought processes back then. They talk about CAP trials and if you have a CAP trial that shows efficacy for Strep pneumo and H. flu, then, in that circumstance, perhaps a single trial for otitis media, bronchitis, or sinusitis would be a reasonable approach.

Then, they go on to provide sort of a contrasting example where they talk about uncomplicated urinary tract infections being cause by E. coli and noting that this would not really provide much assurances to the drug's efficacy and the treatment of bacteremia caused by E. coli.

[Slide.]

The draft guidances 1998 describe some relationships between complicated UTI and prostatitis are similar to what we have seen before. They also talk about concordant microbiology data being derived from CAP or HAP studies being able to support AECB, and also note a relationship between CAP and HAP.

[Slide.]

This list just mentions a couple of NDAs where, in fact, these principles are relying upon data from one indication to support another, and this is not meant to be an exhaustive list. Certainly, a more extensive search could probably turn up more examples, but Sporanox injection, oral solution was improve for empiric antifungal therapy for febrile neutropenia based upon one trial and supportive data from treatment trials of fungal infections including treatment of aspergillosis and also esophageal candidiasis.

Other examples include the studies for prevention indications for Pneumocystis carinii pneumonia and Mycobacterium avium, which were supported by data from treatment studies of illness caused by these same pathogens.

[Slide.]

Just to get people thinking about this a little bit, the rhetorical questions of the relationship between CAP and HAP, same tissue site or same anatomic location, and then a contrasting example of uncomplicated urinary tract infection support CAP, and then complicated skin supporting HAP, and these are really just meant to be provocative examples and really not to ask the question of yes or no, but more to say why are people saying yes, why are people saying no, what is going through people's minds that is leading them to say that either one can support or one cannot.

[Slide.]

I think the factors that people are probably considering are the things that John has mentioned and also that we have here on this slide with microbial etiologies, tissue penetration, severity of disease, and host in which the infection occurs.

[Slide.]

So, this really leads us to the proposed criteria for when data from one indication might be able to support another indication within a multi-indication NDA. I will read through this

because they are the subject of what we would like folks to discuss, and we will talk about more with regards to the questions.

1. The natural history of the disease under study--and that is the first criteria--what is the spontaneous resolution rate and what is the morbidity/mortality without treatment?

So, this issue gets to the degree to which you can understand the treatment effect within a particular indication.

No. 2. Factors other than the antimicrobial which may affect outcome in a given indication, for example, in complicated intra-abdominal infection, part of the therapy would be the surgical debridement, and another example, ABECB, where there therapy is not only the antimicrobial agent, but also can be corticosteroids, can be beta agonists, and other interventions that may influence the outcomes.

No. 3. The characteristics of the study drug. Here, for example, we are talking about the pharmacokinetics of the drug, does it reach the site of the infection, what are the levels within those tissues, and are there any other effects that need to be considered, such as the pH at the site

of action of the antimicrobial agent.

[Slide.]

No. 4. Then, other criteria that may influence the data that can be inferred from a particular indication is whether the infection is a monomicrobial or a polymicrobial infection. An example here would be enterococci in the setting of a polymicrobial intra-abdominal infection where surgical attention would usually be needed, and then also antimicrobial therapy directed at the spectrum of microbials infecting, and not necessarily including enterococci would probably affect effective therapy.

No. 5. Similar sites of infection, for example, the lung where both community-acquired pneumonia and hospital-acquired pneumonia would occur, so another consideration as whether one can use data from one indication to support another.

No. 6. As Dr. Bradley has already mentioned, too, the host effects. Certainly, there are host differences as we move from one indication to another. For example, the patient who gets community-acquired pneumonia may have different host factors than those patients who get hospital-acquired pneumonia.

No. 7. Then, importantly, the seventh criteria, the similarity in spectrum of organisms causing disease, and while there may be some overlap with the organisms causing community-acquired pneumonia and hospital-acquired pneumonia, there are significant differences as one moves from CAP and HAP and gets more to gram-negative pathogens and also more Staph aureus.

So, these are the factors that we have come up with, that we are proposing, that we would like the committee to discuss with regards to using these criteria to determine when it might be appropriate to use data from one indication to support another indication.

[Slide.]

Some of the other considerations, and Dr. Bradley has also mentioned these, is almost sort of a directionality of support, can a severe disease support a less severe disease? How about vice versa?

Some examples here would be an I.V. CAP study in relationship to I.V. HAP, and then to contrast that oral CAP versus I.V. HAP.

Other considerations might be the similarity of dose, duration and the formulation.

If one study uses a different dosing regimen, how does that help us in inferring efficacy with regards to another indication.

And then an underlying question here, too, is also if data from one indication is to be used to support another indication, what is the weight of evidence that that supporting data can provide.

[Slide.]

Some practical issues that I think deserve mention are if there is a greater dependence on a single study in a subject indication, reliance upon other supporting data, with regards to that single study, it is important that that be a high-quality study, have a rigorous study design, and that it be well performed and have very well done clinical and microbiologic endpoints since there is a greater reliance upon that data from a single study within the overall multi-indication NDA.

Some other practical considerations are that within a highly interdependent program, such a program may have less resiliency if unexpected findings are encountered within the program. That can be either in a supporting clinical study, for instance, if efficacy is not demonstrated in the supporting study or that would certainly create

some difficult questions that would need to be answered about the overall indication.

Then, it is also important that the more streamlined approach also still provide sufficient quantity of data to adequately characterize safety, and then we really sort of already mentioned this, and that is, in situations where there is a more streamlined program, if an unexpected safety finding does come up, it may be more difficult to address that within the more limited clinical program.

Then, I have got as the last bullet, other issues here just because as we discuss this, there may be other things that become apparent in the discussions today for other practical issues that need to be considered within a multi-indication NDA that is planning to use a single study within a particular indication.

[Slide.]

Then, just to put out a hypothetical example of a dependent development program for a drug that was being developed for more serious infections, just a hypothetical example of two studies in community-acquired pneumonia, one study in hospital-acquired pneumonia, and one study in

complicated skin and skin structure infections along with supportive data.

Important to remember is that this data would provide both the efficacy data and then should also be able to provide the necessary safety data for the drug development program.

[Slide.]

Because there are numerous indications, as we showed on an earlier slide, I put this up really just to get people thinking about this question, and have sort of put down some of the thoughts so far.

This is not meant to limit the discussions and all, but maybe just sort of focus the discussions initially by providing some indications where there appears to be a relationship by organ system, and you will notice that some of the arrows are one directional and others are bidirectional, and then also other relationships that might be used in relating indications, and these are a little more based on the microbiology than they are the anatomic location.

[Slide.]

What I will do just to give folks an impression of where we are headed to is just to run

through the questions and then I will sit down and take questions if folks have questions, and then we can move from there on into the discussion.

[Slide.]

So, the first question and just so people know where we are headed is to please discuss the concept of data from studies in one indication supporting studies in a different indication.

It would be helpful to have a conceptual discussion about this use of data from one study supporting studies in a different indication within a multi-indication NDA. It would also be helpful in your discussions if you could please also discuss the proposed criteria that are intended to identify factors which should be evaluated when considering the evidence from studies in one indication supporting studies in a different indication, and from the list of factors, are there factors that should be added, modified, or removed.

Question 2. Please discuss which indications may provide supportive evidence for a single clinical study in another indication.

Question 3. Please discuss whether data for a more serious indication can support safety and efficacy in a less serious indication, and are

there situations where the converse could be considered, that is, a less serious disease supporting a more serious disease.

As we get to the questions, we can put up some other slides just to remind people what those criteria were, but at this point, I will take my seat and be happy to take questions.

DR. LEGGETT: Are there any questions for Dr. Cox?

[No response.]

DR. LEGGETT: Obviously, an entirely lucid presentation. Let's hope our discussion can come someplace close.

Committee Discussion

It is now about 2:30, so we have a couple hours at least to come to these proposed criteria and discuss this.

So, why don't we just jump off with Point No. 1, and I would like to hear some people's ideas about the concept of using data from one indication to support studies in a different indication.

I think that the points that were brought up in the final page, looking at the relating indications on that final page that Ed talked about. Why don't we use those as sort of specific

example to try to flesh out what we like, don't like, or other thoughts we have.

Since a lot of yesterday's meeting was devoted to community-acquired pneumonia, why don't we start with can we use community-acquired pneumonia data into the hospital, or can we go the other way around?

Go ahead, Barth.

DR. RELLER: To help get the discussion started, there was a reason that we have community-acquired pneumonia and hospital-acquired pneumonia. Earlier, it was lower respiratory tract infections and upper respiratory tract infections, and I think the reason for the delineation and the arduous discussion of the past, that to lump everything in lower respiratory tract infections did not give sufficient delineation about severity of disease, about differences in pathogens and that one might take easy ones and inappropriately extrapolate to the more difficult ones led to these basic splits.

I think the natural spectrum of organisms in community-acquired and hospital-acquired infections, and the added complications in many of the hospital-acquired infections also being

associated with ventilatory assistance, makes these sufficiently disparate that there is very little that one can extrapolate in one direction or the other, not because if you had a hospital-acquired pneumococcus, it wouldn't act like both of them bacteremic with a community-acquired pneumococcal pneumonia, but just that the frequency with which that happens is insufficient to put much effort into the extrapolations with these two entities.

There was a reason why they were split into this, and not lumped into lower respiratory tract infection.

DR. LEGGETT: Michael.

DR. PROSCHAN: But what you are talking about is not--I mean you are talking about just requiring one study rather than two, and then using information from other similar diseases, right? You are not talking about relying entirely on the other diseases, but on not requiring quite as strong evidence for the particular one.

DR. LEGGETT: That was my understanding, that it would not be two community-acquired pneumonias studies, but one required community-acquired pneumonia, but then if you wanted to get a hospital-acquired pneumonia, what

would you have to do, what kind of data could be transferred or could it be transferred at all.

I don't think we are talking so much of safety at this point although there is some degree of that. I think at least right now we should focus on the efficacy part of it. What sort of that sort of data can we transfer?

Ellen.

DR. WALD: Well, it seemed like in general that you could feel comfortable going from the more complicated infections to the less complicated, so if you are talking about urinary tract infection or soft tissue skin infections, then, you established efficacy in the more complicated, that you could feel I think assured that the uncomplicated would do as well.

DR. LEGGETT: By that, do you mean that if, for instance, taking this hospital-acquired pneumonia that is more complicated, the patient is more complicated, and it's Staph aureus, could you the extrapolate to pneumococcus in the community?

DR. WALD: I would make my remarks confined to the two things I suggested, that is specifically soft tissue and skin, as well as urinary tract infection.

DR. LEGGETT: Go ahead, John.

DR. BRADLEY: In look at getting a good study for both CAP and HAP, Dr. Powers and I talked about this a little bit yesterday. In setting up a clinical study for, say, community-acquired pneumonia, there are certain criteria that we have in order to enroll a patient in the study, and we are looking for a certain percentage of bacteremic pneumonias, and certainly if there is a very motivated investigator to get sick bacteremic consolidated pneumonias and the number of enrollments is actually fairly small, to target that group.

If, on the other hand, the investigators are just there to enroll every child with abnormalities on chest film, knowing, as Dr. Wald had said yesterday, the viral pneumonias are far more common, then the number of children enrolled in that CAP study with viral disease, not true bacterial disease, will be excessive and the quality of the study won't be sufficient for us to feel good, so if there is a community-acquired pneumonia study where 10 percent of the children, 20 percent have bacteremic pneumonias, I will feel really good that that high quality study in

community-acquired pneumonia with one study in hospital-acquired pneumonia would make me comfortable with not doing a second community-acquired pneumonia study.

My point in all of that is to say it's not just how many studies you do, but it is the quality of the study.

DR. LEGGETT: I have a caveat to that. I agree that the harder your target, the small the N you need, but on the other hand, if you are only going to use a single study, the more comprehensive your analysis and correct your analysis has to be as was allowed with the animal data.

It is not the animal model, it's how your good your analysis is of that animal model. For instance, while we were talking about numbers of 15 or 25, that is good to know that for that particular bug, say, pneumococcus, that we can sterilize 25 out of 25 bacteremic sick hospital patients, but unless you have got some data that will extrapolate those 25 cases to 5,000 people that you have done Monte Carlo simulation on, so that you know the kinetics are going to be the same in the 70-year-old liver failure, ICU patient as my 18-year-old pneumococcal bacteremia, I am not going

to buy that. In other words, we can't extrapolate too far.

Mike.

DR. PROSCHAN: Part of this business about two studies is really sort of artificial. I mean if you took one huge study and then you just broke it into two and said, oh, here, here are two studies, I mean that shouldn't be regarded as any stronger evidence than the one study.

It doesn't make sense from a statistical point of view to just break it into two. So, part of the reason it's more convincing to add two studies is that they were done in perhaps slightly different patient groups and maybe there are other factors that were somewhat different. Otherwise, it wouldn't make sense to require two.

DR. LEGGETT: What would you say about the N in each of those two studies? If it's one big study, should it have the same N as the two smaller studies or, quote, "two separate studies?"

DR. PROSCHAN: Well, what I was saying is like suppose you had one study and you used the number of people such that if you cut it in half, each one of those would have high power, 90 percent power, say.

Then, in that situation, it is certainly not more convincing to break the study into two and run two separate tests and say yes, look what happened than it is to just put all the data together and compute the test statistic on the full data. I mean it just wouldn't make sense to do it any other way.

That is what I am saying, that one of the reasons why it is a good idea to require two different studies is because they are usually in different patients or, you know, somewhat different anyway, and there are other things that are slightly different. That makes it more convincing.

DR. LEGGETT: What is you required a priori that you had to have a certain percentage of folks that would give you those two populations, could you then have one study, you have to analyze it knowing that your population was heterogeneous. Does that make it stronger or weaker?

DR. PROSCHAN: I am sorry, if you did what?

DR. LEGGETT: You said you have two studies, you have got one of old folks in the nursing home and one of adolescents on the street. If you put both of those into one study and

analyzed them as one group, is that stronger or weaker?

DR. PROSCHAN: No, that's weaker. I mean in that situation, to me, that situation is different because I want to know separately whether it is working in both groups. You put them all together, you could increase the variance to such an extent that you may not see anything.

DR. LEGGETT: And if we use one study in a hospitalized pneumonia with a larger study in community, and then try to go across it, aren't we doing the same thing?

DR. PROSCHAN: If you go across?

DR. LEGGETT: If you try to use your data from your community-acquired pneumonia to then tell you something about hospital-acquired pneumonia, isn't that doing the same thing?

DR. PROSCHAN: What I would do, to me it seems like a reasonable approach is you already have some results on community-acquired pneumonia, and I would still require a study in hospital-acquired pneumonia, but then if I had that study that was positive, then, I would also try and use the information from the community-acquired, as well.

So, I think you still, you know, you have got to have a study that shows it in the particular one that you are interested in, but perhaps not two. I mean you could borrow the evidence from the other one to help corroborate the results.

DR. LEGGETT: Dave, you look like you want to say something.

DR. BELL: I just wanted to add that I am not in disagreement with the general tone of this, but I think there is value in two studies that goes beyond just different population groups studied. I mean the investigators are different, the institutions are different, geographic region of the country, of the world is different. It adds a certain robustness in terms of whether there might be biases.

DR. LEGGETT: You knew that was a surrogate for all variability.

DR. BELL: Okay.

DR. PROSCHAN: I agree with that. I just was struck, one time I reviewed something where they said yes, we have done these two different protocols and, you know, they were done exactly alike, they had the same investigators, and to me, they did what I said you probably shouldn't do, you

know, they basically just cut one study in two, and that is not more convincing. But I agree with you that all those things are important, the fact that, you know, there other differences, as well.

DR. LEGGETT: Alan, you looked like you wanted to say something.

DR. CROSS: We saw yesterday, I think that there were four control studies presented off of the same indication, and one of the four was markedly at odds with the other, so I do think what everyone else has been saying.

First of all, that no studies are done exactly alike and that there is a greater confidence when we see that there is at least more than one study going in the same direction, and also in terms of comparability, I agree with Barth that it is very hard to extrapolate hospital-acquired to community-acquired because of the obvious multiple differences between the two syndromes.

DR. LEGGETT: Could you elaborate on what kind of differences you are talking about, differences in the host, not just different pathogens?

DR. CROSS: First of all, the organisms

and comorbidities, and therefore perhaps how the drug has to be delivered.

DR. LEGGETT: Orally rather than I.V., you mean.

DR. CROSS: Yes.

DR. LEGGETT: In terms of the analogy that Ellen made about going from complicated to uncomplicated, wouldn't you think that that same analogy could be from complicated to hospitalized sick patients to folks with less, quote, "complicated"?

DR. CROSS: If they have the same organisms, but I don't think what we are talking about are two completely different organisms, but, in general, if one were to have a more severe hospital-acquired pneumonia and extrapolated to perhaps lesser severity, that is obviously acceptable.

DR. LEGGETT: Go ahead, John.

DR. POWERS: Alan, let me ask you for a more specific example here, because clearly, there are different pathogens between community- and hospital-acquired pneumonia, but suppose the drug sponsor came in with, say, a carbapenem type drug, which looked like it had, in the test tube,

activity against Pseudomonas, Acinetobacter, and Strep pneumo, H. flu, Moraxella, and the common ones, and they did first a community-acquired pneumonia trial, and they got, unlike what we saw yesterday, a whole lot of Fine Class V people in there, severely ill people.

This is probably assuming this is going to be I.V. drug. Then, you get, as John pointed out, a high-quality, hospital-acquired pneumonia trial, one of them, and assuming it works, because that's the other issue, what we saw yesterday. If your one trial was that one gemifloxacin trial that didn't work, you have got a problem.

But suppose that that trial actually shows it works, are you convinced by that one hospital-acquired pneumonia trial, based on what you saw in a community-acquired pneumonia trial?

DR. CROSS: Well, I think a real wildcard is certainly in hospital-acquired pneumonia, one of the variables you don't have in community onset is the appliance, the endotracheal tube, and the situation is, first of all, that it is much more difficult to clear organisms in the presence of a trach tube.

But the other aspect of it is that, as I

see it, there is a lot of disagreement in terms of just defining the bacteriology of ventilator-associated pneumonia, for example, is Staph epi truly a pathogen, and if so, do we have to evaluate a drug efficacy there, which you would never do for community onset.

DR. POWERS: I guess what we are getting--maybe if I can make it clear--we are not saying that you do no trials for hospital-acquired pneumonia, that is not even on the table, so let me phrase the question another way.

Somebody does a CAP trial for this carbapenem type drug or let's say they do two of them, like Ed used in his example, and then they have one hospital-acquired pneumonia trial, and it works, and the drugs works, and it is a well done trial.

What is the second hospital-acquired pneumonia trial going to tell you?

DR. CROSS: You mean aside from the reproducibility of that.

DR. POWERS: Exactly, because that is the question we are asking. So, you have got two CAP trials with a drug and it works, and now you have got one hospital-acquired pneumonia trial, and what

we are asking is assuming all those things, that is a well-done trial, and that the end results show the drug is actually effective and safe, what does the second trial in that indication actually add to that?

Now, there are a lot of ifs in there, that is what I am saying, and, of course, the risk there, too, if your one HAP trial and the drug fails, you have got a problem.

DR. CROSS: If what you are saying is on the community onset one, that you have sufficient number Klebsiellas, Pseudomonas, et cetera, then, I might not have as much difficulty, but it seems that most of the drugs which we have evaluated for CAP are really looking at the atypicals plus Strep pneumonia, so I think it depends how much emphasis you wish to place on, let's say, gram-negatives, in that situation.

DR. POWERS: So, I guess what I am hearing, then, to sort of summarize that, would be that perhaps in a single hospital-acquired pneumonia trial, you would still need an adequate number of organisms more commonly seen in HAP than community-acquired pneumonia to give you some confidence of what was going on.

So, that would go to sort of the size of the HAP trial and again the quality of the data that you are getting.

DR. CROSS: Well, again, it might be size, but I think also what we have been discussing is, is there an intrinsic value to having a study done under one protocol by certain investigators reproduced at least a second time, and I should say it does not have to be a huge trial if the patients included are, as we say, informative.

DR. LEGGETT: Keith.

DR. RODVOLD: Actually, your comment in the beginning is what I actually observe out in the field, is that most of the pharmaceutical companies, no matter what kind of compound it is, go two CAPs and come to one HAP, and despite the compound, it is probably better for HAP than it is for CAP, because when they get through and get their numbers for safety, as well as build up a database off the CAP and then make the flip to HAP, and kind of come through smaller.

When you look at those pathogens, and I think the message came up pretty strong this morning, and I agree, that there is nothing in the pipeline for gram-negatives, and really nothing,

that if it was in the pipeline, has really been developed for serious gram-negative infection indications.

If it has got enough gram-positive coverage, which they almost slip in on the compound today, so they can get into the community indications first, that is where they go, and here is no incentive for them to kind of come the other way.

My point is that I think you need to think, I agree with everything, that the diseases are different, the patients are different, that there is no doubt that the bugs are different, but if you really want to be serious about getting people to develop drugs and gram-negatives, and get nosocomial type infections on board, you have got to do something to make them come that way, because they are not coming that way, and they are not going to come that way at the price of drug development and delays they could face.

So, that is where you are going to have to get the caveat or carrots out there to get them to come and to hopefully develop drugs that give us that, because I don't think there is any incentive for them to do it, and that's just what I am

constantly seeing, and I think the example you put is one that is out there already, a big carbapenem, but it doesn't have nosocomial, and they are teasing now with how to get it in CAP guidelines. I am like going really.

DR. COX: It sounds like what I am hearing is that people are thinking really in terms of the criteria and essence, but it seems that efficacy within the lungs is not enough, there is reservations about using that information derived from a CAP study with regards to HAP, and it sounds like the point there is actually, really to the microbiology and the host factors.

So, those are a couple of the criteria that we have there, but it sounds like there is some reservation with regards to that use of supporting information from, say, two CAP studies to a HAP study.

Do I characterize that correctly?

DR. LEGGETT: Especially the lack of bacteriologic data that seem to be coming of CAP studies.

John.

DR. BRADLEY: I am still supportive of one CAP and one HAP, and there is an example that I can

give you right now. We are in Phase III trials of ertapenem with CAP, and ertapenem is a very potent antibiotic, and I don't know if I am going to use ertapenem for CAP for the routine, run-of-the-mill well child that comes into the hospital with pneumonia, assuming the drug is approved.

So, I don't want to do two CAP studies with ertapenem when I see the value of the drug being one for hospital infections and outpatient infections. So, I don't you to ask the company to do extra studies in an area where, at least in pediatrics, it may not have its strength.

So, a CAP study, which is one, well-done, well-powered with high-quality study, where the HAP study, I think will help me.

Now, the gram-negatives that we are talking about, that cause HAP, if there are other supportive data in treatment of those gram-negatives in other tissues, such as complicated urinary tract infections, I will feel better about using the drug for those gram-negatives when they appear in the lung for HAP, especially if I have CAP data to show that I have got good drug penetration, and we are actually doing a complicated UTI study, as well, with the

same drug.

So, I use drugs, the studies, to help complement my confidence in using the drug for pathogens in the lung when they come from another tissue site.

DR. LEGGETT: Mark.

DR. GOLDBERGER: Just to follow up what Drs. Rodvold and Bradley said. I think we would agree that in the perfect world, we would want, for each indication, multiple studies. I think everybody would feel most comfortable about that.

But we live in a world, of course, that has various constraints. One of the constraints is that it takes a certain amount of resources in order to perform all these studies. So, the question really we are sort of asking is, in part, in order to encourage and facilitate the development of new antimicrobials, you know, recognizing the fact that companies have to make decisions about how to apply their resources, what are the things that we can do to sort of expedite the development program, and the big clinical trials are ultimately fairly expensive to perform.

So, we are sort of asking this question, not in the perfect world, but also in the

constrained world in which we live, to try to understand what things might conceivably be reasonable.

We acknowledge, of course, this issue that was raised, that the microbiology in HAP is different than the microbiology in CAP, and how much overlap there is depends on a lot of factors, but clearly it is different as well as the patients themselves.

Now, we have, for instance, the opportunity in a multi-indication development program to also, for instance, explore complicated intra-abdominal infection, which gives us the opportunity to look at fairly sick patients over a wide variety of ages, who will have significant gram-negative infections.

Now, arguably, surgical intervention is a component there, and that is an issue, as well. We also have the opportunity to look at complicated skin including diabetic infections, again where there are issues of significant gram-negatives.

Now, are these perfect surrogates, for instance, what goes on in the lung? No, it depends in part on how much information you have acquired about comparative tissue levels as part of your

development plan, but we are faced with dealing at one level with a somewhat constrained environment, and the question is what can we do with that environment recognizing that this is less than what we would normally do perhaps in the perfect world, and in those circumstances, what is our level of comfort and what is the things we really want to sort of look at and think about in order to make reasonable accommodations.

DR. LEGGETT: Mike.

DR. PROSCHAN: We have been making it kind of simple here by considering only HAP and CAP, but there might be several related bugs, and the question is should you take into account information on the other ones. I think definitely, you would have to say yes.

I mean if you found one clinical trial that showed efficacy for HAP, but all the other things that you think ought to be similar, the drug doesn't work for, then, you would probably want to see another study. On the other hand, if it is consistent, all four are showing the same thing, then, that might be a situation where you would be happy with just the one.

DR. LEGGETT: Again, I come back to my

point of how good the study is. My view of studies of complicated skin and soft tissue infections close up is it looks pretty bad. You can swab somebody's open foot ulcer and its complicated skin and soft tissue, but that is not at all what I would worry about if I was treating somebody with nosocomial pneumonia who had the same pathogen in their lung.

Then, the question I get to is can we redefine the criteria of how many people or what kind of person you have got, and how much has to be bacteriologic hard data in your CAP trial.

DR. POWERS: Let me switch out of indications where this might even be more relevant, because this committee has discussed this only a few months ago.

If you take a look at one of the things we have on the bottom there, of sinusitis compared to otitis media, now, those are two infections where the organisms are almost identical for those things, but we could make the case of what kind of quality data do we see for those kind of indications.

As you are saying, Jim, when one is going to use those to support the other, does the kind of

clinical-only trials that we saw in the past, with no microbiology, or a microbiology trial with no clinical information along with it that is open and non-controlled, what does the committee think about that if we are then going to use that to relate one disease to the other?

DR. LEGGETT: I don't like it.

DR. RELLER: No numbers can make a lousy study a good one. I have no problems whatever extrapolating from otitis media to sinusitis and vice versa if we have got sinus taps and tympanocenteses with microbiology and eradication of the organism.

Coming back to CAP and HAP, it is not that they could never be extrapolated one to the other. It is just that the probability of having comparable organisms is so small, and even if one had a drug that was active against Enterobacter in HAP, and it was active against the Pneumococcus in CAP, I am not willing to extrapolate drug X's data for the Pneumococcus to the Enterobacter in HAP even though they are both susceptible organisms to this putative compound that you mention.

When we come to two studies/one study, I am actually much more interested in the numbers

that I know that they have the entity, the bacteremic pneumococcal pneumonias in CAP, the ones that had an expectorated sputum where the organism was seen on Gram stain, and it was grew and it was devoid of epithelial studies, the HAP studies that have quantitative cultures obtained by endoscopy and bronchial brush.

I mean those where you have got the best possible chance to be sure of what you have got, and then those, of course, accompanied by bacteremia, to me, mean a lot more, and these clinical studies that we have had in the past with otitis and sinusitis, they don't tell us very much, and they certainly don't tell us very much with the kinds of organisms that Dr. Jorgensen described earlier.

DR. LEGGETT: Keith.

DR. RODVOLD: I agree with Barth in the type of patients, and I think the agency themself has used this as an example. It's the levofloxacin data, when that came through to us. I was on the committee, Barth was there, and what was convincing was the story, the whole story. I mean they had a reasonable number of patients, the quality of the patients, and what they had recovered, but they

also had the kinetics, the dynamics, the in vitro models with it, and the story was very consistent to get into a smaller group of numbers of quality people, and it rolled along.

What I would throw on top of that these days would be what Jim brought up, was doing some simulations on top of that information to kind of project out of the worse scenarios, the people that have a very fast clearance to a slow clearance, to someone with a high MICs to low MICs, to again give people comfortability levels, just like what they have been doing at NCCLS more recently of 80 percent of the time, you are going to hit the target even if it's someone that is a poor eliminator or a fast eliminator.

I think that building that whole story around one good study that has good quality patients that are really sick, that have the real pathogens, is more convincing that two trials that have kind of some numbers, and I think that is still the best example you have to share with people.

DR. LEGGETT: Mimi.

DR. GLODE: I just wanted to comment on the issue of trying to establish safety and

efficacy in the same study, so sort of torn between we want to enroll a lot of people, so we have some safety data, but then really, often inadvertently, if you will, contaminating the population and sacrificing quality of the study.

So, particularly, I know it is very hard for everybody, whether in pediatrics or internal medicine, but community-acquired pneumonia, trying to figure out who has got a viral respiratory disease that is going to get better no matter what you give them, who has got mycoplasma that is going to get better no matter what you give them, and who actually has bacterial pneumonia that presumably will definitely get better faster and needs an antibiotic, you know, means the best microbiology, it means pneumococcal urinary antigen, as Barth mentioned yesterday, potentially, I mean quantitative CRPs, I think there are better ways to narrow that population and then study that population, because if you inadvertently contaminate them, you create this effect of making the drug look fabulous in this population, and that is not the critical information you really want.

So, as long as you are inadvertently contaminating them, it is elevating the efficacy of

the drug inappropriately and misleading everybody.

DR. LEGGETT: Ellen.

DR. WALD: I think the infections in which you would have the greatest ability to extrapolate one to the other are the ones in which the microbiology is the same, and so, you know, acute sinusitis and acute otitis media are identical for all intents and purposes.

Some have made the observation that the middle ear is a paranasal sinus, and I think there is truth to that when you think about the eustachian tube as a sinus ostea.

I think a question that you could ask from there is how similar is that bacteriology to the microbiology of acute exacerbations of chronic bronchitis, and then at least in children, for the bacteriology of a community-acquired pneumonia, which, of course, is something we don't exactly know what the bacteriology of community-acquired pneumonia is in children short of the pneumococcus, because that is the only thing that we grow from blood cultures in pleural effusions, although it may not be the only cause of bacterial pneumonia.

So, I think where you have similar microbiology, you have the greatest ability to

extrapolate, and I think, though, it puts a tremendous burden on the quality of the first study that you do for any of those for it to be really high quality, and to have as much microbiology as possible.

DR. POWERS: Could I ask a follow-up question about that, because you named three respiratory diseases and two of them are a little different, and that for otitis media and sinusitis, they are both normally sterile body sites where we can get that microbiology by tympanocentesis or sinus puncture.

On the other hand, acute exacerbations of chronic bronchitis is a disease where, if you culture those people when they are not having exacerbations, you are going to find those bacteria there, as well.

So, does the certainty of diagnosis of what that microbiology means also play into part of this?

DR. WALD: Well, I think if we are willing to suspend certainty for a moment, since we really talked yesterday and I think everybody was sincere about the need to do an antibiotic versus placebo study, but if for the moment, we accept that it is

a real entity that is caused by bacteria at least in some proportion of the cases, then, microbiology is really very similar to the others. Maybe there is a little shift in proportion of the organisms, but they are really pretty much the same organisms.

DR. LEGGETT: Would you be willing, assuming that acute exacerbation of chronic bronchitis or bronchitis, assuming antibiotics help,. would you be wiling to go from community-acquired pneumonia to that indication with the one study?

DR. WALD: Yes, I would, because again, I think going from the more complicated to the less complicated is a direction that has an ease associated with it. So, in a more stringently, better defined infection, i.e., CAP, a drug proves to be effective, then, I think that one could comfortably conclude that in a lesser infection, acute exacerbations of bronchitis, that it would perform equally well.

Again, if we have bacteriology that includes non-typeable Haemophilus and Streptococcus pneumoniae as being probably the major players in both of those infections.

DR. POWERS: Let me extend that a little

bit, asking about the directionality question. So, if you had otitis or sinusitis, that might be supportive of acute bacterial exacerbations of chronic bronchitis.

I am assuming that these trials are doing at different times because a lot of what we see is they are done simultaneously and we can use them to support each other, but suppose the ABECB trials gets done first, how supportive do you think that is in the other direction of, say, sinusitis or otitis media?

DR. LEGGETT: None.

DR. POWERS: Because that is the stuff we are dealing with is, you know, is there a directionality to this, and the CAP one is clearer, better, ABECB is a little different.

DR. LEGGETT: Jan.

DR. PATTERSON: I was going to say I agree with Ellen, and that I think you can go from CAP to ABECB, but not the other way around, and also from acute bacterial sinusitis to acute otitis. In adults, I have a little reservation about going from otitis media to acute bacterial sinusitis because I think adults have staph sinusitis sometimes, but if you had an acute otitis media

study and you knew that the compound had good staphylococcal activity, then, I might go for that.

That kind of gets to the point of, you know, with some of these resistant organisms, they have had sort of pathogen-directed indications like VRE, bacteremia, and that kind of thing, and I think if you had an antibiotic that was successful in treating bacteremia, that it would most probably be successful in treating UTI and lesser sorts of things, but I don't know how much you want to go for pathogen directed indications.

DR. LEGGETT: People are trying to get multiple indications. If they are only trying to get one, is it still two studies and supporting data?

DR. POWERS: Yes.

DR. LEGGETT: I just wanted to make that clear.

Could the two studies, one is controlled, and could the other be one of these enriched pneumococcal antigen, or do they have to be controlled, blinded, the variability problem?

DR. POWERS: That goes to the reproducibility of the information. Whether one could then do two studies and then some other kind

of open-label trial trying to accrue more resistant pathogens might be one way to go.

DR. LEGGETT: Barth.

DR. RELLER: One example of this question about one study/two studies, if you had a good efficacy demonstrated for the pneumococcus Moraxella catarrhalis, I mean the respiratory pathogens with the community-acquired pneumonia study, and one had a single acute exacerbations of chronic bronchitis that was placebo-controlled, I don't think anybody would have any trouble extrapolating.

I mean that would be one nice example of a single study would be all you would need if it was a good one, on the one side, and it was a good one on the other, and then the transfer of the information. I would like to see more of those.

DR. POWERS: I think one of the issues we are trying to get at is what I think I heard yesterday a couple of times was what is the incentive for anyone in industry to go out and do a placebo-controlled study of acute bacterial exacerbations of chronic bronchitis, so in this way, it sounds like this might be some incentive if it streamlines the drug development process in some

way.

The other issue I think that we didn't talk about much yesterday is a placebo-controlled ABECB trial has fewer patients in it than a non-inferiority trial of ABECB does, therefore, there is two benefits to a company doing this. Do I think we are going to see this? I am a little skeptical from what I have heard, but at least we can at least hold out that there is some benefit to industry to actually do things this way.

If there is not, why should anybody do this?

DR. RELLER: Yesterday, I would have to pull out the books, but, what, 2- to 300 in three different trials with acute exacerbation, or were there four? There were three or four trials for acute exacerbations of chronic bronchitis.

DR. COX: You mean in yesterday's discussion?

DR. RELLER: Yes, yesterday. I mean at least three, three, four or five. Let's take four trials, 250, 300 patient apiece, I mean one good trial would have I think given us more useful information than all of the material that we wrestled with yesterday with acute exacerbations of

chronic bronchitis.

DR. POWERS: You are hitting on my pet topic here, so I have another question for the committee related to this. So, if it's okay to expose 800 people to a non-inferiority trial in ABECB, one of the things we hear is it is unethical to do a placebo-controlled trial.

Well, how ethical is it to expose all those people if we don't even know if the drugs have any efficacy in that disease?

DR. LEGGETT: Correct, but they are not going to die. I think that people draw the line at when you are going to die.

DR. POWERS: I am trying to address the question of why is it unethical to do a placebo-controlled trial in ABECB.

DR. WALD: Who says that it is unethical?

DR. POWERS: Ever since we had this discussion in November, we have tried to ask drug sponsors saying based on what we heard, that we think that these trials should be placebo-controlled. No one has expressed a willingness to do so, and one of the reasons we hear is that IRBs have a problem with this and that it is not ethical or supposedly not ethical to do a

placebo-controlled trial in this disease.

DR. LEGGETT: Barth.

DR. RELLER: What a wonderful opportunity for a sponsor. We have got the Infectious Disease Society of America participating in the meeting saying that placebo-controlled trials are necessary, and even the Institute of Medicine saying this is something that should be brought up to the NIH for funding because this is important.

I mean I would think that there are sufficient published consensus bodies experts, I mean it should be a slam dunk within IRB. I mean we have emphasized here the tympanocentesis study with the demonstrations, the taps, that it can't be done, the amount of useful information in what the potential benefit of knowing what somebody actually has as opposed to the pitfalls of empiricism in a world of unexpected resistance, I think the time has never been better to tighten the science and thereby achieve also economies of having more useful information involving smaller numbers.

DR. PROSCHAN: Would you expect the drug companies to say we don't want to do that because our drug might not be any better than the placebo? Of course, there is an incentive to say it is

unethical.

DR. LEGGETT: Ellen.

DR WALD: I think it may help. You know, there are certainly some published statements from recommending agencies suggesting that these things are ripe for investigations, and I think the timing is right, but I have to say that the IRBs now are particularly skittish.

I think that they are feeling a lot of pressure because of the kinds of things that have recently been reported in the press about mistakes of protocol implementation, whatever, and we just had an experience at Pittsburgh where, in fact, our IRB has declined approving a placebo-controlled trial of acute otitis media, and we are going to be sending it to the FDA to get their ruling on that.

I think that is despite the fact that, you know, there is a lot of media now looking at watchful waiting as a strategy. So, I think that maybe in the minutes of this meeting, if we can make a formal statement about how important these studies are, that it will create a sense of equipoise, which I think is what is necessary to engage in any of these kinds of investigations.

I think that we can, in fact, state that

equipoise, because I think we don't know the answer.

DR. LEGGETT: Keith.

DR. RODVOLD: I agree, that, you know, being a past IRB member plus dealing with the IRB constantly, that every IRB is its own animal basically, and the only way you get through it, especially where a lot of people do trials, they go through IRBs that are way different than the ones that I think most of the people sitting around this table go through as an IRB, and you would need to not only gather the literature, but I think you probably would have to make a statement that would go right in the packet.

That does lend credence, a lot of credence, in areas of untouched territories or uncomfortable territories, and I can tell you one of our IRBs, when you bring up placebo-controlled, are just like what Pittsburgh is running into, it's almost a no go until you can just really show them with convincing data and convincing endorsement from the Federal Government that this is a possibility.

DR. LEGGETT: Go ahead, John.

DR. POWERS: Having been on an IRB myself,

I agree that it is the quality of the data that gets presented to the IRB that sways them, and one of the things that always comes to my mind now when we talk about levels of evidence is the trial that was done on hormone replacement therapy in women that was published just last year.

Loads of observational data saying that that therapy actually prevented cardiovascular disease, one very well-done placebo-controlled trial shows it does not, and those are the kinds of things that I think are convincing to IRBs, look, we have all these trials done in the past that prove absolutely nothing to us, we want to do a kind of trial like the hormone replacement trial to answer this question definitively.

Jim, could we maybe look at some of those criteria?

DR. LEGGETT: Sure. Don wanted to say something and we will do it.

DR. PORETZ: In certain areas like cardiovascular disease, you look at endpoints with events like how many myocardial infarctions you are going to have or how many deaths you are going to have if a person does or does not take a certain drug.

In infectious diseases, when you are doing drug studies, antimicrobic studies, who determines the total number of patients for validity of a study, is the pharmaceutical company and their statisticians, is it the FDA and their statisticians, who determines?

DR. POWERS: That is something we usually work on together and it usually depends upon what the endpoint is and how effective you estimate that your drug is going to be, and then it gets into the dreaded delta issue of how effective you want your drug to be relative to whatever control that you are happening to use, but that is usually something we talk about, that the FDA and the pharmaceutical sponsor, we talk about together.

DR. LEGGETT: So, what we are saying basically is if we are going to be able to change things and improve the single trials, that you guys are going to have to require more stringent criteria on your part.

Ken.

DR. BROWN: If I understand the discussion, I am a little uncomfortable with the idea of CAP to HAP or reverse, unless we are absolutely stringent on the organism, be a

case-by-case by organism. The pathology of Pseudomonas pneumonia is so dramatically different from the pathology of Pneumococcal pneumonia that I can't conceive that we could let anybody get a claim for both regardless of where they came from.

I think a parallel exists in my discomfort with otitis media and sinusitis. After the first or second bout of sinusitis, I believe that you no longer have acute sinusitis, you have acute exacerbations of chronic sinusitis.

Joe Fredericks showed in around 1964 that if you do cultures for obligate anaerobes, and not just facultative anaerobes, you always get anaerobes in those sinuses, which means to me that the drainage procedure may be more important than the antibiotic in those cases, but certainly we shouldn't be using antibiotics which don't have anaerobic coverage for those people.

DR. LEGGETT: I think one would have to specify there are big differences between adult and pediatric populations in terms of sinusitis.

Here are the proposed criteria. No. 1, the natural history of the disease under study - what is the spontaneous resolution rate and what is the morbidity/mortality without treatment? This is

where we have been talking about acute exacerbation of chronic bronchitis.

Are there some others in terms of we are talking about various different models where that might apply other than the otitis that we have just mentioned?

Go ahead, Ed.

DR. COX: One of the things that might be helpful would be this morning, some of the criteria were actually ranked as far as level of importance, and I think that might help us get a better feel. I think we had some discussions about where there are criteria that are more important than others at least from the discussions we had going on here.

That would actually be helpful to us, I think, if we had some discussion of the criteria, which of these are of the most importance and which ones are of lesser importance.

DR. LEGGETT: The diseases that we get the most irrelevant data on are the ones that have the fewest hard endpoints, and that is the upper respiratory tract type problems. That, to me, is probably the strongest argument for a placebo-controlled trial in a disease of that nature.

Don.

DR. PORETZ: Another example of 1 would be chronic bacteriuria, chronic urinary tract infection in elderly women where most people now would not treat asymptomatic bacteria. I mean you can put them on an antimicrobic, get rid of the organism, just like chronic bronchitis, it means nothing.

DR. LEGGETT: What about something like skin and soft tissue infections, whether it's complicated or uncomplicated, we are going to let clinical data go where we can't get bacteria? That is another example of two things that I can think of where we don't really get reliable data, but we know from antibody studies that 90 percent of them are group A strep, at least in uncomplicated.

What kind of numbers do we need for that? Are those going to resolve by themselves, does anybody think?

Go ahead, Alan.

DR. CROSS: Not with group A strep or Staph aureus.

DR. LEGGETT: Or Staph aureus.

DR. CROSS: But perhaps I can take this opportunity to ask a question, and that is, we

heard from the pharmacokineticists and dynamics folks that if we had an AUC of greater than 100, it is highly predictive of efficacy, so I am just wondering, in the case of like a skin infection, if we actually were able to measure the antibiotics in the skin and actually calculate how much of a dose actually gets in the skin.

Can that type of data be extrapolated to other organisms?

DR. LEGGETT: So, in other words, the question is sort of will you guys allow in vitro or in vivo model extrapolations.

DR. POWERS: That is actually No. 3, the characteristics that is up there about looking at the pharmacokinetics of the drug. How to use pharmacodynamics is something that we have been discussing internally and that got brought up in November, and the FDA has an internal exposure response working group, which is actually trying to look at this information of how can we actually apply some of that data.

DR. COX: I think, too, I mean we are focusing here today on clinical data and really the reliance and inference that can be drawn from other indications, so I think it is more clinical that we

are talking about here today.

DR. LEGGETT: To finish up with the natural history stuff, does anybody here believe that prostatitis or urinary tract infection is going to go away by itself, and what are we going to do? Uncomplicated urinary tract infection, you know, post-coital cystitis, do we need placebo control is what I am saying or do we have to have controlled data? I am just making sure that we flesh this whole thing out before we go. No.

The only thing I can think of unless somebody tells me otherwise that we are going to have placebo control is that upper respiratory tract.

DR. POWERS: But our real question is how they would be supportive of another disease. So, I guess what I was hearing was acute bacterial exacerbations of chronic bronchitis trials wouldn't be supportive of anything else unless you did a placebo-controlled trial.

DR. LEGGETT: Right. That is the lowest on the totem pole, everything is above that.

A question that sort of jumps back in terms of what do you propose. If you have a very good, tight puncture of the ear trial with data,

and you have one puncture trial of the sinus data in kids, can you use them back and forth, or do you need two in the ear and then one in the sinus?

If we have just made the argument that they are the same, why do you need two in one and in the other except for the best possible world validation?

DR. COX: I think it gets to the issue of level of evidence, and having the one indication or anchoring the initial indication in a couple of studies, and then moving on to use that information to support other studies, so it is all level of evidence question, and we have had some discussion about the number of studies, one big study versus smaller studies.

John mentions another good point, too, and that is, you know, accruing sufficient numbers of patients in order to be able to adequately characterize the safety of the drug, too.

DR. LEGGETT: Right, the same globalization.

Jan.

DR. PATTERSON: Just in terms of priorities, you were asking about priorities. I think one of the things that have spent a lot of

time talking about is that No. 7, similarity in spectrum of organisms causing disease. I think I would put that pretty high, like towards No. 1.

Then, No. 5, similar site of infection, you know, respiratory versus urinary versus skin and soft tissue, complicated versus uncomplicated, we have been talking about that, too, so I think that would also be pretty high up, maybe No. 2.

I would see those two as being a couple of the more high-priority ones.

DR. LEGGETT: So, what you are saying, for No. 5, was we don't really seem to like the CAP/HAP thing. You are saying that urinary, complicated/uncomplicated, skin, complicated/uncomplicated, and how about urine and prostate?

DR. PATTERSON: Complicated UTI.

DR. LEGGETT: Yes, complicated UTI.

DR. PATTERSON: Complicated UTI, then, I would go for prostatitis, yes.

Go ahead, John.

DR. BRADLEY: In extrapolating between the same site of infection, but different scenarios, like HAP and CAP, knowing that they are different types of organisms, in my suggesting that all you

would need is one study of each, the implication was that you would need to study a certain number of Pseudomonas infections either in that HAP trial, so that you would know that it would work in Pseudomonas, hospital-acquired pneumonia, or have just a few in hospital-acquired pneumonia and then Pseudomonas in another complicated tissue site that you would not expect any spontaneous resolution, so some sort of complicated urinary tract infection, hospital-acquired urinary tract infection, or deep surgical wound infection, a mediastinitis.

There are certainly situations where you can collect information on the drug's effect on the organism, so what I am trying to build is taking a certain amount of information on efficacy at a tissue site, but requiring a certain amount of microbiology that is either from that site or a comparable site.

So, if you can treat Pseudomonas or Enterobacter or Klebsiella in a complicated intra-abdominal infection, because even though you require surgery, the antibiotics are part of the whole treatment process, if I can get efficacy data in those pathogens in another tissue site, I will feel comfortable extrapolating into a pneumonia

site and requiring fewer of those cases in a pneumonia.

You had in the other slide complicated intra-abdominal infection towards complicated skin and skin structure. Well, you don't get Staph aureus very often in a ruptured appendix, but it's a deep tissue space where there is a low pH, lots of white cells that requires drainage, so the same thing would be true of a cervical adenitis that requires drainage caused by staph in terms of the environment, but the organisms would be different.

So, I wouldn't go from intra-abdominal into complicated skin and skin structure unless I had data on Staph aureus supporting skin and skin structure, and where you would get that other data, I don't know, certainly not in intra-abdominal infections.

Then, you have got complicated skin and skin structure supporting complicated intra-abdominal, and again the same concept is there. The organisms are completely different even though the types of tissue environment would be similar, both deep tissue, both requiring drainage.

DR. LEGGETT: To follow up on that, what about monomicrobial and polymicrobial, so staph is

one of your polymicrobial in your intra-abdominal, whatever process, and then your skin and soft tissue is staph, do you think you can extrapolate?

DR. BRADLEY: I think it would be difficult to extrapolate polymicrobial to a single drug simply because in the abdomen and in deep head and neck space infections where you have got so many different organisms, the quality of pathogenesis and rapidity of spread seems to be a function of the multiple organisms rather than the single, and it may be easier to treat a single organism than once you get them all together, and their separate pathogenicities add or are synergistic with each other.

DR. LEGGETT: To face the other issue, what about an enterococcus in a polymicrobial versus an enterococcus someplace else? I am not sure I would buy that either. So, I am not sure we can use this polymicrobial/monomicrobial in terms of going from one to the other, if that is what you guys were trying to get at.

DR. POWERS: I guess what we are asking is suppose you had some complicated intra-abdominal cases, and some of those were, say, abscesses that grew pure enterococcus versus you had another drug

that studies the same thing, and then you get enterococcus and a whole bunch of other stuff.

DR. LEGGETT: Nope.

DR. POWERS: But would the pure cases of enterococcus be more convincing to you?

DR. LEGGETT: Yes, to me, yes. I will defer to everybody else. Go ahead, Alan.

DR. CROSS: If you had a pure case of enterococcal abscess in the belly, I would be impressed. I just recall early on when the coverage for intra-abdominal sepsis used to be Keflin and kanamycin and, you know, absolutely no enterococcal coverage. People have studied it, including Dr. Tally in his earlier days, it just hasn't been a problem in patients or animal models, so I would be hard pressed.

DR. LEGGETT: The same applies to clinda/gent.

DR. PATTERSON: I guess one comment about enterococcus is kind of getting back to the pathogen-specific issue. If I knew something worked in enterococcal bacteremia, then, I would use it for an abscess or skin and soft tissue, and I think there are times you see significant intra-abdominal infections, for instance, in liver

transplant patients, so I mean I think you do see them sometimes.

DR. POWERS: And that is the point. I have seen pure enterococcal abscesses, but it is in somebody that is throwing bucketloads of antibiotics, you know, in their third operation after they get it.

DR. LEGGETT: Right, where it is in their liver.

DR. POWERS: Exactly. I think it can exist, it is just unusual.

Mike.

DR. PROSCHAN: Could the FDA say, you know, ordinarily you need two well-controlled clinical trials, but if you think you can make the case based on related bugs, then, you are welcome to try, and then the advisory committee sees if they made the case.

DR. POWERS: What we are trying to do here is outline the criteria that decides whether you make the case. Rather than have the company come in and just have to de novo make this up, we are trying to outline this of the things that would allow them to say we meet these criteria that the advisory committee outlined, which is what we are

asking you guys today, so that they have some template upon which to build their case.

DR. LEGGETT: I would think it pertinent in terms of that, in your No. 1, the natural history of the disease, it is not only the disease, it is natural history of the bug disease complex. As we were saying, that enterococcus melts away when you don't treat it in the presence of a bunch of other stuff, but VRE bacteremia, if it's persistent, you know, if somebody is looking for a VRE thing, they have got a VRE liver abscess, and then a VRE bloodstream, and then a VRE someplace else, could they lump those together and say yes, I would think you could make a case for saying yes.

Barth.

DR. RELLER: That is basically what was done with quinupristin-dalfopristin.

DR. LEGGETT: That is an example, going forward to drug-resistant pneumococcus, or VRSA, or something like that.

DR. RELLER: To me, the critical issue is the rigor of the database, and I would add a little caution in trying to get things too delineated because then if those things are met, you still may be uncomfortable.

I think about yesterday's discussion, well, the company did what they were supposed to do, but, you know, the lingering discomfort of the solidity of the science, so that I think maybe 95 percent of the way there, but just checking them off shouldn't be--it should be defensible, not only there, but also rigorous, and I think some of the attempts here is to raise the bar, or put another way, you get what you ask for, and it also applies to the agency what is required.

DR. LEGGETT: Going back to how hard the sort of persistence question of the pathogen can be applied, not when you are only trying to do one bug, but when you are trying to do nosocomial-acquired pneumonia.

Lots of the times, MRSA in the sputum, I deliberately don't do anything with in the ICU with somebody who has got an infiltrate. That data has to be tightened up. The not normally sterile site, you know, but the data that I am aware of, and that we have tried, looking at all the sort of protected specimens in the quantitative, is if anybody has had a whiff of antibiotics, you don't get anything.

It is only in France where they don't give antibiotics to anybody before they do the

bronchoscopy that they get anything, and it is only in those one or two places that could publish those studies, nobody else can replicate that.

DR. POWERS: So, it sounds like what I am hearing is there should be an eighth criteria on here, and that has to do with the quality and rigor of the trial.

DR. LEGGETT: Definitely.

John.

DR. BRADLEY: Looking at 7, thinking of organisms, in most of the studies that I have done, and in what you said earlier, John, that the FDA looks to treat infections, when there is a clinical trial, when a patient comes into the hospital, we are looking for infectious disease diagnoses, and then we look to see if that patient qualifies in terms of the types of pathogens that we are interested in treating, but what Dr. Reller is saying, and you seem to have agreed with, particularly with dalfopristin-quinupristin, is supplementary data that is organism-specific, not site-specific.

Am I hearing you say that if there is a particular indication like pneumonia, and a company would like Pseudomonas as an indication for

pneumonia, that you would accept my screening from the micro lab and taking Pseudomonas infections other than pneumonia, so bacteremias, endocarditis, prosthetic joint, you know, all range of things that are not pneumonia--

DR. LEGGETT: Except UTI.

DR. BRADLEY: Except UTI, you know, the quality of data, serious infections that you need the drug, and provide you with supplemental data for the organism that is organism-driven, not infection-driven.

DR. GOLDBERGER: I think that basically we recognize, and this is something we have sort of touched on a couple times, that for some of the more difficult-to-study organisms, including some that despite the fact that they are difficult to study, in no way means that they are not important. We talked about an Acinetobacter, there are other examples.

It is going to be necessary, I think, to be able to pool data across more than one indication, and I think you can recognize that much of the discussion that we have had today about how indications support one another is the kind of discussion that is necessary as part of thinking

conceptually how we can take organisms across the different sites and pool them, but I think it is inevitable if we are going to be able to draw some kinds of conclusions about whether a drug works.

You can argue, on one hand, the goal from the pharmaceutical company is, of course, to get this in their product labeling, which is fine because they need to have an incentive in order to do all this work, but realistically, that is hopefully intimately tied to the idea that we can actually draw some meaningful conclusions about whether the drug actually performs.

In order to do that, it is clear it is going to be necessary to do this, so in addition to a lot of obviously the traditional indications and listing some organisms, it is clear in certain circumstances we will need to be able to grant some sort of organism-specific approval that will utilize data across more than one indication. I think it is inevitable.

What we want to do is to do it as well as we can. I think if you think about what everybody is saying here, what everybody is saying is and almost irrespective of whether we were having the discussion we are having, is that there are issues

still in how the clinical trials are performed, and they could be done better.

We have talked about it for sinusitis, we have talked about it for otitis, we have talked about it for pneumonia, we have talked about it for almost every--well, and that is what we are moving toward.

On the other hand, what we are also hopefully moving towards is providing an incentive for industry to be interested in doing it better because instead of doing a lot of trials that are at best so-so, ultimately, the goal is to move to a fewer number of trials that are better performed with better endpoints, with better microbiology, and the link to that is this further incentive of how organisms can sort of be used across more than one indication.

That is really what we are trying to do.

DR. LEGGETT: Could I go back to sort of the real world situation? I don't know if, say, piperacillin or piperacillin-tazobactam, or some drug, for instance, that did not get intra-abdominal and went for pneumonia, or got intra-abdominal and then did not go for a pneumonia trial, but you knew the MIC and the susceptibility

data in real life, do you not use your pip-whatever it is in the belly after you have used it before in the pneumonia, and vice versa?

So, how much higher does the hurdle have to be, which is I think what you are trying to get at, so we should think about the way we actually treat people with antibiotics when we are discussing this.

DR. POWERS: Can I sort of follow up on that for a second, because one of the things I think that came out of the last meeting we had in February was a misunderstanding of what we were saying when we were saying accepting pooled information.

That would still need to be held down by efficacy data in the disease in which that resistant pathogen is most likely to be found. So, in other words, suppose you wanted to go for methicillin-resistant Staph aureus, the two places you would most likely see that would be complicated skin and, say, hospital-acquired pneumonia.

So, if you did a hospital-acquired pneumonia trial and only came up with a few MRSAs, you could then do this other trial, pooling the information, but if you just come to us with all

that pooled information and no hospital-acquired pneumonia trial, that is not very helpful.

DR. LEGGETT: Jan.

DR. PATTERSON: I was just going to say about extrapolating from the non-pneumonia infections to pneumonia. I think that is where Criteria No. 3 would come in as pretty high priority about making sure you had tissue levels, because not all antibiotics get into the lung equally well, so that would become important.

Then, just thinking about Pseudomonas pneumonia, I mean even if you had a complicated skin and skin structure infection due to Pseudomonas, I think Pseudomonas pneumonia is harder to treat. For instance, you would definitely use combination therapy for Pseudomonas pneumonia, whereas, with the other one, if you combined it with surgery, you might not need combination therapy for as long at least.

So, I think for that particular pathogen, you would have to be a little bit careful going from non-pneumonia to pneumonia.

DR. LEGGETT: To bring No. 2 back into this, Pseudomonas, would you accept an intra-abdominal abscess that got drained, that had

the resistant Pseudomonas in it, if you had lung data or vice versa?

In other words, a good study in pneumonia that cleared the resistant Pseudomonas, and then you had other supportive data, say, an intra-abdominal abscess drained or had surgery, would that be acceptable? Trying to get at No. 2.

DR. PATTERSON: Going from pneumonia to the abscess, you mean?

DR. LEGGETT: Yes.

DR. PATTERSON: Yes, I would accept that.

DR. LEGGETT: And is it a directionality, would you not go the other way?

DR. PATTERSON: Well, that is what I am saying. I don't know that I would necessarily go the other way for Pseudomonas, I might for some other pathogens, but I would want to know about the tissue levels if I was going the other way.

DR. LEGGETT: Back to No. 3, there are some significant differences in the surface-to-volume ratio in the abdomen than there is in the lung, so I would be very hesitant going from the belly to the lung personally.

Keith, what is your take on what can be done in terms of No. 3, in terms of helping with

resistance trials and in vitro, in vivo, and stuff?

DR. RODVOLD: Well, in 3, where you are looking at basically tissue levels or concentrations of fluids, is that again I think, as you are putting the whole package together, it lends you support in that disease state.

The problem in the area is that tissue samples, I have never been hooked to efficacy to a significant degree, and someone that does research in the area that I do, I mean that is the common criticism we get, you know, elegantly designed study, data is really meaningful, but there is no link to showing that those samples and those levels of concentrations prove that efficacy is going to occur.

It gives people a comfortability level, I think that is what it does, and supports, as you trying to say I have got 10 Pseudomonas and I have concentrations in the lung that equivalent or higher in the plasma, and it works in the plasma, it is going to probably work there, as well.

DR. POWERS: Let me give you an example of where we encounter something like this. Norfloxacin is indicated for urinary tract infections. Do you feel real good about using it

for pneumonia, and if not, why not?

DR. RODVOLD: Well, in that case, it doesn't have any systemic levels in the blood, in the first place.

DR. POWERS: That's what we are talking about. Maybe we didn't phrase this like tissue levels is not the right word. I guess maybe we should broadly say gets to the site of infection at all.

DR. RODVOLD: I think that most people believe that it needs to be in the site of infection, but if it's there, it doesn't necessarily still link you to efficacy.

DR. POWERS: Right, not relative concentrations, just the fact that it has to get there at all.

DR. RODVOLD: But, again, I think it's a supportive tool, and especially for the industry, from the industry perspective for them, is that you are trying to make them fast-track to get an approval or get it in their package, it's another thing if they have it, it allows you to be a little bit more comfortable, but they still need efficacy data in the indication.

If you have 10, 15, or however many

pathogens, I think most people feel more comfortable with it. The whole kicker with that is, though, I can tell you from the number of phone calls I get and the conversation with people is that the quality of those studies have got to be done right, as well.

Most people call me to ask me how we do the studies, and they are not sure what they are going to do and how they do them, and there is only a few sites around the area that really know, in a specific tissue, how to do them.

We do lung, but I don't do a lot of the other ones, so I am very cautious in jumping over there until we make sure we have the methodology done right. So, the methodology, again, good data is going to come to you.

DR. LEGGETT: Barth.

DR. RELLER: Maybe a comprehensive way of putting this is the necessary, but not sufficient concept, the necessity of having adequate concentrations at the site of infection, and this also extends--well, there are high concentrations in urine, but it is also the recognized published quantitative relationships that are necessary.

NCSF, the 10-fold margin of bactericidal

activity, that many drugs get into the urinary tract, but not all drugs get into the urinary tract, and the ones that don't get in there are not good agents for urinary tract infections, so without which, you can't expect efficacy and that alone doesn't necessarily constitute efficacy of adequate concentration, and adequate has some quantitative concentrative relationships that are recognized in some sites that are more important than others.

Coming back to what we haven't discussed a lot is complicated intra-abdominal infections. The integrity of the database and what you can rely on microbiologically, I think there is more recent published data in this area, as well.

For example, the microbiology that you can rely on in intra-abdominal collections of pus, drainage or not, are the initial CT-guided aspirates, not what is draining out of the pigtail catheter on the fourth, fifth, sixth day, but what is achieved initially. That is one point.

Secondly, if one has multiple, which is frequently the case, collections in the abdomen, that we know that they need to be drained, you know, over a certain size, but I mean if there are

multiple collections, there are multiple sites that need to be drained, but they also need to be sampled.

There are also good published data on the lack of complete correlation between one collection and another collection in terms of the microbiology, so that clearly, drainage is necessary, but I think with some of these organisms, it is not sufficient, and what used to be true is not necessarily, as Jan and others have pointed out, for example, with the enterococcus that may have been dismissed 20 years ago in a polymicrobial collection, it is not necessarily dismissed in a post-liver transplant with a collection of pus.

We know that it is real when it's associated with bacteremia, but it is probably real even without always demonstrating the bacteremia when it is got by CT-guided aspirate. So, I think the techniques for getting the microbiology are better than they used to be, and we need to look at first tap and each one drained tap information in the microbiology and the correlation with efficacy of these agents in complicated intra-abdominal infection.

And then having those data and what the response is adds support to the potential, not the automatic, but the potential in the resistant organisms of some extra utility in considering the efficacy of the compound against a given resistant pathogen across body sites.

DR. LEGGETT: In terms of across body sites, I was looking there. I don't think I would allow that resistant pathogen in bronchitis or just a sputum without some illness at all, ever, unless it was part of a trial that was placebo-controlled.

What about the situation in which you have a pathogen that is hard to come up with like drug-resistant pneumococcus, and you use penicillin-susceptible pneumococcus with great data, bacteremic pneumonias, and then you do your animal model trial that tells you that you are going to kill it dead from your PK/PD modeling, how much more data do you think is reasonable before you are going to use that in real life, in other words, is this a situation where you would allow 15 bacteremic pneumonias that are treated with this drug when you had all that supporting data and PK/PD modeling?

DR. RELLER: Well, I think if you have the

PK/PD data, the animal model, a relatively small number, but those are golden cases, you know, accompanied by bacteremia, and you have got the NV drode [?], legitimate, NCCLS methodology data that the, quote, "resistant" organisms are susceptible to compound X, and the mechanism of resistance, there are good data in vitro, that there is no cross-resistance whatsoever, the resistance mechanism isn't totally different, you know, you don't need 100 cases of resistant when you put all of the components together.

I think Keith was talking about that earlier. I mean if you have got a beautiful package that passes muster based on what is known about mechanisms of resistance, doing everything that you have done first-class, you don't need the numbers.

DR. LEGGETT: The reason I brought that up again is because I want to go back to the one dose azithromycin for the ear.

Suppose we get into a situation where you have got dueling PK/PD stuff, are we going to hence forward say you are going to have to show us more data, or what happens if the company comes up with some clinical points or has a few bugs, but the

PK/PD says it shouldn't work or, as Dr. Schentag said earlier, they aim at 25, and we know we want 100 if we are not going to see resistance in a couple of months, I think those things need to be fleshed out in terms of your criteria for allowing resistant pathogens.

You were going to say something, John?

DR. BRADLEY: I was just going to support the statement that you made when there was that long pause that no one was saying anything and Barth agreed with you, and I think everything Barth said regarding the package, the complete package, is absolutely correct.

DR. POWERS: One of the things that we deal with is when the package doesn't hold together. I think this brought this up earlier today. What we saw yesterday was some information on quinolone-resistant organisms in a drug that had zero anti-pneumococcal quinolone isolates in its clinical development package, and showed an animal study that showed lack of eradication when the drug was given twice a day compared to when it was given once a day in an animal model.

So, what we do we do when that information package doesn't hold together?

DR. LEGGETT: I personally, if it comes across again, I am going to be much harder than I was yesterday. That was a terrible model. It wasn't a model of infection, it was a preventive, prophylactic model, and you could see the dropoff right at 0.25, you know, 0.5 was certainly a dropoff, but I didn't want to go too far down the NCCLS road because you are going to be doing that later, but that was really very disturbing to me especially with them trying to say that they were going to get quinolone-resistant--no way in m view.

Alan.

DR. CROSS: I think we also have to be careful when we talk about animal models between the PK/PD models versus infection models. I think certainly in terms of the latter, it is very difficult to have a uniformly accepted model that everyone is comfortable with the data that is collected and how it is interpreted.

I just have to always harken back to in the area of sepsis where there really isn't one uniformly accepted animal model, and I would probably hazard that is probably the same in terms of the--

DR. LEGGETT: Yes, in that little package,

that was definitely just an animal model, and not a PK/PD model, which to me what you take from that is the goal that you are going to use in your clinical studies, not that it works or not, and that you can then sort of use it as a surrogate endpoint, no.

DR. BRADLEY: You said that you have got a PK/PD working group, and I think when a sponsor comes to you with a request for an indication, you can share with them the animal model that you think would best fit the types of indications that they are ultimately looking for.

As I understand it, you know lots of the information that the sponsor is looking for ultimately when they come to you, and there is much more dialogue upfront rather than waiting for a sponsor to just come up with data, dump it in your lap, and say, "and here is the animal model we used," and have that not be the appropriate one that you feel is the best and most predictive model.

DR. POWERS: I think in the future, at some point we will need to have a more detailed discussion about this issue of pharmacodynamics, but some of the issues of how these studies are done are important in that realm, as well, as far

as when you actually measure it, how long you wait, et cetera.

Although we have heard several times from people at this advisory committee, there are other folks within that field that feel differently about how those studies should be done, and we need to probably address that at some point in the future.

DR. LEGGETT: Ellen.

DR. WALD: In the practice of clinical medicine, one of the things that makes interpretation of microbiologic data difficult, especially in things like intra-abdominal infections, is that the patient has often received a few doses of antibiotics before the material is available for culture.

I am participating in a pneumonia study now, and it really surprised me, but I presume that you guys okayed this, which allows me to enroll patients 24 hours after they have received another antibiotic. Now, I can't do that in good conscience, and so I am not doing it, but I suspect that other investigators who are entering patients in this trial are.

What do you learn from that and what should be the posture?

DR. POWERS: This goes to something Dr. Goldberger said earlier. In a perfect world, one would obviously like to enroll pristine patients that didn't get any antibiotic. It becomes very difficult, though, to enroll people that way especially--you know, when I was an infectious disease fellow trotting in at 3 o'clock in the morning to enroll those people in those trials.

The flip side of that, though, is that would you expect one dose of a different antibiotic to cure the patient, and in the long run, what we want to look at is, you know, what was the actual effect. So, if a person gets one dose of ceftriaxone and then gets nine more days of drug X, is it the ceftriaxone that cured them or not.

This goes to a bigger issue, though, and that is, you know, when the perfect becomes the enemy of the good, where if we require people to do trials that way, and the companies say forget it, it's too hard to do it, and then we get no data.

DR. WALD: Well, I would say that ceftriaxones are a pretty powerful drug, and I would really not know the answer to the question that you posed, is the clinical outcome a consequence at least in great part from one very

powerful drug and some other not so powerful drug.

DR. LEGGETT: I think people are going to have to be a little bit more inventive of trying to enroll people's pathogens. If you use your pneumococcal urine antigen after you have received one dose of ceftriaxone, and then you use your drug X for 10 days, I will buy that, but just allowing clinical data because, quote, "you had this infiltrate," and you enrolled somebody on ceftriaxone is a much weaker endpoint. I think that is what Ellen is getting at.

Whether this would have a lot of bearing on anything except drug-resistant pneumococcus is unclear in that example, but I mean I could think of other situations.

I had a question. In the proposed criteria for resistant pathogens, No. 6, host effects, what sort of things were you guys thinking about in terms of the criteria?

DR. COX: I think what we are talking about here are if we are looking to take data and use that to support another indication, if there were significant differences in host factors, say, for instance, one indication was in the study of immunocompromised patients, patients who were

ventilated or other factors, I mean it would certainly seem reasonable to have some degree of reservation about extrapolating that data from a more immunosuppressed host to a less immunosuppressed host.

So, I think that is sort of what we are trying to get at there and trying to characterize that, and we are looking for comment on that.

DR. LEGGETT: Do you want to start, Alan?

DR. CROSS: I am sorry, I am not sure I followed your comment. Are you saying or asking is it possible to extrapolate from a more compromised to a less compromised patient?

DR. COX: What we are getting at is the host factors. If you had a more immunocompromised patient, it would seem reasonable to have some degree of hesitancy to extrapolate that data to a less immunocompromised host, so we are looking at this as sort of criteria that would allow us to assess whether one indication could support another one, and host factors seem to be important.

So, yes, I mean I guess we are asking the question of in what situations would host factors give you hesitation to extrapolate data or not extrapolate, but using supportive data from one

indication to support another indication.

DR. POWERS: If a drug was indicated for febrile neutropenia, bacterial drug for febrile neutropenia, how good would that make you feel about hospital-acquired pneumonia in non-immunocompromised population?

DR. CROSS: I will give you a different example. I see lots of patients who are neutropenic, who have VRE, so they have host defenses that are compromised, there are a bunch of other immunosuppressive drugs. If I have an agent that is effective in clearing the VRE in that patient, I would have no hesitation going in the other direction.

DR. POWERS: But remember we are talking about a different indication. We are not talking about the same indication in neutropenic versus non-neutropenic. We are trying to extrapolate across different disease states.

That is why I used the example of two different diseases all together, of empiric therapy for bacterial infections in neutropenic patients compared to some other completely different disease, not empiric--well, you don't give empiric therapy to non-neutropenic patients.

DR. LEGGETT: How about you grow Pseudomonas out of the bloodstream when you are neutropenic, and then you have got a normal host with a complicated skin and soft tissue infection, would that data, if you cleared that, would you like to hear that at this meeting?

DR. CROSS: Yes, I would feel pretty comfortable with that because I know the importance, let's say, of neutrophils in Pseudomonas infections, and if it worked in the absence of it, I would think in someone who had it--

DR. POWERS: How about the other way around, complicated skin infections with Pseudomonas, and then referring that to the neutropenic compromised host?

DR. CROSS: I wouldn't know what the contribution of the neutrophils is in that situation.

DR. POWERS: So, there would be a directionality to this.

DR. LEGGETT: What about Pseudomonas bacteremia from presumed GI tract in your neutropenic with no infiltrate to Pseudomonas pneumonia in a hospitalized patient who is not

immunocompromised?

DR. CROSS: I think as Jan pointed out, at least historically, Pseudomonas pneumonia with bacteremia is a horse of a completely different color.

DR. LEGGETT: I don't think I would feel comfortable going from a neutropenic bacteremic patient no matter what--unless it was the pneumonia, the source, to the lung in a non-compromised person.

Barth.

DR. RELLER: The issue is the enormous numbers of organisms and what you are asking the antibiotic to do. Maybe there is one place, not that this comes up very commonly even though it is occasionally seen, and that is the sort of stringency required for Pseudomonas meningitis, so if it worked in Pseudomonas meningitis, maybe you could have some benefit to the lung.

John asked earlier, and I want to not miss the opportunity to be a little provocative on this one, you said what do we do when the data don't hang together in a package. Well, I would hope you would exercise your regulatory responsibility and consider the advisory committee exactly what the

name says, advisory, and that you would give no broader indication than what the substantive scientific data allowed until additional information was forthcoming that would allow expansion of the indication as regards organism or site of infection.

DR. LEGGETT: Are you implying a ruling committee or advisory committee?

DR. RELLER: What I am saying is that the agency is privy to the entire package. I mean there are limitations to what any advisory committee, no matter what its composition and how hard they work and how carefully they think, can do in the course of a few hours relative to the detail that the agency is privy to. That is all I am saying.

DR. LEGGETT: Beyond that, there is all the information that is not yet done when we are meeting, that comes up later, for instance, as well as all the stuff that went on before.

One thing maybe to consider would be another--well, I don't know if you guys can even do this--but another venue to then get secondary feedback if more information comes in, but the package still doesn't look good, you know, without

going through the whole process, is there any way of getting a "second" look or something like that, or what is the rules?

DR. POWERS: Usually, we can bring it back here a second time.

DR. LEGGETT: Are there any of these other criteria that you want to run through more at length?

DR. POWERS: I think we can probably sum this up. It sounds like what we heard was that these seven criteria are pretty good, they need to be arranged in a certain way, putting the microbiology of the disease and the similar site up at the top as No. 1 and 2, and then we need to add an eighth criteria to this, to say that these studies need to be also of high quality and rigor.

DR. LEGGETT: That is close. I will tell you the way I did it.

No. 1 is the similarity in spectrum, which you guys have as 7. No. 2 is the rigor of the trial. No. 3 is the similar site, and then it gets less. No. 4 is the characteristics, which you guys have as No. 3. Then, No. 5 is the similar--sorry, I am getting lost because I numbered them again--at some point, No. 5 or 6, or whatever the next number

is, is your guys No. 2, the factors other than the antimicrobial.

The final two, the next to the last would be the host effects, and the last one is the monomicrobial versus polymicrobial.

Jan, you were the original re-arranger of the list.

DR. PATTERSON: I think I had put No. 5 as No. 2, but I think the rigor of the trial is very important, so I think that is very important to have up there.

Summary

DR. LEGGETT: Any other comments by anyone? Okay.

I think basically, this morning we heard about linkage of resistance determinants in bacteria and we looked at and basically didn't have much to say about a draft of criteria of listing pathogens of public health importance, so I think that means they are probably pretty close, and we heard an industry perspective.

We spent lots of time discussing the criteria that was presented, but I think we came up with a little fundamental change and lots of tweaking that may or may not be useful. I think

the FDA's list is coming close to being finished and the pathogens of priority further analyzed to get more data.

This afternoon we heard about being sure to incorporate PK/PD concepts not only into the new drug approval process, but also in prioritizing the list of pathogens for targeting drug development, the complexities of relating clinical data from one disease state to the other, and then some, and how clinicians eventually try to make sense of the bug-drug host interactions in treating people after all the above is said and done and behind us.

I think that you might want to draw upon your own clinical experiences as you guys start thinking about the clinical trials things, and thinking more the way we were talking there in real life, if you know the drug works against the bug in one situation, would you use it in another, and I think let reality sort of filter into regulation in terms of trying to come up with what you feel comfortable with.

In the few minutes we had today, I don't think we spent enough time thinking about all the permutations of that.

Anybody else have anything to say?

[No response.]

DR. LEGGETT: Thank you all for putting up with a long day. Tomorrow, we are going to start at 8:00. Thank you.

[Whereupon, the committee was adjourned at 4:05 p.m., to reconvene at 8:00 a.m., Thursday, March 6, 2003.]

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CERTIFICATE

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

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