UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

(AIDAC)

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MEETING

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WEDNESDAY

FEBRUARY 20, 2002

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The Committee met at 8:00 a.m. at the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. L. Barth Reller, Chairman, presiding.

PRESENT:

L. BARTH RELLER, M.D.	Chairman
GORDON L. ARCHER, M.D.	Member
DAVID M. BELL, M.D.	Consultant
P. JOAN CHESNEY, M.D.	Consultant
STEVEN EBERT, Pharm.D.	Consumer Representative
MARY GLODE, M.D.	Consultant
DON GOLDMANN, M.D.	Guest
CATHERINE HARDALO, M.D.	PhRMA Representative
JAMES E. LEGGETT, JR., M.D.	Member
CELIA MAXWELL, M.D.	Consultant
JOSHUA P. METLAY, M.D., PhD	Guest
MARISSA A. MILLER, DVM, MPH	Guest
JUDITH R. O'FALLON, PhD	Member
JAN A. PATTERSON, M.D.	Consultant
JULIO A. RAMIREZ, M.D.	Member
LOUIS B. RICE, M.D.	IDSA Representative
COLEMAN ROTSTEIN, M.D.	Guest
DAVID SHLAES, M.D.	PhRMA Representative

PRESENT: (continued)

CIRO SUMAYA, M.D.	Consultant
GEORGE H. TALBOT, M.D.	IDSA Rep
FRANCIS TALLY, M.D.	Cubist Pharmaceutical
JANET WITTES, PhD	Consultant
LIANNG YUH, PhD	PhRMA Representative
TARA P. TURNER, Pharm D.	Executive Secretary

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

CHAIRMAN RELLER: I would like to call today's meeting of the Anti-Infective Drugs Advisory Committee to order and begin the day with introductions.

I am Barth Reller, Division of Infectious Diseases, Director of Clinical Microbiology, at University of -- Duke University. We will begin our introductions, inclusive of all of the tables, and start at my far, far right, Dr. Metlay.

DR. METLAY: Josh Metlay, University of Pennsylvania, Departments of Medicine and Epidemiology.

DR. YUH: Lianng Yuh from Astra Zeneca.

DR. SHLAES: David Shlaes from Wyeth-Ayerst.

DR. TALLY: Frank Tally from Cubist Pharmaceuticals.

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

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

DR. SORETH: Janice Soreth, Division of

Anti-Infectives at the FDA.

DR. LEGGETT: Jim Leggett, oregon Health Sciences University.

DR. SUMAYA: Ciro Sumaya, School of Rural Public Health, Texas A&M University System Health Science Center.

DR. GLODE: Mimi Glode, Pediatric Infectious Disease, University of Colorado.

DR. O'FALLON: Judith O'Fallon, Cancer Center Statistics, Mayo Clinic, Rochester, Minnesota.

DR. RAMIREZ: Julio Ramirez, Division of Infectious Diseases, University of Louisville, Kentucky.

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

DR. EBERT: Steve Ebert, Meriter Hospital and University of Wisconsin, Madison.

DR. BELL: David Bell, National Center for Infectious Diseases, CDC.

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

DR. ARCHER: Gordon Archer, Adult Infectious Diseases, Virginia Commonwealth University in Richmond, Virginia.

DR. CHESNEY: Joan Chesney, Pediatric Infectious Disease at the University of Tennessee Health Science Center in Memphis.

DR. WITTES: Janet Wittes, statistician, Statistics Collaborative, D.C.

DR. MILLER: Marissa Miller, National Institute of Allergy and Infectious Diseases.

DR. ROTSTEIN: Coleman Rotstein, McMaster University, Hamilton, Canada.

DR. GOLDMANN: Don Goldmann, Pediatric ID, Children's Hospital, Boston, representing the Bacteriology and Mycology Study Group of NIAID.

DR. TALBOT: George Talbot, Talbot Advisors, representing IDSA.

DR. RICE: Lou Rice, Medicine and Infectious Disease, Cleveland VA Hospital and Case Western Reserve, representing IDSA.

CHAIRMAN RELLER: Thank you. Dr. Turner.

DR. TURNER: Thank you. The Food and Drug Administration has prepared general matters waivers for the following Special Government Employees: Julio Ramirez, Steven Ebert, Jan Patterson, Celia Maxwell, Ciro Sumaya, L. Barth Reller, Alan Cross, Gordon Archer, James Leggett, Jr., Joan Chesney, Celia Christie-Samuels, and Janet Wittes, who are attending

today's Anti-Infective Drugs Advisory Committee meeting on the approaches to development of anti-microbial agents for the treatment of resistant pathogens being held by the Center for Drug Evaluation and Research.

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.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability such as the topic of today's meeting involve many industrial sponsors and academic institutions.

The Committee members have been screened for their financial interests as they may apply to the general topic at hand. However, because general topics impact on so many institutions, it is not prudent to recite all potential conflicts as they apply to each member.

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 guests,

there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Don Goldmann owns stock in Pfizer and Merck. He is also a consulting contractor with BioSynexis and receives consulting fees from a law firm representing Novartis on a legal case.

Dr. Joshua Metlay lectures and is a scientific advisor for Aventis.

Dr. Coleman Rotstein serves as a researcher and has contracts and grants from Pfizer, Merck, ICOS, Schering, Wyeth and Fujisawa. In addition, Dr. Rotstein consults for Merck, Schering, Pfizer and Pharmacia. He also lectures for Pharmacia, Pfizer, Bayer, Merck and Fujisawa.

In addition, we would like to note for the record that Doctors Catherine Hardalo, David Shlaes, Liangg Yuh, and Chrisy Chuang-Stein from PhMRA, and Dr. Francis Tally from Cubist Pharmaceuticals are participating in this meeting as industry representatives acting on behalf of regulated industry. As such, these participants have not been screened for any conflicts of interest.

Also, Doctors George Talbot, Dennis Wallace, and Louis Rice are participating in this

meeting on behalf of the Infectious Disease Society of America. As such, these participants have not been screened for any conflicts of interest.

I have one announcement. If you wish to enter a statement for the record, comments on this meeting topic may be submitted to Docket No. 02N-0047 titled "Development of Antibiotics for Resistant Pathogens."

We have prepared a handout which is available at the registration table. It's a blue handout. Thank you.

CHAIRMAN RELLER: One reminder. When you speak, tap the button on the bottom of your microphone that lights up the red ring.

If you are not at the table and already have introduced yourself, please give your name and position, if you come to a microphone for the comments from the group later.

Next we shall have an update on antibiotic resistance presented by Dr. Janice Soreth, Director, Division of Anti-Infective Drug Products at the FDA.

DR. SORETH: But first Dr. Goldberger will make some opening comments, I think.

CHAIRMAN RELLER: Ah, indeed, he will. Dr. Goldberger.

DR. GOLDBERGER: Well, in the interest of that, I will make my remarks particularly brief today.

Basically, we would again like to extend our welcome to Advisory Committee participants, invited guests, consultants, and members of the audience.

As I said yesterday, and it's certainly still true today, the goal that we have is to ensure that there is adequate antimicrobial therapy to meet the therapeutic challenges that we face. In this case today, we will be focusing on primarily resistant organisms and, I think, some of the serious infections that they are often associated with.

Again, I want to emphasize, we view this meeting as the beginning of a process. This meeting will be followed by a docket that will be open, I think, for at least 120 days for additional public comment, and that will be followed then by at least one other subsequent meeting to discuss perhaps in more detail both some of the issues that have been raised here, as well as the issues that have been raised in the docket, and other information and comments that we receive from other groups.

I think we certainly believe that it is appropriate to be flexible in the approach to products

that add value, particularly in more serious diseases and, certainly, oncology drug development and HIV drug development certainly are good examples of that, and we believe that the development of agents for resistant infections clearly falls into that area.

We do think that, as we consider ways to expedite the development of such products, we must also consider what approaches might be appropriate that would preserve the value of these products. Fundamentally, we would like, if possible, to restrain a little bit the built-in obsolescence that does seem at times to be a component of many new antimicrobials that are developed.

There are clearly a number of approaches to developing drugs for resistant indications. There are a number of situations that occur ranging from drugs that are fairly toxic, intravenous only, that are probably ideal for fairly limited situations to oral and IV or oral only broad spectrum agents that would be effective against resistant organisms as well as many others.

The approaches that one might take to the development of products like that differ widely. At today's meeting some of the suggestions we will be presenting will focus on a couple of aspects of this,

probably initially more on an intravenous, more toxic type of drug.

We do not want to give the impression that, by any stretch, that is the only way to proceed. We do feel, however, that that may be the best way to initiate the discussion, with the understanding that subsequently in forums like this as well as in interactions with industry, there will need to be discussions of the broader range of possibilities.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Goldberger. Dr. Soreth.

DR. SORETH: Good morning. Leo, if I could have the first slide, please.

I wanted to give an update this morning on recent developments and history within the FDA Center for Drugs for development of products for antibiotic resistance.

By way of overview, I would like to briefly summarize some of the meetings that we have had within the Center that come largely in two flavors, both general meetings on antibiotic resistance and drug development, as well as specific product meetings, talk about some of the important lessons learned within those meetings, and finally

talk briefly about what's new in 2002.

The reduction in morbidity and, here, mortality from infectious diseases in the United States in the past century is certainly one of the great public health success stories. However, recent trends are somewhat concerning. Next slide, please.

We know that bacteria wisely adapt to pressures, one of them being the use of antibiotics. So that the rise in resistant pathogens shown here threatens to thwart or wipe out the gains that we have realized in the previous century by leading to untreatable infections.

So we've met and met again almost on a yearly basis, sometimes twice yearly since 1998. When we began in July of '98 a dialogue, a workshop, a word I heard a lot about yesterday, the '98 July meeting was a meeting between FDA and largely with industry to get input on approaches to developing new products for resistant pathogens and to try to talk very seriously about streamlining that process.

In October of '98 we expanded the discussion to members of this Anti-Infective Advisory Committee, to academia, to other public health agencies, as well as other regulatory bodies and the industries whom they regulate, to define antibiotic

resistance, to discuss the use of information like pharmacokinetics and pharmacodynamics in drug development, to talk about prudent use of antibiotics so that we might preserve or maintain those agents that we already have on the market that we wish to be able to use for many years to come.

Finally, in October of '99 we had our last general meeting on antibiotic resistance, and this dealt with a guidance, in this case a guidance on catheter-related bloodstream infections which are often associated with resistant pathogens, with the intent to encourage development of products in this arena.

From the product-specific meetings -- Let me just go back to that slide, Leo, please. From the product-specific meetings beginning with Synercid in 1998, Levaquin in October of '99, Zyvox in April of 2000, and finally AugmentinES, January a year ago, I think we gained a lot of knowledge, and the deliberations of the Committee were certainly important in helping us to reach conclusions and come to an action that led to the registration of each of these products some months after the Advisory Committee meeting. Next slide, please.

What were some of the important lessons

learned, both from the general meetings on resistance as well as the product-specific meetings?

I think that we have found that regulatory tools may encourage development and facilitate registration. I think, particularly in the Synercid deliberations, the use of surrogate markers in the clearance of bacteremia were an important tool, part of Subpart H David Ross will go into a little bit more, that it enabled us to reach a conclusion that this represented substantial evidence that would lead to the registration of Synercid for treatment of vancomycin-resistant enterococcus faecium infections.

I think that we recognize fully that greater flexibility is something that we all need to have when therapeutic options are limited and when there are no approved drugs on the landscape.

Novel approaches to study design need to be considered always. The traditional way that antibiotics for routine infections are developed don't easily apply here, don't readily and quickly enable companies to amass data to support resistant pathogens.

What are some of these novel approaches that we have used in the registration of the products in the previous slide? Well, I think with the

development of Pharmacia's linezolid or Zyvox, we had the luxury in the anti-infectives of having a dose response trial, again in the setting of vancomycin-resistant enterococcal infections, when at the time of that product's development there were no proof comparators, where we learned that historical control is really difficult and that we might gain an important body of data by employing what I think in non-anti-infective realms of drug development might be used more commonly, the dose response trial. But it's not a one-size-fits-all gain.

We recognize that, if one has a product with a very narrow safety therapeutic margin, something like a dose response trial probably isn't feasible.

Furthermore, I think there are ethical considerations that can be raised with dose response trials, for the key in a dose response trial is to pick pharmakinetically distinct enough doses that one can hope to show a difference, while at the same time picking a lower dose that is not a thinly veiled placebo.

Enrichment strategies can help, and I think we have seen this strategy work, particularly in the realm of otitis media and the development of

products for penicillin-resistant Strep. pneumoniae.

We've talked at committee meetings like this about what some of those enrichment strategies are in otitis, studying children under the age of two, studying children with a history of difficult to treat or many prior infections with otitis, studying children with siblings, children in daycare, etcetera.

Those strategies have helped, but again it's not one-size-fits-all for all indications, because I think, on the other hand, in the realm of community acquired pneumonia, enrichment strategies haven't worked or they haven't worked as well, as readily as they have in developing drugs for otitis.

Overall, we know that the total body of evidence and everything that's in the package is helpful, and that includes experience from susceptible isolates. They are an important part of the overall picture, and tell us something about how a drug performs as an anti-pneumococcal agent, as an anti-staph agent.

A strategy of what we like to think of as working backwards has helped, certainly in the arena of MRSA, methizone-resistant staph aureus infections, where a product's development may include site specific protocols, a pneumonia protocol, a skin and

skin structure protocol.

That's augmented by another umbrella or catchall protocol that would work backward from positive cultures to the patients represented to have those infections for overall augmentation of experience with a particular isolate. Next slide.

While regulatory tools have helped, it is still a challenge to accrue organisms. We hear that time and time again from colleagues in the pharmaceutical industry, and great resources are spent to develop a drug for resistant pathogens, great resources both when the claim is an in-class claim as well as out of class.

I think we need to think about that and, as we recognize resources are limited, decide is that is a direction that is wise to continue to go in.

As I mentioned, historical controls can be used when there is no proof comparator, but they may be -- they usually are problematic.

Finally, more data do not necessarily equal better data. At the end of the day, if we have 1,000 patient experience, a 1500 patient experience, but we really can't form a conclusion about what those data mean, it's a very difficult position to be in, both for drug developers, the investigators who

participated in the trials, the patients who were exposed to the medication, and we as regulators.

Bottom line, very simply: We recognize that new drugs are still needed, as is preservation of the already marketed ones. The pipeline is not bursting with new products. We need to maintain what we have as well as try to encourage development of new. Next slide.

Well, what is new in 2002 with regard to resources, surveillance, education, and future approaches, which I will only touch on briefly as the final bullet is the subject of Dr. David Ross's talk.

We have received at the FDA Center for Drugs resources earmarked specifically for antimicrobial development and resistant issues, and we intend to increase our staff who can deal with these.

We plan to augment our access to surveillance information, in collaboration with colleagues at the Centers for Disease Control as well as with the private sector. The goal here is to better approach anti-microbial drug development and usage.

As far as education is concerned, we know that we have to target both the health care professional as well as patients, and we plan to

address antibiotic resistance and prudent use in product labeling, and anticipate an impact on promotional material.

We are cognizant of the fact that more information in package inserts are not the sole solution to getting information out about antibiotic resistance and antibiotic utilization, but feel for us it's an important first step.

In September of 2000, the Federal Register had a proposal to amend regulations that would require all systemic antibacterial products intended for human use to contain additional labeling information about the emergence of drug resistant bacteria.

The intent here is to encourage physicians to prescribe antibiotics only when they are clinically necessary, and to counsel their patients about the proper use of antibiotics and taking them as directed.

At this point the proposed rule has received comments. I believe those comments are in the process of being collated, as we anticipate an issuance of the final rule. Next slide.

A CDER effort is underway to develop advertisements on the prudent use of antibiotics, and we envision a variety of media to do this, both in print advertisements in professional journals, patient

leaflets, and public service announcements, again in collaboration with other agencies like CDC who have already been doing this for a number of years. Next slide.

As to future approaches to anti-infective development for resistant pathogens, we recognize fully that they require creativity and flexibility on our part. We are cognizant of the limits of resources, patients, time and money, that go into developing an antimicrobial product, period, especially an antimicrobial product for resistant pathogens.

As Dr. Turner mentioned at the outset of this meeting, we welcome your comments, written comments, on approaches to anti-infective development for resistant pathogens, and you may submit them to Docket 02 -- I left out the N for Nancy -- 0047. Next slide.

In summary, I think we have made some progress in getting antimicrobial products registered for patients with resistant pathogens, but clearly more are needed. We also need to preserve the antibiotic treasures that we do have, through education, through prudent use.

Finally, we recognize the need to strike a

balance between available resources for performing clinical trials and level of certainty in determining effectiveness.

I thank you, and will turn the podium over to Dr. Ross.

CHAIRMAN RELLER: Dr. David Ross is a Medical Team Leader at the Division of Anti-Infective Drug Products at FDA, and will speak to us about developing drugs for resistant pathogens: problems and possibilities.

DR. ROSS: Good morning. I am going to be speaking this morning about problems and possibilities in terms of developing drugs for resistant pathogens. I think one thing we want to emphasize is that this is what is the continuation of a wide ranging discussion about how to deal with this extremely serious public health problem.

Let me first mention my colleagues in the Office of Drug Evaluation who have been working on this area with me: Dr. Edward Cox from the Division of Special Pathogens; Dr. Brad Leissa who is now working on bioterrorism issues; Dr. Jean Mulinde; Dr. Janice Soreth from the Division of Anti-Infective Drug Products; Dr. Renata Albrecht from the Division of special Pathogens and Immunologic Drug Products; and

Dr. Mark Goldberger from the Office of Drug Evaluation IV. Next slide, please.

What I would like to do is talk briefly about some trends in antimicrobial drug resistance, review briefly some of the problems in developing drugs for resistant pathogens -- and I know we will hear more about this from our colleagues in industry and from our colleagues at the IDSA -- and then talk about one -- and I want to emphasize one -- possible solution which is focused development.

It is not the intent that this serve as the template for all future efforts to develop drugs for resistant pathogens, but as one potential element. Next slide, please.

I've just listed here some resistant bacteria that are of public health concern. This is not intended to be an all inclusive list, but it's some organisms that clearly represent a problem: Methicillin-resistant staph aureus; methicillin-resistant coagulase-negative staph; VRE; multidrug-resistant Klebsiella and Pseudomonas as well as other gram negative rods; and in the community setting penicillin-resistant strep pneumo and multidrug-resistant nin-typhi salmonella.

I think it's important to remember that

there is interchange between these two environments. So these categories are somewhat artificial and will continue to blur. Next slide, please.

These are just some prevalence and incidence estimates of various resistant organisms. Just as a note of clarification, I want to mention that these bloodstream estimates represent my own quick calculations from a paper by Edmond that was published in CID a few years ago using a figure of 250,000 bloodstream infections per year.

The point I want to make is that these numbers may seem at first glance low, but the impact of these infections on the public health is extraordinary, because we don't have effective treatment or what we regard as very good treatments for a lot of these patients, and these are, obviously, transmissible pathogens.

In the briefing package I also presented some very, very, very crude estimates drawn from Dutch data of the burden of disease due to resistant pathogens. One thing I would like to emphasize is these are almost certainly, as are these, extreme underestimates, and we look forward to more definitive robust analyses from our colleagues at CDC.

I think, even given the conservative

nature of these estimates, this is clearly a bad problem. Even when you have a low prevalence -- for example, for fluoroquinolone-resistant gonococcus -- this translates into a substantial public health problem. Next slide.

It is not a static problem either. We all know it's getting worse. This is a slide that people have seen not only in this presentation but in a number of others a variety of times. One thing I want to point out that's missing from this slide, which is gram-negative rods. I would like people to keep that in mind as one component of the resistance problem that we need to address as we move forward in our discussions. Next slide.

Well, in response to this, the Public Health Service convened a task force chaired by CDC, NIH and FDA with input from other Federal agencies and other stakeholders to deal with this crisis. There's a number of components to this action plan.

There is prevention, research, surveillance, and product development. Under each of these elements there are a number of action items, and I want to just cite two for product development.

One action item, 82, calls for streamlining the regulatory process. I'll just

mention here that the action plan is -- The report and the action plan are available on the CDC's website and on the FDA's website, if people would like more details.

Another action item that's quite important is identifying ways to promote the development of priority antimicrobial resistance products, Action Item 80. This includes incentives. While we will not explicitly be discussing incentives today, that's clearly one component that needs to be considered in any response to this problem. Next slide, please.

What are the regulatory tools that we have at hand right now to implement the product development aspect of the response to resistance? Well, briefly these are -- and I'll go into these in more detail -- Subpart E, Subpart H, fast track, and market exclusivity, and I'll talk about what each of these mean in a minute.

I want to make the point that these are intended to deal with -- These are written in a fairly general way that allows us to apply them to antimicrobial resistance. They are not, in and of themselves, explicit economic incentives except for market exclusivity. Next slide, please.

Subpart E -- and I'll forgo citing the CFR

section, although that is really one of the joys of being a bureaucrat -- is intended to address life threatening and severely debilitating illnesses. It calls for utilizing risk-benefit analysis in the decision making process.

It promotes early consultation between the FDA and pharmaceutical sponsors as well as increased communication, which can be crucial in a successful development program and, finally, provides for earlier approval in the drug development process than one traditionally sees. Next slide.

Subpart H, which is also known as accelerated approval, addresses serious or life threatening diseases and targets agents that provide a meaningful therapeutic benefit over existing therapy.

One major feature of Subpart H is the use of surrogate endpoints as the basis for accelerated approval, and this refers to surrogate endpoints that are reasonably likely to predict clinical benefit.

I'd like to just take a minute to talk about that, because one focus of the discussion yesterday was on surrogate markers that could be useful in development of drugs, and I would like people to keep in mind that these markers have both

strengths and weaknesses.

They may allow us to develop drugs much, much more rapidly. A classic example is the use of HIV viral load in development of antiretrovirals, and that's been extraordinarily successful.

It's important to keep in mind that surrogates are just that. They are not direct evidence of clinical benefit, and you can go wrong sometimes or get fooled. Another classic example occurred as the cardiac arrhythmias back in the late Eighties.

It was noted that there was increased mortality in post-MI patients who had an increased number of ventricular premature contractions, and it made sense that if you suppressed those VPCs, you would reduce mortality. This led to the cardiac arrhythmia suppression trial in which patients who had been shown to respond to these drugs were randomized either to the drug or to placebo.

t was argued actually that this might not be an ethical trial, that this was becoming the standard of care, consensus standard, and therefore, it wasn't ethical to a trial where everyone knew that this was the thing to do.

In fact, the patients who were treated

with anti-arrhythmics had a markedly increased mortality rate as well as cardiac arrest rate due to arrhythmias, and this trial showed that VPCs as a surrogate marker were not predictive of benefit. Just the opposite.

So we need to be careful about using surrogate markers. They can be very helpful, but they are not clinical benefit or evidence of clinical benefit in and of themselves. For that reason, Subpart H calls for post-marketing confirmatory trials.

If a clinical benefit is not shown, there are provisions for expedited withdrawal. In addition, Subpart H also calls for prior submission of promotional materials and carries the potential for restricted distribution and use. Next slide, please.

Fast Track designation, which is part of the FDA Modernization Act, combines Subparts E and H. It includes a provision to accept for review a portion of a marketing application prior to submission of the complete package.

A final regulatory tool that is available to us is market exclusivity. Without going into the economic aspects of this in great detail, essentially this is protection of a product from identical

products being introduced in the market, and represents an incentive for companies to spend the money to develop a drug and get their investment back.

There's a number of different forms of this: Orphan Drug exclusivity which applies to agents intended to treat a condition affecting 200,000 patients per year or less. This represents seven years of stand-alone marketing exclusivity for each indication for which it is approved.

Pediatric exclusivity: If a sponsor performs studies requested by the agency, six months of exclusivity can be added onto other forms of exclusivity, such as patent protection.

Then finally, there's a form of exclusivity called Waxman-Hatch that provides for three to five years of marketing exclusivity. Next slide.

Now our job at the agency is to look at the data and say do we think this drug is safe and effective? But we cannot ignore the fact that, as Dr. Andriole said yesterday, drugs are developed by drug companies.

What are some of the considerations that a sponsor looks at when they develop drugs, and I'm going to talk about this very briefly. I know that

again our colleagues from industry will be talking about this more.

Some obvious things to look at are market potential. How many patients have got the condition that you are studying the drug for, and how long will they be receiving the drug? There's a big difference between giving an agent for two weeks versus giving it for the rest of a patient's life, an antibiotic versus a cholesterol lowering agent.

What's the feasibility of doing a study? How long will it take? How many patients do you have to screen to get there?

How complex is the trial? How many patients do you have to accrue? How hard is it to accrue them? How do you document the diagnosis? One thing to remember is that, as opposed to many other therapeutic areas in infectious diseases, the diagnosis is generally established during the trial. It's not like, for example, colon carcinoma where patients may come in with the diagnosis already established.

Then finally, what's the development time? How long does it take to develop the drug, and what is the regulatory review clock? Next slide, please.

In terms of market potential, I just

wanted to briefly talk about this. The point I want to make -- This is just a summary of data from IMS Health -- about 15 or so classes of drugs account for half of all drug sales in this country.

Antimicrobials -- and this excludes antiretrovirals -- account for about four percent of all sales. So this is a small but critical portion, but clearly, there are many other therapeutic areas that a pharmaceutical company may choose to invest its time, money and resources in.

Furthermore, if you blow up this four percent or you expand this four percent, I should say -- next slide. This is data from Linda McCaig and James Hughes at CDC -- the majority of prescriptions are written for upper respiratory tract infections, and Dr. Thompson showed this slide yesterday. Again, this is from ten years ago.

The situation is probably about the same or more extreme today. The sort of serious infections we're talking about, meningitis, endocarditis, nosocomial pneumonia, represent a much smaller portion of this pie. Next slide.

In terms of feasibility, I would like to show some results from a recent trial of community-acquired pneumonia. This is not necessarily typical,

but I think it's illustrative.

This trial enrolled 745 patients. 561 of these completed the protocol. 191 of these had a pathogen isolated. 146 of these patients had pneumococcal pneumonia or what we thought was pneumococcal pneumonia on the basis of sputum and blood culture data.

In terms of who we really felt sure had pneumococcal pneumonia, there were 54 patients who were bacteremic, who had what we regard as definitive evidence of invasive pneumococcal disease. None of these patients had a highly resistant pneumococcal isolate.

So does this mean that those patients aren't out there or this isn't a problem? Of course not. What it means is that clinical trials that are being conducted have difficulty capturing these patients, and it's easy to understand why.

If there is a requirement that patients not be exposed to antimicrobials for a prolonged period of time before entry, well, that's one major risk factor for pneumococcal resistance.

So even large controlled trials for common indications -- Dr. Powers mentioned yesterday that there's about 4 million cases of CAP in this country a

year -- may not be sufficient to obtain the sort of data we would like to get about treatment of infections due to resistant pathogens. Next slide.

In terms of dealing with these problems, I'd like to consider four broad categories of drugs, and these are not the way that we look at things from a regulatory perspective but just -- this is a convenient way of classifying drugs as far as their applicability to the problem of resistant pathogens.

What I'd like to do is focus on new -- that is, unapproved -- drugs that are targeting a narrow range of indications, category 3. I want to emphasize, this is not the only possible category that could help address the resistance problem. We are going to focus on it today, but drugs in the other categories could also be quite useful. Next slide.

What we would like to throw out for consideration is looking at category 3 drugs, those that have not been -- are not on the market yet and have a potential narrow range of indications as candidates for focused development.

What do we mean by that? Development specifically for serious indications due to resistant pathogens. Why focused development? This is called for or mentioned in the action plan, and it may allow

marketing of agents that would not otherwise be developed, either because of toxicity concerns or market considerations or other reasons.

The safety profile of the drug may preclude a broader program, and approval of these agents may rely on Subpart H, using surrogate markers and confirmatory trials with restricted distribution and labeling. Next slide.

What are some of the characteristics of a candidate agent for focused development? Obviously, it should have activity against the resistant pathogen. There should be an absence of alternative or comparable therapy for the pathogen, subject pathogen and subject indication.

The subject pathogen and subject indication should represent an important public health problem, and the safety information on the drug's risk profile should support an acceptable risk-benefit profile, assuming that there's going to be a limited population exposure. That's why we are targeting specifically category 3 drugs. Next slide.

I think it's helpful to quote here from the rule for Subpart H that was published in the Federal Register, which states that "these procedures" -- that is Subpart E -- "generally reflect

the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses"

It's a tradeoff. We are willing to accept more risk if there is evidence of added benefit, especially when there are no therapeutic alternatives, or few therapeutic alternatives. Next slide.

What would a development program for -- our focused development program look like? Well, Phase I would look similar to the traditional program, with dose ranging studies, pharmacokinetics performed by either traditional or sparse sampling techniques, and special population studies in the elderly and patients with renal and/or hepatic impairment. Next slide.

I think the real differences arise in Phases II and III. A program would call for dose finding, to find an optimal dose, and proof of concept that the drug can treat serious infections due to a resistant pathogen, and the data would have to demonstrate safety and efficacy.

If there was sufficient data from controlled trials, then the traditional strategy of

adequate and well controlled trials could be followed, combined with enrichment strategies, as Dr. Soreth mentioned.

If there's insufficient data from controlled trials, which is the situation that we are confronting, what do we do then? Well, then we might want to look at clinical data with historic controls, keeping in mind the problems that historic controls can give rise to.

Data from infections with susceptible organisms may be helpful. If we don't think that there's a difference in virulence between susceptible and resistant pathogens, then efficacy against infections caused by susceptible pathogens could be supportive.

There's a couple of important caveats to this, the major one being that the populations of patients with susceptible organism infections and resistant organism infections would have to be comparable or at least one would need to try and adjust for differences, since that could affect outcome.

The use of surrogate endpoints could be very helpful. Bacterial eradication of -- or serialization of the CSF meningitis was mentioned

yesterday. Again, we need to make sure that this is a surrogate marker that is reasonably likely to predict clinical benefit.

One example that was mentioned yesterday was the use of clarithromycin in treatment of MAI where eradication of the organism from the blood did not correlate with survival. In fact, it showed just the opposite.

Then finally, as we will hear about, pharmacokinetics and pharmacodynamic data may be very helpful in supporting the clinical data. Next slide.

What sort of data requirements would be needed in a focused development program? Well, I think one crucial point is the quality of the data is more important than the quantity in this situation.

It may be that relatively small databases of 300 to 500 patients could sufficient as opposed to the typical NDA database where one sees upwards of 2,000 patients.

For conditions that are known to have a high mortality -- for example, VRE or MRSA, endocarditis -- a small number of successes could suffice if one sees an acceptable cure rate.

It's important to remember the tradeoff with a small database. Limited data may mean limited

availability, because again we are targeting and focusing development on a specific indication. Next slide.

Let me just contrast traditional and focused anti-infective development in terms of how I've outlined it. Traditional development looks at many indications. Focused development would concentrate on one or perhaps a few indications.

There would be a large Phase III database in traditional development and a small Phase II/III database in focused development. In traditional development controlled trials are pivotal to efficacy demonstration. Other data is supportive but not central.

In focused development, safety and efficacy would be examined using clinical data, surrogate markers, data from infections from susceptible pathogens, historical controls and PK/PD.

In traditional development a toxicity profile may preclude further development, because if one is targeting a broad set of indications, toxicity may mean that the risk-benefit balance is not there. In focused development the toxicity would be weighed versus the benefit and would not necessarily preclude development.

Finally, as I've mentioned, one is looking at broad availability for a wide range of indications in traditional development, and focused development would look at limited availability for a narrow set of indications. Next slide.

Some of the questions that such a program would raise include the following: At what point should a drug enter focused development? At what point do we know enough to say this drug is a candidate?

If there are potential toxicities, what populations should be studied? If one is trying to look at, for example, susceptible pathogen data and there's alternative therapies, it may not be ethical to expose patients to a toxic agent when there are less toxic agents available.

Finally, is the incentive of focused development with smaller databases and potentially lower costs and shorter development times worth a limited market? Next slide.

So in summary, focused development may increase market incentives by decreasing the costs and increasing return on investment; increase the feasibility of clinical trials; decrease the complexity of drug development; and decrease clinical

development time.

I think that it's important to emphasize that this is just the beginning of the discussion about these sort of strategies, and there are many other potential solutions. Next slide.

Just by way of illustration in terms of what we are looking for, this is -- People probably know this, but this is "C.C," the world's first cloned cat. I think I'd just like to use this briefly as an illustration of what we are looking for.

It took 190 attempts to clone this cat. So we are looking for something that we recognize is going to require a lot of work, is going to make us feel good, but also represents real science, and hopefully, it's not just a ball of fluff.

So let me stop there, and I thank you for your attention.

CHAIRMAN RELLER: Than you, Dr. Ross. We will have the industry presentation now by Dr. David Shlaes, and then we will take some questions if time remains before our break at 9:30 or thereabouts. Dr. Shlaes.

DR. SHLAES: Thank you. I am glad to be able to be here today. I'm David Shlaes. I run the antimicrobial discovery group in the therapeutic area

for infectious disease at Wyeth -Ayerst, and I'm here today to represent PhRMA.

I did spend about 16 years in academic medicine where I had a research interest in antimicrobial resistance. So this is a topic near and dear to me and, of course, I took care of patients during those years.

So today I'm here represent PhRMA -- and is there a pointer? Thank you -- and PhRMA's Antimicrobial Working Group. Next slide, please.

The Antimicrobial Working Group of PhRMA offers a forum for exchange of scientific information among PhRMA companies with R&D commitment to anti-infective drug products.

It provides industry's scientific perspective in response to proposed rules, draft guidances, and relevant issues affecting anti-infective drug products. Next slide.

This is just a list of the companies who have been participating in the Antimicrobial Working Group, in at least this recent past. All of these companies contributed to the presentation that I am making right now. Next slide.

So PhRMA's Working Group applauds the efforts of the Interagency Task Force. I think the

Interagency Task Force could be a model for a way forward to improve communications not only within the different agencies within HHS, but between Departments in the Federal government and between these agencies and industry and academia. So I think this has been at least a positive step forward.

Obviously, there's room for improvement here, but I think this is a very positive step forward. As Dr. Ross and Dr. Soreth just pointed out, the action items from the Public Health Action Plan included efforts to stimulate the development of priority products to treat antimicrobial resistance, a streamlining of the regulatory process, and to identify ways, financial and other incentives, to promote the development of new antimicrobial agents, and we applaud these efforts. Next.

Now one of the things that I don't know how much you are aware of, but it is extraordinarily difficult to find or to discover new antibiotics that can actually be used successfully in people.

There have been a lot of companies working on this for a very long time, and this is extraordinarily difficult. The resources required to come up with an NCE that will successfully make it to the marketplace are large.

Now when you talk about the problem of resistance, we are talking about generally low incidence pathogens. Obviously, if we want to anticipate the emergence of resistance, then this is going to be a special problem in that regard, especially if, for example, you start out with something like the glycopeptide intermediate strains of *Staph aureus* now, which are very low incidence, and you want to be sure that -- or try and be sure that you have a compound that is active against those strains in the clinic. You know, how will you do that in any kind of trial setting?

The other issue is that these strains are not generally limited to a single infectious disease indication. So you may get one case in a skin infection, one case in a pneumonia. They are in a variety of infections.

As you pointed out -- As the agency has pointed out, the development timelines can be long. they are uncertain, and this is in spite of a current and projected public health need. Next slide.

I think issues for the future, no matter how we look at this, I think fewer companies are going to be developing novel antibacterial agents. The reason for this is market concerns and the difficulty

in actually discovering new agents that we have all experienced over the last decade or so.

This means that fewer new antibiotics will be developed, especially parenteral antibiotics. So the very products that you would like, I would view as being less likely to be developed, because -- partly because the patients that are available for treatment with such agents tend to be limited.

Other issues: The development costs continue to rise as the size of databases required for efficacy and safety are increased. So this is another issue. Along with this, therefore, because of continued reliance on older classes of antibiotics, resistance is going to continue. I think the incidence will be low to be well studied in traditional indications, but clearly VRE is going to continue.

I think multiply resistant Gram negative bacilli, as Dr. Ross mentioned, is the threat over the horizon, and there is very little in the pipeline for these organisms. I can only think of one compound in the pipeline that would address these organisms.

Kind of bottom line, novel breakthroughs are going to be few, unless we can identify adequate incentives for these high risk and limited gain

indications. Next slide.

Now I'm not going to spend too much time on this, because this has already been covered. But one of the points I wanted to make is that clinical trials are not "real life" We've discussed this a little bit yesterday, but the fact is that the entry criteria that we use for clinical trials are actually very artificial compared to the patients that one sees on the wards and in everyday setting.

This leads to situations where, in spite of the fact that resistant organisms may be not so uncommon in clinical practice, they are very uncommon when you try to enroll patients into clinical trials.

So one of the things that I think we all need to think about as a group is how can we make clinical trials more "real world"? Is there a way that we can -- Instead of thinking about the traditional clinical trial design, is there a way that we can design approaches to this that would more adequately reflect real life, and we have a couple of suggestions that we will talk about. Next slide.

Now one of the issues that I think the agency is touching on is the fact that right now there's not really much of a balance. There are fewer companies in R&D for antibiotics. There's an emphasis

within the industry on blockbuster drugs.

There are limited agents now for novel targets, novel bacterial targets with known safety profiles, and one of the issues that's come up lately is that the patent protection that you might have might be taken away from you in the case of a public health emergency.

Other things that have been discussed: More restrictive labeling; prudent use of novel agents, which is something that we all, I think, would support, prudent use of novel agents; and more safety requirements. Obviously, nobody wants to widely market a drug that's not safe.

These all kind of make it more difficult. It makes the risks higher and actually the return on investment lower. At the same time, we have growing resistance problems, and I will emphasize the Gram negative resistance here. Fungal resistance is another consideration, and the growing cost of studies as safety and efficacy requirements increase lead to a lack of balance in our approach to this problem. Next slide.

So what is needed? I think an early definition of regulatory guidance which include reasonable barriers to entry for new compounds is

something that we have to aim for.

We need to define mutually acceptable registration strategies such that efficient and cost effective development programs for very small but significant public health needs can be identified, and we need to facilitate registration of safe and effective antibacterial agents.

Another thing we need to do is we need to identify incentives to develop antimicrobial agents to treat niche indications, and this is something that, obviously, you just talked about, but I'd like to expand that a little bit.

Clearly, exploring supportive data in addition to clinical trials, the issue of patent protection and exclusivity -- I think one of the points I wanted to make was that the market exclusivity for relatively small products has not been enough of an incentive for industry in the past. I don't think it will be enough of an incentive in the present.

The other issue is that, when you correct for inflation, those later years are heavily discounted. So that it's just not going to be enough of an incentive, I think, to get us where we would like to go. So I think other incentives need to be

considered. Next slide.

So we need to strike a better balance. We need to actually reduce the cost of development and maintaining licensure. We need to protect intellectual property. We need to maintain a level playing field, and we need to reduce barriers to entry into this arena.

At the same time, I think the prudent use of novel agents can be supported and, in fact, the PhRMA companies have been supporting prudent use campaigns and antibiotic resistance awareness campaigns since the early 1990s.

We also need to encourage better postmarketing surveillance for safety, and I would say for efficacy as well. I think the current requirements for postmarketing surveillance for resistance is to be commended.

These kinds of approaches may lead to an acceptable risk for reasonable overall return on the part of the companies, and may ultimately lead to more effective and timely responses to emerging public health needs, such as the fact that you might have a pipeline of the antibiotics that we can turn to, which is what I think we desperately need. Next slide.

So we've put together a few proposals for

consideration, some of which you have also mentioned. Clearly, acceptance of PK/PD data as evidence of efficacy is going to be a linchpin of our ability to bring these products forward.

As we talked about yesterday, these studies are increasingly utilized in academia and industry, but have not yet been accepted as evidence for approval. Also, we in infectious disease in antibacterial infections have a number of well understood animal models of infection that can be a useful source of evidence for approval.

Obviously, surrogate endpoints such as time to clinical response, rate of progression, surrogate endpoints as we talked about yesterday and this morning such as resolution of bacteremia all are approaches that might allow us to move things forward more quickly and more reasonably. Next slide.

I think pooling of pathogen experience across related body sites is another approach that actually has been used and can continue to be used, so that you have indications by pathogen across multiple indications for these rare pathogens.

Another approach which, I think, is a more real world approach is using observational cohort studies along the lines of the kinds of studies that

Victor Yu has carried out. This would be something that would be used, I would think, for a marketed product, but if we can think of a way to do this for something that's not marketed, I'd like to hear it.

You could do something like this for a marketed product as evidence of efficacy against a resistant pathogen. So in this case you would collect well documented cases of infection with a resistant pathogen. You would look at outcomes for study drug versus standard of care, and this can be highly representative of real world practice. Next slide.

So one of the things that we were asked to actually talk about are kind of more general incentives that could be provided from a regulatory perspective, that would not require legislation. So we have put together a list.

Clearly, reducing the cost of development is high on the list. A smaller N for initial registration, fewer assessments per patient, and again acceptance of other supporting data outside of the clinical -- of the specific indication clinical trial setting would be very helpful.

Reducing time from discovery to market: Obviously, a smaller N, would be helpful in this regard. Accelerated approval, obviously, would be

helpful.

Ways to increase the value proposition for industry would be very helpful, such as enabling pharmacoeconomic claims. I think Dr. Ramirez mentioned this yesterday. So that might be helpful not only to industry but to clinicians who use drugs. Quality of life claims, I think, would be helpful for everybody. Compliance claims might be helpful.

So there may be ways to increase the value proposition for everybody and provide useful information in label for physicians and patients. Next slide.

So another thing that I think would be helpful would be to get together a consensus conference to enumerate a list of resistant pathogens for priority attention over the next ten years. I think we all know about the Gram positive pathogens, but what are the other pathogens that are going to be coming along in the next ten years, and where do we need to focus our efforts?

We could consider an approach where a multi-indication registration might be available, based on one study per indication, rather than the current norm of requiring two studies per indication where one indication would support approval for the

other.

We could consider a potential role for placebo controlled trials, as we discussed yesterday, in non-life threatening disease with rapid exit for patients who fail to respond early. This should help reduce the sample size for some of the infections that we look at. These all might be kind of regulatory based incentives that we could examine. Next slide.

Again accelerated approval paradigm for resistant pathogens that Dr. Ross mentioned already. I think the issue here is that I'm not sure that we would be able to develop compounds just for resistant pathogens, because the usage would not be enough to justify the investment. So I think it's unlikely that you would see that.

I think the other issue, by the way, of that strategy is the absence of beside diagnosis. I think that, in fact, the technology just isn't there to allow for that to occur within the next decade or so. So I think that is going to be a limiting factor in providing these very focused therapies.

So I think for the next period of time the most narrow spectrum drugs that are reasonable are probably those that would be directed against the Gram positive pathogens, but clearly, we need more than

that, because as I said, I think the Gram negative pathogens are about to bite us. Next slide.

So we would ask that the July 1998 draft antimicrobial guidance be finalized using a workshop approach, including clinical investigators, IDSA and other stakeholders.

I think a resistance workshop among stakeholders, including FDA, PhRMA, IDSA, other industry, and Europe, including European PhRMA, would be very helpful; because, obviously, these are global issues. It's not just a United States issue, and there may be others that one would want to include here.

The goal of this would be to develop a mutually acceptable resistance policy, and an U.S./EU resistance guidance document would be very helpful for all of us, I think. Next slide.

So in summary, PhRMA recognizes the importance of the discovery and development of new drugs for resistant pathogens. We welcome dialogue on approaches to stimulate and foster development and registration of such products, and we will organize and/or participate in workshops with other stakeholders to foster progress in this area.

Thank you very much.

CHAIRMAN RELLER: Questions for Doctors, Shlaes, Ross and Soreth? Dr. Chesney?

DR. CHESNEY: Three comments, the first one for Dr. Soreth and Dr. Ross. The community acquired non-health related MRSA are becoming a major problem, and I think it might be worth adding a separate category to your slide of resistant organisms, because they are very different in terms of susceptibilities, and we are seeing a lot of that now.

The second thing: In terms of groups to relate to, most of us are members of the IDSA, but I would also encourage that, as this issue goes forward and you get workshops together, as Janice says, that you include pediatric groups.

I know you've thought of this, but I think the resistant pneumococci kind of got ahead of everybody, because the pediatricians were not maybe having enough input.

The third thing: Dr. Shlaes, I wondered if you could explain on slide 10 your issue of reducing the cost of maintaining your license. That's something those of us not in the area maybe don't quite understand. What kind of costs are we talking about?

DR. HARDALO: Actually, I can probably

answer that for you. There's a certain amount of surveillance work that has to do with not only reporting safety events but also doing follow-up surveillance requirements to look for the emergence of resistance.

One of the things that had been mentioned in the documents is the need for ongoing surveillance, both of antibiotic use and outcomes as well as laboratory based surveillance.

Now as David mentioned, many of the companies already do this for their products in an effort to support more prudent use. However, this is somewhat spotty, and if each of the companies is required to do this in order to provide data every five years or however frequently, it's an incredible cost that goes into maintaining one's license and, if this is required, not only in the U.S. but in Europe, we would at least want to know what surveillance, where, how many isolates, what is it representative of, and make it much more reasonable and useful to support prudent use.

DR. CHESNEY: This may not be fair, but can you give us numbers? I mean, I understand it would be very expensive. Are we talking millions of dollars?

DR. SHLAES: Yes, definitely millions of dollars.

CHAIRMAN RELLER: Dr. Patterson.

DR. PATTERSON: I had a question for Dr. Ross. You mentioned the limited availability. I wondered how that would be implemented.

DR. ROSS: I think there's a number of mechanisms that one can look at. There can be, for example, restriction to inpatient facilities. One can have, for example, in the case of a drug such as thalidomide where there is a clear risk-benefit equation that one wants to keep in mind restricting it to its use in terms of women who have childbearing potential, those sorts.

So there's restrictions in terms of who can prescribe it, who can get it, and there's a number of mechanisms for doing that. I don't know if Dr. Goldberger wants to add anything.

DR. GOLDBERGER: I think that there is a very broad range. One extreme probably represents the type of program that's used for thalidomide, which is very intensive, requiring registration of pharmacies, practitioners, etcetera.

The other extreme is simply statements in product labeling, just indicating when the drug should

be used, the situation, you know, and reminding people perhaps of its limitations, not necessarily using it broadly for more minor infections, assuming this is something for more serious disease, with the idea that those statements would then be part of promotional material.

Those represent, I think, the extremes that exist in terms of thinking about restricted distribution. Actually, we were talking right before the meeting started, and you know, there is a concern, not surprisingly, from the industry perspective that, if something too strict is a component of this, that the attraction for developing drugs this way will be reduced.

On the other hand, I think there is the concern that, if you do develop a product that really offers something, if it is used very widely, then what will be the life span of the usefulness of the product?

I think one of the major issues in terms of thinking about development for resistant indication, whether it's an IV only product, IV/oral, oral only, etcetera, is getting to this issue to strike a balance, on one hand, to provide an adequate economic incentive for the development of the product,

but also some means of ensuring that the product will actually do what it's supposed to do for a while.

I think that this is one of the most difficult issue, in fact, in thinking about this problem. We ourselves at this point don't have a particular strategy with regard to any type of restricted availability that we would put forward. Rather, I think it's appropriate to give the range.

We do feel it's appropriate at least to bring forward the concept, so discussions about the pluses and minuses of this can be included in the broader discussions about this whole issue.

CHAIRMAN RELLER: Dr. Patterson?

DR. PATTERSON: The other, I think, is just a comment, that I agree with Dr. Shales that I think the multi-drug resistant Gram negatives are really the biggest specter on the horizon right now. I think *Klebsiella* and *Pseudomonas* were the two that were listed, but you know, we are seeing *Acinetobacter* that are resistant to everything, and *Enterobacter* and *Citrobacter*.

So I think, if we are going to consider, you know, by specific pathogen, then we ought to include those as well.

DR. ROSS: I absolutely agree. We had a

physician call up recently asking for use of a drug for treatment of *Acinetobacter* osteomyelitis with a highly resistant isolate, and I think the list was certainly not intended to be all inclusive. It's just an example of some, but certainly, there's others that we could add.

CHAIRMAN RELLER: Dr. Ebert, and then Dr. O'Fallon.

DR. EBERT: Just to expand on that briefly, one of the issues that was, I think, alluded to but not really addressed was the fact that we're focusing primarily on treatment of resistant pathogens, but another strategy that I think should be explored is to encourage the development of either drugs or drug regimens or strategies that would minimize the risk of developing resistance.

So that this may be a way where these products can have a wider indication or wider use than just in the treatment of resistance, but if companies can devise strategies where their products either have an advantage by having less development of resistance or perhaps even in partnering with other compounds in different strategies, that may also be an advantage.

DR. O'FALLON: I have a question for Dr. Ross. In your slide number 5, you give the prevalence

and incidence estimates of the various nonsusceptibles or resistance. Are those cases or are those people? I mean, are those incidents or are those people?

What I'm thinking about is someone might have three or four different, you know, cultures taken, and I was wondering, are these people or are these specimens, if you will?

DR. ROSS: Well, first off, I am definitely -- I sort of hesitated before even putting this slide up, because people refer to being statistically challenged. I'm in some ways epidemiologically challenged. So I think the best answer to that would be that these are cases.

It may represent more than one infection per person. I think this is one reason that we are -- I think more definitive numbers will have to come from the people who do this for a living, and that would be Dr. Bell's domain.

CHAIRMAN RELLER: Dr. Goldmann?

DR. GOLDMANN: I'd like to engage in a little dialogue with Dr. Shlaes over his proposal that observational cohort studies might be a mechanism for real life clinical trials. Could you elaborate on what you had in mind there?

DR. SHLAES: Actually, I had in mind -- I

should say we had in mind the models of the kind of Victor Yu sorts of studies. There have been several *Enterobacter* bacteremia, *Klebsiella* bacteremia where you kind of take all comers in a prospective way. You don't -- The therapy is not encouraged or discouraged. You just watch, and this allows you to examine in a cohort fashion the response to various regimes.

DR. GOLDMANN: So the idea there would be to take a prospective agent and to introduce it into an ICU and allow people just to use it, but they would still have to have IRB, informed consent, very detailed data, documentation for safety and efficacy? I'm just a little unclear as to how you do this with a novel agent.

DR. SHLAES: Right. This would have to be a marketed agent. This would be a marketed agent where -- unless somebody can think of another way to do this, but this would a marketed agent where you want to get an indication for activity against, you know, some sort of new indication which is rare or otherwise difficult to study, such as resistance.

DR. O'FALLON: So this would allow you to look for what the size both of the market and of the research pool, if you will, is here. That's why I was trying to find out if we had to divide it by three or

four, you know, it made a difference.

Okay. What you were just saying about these observational studies, I would like to suggest that you think in terms of using the Phase II design strategy with -- I think that would work pretty well in a rare disease.

I am very concerned about the idea that surrogate endpoints can be -- give us very dependable information about clinical events. So I think that any indication really ought to have some decent clinical data about the effectiveness in human beings using truly clinical endpoints. But I understand the problem of the small samples.

So I would -- It occurred to me, just off the top of my head, that there would be a couple of ways that a Phase II design could be done. Since we don't have the bedside diagnosis in -- say you are preparing a new drug; I'm thinking of the category 3 now.

You're working on a new drug. As you identify in the course of the drug the ones with the resistant pathogens, you could perform a subset analysis of those people using a well controlled -- no, well conducted Phase II design where you would set up what a success rate would be that you would

consider important for marketing purposes. I mean, somebody has to do this. What is an effective drug, say 50 percent or something like that. That's off the top of the head.

You could then do -- conduct a Phase II trial using the ones that you find in your study that are showing up. If they are coming up this often, you should be able to find them. It might take a while, but you could at least come in with evidence of clinical effectiveness. They either did or didn't pass the bar for clinical effectiveness using the normal endpoints for the particular disease.

Now that's one thing. Another thing would be, again using the marketed drugs, what you are talking about, again using a Phase II design, which is usually set up using -- The parameters for it are chosen. You know, success rate and things like that are chosen based on the historical knowledge, but then again you would be doing your study in your IC unit or whatever of these people, but you look for a proper clinical success rate to find out whether it's -- You could come in with evidence that it's actually clinically effective, not just a surrogate endpoint that it like clears out the -- it sterilizes the system.

This sterilizing the system -- I was listening to it yesterday. It is clearly a necessary condition, but it isn't a sufficient condition for clinical success. Obviously, if you can clear 98 percent of the patients, but only 50 percent of them actually respond clinically, there's more that's needed.

The problem here is that a surrogate endpoint may be fine for one type of drug, but it won't be fine for another type of drug that works a different way. So you are going to have to have special surrogate endpoints for each of the different kinds of drugs in order to make them very predictive of clinical outcomes.

CHAIRMAN RELLER: Dr. Ross. Then Dr. Shlaes and Bell.

DR. ROSS: Just a couple of quick points. In terms of the issue of an observational study, this is a question that we're examining. There were a couple of papers about, I think, two years ago in the New England Journal, one from Ralph Horowitz's group at Yale and the other by Harts and Benson, arguing that observational studies, cohort studies, may actually be better in some respects than randomized controlled trials.

As people who have been following this literature know better than I do, there's been sort of a fierce debate about whether that's really true, but certainly it's a question we are examining.

I wanted to also just touch briefly on the point that Dr. O'Fallon made. I think, in terms of a surrogate marker for accelerated approval, one point that is important to keep in mind is that the surrogate marker has to be reasonably likely to predict clinical benefit.

It doesn't have to be, for the purposes of accelerated approval absolutely predictive, and that's the reason that we want a confirmatory trial. If you look at sort of classic surrogates, like blood pressure is a predictor of the risk of stroke or heart attack, those are not perfect surrogates either.

So we don't demand that the surrogate be perfect. We do demand certain things of it, though.

DR. SHLAES: Actually, I just wanted to get back to Dr. Ebert's comments. I think most companies actually in their discovery process try and identify targets that would delay or preclude resistance. Examples of that are pathways.

So I think everybody has this in mind, but it is so extraordinarily difficult to actually find

something that you can develop that it's taking a long time, and you see that the pipeline is relatively empty. But I think everybody is working toward that end.

CHAIRMAN RELLER: Dr. Bell.

DR. BELL: I would like to make a side comment about numbers of cases, since this has come up. We realize at CDC that we need to do a better job in our surveillance projects of monitoring or at least estimating the actual numbers of cases as opposed to the way we have traditionally reported surveillance data, which is the percent of bugs resistant to certain drugs.

We are in internal discussions about how to do this. It's a bit like turning the Queen Mary, you know. I should say some surveillance projects are population based, and won't be too hard. But others are sentinel systems, and coming up with numbers of cases, it's going to involve some work and estimates. But we know for a number of reasons that we very much need to do this, and we are working on it. At least, we are going to start with certain target pathogens of which *Staph aureus* is one, for example, that's been mentioned frequently.

CHAIRMAN RELLER: Dr. Sumayo has a query,

but before coming to him, with the speakers we have just heard from, I wondered with this concept Dr. Shlaes emphasized in his presentation of the possibility of cohort studies of existing data or data being collected prospectively and the interagency task force, is there any way, Dr. Bell, to capture NIS eyecare results, therapeutic results?

The CDC has been involved in many cohort studies. Are there -- I mean, you've got the responsibility for surveillance of the largest number of resistant bloodstream infections, etcetera, in the nation. Are there outcome data? Could there be outcome data captured? Could there be response to antimicrobial therapy captured that would satisfy or provide ancillary data along the lines that Dr. Shlaes suggested at a cost that we could all live with?

DR. BELL: Well, that's the big caveat. You know, we also know that we need more information on outcome, and actually the Division of Healthcare Quality Promotion, which used to be called Hospital Infections Program, as you may know, has a group that's particularly interested in this.

It's a complicated subject, and it's going to take resources to do it well, but it's certainly something that is being discussed.

CHAIRMAN RELLER: You're counting the problem. I'm wondering if part of the solution may be in the same or could be in the same database.

DR. BELL: Probably not. I mean, that's a whole -- You know, outcome is quite an involved -- In order to interpret the data properly, you need to get a lot of other information. We need to do it, but it's not going to be inexpensive.

CHAIRMAN RELLER: Dr. Goldberger, and then Dr. Goldmann. Then we need to come back to Dr. Sumayo and Dr. Metlay.

DR. GOLDBERGER: Yes. I was just going to say, we certainly have been thinking about this issue as well, with one recent approval. We, in fact, talked to a company about what kind of data would be available postmarketing. Realistically, what we are interested in would be finding out how a drug is actually being used in the hospital setting, for instance, after it's approved. Who is getting it? What happens to them? What was their diagnosis, maybe even their concomitant medications, etcetera?

That type of information could be extraordinarily useful. There is a question about how available it really is at the patient level. In other words, you can sort of get, I guess, aggregate data,

but there would be some interest from our perspective in actually getting it to the patient so you could really see what was going on with individual patients.

I would have also thought from an industry perspective that there would be an opportunity here for industry -- for companies to cooperate in terms of funding something, since this type of study could, of course, be applicable to many products, not simply one given product; but if a study is set up across a range of hospitals, many patients on many different products will be studied, which would also make the cost potentially more reasonable.

CHAIRMAN RELLER: Dr. Goldmann.

DR. GOLDMANN: I just wanted to get back to the observational cohort study issue and, second, Dr. Bell's comment about the lack of really good outcomes data in the databases that the CDC and other surveillance networks have developed.

Really, the data not only aren't there, but when there are some data, they are really not adequate for this purpose. The issue about getting high quality patient level data for these kinds of studies is really important.

The epidemiologic methods for examining large cohort dataset techniques such as propensity

scores and so forth really have become more sophisticated, and I would urge FDA and other interested agencies to put together a small working group to really look at this issue, understand what the resources might be, and to proceed accordingly.

I think that what you are really asking for is a group of hospitals or intensive care units to work together as a laboratory for this purpose and to collect very high quality patient level data in a perspective manner.

You have to remember that the diseases, by definition, we're talking about are rare, and if they are rare, you can't just overcome the problem by looking at a large cohort. You still have to allow for the biases of confounding that are going to be in your dataset.

So it would have to be, I think, a multi-institutional laboratory to really do these studies right. Again, I would urge a working group to look specifically at the problems potential in this approach.

CHAIRMAN RELLER: Given the incredible cost for infrastructure, a question that comes at least to my mind is: Is it more expensive to set it up from scratch or would it be wise perhaps on a pilot

initially with a smaller subset of NIS hospitals to spend the money to improve the system or expand the system as opposed to setting it up from the very outset?

I mean, there's already been a huge investment, and there's a demonstrated track record of what can be captured and what is inadequately -- I mean, is not designed to capture. So can you improve the existing as opposed to starting something new, given the emphasis in the task force of better interagency cooperation, collaboration and helping each other get their respective jobs, mandates, accomplished?

Let's see. We have Dr. Sumaya, and then Dr. Metlay before our break.

DR. SUMAYA: I had a question of clarification from the presentation by Dr. Shlaes, and that was slide 6 where he mentioned anticipated issues for the future: Fewer companies developing novel antibacterial drugs and related antibiotics being developed, especially parenteral.

Could one -- Is the assumption that fewer companies -- Could that be compensated by other companies or increasing novel antibacterial drug development to compensate for that? And also where

does this relate to quantity versus quality? if we are doing less, are we doing the few in a better fashion? Could you clarify that?

DR. SHLAES: Well, first of all, I think you have to understand that this is just us trying to look into a crystal ball. But I think the fact that fewer companies are in the antibacterial research and development business right now is clear. That's happening. So that's not the future.

I think it's likely, therefore -- Because of the extraordinary effort that is required to discover these new drugs, it's likely, therefore, that our chances are diminished, since there are fewer resources being applied to the problem.

So I think that's what I was trying to get at, and the issue for many of these companies has to do with prioritization of antibacterial compounds compared to the other therapeutic areas, as was actually discussed by Dr. Ross, I think.

So I don't know if that answers your question, but that's what I was trying to get at.

CHAIRMAN RELLER: Let's have Dr. Metlay, and we need to take our break so we don't get too far off schedule. It's great that we have a vigorous discussion, and we want to keep this going after the

break. Dr. Metlay, and then we'll have our break.

DR. METLAY: Well, I just want to throw my hat into the observational study ring a bit. I absolutely agree with Dr. Goldmann that there are good ways to do it and bad ways to do it, and I think the FDA should clearly define what is meant by a good observational study, and I think there's a lot of guidance there.

That said, I would challenge some of what Dr. Ross said in one of his comments regarding the relative value of observational studies over a clinical trial. This is a tricky business, I think, indeed, and there are some specific issues that need to be considered when an observational study is really giving you useful data on drug effectiveness.

In this setting, I think, you know, there's good news and bad news. I can imagine that in some sense the selection is in the favor of new compounds to the degree that they may be used in sicker patients who are failing therapy, and so benefits for those compounds may be meaningful and could be interpretable.

On the other hand, there are lots of things we don't know about the impact of resistance on the natural history of the disease and the virulence

of the organisms, for example, in ways that could seriously bias these kinds of studies in the wrong direction.

So I think this is a difficult business, and I would certainly not like to see a lot of observational data replace the value of good clinical trial data in assessing these new compounds.

CHAIRMAN RELLER: Let's have our break and reconvene at five minutes after eleven, and we'll continue with Dr. Ross's query and others in our discussion. Excuse me. That's five after ten that we reconvene.

(Whereupon, the foregoing matter went off the record at 9:50 a.m. and went back on the record at 10:09 a.m.)

CHAIRMAN RELLER: A couple of reminders. Because of the reduction in number of flights going west, time constraints of Committee members, we seek to finish between three and 3:30, preferable closer to the former.

To accomplish that, Dr. Schentag will present -- start the open public hearing at 12:45, and we will break for lunch somewhere between 11:45 and 12:00 Noon.

To aid a 45 minute lunch, Tom Perez and

Dr. Turner have requested availability of sandwiches for those who want a simpler lunch, and we will readjourn here at 12:45, also buffet available.

Dr. Tally?

DR. TALLY: Thank you, Dr. Reller. I'd like to thank the FDA for inviting me to talk on this subject. As David Shlaes said, he and I both come from academic backgrounds. We have both been in big industry, but I have also been in biotech industry for the last seven years, attempting to develop antimicrobial agents.

I would like to focus this talk a little differently than David's talk and look at it from the biotech perspective. Regulatory-wise, we have to fulfill the same criteria to register a drug as big pharma does. We just have a smaller company with a smaller number of resources.

What we can do is probably make decisions a little faster and turn a little faster. That may shorten up some of the development time, for when you look at development times from discovering a drug to getting it on the market, approximately eight years, and huge costs, we have problems that are in common for both big pharma and the biotech industry.

I'd like to comment on some of the points

that were in the briefing documents that were sent to us and comment on some of the points that I -- I was telling Mark the other day that it's de javu. I was at the October 16, 1998, Advisory Committee meeting on points to consider for rapidly developing drugs.

We have made some progress in this area with the multiple committees. We still have a long way to go in defining what we have to do. Since that time, we have actually had two drugs approved. That's Synercid and Zyvox.

We have had some drugs that were potential drugs for treating resistant infections drop out, and there has not been a lot of additions to the pipeline that was available back then, and I'd like to go into that in development.

I think there are decreased numbers of drugs in development. As David pointed out, discovering new antibiotics is a very difficult problem, and all the low hanging fruit has been picked off in the last 40 years.

The pharmaceutical industry has actually done a very good job in bringing forward both synthetic molecules and natural products. It's about a 70/30 split, and we have multiple drugs in each of these classes. But discovering new classes has been a

very difficult job.

As I said yesterday in the meeting we had yesterday on deltas, a company has to have a very good reason to bring a drug forward, and has to have very good preclinical data to substantiate that, both *in vivo*, *in vitro*, and in safety data in order to bring it forward.

The three reasons you bring things forward is the microbiological advantages, pharmacological advantages, and finally your safety advantage over currently available therapy.

Today we are focusing on the first, microbiological advantage, and specifically the activity of drugs against the emerging resistant pathogens. We can look at that emerging pathogens really in a couple of ways.

We've talked about looking out ten years, and what will be the potential pathogens. We can make our best estimates, and there's nothing like data to prove estimates wrong, but we have to do that to plan forward. I would agree. I think the next wave on the horizon is the Gram negatives, and we are going to hear about that, I think, today.

Well, what are the preclinical characteristics that you're looking at in order to

justify bringing a drug into development? You want therapeutic potency versus resistant pathogens, and it would be nice to have a novel molecule that does not have cross-resistance with other classes of drugs that you have now and where resistance doesn't a priori exist out in the environment because these drugs have been used in some other industry.

We've heard that we would like a cidal drug to treat certain infections such as meningitis, endocarditis, and possibly the granulocytopenic hosts. There's been a very good PR on cidal versus static drugs, but when you go and look at the actual data in ordinary infections, there's not a lot of data to support cidal over static. But if you ask 100 physicians to line up on which one they would want, they would all want the cidal drug.

We have a lot of good static drugs out there for the treatment of a lot of infections, but to treat the life threatening bacteremic infections, one would prefer a cidal agent.

Finally, you want a drug with low resistance rates. It doesn't make sense to have resistant emerge as soon as your drug comes out, because it will very rapidly fall out of use, and you will have the same problem with the agents that we

have out there.

So it is one of the rigid criteria that David talked about that you try and predetermine this before you bring a drug forward.

You want efficacy in key salient models against resistant pathogens. Pharmacokinetics: For serious infections, you are going to require an IV agent. You can't rely on oral absorption in patients that are seriously ill. And it would be nice to have an oral compound or analog of that drug to switch over to oral therapy, and I'll come to that in a minute.

In safety, you want to balance the risk-benefit with the type of infection. To treat outpatient infections where you are going to be treating millions of patients for common diseases, you need a very, very safe agent.

If you do have an adverse event, it would be nice to have one that's easy to recognize and is totally reversible.

We've talked, and we've heard about the use of IV drugs. Having an IV-only drug is a double-edged sword. It may be a double-edged sword in resistance in that it's not being widely used. So you will get slow emergence of resistance, and I think the one example of this is vancomycin.

We have had vancomycin around for 35 years, actually longer than that, almost 40 years, and emergence of resistance only occurred ten years ago, and it was slow, and it's only in one species at this point in time, common species.

There are other examples, too, of drugs staying around for a longer period of time. Clindamycin with a black box warning back in the Seventies became mostly an IV-only drug for anaerobic infections, and indeed it was a long time for the development of resistance that Jay Kistlack and I first described Bacteroides in the seventies to emerge into the eighties. So an IV drug that is used under the right circumstances will have a long period of usefulness.

We talked yesterday about biocreep. In treatment of serious infections, I don't think there's a lot of biocreep that goes on, because the FDA investigators and ethics committees demand the best therapy for patients that have a high mortality.

David Ross talked about the amount of MRSA bacteremia. When you couple even 12,000 cases with a 30-40 percent mortality, that is a huge mortality, and the physicians want the best drug to treat their patients, because the objective is the survival of

their patients.

What are the added problems with an IV-only drug? It's in-hospital use versus stepdown or home IV care. It's a major problem in the United States. You can do it at a few centers, but most centers you can't do this in.

So one of the problem areas we have with an IV-only drug is with the practice of medicine in the United States and in Western Europe, patients are discharged from hospitals very rapidly, and the availability of an oral stepdown drug is important. I think that helped Pharmacia in their trials with linezolid.

With other IV-only drugs, we have to look at some criteria for oral switch on whether or not that can be incorporated into the process of speeding up the enrollment of patients, of evaluable patients in these studies, and consider it. Right now, if you switch a drug to another class of drug, we lose that patient as an evaluable patient in the studies that we have been doing.

So we go to all lengths to try and make sure we continue full IV therapy with a compound we are using.

I took this right out of the documents

that were circulated by the FDA on the nosocomial pathogens that are a problem. They have the Gram positive organisms and the Gram negatives.

The Gram negatives continue to be a major problem, as we've heard about, and they will be in the future, but I would like to concentrate on the Gram positive pathogens because that's the problem we have today.

The problem is much more complex. In doing a large *in vitro* study looking at surveillance from 50 centers across the United States -- and this was done in 2001 -- with large numbers of bacteria, *Staph aureus*, *Strep pneumo*, *E. faecalis*, and *E. faecium*, what we've tried to bring out in this slide -- It's not just methicillin resistances, illustrated by the oxacillin resistance here.

What the problem is is there's multi-drug resistance in the Gram positives to several classes of drugs. So the drugs that are available to treat these infections are very limited, and we are seeing this in Strep pneumonia with macrolide resistance and sulfa/trimethoprim resistance.

Fortunately, *E. faecalis* multi-drug resistance still remains low, but in *E. faecium* it's a major problem. So it's a multi-drug resistance, not

just one particular drug, which is the therapeutic problem.

So I would like to go back in history a little bit to show the versatility of *Staphylococcus aureus*, because as Dr. Chesney pointed out, that's the problem. The major problem right now -- and if you look at penicillin resistance -- I'm dating myself, because when I was in medical school, we could treat patients on the outpatient with penicillin, because penicillin resistance wasn't very prominent on patients coming in from the community. It was a hospital problem.

You can see the hospital problem here with penicillin resistant *Staph. aureus*, and by the time I was in medical school in the Sixties, it was a major hospital problem with low community. It took about 15 years for the community to catch up. It's just telling you what *Staphylococcus* is going to do, because what is going to go on next?

Well, we've seen a bunch of slides about the nosocomial methicillin resistant *Staph. aureus*, and that's the period from '45 to '55 or '60, if we look back at penicillin.

If we look at some data I borrowed from Chip Chambers in a CME program he ran for us, if you

look at methicillin resistance at San Francisco General Hospital, they peaked at over 50 percent in '98, went down a little in '99, and went back up in 2000.

What was more disturbing from the data that Dr. Chambers presented at this meeting was that, when he went out and surveyed the San Francisco Bay Area to look at the carriage rate of *Staph. aureus* in the population, it varied from a low of 18 percent to a high of 34 percent. But what was very disturbing was the incidence of MRSA in this population out in the community. I think that's what Dr. Chesney was talking about.

Well, we also reviewed the literature and looked at different periods from the late seventies to the late nineties, looking at the rate of MRSA in hospital, growing, and looking at the number of studies where there was community acquired infections with MRSA talked about.

As you can see, we are starting to see a lot of these studies, and now we are starting to see it in children, and the deaths reported from the Midwest in children that were never exposed to antibiotics or to a hospital environment before.

So MRSA is catching on in the community.

Quite frankly, I don't think we have adequate agents to treat it right now, and I don't see anything coming down the pike to treat MRSA out in the community when they are multi-drug resistant. So we are in a major problem at this point in time.

Finally, the other major nosocomial pathogen is the enterococcus, and vancomycin resistant enterococci have been talked about tremendously. So in a search for drugs to treat the current resistant pathogens in hospital, one has to have a drug with activity against both MRSA and VRE.

That's a very limited set of drugs. I showed them yesterday, and you can count them on one hand. We've had two approved. That's Synercid and linezolid. We have oritavancin, a glycopeptide. We have daptomycin, a lipopeptide. We have tigecycline that David's group is developing, which is an analog of mynocycline.

There are very few other agents. There's a possibility of a couple of cephalosporins coming down, but they have activity against MRSA and not VRE. They have not made it to the clinic yet. So the pipeline is very sparse.

I think what we are going to have to do is develop new chemical entities, because I think most of

the tricks to make the old classes of drugs active against resistant strains have been done. People are still trying to do it in research groups, but as you heard from David, that type of research has been well worn, and most of the tricks have already been done.

So the new chemical entities that we are developing, we have to find out what type of infections they are for. Are they for mild infections, for otitis media or UTIs? The need here is not as great as in the hospital, and where we need the therapy is for serious infections and severe infections where we may have resistance.

The general recommendation now is two well controlled trials with appropriate sizing. Usually with safety, it requires with a new chemical entity at least 1,000 patients, so we can get a clear idea of what the major adverse events and dose limiting organ toxicity you may run into for that class of drugs.

To get 1,000 patients, you need comparative studies, and you can estimate the size of those studies; and I would call this a small study, from 2500 to 3000 patients when you start to include all of the Phase I, Phase II and Phase III studies that you need.

So being able to approve a new chemical

entity with just 500 or 600 patients, I think, would be a major undertaking.

In preparing for this talk, I went back to see our actual cost today for the year 2002, clinical cost in a program developing drugs for serious infections, and we are looking at VRE patients and endocarditis bacteremia patients. My cost for clinical studies is $30,182 per patient.

This is fully loaded, but does not count any of the preclinical costs we have developed already and does not include manufacture of the drug. So this is a costly process. The cost -- and because we are a biotech company, we are not spared those costs.

If you have to do larger studies, you can see the costs just escalate for the clinical development. I don't want to get into a discussion of cost. I mean, that's raging between the two different groups, the Tufts group and then the advocacy groups, up to $800 million for new drug. I'll settle on $400-500 million is probably the cost of a drug, but that's the cost today to bring a drug forward and to get it registered.

For the antibiotic, it's already been proven and shown how to manufacture it and have an IND in place. My company has already spent $180 million

to bring it this far. So these are expensive endeavors to bring drugs to market.

I'd like to turn my attention to some of the action items that were discussed in the documents that were provided. There is one on Action Item 82 which is streamlining the regulatory process to bring antibiotic resistant products to market efficiently while assuring safety and efficacy.

Assuring safety and efficacy is why you need the large studies with over 1,000 patients, so you can get a good idea of what the safety of your new compound is.

We've talked a lot about surrogate endpoints. With bacterial infections I think it's the resistant pathogen or the susceptible pathogen is the endpoint, and you really can't get around it. It's actually in one of the classes that you look at. You look at microbiologically evaluable patients, and so that's where bacteriology counts.

One potential surrogate marker that was talked about today is using susceptible pathogens in the same species to get an idea of how a new chemical entity works against that species, and having adequate numbers then of the resistant species, isolates in that species, are required to register a drug.

I agree, animal models give us a lot of guides to how to study this, but it is to a true surrogate for patients.

Continuing on Action Item 82 is antibiotics for resistant organisms with life threatening infections and to focus development with selected infections. That makes sense with MRSA.

There's a high enough incidence of MRSA that, from your clinical studies in the United States, you should be able to get enough patients to answer the question of (1) does it work against *Staph. aureus*, and indeed does it work against *Staph. aureus* that has methicillin resistance; and with the high incidence of *Staph. aureus* in complicated skin and soft tissue infections?

In studies in the United States, if you can accomplish this, you should have enough patients to be able to come to a conclusion.

Clearly, in bacteremia and bacterial endocarditis, whereas we talked yesterday *Staph.* has become a major problem, you should also be able to get it there.

Finally, in nosocomial pneumonia *Staph. aureus* is a major problem. It's in ventilator associated pneumonia, and it's also a problem. But

also this is an area where you need multi-drug therapy to cover both the Gram-negatives and the Gram-positives, and in this instance when you look at the mortality of *Staph. aureus* in MRSA, in pneumonia, it approaches 50 percent. So this is a very difficult area to study.

When you look at VRE, the incidence is actually much lower, and it goes across a number of different clinical indications. So you will not be obtaining enough data from one system indication, such as intra-abdominal or UTI or complicated skin. There just aren't the number of patients with enterococcal infections.

So as David suggested with certain of these infections, this is where you have to pool data across a number of different infections and come to a microbiological claim for VRE, using a number of different infections to gather enough data to prove that.

Are Vancomycin susceptible enterococci suitable surrogate markers? Well, you can get an idea whether the new drug works against the enterococcus, and you will know that against both faecium and faecalis, and then with an adequate number of resistant isolates, you could then, I think, come to a

reasonable conclusion with these types of agents.

To promote development and appropriate use of priority antibiotic resistant products, what about restricting labeling to antibiotic resistant organisms?

That's one of the problems that has really frightened a lot of people out there in big pharma, on Wall Street, and on really whether or not they should be funding this area; because when this is talked about, it comes back to the question the amount of return on investment that you can get.

With MRSA, though, with the high incidence that we have now and the amount of empiric therapy, you can still justify it. You can at least justify it for a biotech company that's not looking for the blockbuster drug or a $500 million drug. A $200-$300 million drug is a blockbuster drug for a biotech company. Remember now, it is going to cost you a couple of hundred million dollars to get that drug on the market.

What my belief is, products with safety issues, massive safety issues and activity against resistant pathogens, will be restricted by the physicians, because they have a credo not to do any harm to their patients.

So if they have an alternative, they are going to restrict that drug. We've seen that in the past. I mean, Chloramphenicol is still a very good drug, but highly restricted based on its toxicity that, of course, is aplastic anemia.

So I think it is coming down. It's the characteristics of the drug, and that's what has to be clearly defined in the clinical studies, so at the end we can put it into perspective, as we heard that the FDA was talking about this morning, both Janice and David.

So broad ranges of indications requires large clinical programs. There are two potential sources for the drug, new classes of drugs and approved analogs or approved drugs with novel activity versus resistant pathogens.

This is the area where I think you will see the new drugs coming along. Drugs that are already approved or an analog of a new drug still need this approval, because it's a new chemical entity. You may not need quite as high -- a wide a safety database, but new entities need to be shown to be safe, and they both require adequate studies and adequate doses to retard resistance.

I think that's one of the things we should

be doing, is what is the dose that's really going to clear the bacteria so they can't become resistant. And you have to determine what are the appropriate indications.

Right now we have a lot of drugs that have a narrow range for gram positive infections, and most for serious infections. I don't see any for outpatient therapy. The one exception is tigecycline which is both gram positive and gram negative.

What about old agents that are resurrected that now have activity against susceptible pathogens? We have a lesson already. It's called Vancomycin. If you look at the data, you can superimpose the resistance rates for MRSA climbing in the hospital and then out in the community with the tonnage of vancomycin use.

What is the extent of Vancomycin use in the United States? There are 15 million days of therapy, and this is without promotion; because this is a generic agent that costs about six dollars a vial. So people talk about Vancomycin as a restricted drug. Well, 15 million doses -- days of therapy is not very restricted.

What it answered was there was a use and, if you have a drug that's approved that is safe, then

physicians will use it.

It brings me back to defining what is the characteristics of the drug under development? What you are going to see in the last few slides is really an opinion. I've talked to my colleagues about it, but if anybody has any reservations about this, they can take it up with me. That's what happens when you become a Chief Scientific Officer who is out doing the day to day work.

What is the problem of focused drug development for antimicrobial resistant organisms? We've talked about this. There's very limited drugs in the pipeline, and one of my jobs is to go out and search for new drugs, and I've exhaustively been doing this over the last ten years.

There are not very many drugs coming down for resistant organisms. The promise that genomic sequencing of pathogens, genomes, and combinatory chemistry which was espoused in the first half of the 1990s as the Holy Grail of drug research and the promise of many new antimicrobial agents -- that approach has failed.

There are no drugs currently being developed from the genetic approaches and combinatorial chemistry approaches that have seen the

light of day in animal models even.

Indeed, the genomics companies and the biotech sector are moving out of this area and concentrating on the human approaches and the human diseases, and abandoning antibiotics. They thought it would be easy to come in and discover some antibiotics with the new genetics and combinatorial chemistry.

After millions of dollars, they have realized this is a very hard job, and indeed that is going into the reasons that some of the big pharmaceutical companies are closing down their pharmaceutical groups that discover antibiotics. We've seen that Eli Lilly, and Bristol-Myers Squibb has recently announced that. Other companies are thinking of that.

To realize -- I don't think the genomic approach has failed. It's the genomic approach in combinatorial chemistry that's failed, and there is tremendous potential in understanding these new targets which will be appropriate targets for antimicrobial agents, but it's going to take a substantial investment, both in big pharma and of the biotech industry to realize the potential and to get the very high hanging fruit that will be our agents to treat these serious infections.

One of the problems, I think, of focused drug development, and Dr. Shlaes mentioned this, is what we need to do is clearly define the number of patients with resistant infections required in our efficacy trials. Is it an absolute number or a percentage of infections in these different syndromes that I talked about earlier? How many MRSA versus MSSA do we need to really define the one -- this new chemical entity works against *Staph. aureus*, and indeed then works against MRSA?

I was involved in a project in registering Zosan pipericillin tazobactam when I was at Lederle Labs, and we had the same problem, because we had to prove that Zosan worked against pipericillin resistant pipericillin tazobactam susceptible strains.

It took us enrolling 3,000 patients in the pipericillin tazobactam arms to come up with 256 patients that met those criteria. You can do it, but it takes huge studies to do that when you are looking at it. But it can be done, and we can learn lessons from the past. So if we know what we have to do, we can design our studies to try and achieve that.

Remember the cost. We've talked about it for this new compound. It's very high, and to restrict new drugs for antibiotic resistant isolate

only would really limit the return, and for many companies it would not be justified to go forward with this development.

What is the path that we have been taking with a new chemical entity? In trying to prove efficacy with a narrow spectrum drug that's active against Gram positives, we tried to go to infections that had high incidence of Gram positive infections, such as complicated skin and soft tissue infections.

We attempted to capture *Strep. pneumoniae* in community acquired pneumonia trials. We are planning to do a bacterial endocarditis trial directed at *Staph. aureus*.

Finally, where does the enterococcus come from? Many times it comes from the urinary tract. We've done a pilot study in this area, and indeed you can isolate out the patients, but these are very hard studies to do in the United States, because you can't keep the patients in the hospital with UTIs. So we have to look at a strategy in that particular area.

We need to show that the drug is safe, and we are doing two well controlled trials in many indications. We are looking at specific resistant pathogens such as MRSA and VRE.

We have a 700 patient community acquired

pneumonia trial. We only came up with seven penicillin resistant isolates in that trial. So the problem continues in trying to identify penicillin resistant *Strep. pneumo* in adults.

What is the answer? I don't think there's a simple answer, and that's why we are having these meetings, because if you look for a simple answer, you are going to make a mistake, and you are going to create more of a problem.

So I think antibiotic resistance is really a complex issue, and the NDA Task Force is approaching it that way. I don't think we should look for one simple answer that will satisfy all of us -- the solutions.

Reserving novel new antimicrobial agents for antimicrobial resistant pathogens: It will limit economic return. It will actually decrease both big pharma and biotech's research, if indeed that's what happens, and that big investment we need to develop new molecules just won't be put on the shelf.

Finally, I would contend that actually saying restricting the problem to resistant pathogens probably won't solve the problem. Ceftriaxone was a restricted drug when it first came on the market, but when physicians started using it and found the

convenience of a good drug that worked once a day, that's why it's the largest selling IV antibiotic right now.

We see this with a number of drugs. Many drugs are restricted right at the beginning, and what the clinicians do is find out is the drug working; and if it's working and safe, then they will use it for their seriously ill patients.

So to justify the high investment to develop drugs, the drug -- what we should do is to determine the safety and effectiveness of the agent in focused, well designed clinical studies that allows the clinician to make the decision on what's the appropriate use of this new agent.

I think what I've been trying to do is focus on the molecule and not focus on the rules to restrict it because it happens to have activity against resistant organisms.

The only way this can be done is for industry and regulatory agencies to work very closely together, develop cooperative teams so they can put all these issues on the table and come to the best resolution to develop these drugs for appropriate use, and with that we will develop drugs for antimicrobial resistance.

Finally, I'd like to be a little provocative, because I've heard some recommendations that how can we develop a situation where drugs will be developed for resistant organisms and then put on the shelf?

As from my perspective in biotech, the only way we can do this is massive government funding of an agency to develop the drug, because if you take the profit incentive out by putting that on the shelf, then the only way you can do that is totally fund that with public funds so you can justify putting it there; because with public companies one of the main goals we have is developing drugs to treat patients to get them well, but also is returning a profit to stockholders, and that's the reason that they invest in those companies.

Well, we've covered a lot of different area, but I think, in summary, what we heard today is (1) the pipeline is sparse, and it's going to take a lot of money to develop new drugs. It's sparse for Gram positives. It's empty for *pseudomonas*.

We need close cooperation between industry and regulatory bodies. Here it's the FDA. In Europe it's other bodies. One approach doesn't fit all compounds, and I think each individual molecule's

characteristics must be clearly recognized, developed, and its efficacy and its safety should be clearly worked out in well focused study to allow us to develop drugs to treat a major public health issue.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Tally. Dr. Louis Rice will speak on behalf of the Infectious Diseases Society of America.

DR. RICE: Thank you. I appreciate the invitation to come and speak today. As was stated, my name is Lou Rice. By way of introduction, I am an infectious diseases physician. I also serve as the Chief of the Medical Service at the Louis Stokes Cleveland VA Medical Center, and I'm a professor of medicine at Case Western Reserve University, and as was stated, I am here representing the Infectious Disease Society of America.

The issue of clinical infections caused by bacteria resistance to many and sometimes all available antimicrobial agents is a daily challenge for many infectious disease physicians, as well as for physicians from many other specialties, including surgeons, pulmonologists and hematologist oncologists, among others.

Since the problem of multi-resistant

bacteria has its origins in many places, including poor compliance with infection control measures and overuse of many different antimicrobial agents, it is not likely, nor is it anyone's contention, that novel antimicrobial agents will solve the problem of antibiotic resistance.

Nevertheless, we are in constant need of novel therapeutic agents to address the variety of resistant bacteria that arise to fill the niches created by use of currently available antibiotics in the modern hospital.

As stated by Vince Andriole at this meeting yesterday, the Infectious Disease Society of American stands ready and eager to make available the substantial expertise within its ranks to help resolve these issues in a manner that will be satisfactory to all the involved stakeholders.

In considering what we as a Society could bring to today's discussion of resistant bacteria, I thought that, in addition to discussing some broad statistics of resistance, I will also focus on what antimicrobial resistance means to the individual clinician at the patient's bedside.

By doing this, I intend simply to remind us that this is a real problem. It affects real

patients treated by real physicians. Whatever the appropriate solutions to the problem, some mechanism must be determined to facilitate the entry of new drugs to the marketplace, for while we rest, the bacteria continue to work.

In its preliminary communication prior to this meeting, the FDA has compiled a list of representative problematic resistant organisms. I think it's a very useful list to start from, but as has been stated before, there is one organism that is not included that really threatens to become the top resistant pathogen of the next decade.

That organism is multi-resistant *Acinetobacter baumanni*. The first slide -- you don't have my slides? Okay. Well, there are no slides.

In any case, in data from a consortium of seven New York City hospitals headed up by Brian Currie of Monefiore Medical Center and Albert Einstein College of Medicine indicate that rates of Imipenem resistance in *Acinetobacter baumanni* isolated from intensive care units where *Acinetobacter* is really a problem pathogen, particularly in ventilator associated pneumonia, approached 30 percent; whereas, rates of Amikacin-resistance approached 50 percent.

Acinetobacter strains resistant to both

Imipenem and Amikacin are now common in New York City, and it is common for such strains to be susceptible to only colistin and polymyxin B, two membrane active antibiotics which are highly toxic and which most of us thought were historical curiosities as recently as a decade ago.

In a recent conversation with David Gilbert, who is the current President of IDSA, David offered that three days do not go by without a new York City physician calling him, asking him whether there is anything in the pipeline that can treat these *Acinetobacter* infections. Sadly, he has little encouragement to offer.

One of the most active investigators in the area of clinical impact of antimicrobial resistance is Jim Rahal who is the Chief of Infectious Disease at New York Hospital Medical Center of Queens. In a recent article in Clinical Infectious Diseases, Jim and his colleagues nicely summarized their sequential experience with multi-resistant Gram negative bacilli.

Ceftazidime use in the late 1980s begat multi-resistant -- I'm sorry. Ceftazidime use in the late 1980s begat Ceftazidime resistant *Acinetobacter* and Ceftazidime resistant *Klebsiella*.

Imipenem use to address these resistant organisms then begat Imipenem resistant *Acinetobacter*, which it took seven years to finally eliminate from that hospital, but obviously not from the rest of the New York hospitals.

Imipenem use was also associated with the emergence of Imipenem resistant *Pseudomonas aeruginosa* and Imipenem resistant *Klebsiella pneumoniae*. Lest anyone think that these resistant pathogens were merely colonizers of uncertain clinical significance, a publication by Ahmad and colleagues from Jim Rahal's group as well reported that six of seven patients infected with Imipenem resistant *Klebsiella pneumoniae* died, nor is resistance the exclusive province of exotic nosocomial Gram negative rods.

It is worth noting that during this same symposium that Brian Currie presented his data on *Acinetobacter* in New York City, he also presented data suggesting that rates of *E. Coli* resistance to Ciprofloxacin in New York City hospitals now approached 15 percent.

One week later I was attending a symposium in Chicago and was told that rates were very similar in Chicago. It should be also noted that the symposium in New York occurred October 13, 2001, about

two days after Tom Brokaw advertised the fact that he was taking Cipro and that, in fact, everybody in New York seemed to be taking Cipro. The ultimate results of this huge natural experiment remain to be determined.

The past decade has seen similar problems of resistance in Gram positive bacteria. Just this past year, the National Nosocomial Infection Surveillance reported that the percentage of *Staph. aureus* strains isolated from true clinical infections, patients in intensive care units, has now exceeded 50 percent.

Needless to say, this rising prevalence of MRSA continued to drive Vancomycin use which, among other things, has the effect of driving the spread of Vancomycin resistant enterococci.

If I may, I'd like to briefly review the case of a patient, a true patient, who still lies in a bed in the Cleveland VA Hospital as we speak. He is a 57-year-old male who was diagnosed with acute myelogenous leukemia in late December or in December of 2001.

he initially underwent induction chemotherapy in December, which proceeded reasonably smoothly, although he was noted to become colonized in

his gastrointestinal tract during that period with multi-resistant enterococci, defined as enterococci resistant ampicillin and Vancomycin, fortunately susceptible to Linezolid and Quinupristin/dalfopristin.

He returned to the hospital in January with a relapse of his leukemia, and blood cultures that grew *Candida parapsilosis* and *Candida glabrata*. This responded to removal of his broviac catheter and intravenous administration of amphotericin B.

He then underwent a second cycle of chemotherapy and was soon neutropenic. On January 26th, his blood cultures grew coagulase-negative staphylococci, and he was noted to have diarrhea and abdominal pain, prompting initiation of vancomycin and metronidazole therapy.

He remained persistently febrile, and an abdominal CT scan suggested neutropenic enteral colitis, otherwise known as typhlitis, a serious and life threatening condition that prompted initiation of meropenem therapy.

Then finally on January 31st, his blood cultures grew multi-resistant *Enterococcus faecium*, the same strain that had been in his gastrointestinal tract one month before, necessitating a switch from

vancomycin to linezolid.

There weren't many of us that would have bet on this patient making it out of the hospital. However, over the subsequent two weeks he gradually improved, and as of the 14th of February his white count had now risen to over 3900, and his bone marrow was free of blasts. On linezolid, though, his platelets remained below 20,000.

Although there's been some debate regarding the virulence of multi-resistant *Enterococcus faecium*, a large multi-center study of enterococcal bacteremia recently published by Manny Vergis and colleagues from Pittsburgh in The Annals of Internal Medicine has, it is hoped, put this issue to rest.

Vergis and colleagues showed that after multivariate analysis, the factors associated with mortality in patients with enterococcal bacteremia were resistance to vancomycin, presence of a hematologic malignancy, and APACHE II score.

It is important to note that the patients described in the Vergis multi-center study were patients who developed enterococcal bacteremia prior to widespread availability of linezolid and Synercid or quinupristin/dalfopristin.

Given the multitude of factors present in the patient I just described that would predict a high likelihood of mortality, it is not a stretch to state that the availability of linezolid probably saved this man's life.

As we move into the third week of linezolid therapy, however, and with his platelet counts still below 20,000, additional therapeutic options, of which quinupristin/dalfopristin is the only one, would certainly be welcomed.

The risk associated with accepting large deltas for licensing new pharmaceutical agents is an important one and should not be underestimated. However, it must be understood that antibiotics, and particularly those used for the treatment of serious life threatening infections caused by potentially resistant bacteria, are fundamentally different from other pharmaceutical agents.

The presence of the third factor that is not important for other types of agents, the susceptibility of the bacteria, in combination with frequent intolerance of antibiotics either due to hypersensitivity reactions or well described adverse events means that the "most effective agent" is all too frequently unavailable.

In such settings, we need the availability of drugs that will work, even if not as effectively as the ideal agent. Infectious diseases physicians are commonly forced to employ agents that are not the optimal agent for treating a given infection.

I suspect that every time an infectious diseases physician prescribes vancomycin for *Staph. aureus*, he or she has in their mind a study published by Levine and colleagues in the Annals of Internal Medicine in 1991.

This study reported that the mean time to sterilization of blood cultures in patients with staphylococcal endocarditis treated with vancomycin was nine days, roughly two to three times the historical time for sterilization of blood cultures when treated with nafcillin.

We know that vancomycin is less effective than betalactam antibiotics, but we are certainly grateful to have the option to use it when patients are infected with methicillin resistant staphylococci.

I think it is also very important to note that vancomycin was first introduced clinically in 1958, three years before methicillin resistant staphylococci, the reason for its primary use now -- three years before that was even described.

We do not know what the predominant pathogens will be ten or 20 years from now. We can safely say, however, that the problem of antimicrobial resistance will be with us still. The continued development of novel and effective antibacterial agents in combination with strict adherence to infection control measures and judicious use of currently available agents form the three legs of the stool upon which our ability to treat serious infections will rest.

The IDSA stands ready to assist in any way to ensure that the future development of antimicrobial agents yields maximally safe and predictably effective products.

I appreciate you allowing me this time. I would like now to yield to my colleague, George Talbot, who would like to make a few remarks as well.

DR. TALBOT: Good morning. My name is George Talbot, and I'm pleased to be making a few comments today on behalf of the Infectious Diseases Society of America.

With Dr. Rice's presentation about the dilemmas confronted by frontline providers of infectious diseases care as background, I have several general comments that I would like to make, again on

behalf of IDSA.

My first point is one that is perhaps self-evident or obvious, but I feel it needs to be said. That is that it is extremely encouraging to see the efforts put forth by the agency to hold this meeting, to prepare the briefing document, to present such well reasoned analyses, and in general to give us the opportunity to have these discussions. So I'd like to thank the agency for doing that, and let you know that IDSA and its membership appreciate that very much.

There are several specific suggestions that could be made based on some of the discussion that has happened so far today and that will come later. First of all, the briefing document, as you prepared it, is extremely useful and, as I mentioned, very encouraging.

One step that would help in its relevance to the pharmaceutical industry and to members of IDSA and to members of other specialties is to turn this briefing document, together with the input from today's presentations, into a written guidance.

This would make it easier for those in industry and in the clinical trials arena to anticipate the needs of this regulatory agency and to

produce the best possible data to allow the rapid development and approval of novel drugs for antibiotic resistant pathogens.

In this effort, IDSA stands ready to assist you in whichever way you feel would be most appropriate.

A second point related to any potential guidances is that these guidances should be as specific as possible. Dr. Metlay has already alluded to some of the issues relating to observational cohort studies and has encouraged the agency to provide some specific directives.

While I applaud the proposal of that potential design as part of a constructive brainstorming process, I think Dr. Metlay's comment is very germane and that that area, among others, requires specific thought and some specific guidance.

A similar area is related to the use of historical controls. As Dr. Soreth mentioned, these can sometimes be useful, but in my own experience they are fraught with hazard and not necessarily in the end all that useful.

My final comment is that the IDSA hopes that whatever comes from today's meeting and however it is translated into either action or written

documentation or written guidances, the IDSA hopes that this be done with urgency.

As Dr. Rice's presentation has, I think, so well described, there are patients now who need these agents. There are going to be more patients every day, and the greater the urgency that can be applied to reaching some resolutions and some definitive guidelines, the better for these patients.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Talbot. The presentations from IDSA, industry, PhRMA are open to discussion, comment. Dr. Ross, just before our break, you had your hand up. Still relevant?

DR. ROSS: Yes. Actually, Dr. Talbot made a couple of points about observational studies, and I wanted to follow up on Dr. Metlay's comments about observational studies.

I think those represent one potential resource. I think, as Dr. Metlay pointed out, there are potential pitfalls. We are examining the question of how to use that sort of data and what the pros and cons are.

I mentioned the papers by Horowitz and Hart and Benson in the New England Journal. The follow-up correspondence on those, for anybody who has

read that, was quite fierce. So I think that those are -- I think I just wanted to indicate that those are areas that we are looking at, but we certainly appreciate the input that we need to keep our wits about us as we look at those sort of issues.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: Following the same, I would like to make a comment, that ideally what the agency would like for us is to think outside of the box. We are here to suggest new ways to deal with this problem, because if we want simplicity in MDR organisms, we need to be thinking outside of the box, and then I think that we should probably for a couple of minutes just stop thinking that the ideal situation is the two trials, prospective, double blind with a low delta. Otherwise, anything that we are going to say that is novel is going to be -- probably is going to have potential pitfalls.

Then I would like not to someone come out with an idea, and then the next comment is, well, but you need to do a prospective, double blind trial.

The other thing I would like to -- Another comment is that I think from the clinical perspective -- this was already mentioned, but there are two types of MDR organisms. There is the MDR organism that we

still have antibiotics to treat. If the patient has an infection, we may have limited numbers, but there are MDR with one, two, three, four, five antibiotics.

This is one problem. Then there's the other MDR organism that the patient has an infection, and we don't have any antibiotics to treat. Then fortunately in our -- I don't remember when was the last time in our patient management conference that we discussed a Gram positive infection, but we recently had discussion of the *Pseudomonas* resistant to everything or the *Acinetobacter* resistant to everything.

These are the real challenges. I understand there is also a problem with MRSA, but we have not presented a MRSA case in a long time. Eve though we will not have the idea of antibiotic, we do have antibiotics.

My point is that when I think what do I need clinically, I think that we need to be looking at two types of drug development process. One is when I add a new antibiotic to an MDR organism that already have three or four, and I may look at one way to develop this drug.

The other is when I am faced with a patient with a multi-resistant *Pseudomonas* that I

don't have any antibiotic. Now until not long ago, we used to call for compassionate use for clinofloxacin. There was always something that you can call in trying to get some antibiotic to use for these patients.

I can tell you that you discuss with the patient or the family, nobody is going to be concerned of toxicity or anything with these patients, because these patients with these multi-resistant organisms with nosocomial pneumonia is going to die. And for these type of MDR, I may say that I will be very pleased with a PK/PD, animal data, and just almost somehow jump into the patient, and give me the antibiotic and let me have this antibiotic for compassionate use around the country, and we can come out with a -- If this is done by people with some idea of clinical research, we can come out with a lot of patients at minimal cost, and this can be -- We can have a national RIV approval for these particular antibiotics.

Then I see -- In my mind, I have two different type of problems. One is the MDR, that I have antibiotics, and the other MDR that I don't have antibiotics, and I see that probably the process needs to be two different type of process. Just a comment.

CHAIRMAN RELLER: Dr. Bell?

DR. BELL; I agree with Dr. Ramirez. We need to think outside the box, but first I have two points of clarification I would like to ask.

One is the question I asked yesterday, which is how does the discussion of deltas apply to new drugs to treat resistant infections? I was promised the answer today.

Well, is the typical model a noninferiority study, comparing a new agent against a drug of another class that still does work; because for most pathogens there is still something that -- I mean, we are -- I mean, is that the way this is typically viewed?

In such case, of course, widening the delta is an option, or is the typical way this is approached a superiority study comparing against -- I mean, I'm not sure how that would be done. But if somebody could just -- You know, how does the delta discussion of yesterday apply to what we are about today?

My second question is -- I think it was Dr. Shlaes alluded to the requirements of clinical trials making it difficult to accrue patients with resistant infections in those trials.

I've heard that a lot and don't doubt it, but I wonder if he or someone could elaborate on just what are those requirements that make it so hard to find resistant infections? You know, there also might be an opportunity to make some changes.

So those two questions.

CHAIRMAN RELLER: We have multiple hands up, but first those who wish to provide answers specifically for Dr. Bell. Dr. Goldberger?

DR. GOLDBERGER: I'll answer the first question, or try to. I'll leave it to Dr. Shlaes to attempt to answer the second question. He can think while I'm trying to talk here.

No, you raise a very legitimate question, and I think that in the past, certainly, the development of a drug that would include a resistance claim might be subsumed into the overall development of the drug.

That is to say, to get a claim for PRSP, say, in the setting of community acquired pneumonia, you would have the data in community acquired pneumonia to show from routine trials that the drug was efficacious, data in susceptible pneumococci to show that the drug was efficacious, and then some additional number of resistant pneumococci.

Now in the case, for instance, of a fluoroquinolone where the issue of -- you were sort of out of the class. So you weren't worried so much about penicillin resistance having an impact on fluoroquinolone activity. Whether that's still the case now could be worth some discussion, but in any case we required a relatively small number of patients with documented PRSP infection in community acquired pneumonia to demonstrate that the drug had activity there.

The reason we required any, in fact, since you could argue, well, if their resistances are not linked and you've got an overwhelming amount of pneumococcal data, as we had with levofloxacin, for instance, where there were literally a couple of hundred cases, why have any cases?

Our thinking along those lines was that there may be patient related factors that go along with acquisition of PRSP that those patients may some way either be sicker, either from their infection or from underlying illness, and it would be desirable to show that the drug would work in that setting.

So that's a model that we've sort of followed. I think it's clear that, if we were to move to a model where there would be more focus on

resistance and less focus on broad other claims, then that approach would have to be modified, and that there might not -- I don't know that we would be really using a delta approach to the resistant data.

We might be using an approach similar to what David Ross outlined earlier where there would, for instance, be serious enterococcal or *Staph. aureus* infections, a limited number of patients whose nature of infection was extremely well characterized, i.e., endocarditis, vertebral osteomyelitis with sustained bacteremia, etcetera, etcetera, that you demonstrated that the drug was effective in those patients where there would be little doubt that, absent effective antimicrobial therapy, there would be any spontaneous remission, and that that might then be supplemented by some additional data in at least one other indication to demonstrate the drug's role in treating patients with serious infection.

The latter indication might, for instance, be subject more to a routine delta approach. So that's one part of our thinking. That's, in essence, the reason for presenting this today, was to get some discussion on those issues, because in fact it is an approach that ultimately relies on a smaller clinical experience than what we have generally done, and the

question is: Is this a reasonable way to proceed, which is why we sort of brought it up for the purposes of discussion.

So I hope I've spoken long enough for Dr. Shlaes to have his answer ready.

CHAIRMAN RELLER: So we will have Dr. Shlaes and Dr. Talbot, then Dr. Wittes and Dr. Archer. David?

DR. SHLAES: Okay. So the reason that it's so difficult to accrue patients with resistant infections -- There are probably several reasons. One big one is that one of the major exclusion criteria for entering into clinical trials is prior -- recent prior treatment with antibiotics, which is the very population that tend to have the resistant organisms.

DR. BELL: How recent is recent?

DR. SHLAES: It varies with the trial, but on the order of 72 hours, something like that.

The other issue is that many of these patients tend to have multiple other medical problems, and because these are investigational agents, we tend to exclude patients with a lot of serious underlying diseases, renal insufficiency, sometimes hepatic insufficiency, etcetera.

So that when I had this slide in this set

which said that, you know, clinical trials are not real life, I think if you want to capture patients with resistant pathogens, we have to have an approach that more reflects real life somehow.

CHAIRMAN RELLER: Dr. Talbot?

DR. TALBOT: To comment on the question, and also Dr. Ramirez's point about studying lots of patients in a compassionate use program, we did try that with Synercid.

So I agree with Dr. Goldberger's comments. Let me cast them in a slightly different way. I think one way to think about this is how you study a drug when there is a comparator available is different from how you have to study a drug when there is no comparator available. That was the situation that was faced with Synercid.

In the latter situation, the issue of delta, at least against a resistant organism, becomes irrelevant, because there is no comparator. It's really a question of efficacy as opposed to comparative efficacy.

So in that setting, what could you do? I think you could do pretty much what Dr. Goldberger alluded to, which is: If you build a whole story about the drug's efficacy based on *in vitro*

susceptibility, *in vivo* animal model data, PK/PD relationships, activity against susceptible pathogens and clinical efficacy in other indications, then if you can also show that in a subset of patients with clearly defined infection due to a resistant organism that you have efficacy, I think that that should be sufficient for an approval for that indication. That is a pathogen specific or pathogen driven indication.

CHAIRMAN RELLER: While it's fresh in our memories, the patient that Dr. Rice alluded to, I think, is a good example of how these exclusions would make it impossible to study the very patients for whom the new drugs are necessary.

By definition, other antimicrobial drugs within 72 hours that are irrelevant to the resistance issue at hand are underlying factors, risk factors. This seems to be a rich area for moderation of entry criteria for treatment of resistance.

Dr. Wittes?

DR. WITTES: Thanks. I actually have four comments, and I know I am infectious disease challenged, but I'll try my best.

The first thing actually relates to the number issue and the 72 hours. I've been trying all day to figure out why there can't be large enough

numbers. It didn't make any sense. Given the sample sizes you have put on the board, the slides, of how many people there are in this burgeoning problem and so forth, it didn't make any sense to me that there are no numbers.

If what you are doing is designing trials that are so unlike the patients that you need to treat, and you are excluding wide swaths of them, that doesn't make sense to me.

So if we are talking out of the box, it seems to me this is really put it back in the box. Think about what your -- who the patients are that need the treatment, and design the trials around them. I mean, I must be missing something. Okay, good.

DR. HARDALO: Having been through this with the VRE experience and on both sides, actually, as an investigator and then later as a project director for a pharmaceutical company, on the one hand, when we were doing compassionate trials like the Synercid trial, we were initially told that the patient had to fail all reasonable appropriate options in order to get enrolled in the Synercid trial, which in general meant that you had to wait for the culture to grow, wait for the organism to be identified, wait for susceptibility testing to show what you could use,

try that, have them fail it with a minimum of 72 hours worth of therapy.

Now the epidemiologic data on VRE suggests that most of the morality occurs within the first week. You've just wasted that week trying out the appropriate options.

Okay. Second would be randomize a patient to a controlled trial in which you are looking at a selected comparator, realizing that your VRE is multi-drug resistant, and no one agrees what's the best standard of care.

In that particular case, if there's alternative options in a compassionate use trial for linezolid or Synercid, you won't get patients enrolled in your trial, because they can get the other drugs that they believe may have some efficacy easier.

So it becomes much more difficult when you are dealing with sick patients who have high mortality to force somebody into an investigational trial. Even though it may be academically more rigorous, scientifically more robust, there are significant challenges.

Four thousand isolates may be very different than 4,000 patient cases that are eligible for a clinical trial. So that's where the

surveillance data could be extremely useful in telling us, indeed, how many patients are really out there, how many patients really could consent to a clinical trial and be expected to survive longer than a week so that you could get any kind of assessment of efficacy.

CHAIRMAN RELLER: Dr. Wittes, you had four comments.

DR. WITTES: All right. The second actually, I do have to say something about the observational data, because I, too -- I want to echo the concerns of those people who have expressed concern about it.

I think that to do an observational study of the type that we are talking about where it's been on the table is very expensive, very time consuming, very prone to bias, and really hard to interpret.

I was involved in -- When I was at NHLBI, coming to the FDA to the Blood Advisory Committee asking them -- We at NHLBI were asking the FDA whether we could do the observational study of alpha 1 antitrypsin replacement therapy, and our argument was sort of all the arguments I've heard around the table, and we won the argument. We were allowed to do it instead of a randomized trial. Fifteen years later nobody knows whether it works.

So I just -- From my own experience as well as lots of letters that we read, I just hope that that's not the route that will be taken.

The other issue actually has to do with -- Oh, short issue and then the bigger one. The cost of trials: The 30,000 sounds like a lot, and I don't know whether there's some marginal cost or not a marginal cost. But it seems to me that we spend a lot of money in trials that's really unnecessary and there is a kind of overcollection of -- overprecision that we do that is extremely costly and that we should look at and question.

Increasing sample size can be much cheaper than increasing complexity and the rigidity of certain kinds of ways in which we validate data. So this is an appeal for a little less validity and bigger sample sizes and less costly -- saving money at the margins.

Finally, I think that it seems to me that there is a real interweaving of biocreep of this delta, of the availability of drugs, and what should be sitting on the shelf in case a new resistance arises.

Dr. Tally talked about that people would use -- docs would use the best drug, because -- There's no danger of biocreep, because people use

what's best. I think the issue, as far as I can -- seems to me, that if you are talking about having a large delta, a drug coming on the market with a large delta, and the word noninferiority attached to it, how in the world can somebody know -- a practicing clinician know what's best?

I mean, I think that was the point Erica made yesterday, that if the data aren't there to say what's best, how do you know what's best? So it seems to me that the structure of large deltas, of course, have the potential of leading to this biocreep.

On the other hand, if we are more careful about our language and don't claim that things are equivalent when they are not or when the data don't really support that, or not inferior when the data don't really support that, and admit to the kinds of -- If a drug will be on the market with a larger delta, admit that and have that as well known so that we are not -- Separate the trial and the definition of the delta in the trial from the way in which it's described in literature and label and in practice.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: I am going to ask a question. We discussed yesterday biocreep and delta. We'll treat usually critically ill patients infected

with multi-resistant organisms that without treatment 80-90 percent is going to die. There is not too much room for biocreep.

If you have a drug that works, as soon as you drop one or two times a delta, the patient is going to die. I think that -- I don't know if this is thinking appropriately to adding delta or biocreep, because these patients are -- I mean, sometimes there is no option.

I mean, in nosocomial pneumonia we discussed 50 percent mortality. In these two cases there were presented today, I mean the mortality is close to 100 percent.

CHAIRMAN RELLER: Dr. Ross.

DR. ROSS: I think you are raising a very germane question, one that is very difficult to answer. One of the difficulties comes from the fact that our estimates -- this was discussed yesterday -- of treatment effect differ depending on the situation.

If we are talking about *Staph. aureus* endocarditis, we think that appropriate therapy leads to a very large treatment effect. Not everyone will get better, but certainly more people will get better -- Many more people will get better than if you don't treat.

What is the magnitude of the treatment effect if you have a patient with a single blood culture that is positive for vancomycin resistant enterococci? Let me just say very quickly before I fall into the ice that I do agree that VRE is a real pathogen and leads to bad outcomes, but the question is, in a given patient, if the patient gets better with treatment and you are not quite sure of the significance of a finding for that given patient, what is the exact treatment effect? And it's very difficult to say.

So I think that may be one area where biocreep -- and I might not even use the word biocreep, but in terms of trying to figure out which drug is best, that it can be very difficult.

CHAIRMAN RELLER: In the example that Dr. Ramirez gave, the high probability of death is one issue. The magnitude of what the infection is contributing there is, I think, a legitimate margin for discussion.

I recall Dr. Rice's -- the patient he presented, and some of the discussions that have taken place about using data from compassionate use. When quinupristin/dalfopristin was discussed at this Committee, my recollection is in the order of 3,000-

plus patients in the compassionate use category, and it was exceedingly difficult to assess what information regarding efficacy could come from those patients.

What was seized on is that smaller group of patients who had persistent bacteremia with vancomycin resistant enterococci where this compound was shown to be associated with cessation of bacteremia -- that's my recollection.

So you had large numbers where it was very difficult to tell what was going on and what the contribution of agent was, and a relatively smaller number of patients with a, if you will, surrogate endpoint that was a part of, perhaps a large part, of the decision to approve for this resistant organism.

I'd like to couple those recollections with the constraints that Dr. Shlaes mentioned in enrollment of patients with resistant organisms for exclusion criteria. Would it not be possibly far better to have a trial or inclusion design that captured those patients who are now escaping the trials, because they are getting a compound on a compassionate use, and having them captured in a more structured trial that would focus on issues that might lend themselves more readily to interpretation of

efficacy of the compound as opposed to mortality, bad outcome related to the underlying diseases that are the very place that these organisms are found?

Dr. Talbot?

DR. TALBOT: Dr. Reller, I think that gets directly to where I wanted to go, and it deals with a number of the issues that have come up, beginning with the one with why can't you get patients.

I think part of the answer there is that, when you are studying an antibiotic, as with other compounds, the first thing you want to understand is does your treatment have efficacy in the target population with the target pathogens.

The only way you can do that sometimes is by -- and most times is by eliminating a variety of factors which can confound your interpretation of response. So that's why you have exclusion criteria in clinical trials.

Now that tells you if you have efficacy, but the problem with resistant pathogens is that they tend to occur in patients who have all these confounding factors, and that's exactly what we ran into with Synercid, and other people have had the same problem.

So you have an inherent sort of

contradictory situation, as you would like to study them; but if you study them, then you have all these other things that contribute to mortality and so forth, and what have you got?

So that raises this question. We have talked about surrogate markers, and I'm not sure that we have actually been precise enough in what we mean. A surrogate has sort of a bad connotation, in a way, but as Dr. McCracken expressed yesterday, most of what an ID physician, I think, might expect with an antibiotic is, in fact, to eradicate the pathogen.

If the pathogen goes away, that in fact is the outcome you are looking for, and sometimes it's the only one you can assess, because of these confounding factors.

So I think I'd like to propose that there be some reconsideration of what's a surrogate marker in this field as opposed to what is a valid endpoint that is clinically meaningful. I think that there are probably some clinicians who would suggest that eradication of the bug is not just a surrogate marker. It's actually the clinically meaningful endpoint that you want, and that is, in particular, true when you are dealing with multi-drug resistant pathogens for which there is no comparator agent available to study

in clinical trials.

So if there could be some discussion about surrogate markers and what they are or aren't, that might advance the discussion.

CHAIRMAN RELLER: Dr. Rice's patient again now illustrated that. So maybe we get into something of semantics issue with surrogate markers with what in many cases might be objective endpoints that is the best that we could hope to achieve in the patient presented. It would be a cessation of VRE bacteremia.

Dr. Shlaes, you wanted to say something? Dr. Hardalo?

DR. HARDALO: Yes. I think actually, just as Dr. Ramirez correctly identified the dichotomy of the options that are available for treatment, Dr. Talbot has identified the dichotomy of the endpoints that we need to consider.

That is, there are certain types of infections for which these confounding factors are present and cloud the assessment of efficacy and, therefore, surrogate markers are appropriate as a primary endpoint. Then there are certain infections for which you can assess outcomes more clearly, because there are less confounding factors or there is a better assessment of efficacy.

I believe that we have seen two extremes of precedence, one a dossier as small as 63 patients supporting efficacy in refractory infections, up to a dossier as large as 3,000 patients which has been said that it is inadequate to support efficacy and that it is confusing and it's unclear.

On the one hand, we are saying observational prospective trials are fraught with difficulty but, on the other hand, we are saying historical data should never be used again.

I think, for clarity's sake, we would appreciate any guidance form the necessary stakeholders as to what is it that you want for resistant pathogens, in what setting?

CHAIRMAN RELLER: Dr. Shlaes?

DR. SHLAES: Actually, just to follow up on this a little bit, I think the suggestion that Dr. Goldberger made at the outset, which was to focus on a very small number of very well characterized patients, and I'd like to limit this necessarily to endocarditis and osteomyelitis with persistent bacteria -- But anyway, a small number of well characterized patients in combination with a package of data, including activity against susceptible pathogens in human trials, including PK/PD supportive data, including

supportive *in vitro* data and supportive animal model data.

I think, if you take that as a package and you are willing to approve based on that, you would find a warm reception from the industry. So I think that that is a reasonable way forward.

CHAIRMAN RELLER: If one, for example, took the *Acineto baumanni* resistant organism and one had patients with meningitis with that organism, pneumonia with bacteremia, infective endocarditis, and showed clearing of the organism, this would seem to me to be so much more powerful than trying to make sense out of an intubated patient with hospital acquired pneumonia looking at endotracheal suction specimens with *baumanni* without these other objective eradication endpoints where trying to make sense in a ventilated patient of *baumanni* in an ETS specimen without bacteremia, etcetera, I think is virtually impossible. Dr. Rice, any comment?

DR. RICE: I agree. I think it's just a matter of being able to identify enough of those patients to be able to come to conclusions. But ventilator associated pneumonia studies are fraught with problems, as we all know, and although actually continuing to look at suction specimens probably would

have the benefit of at least telling you whether the *Acinetobacter* will become resistant to the new antibiotic as well, since that's where you are most likely to find it.

CHAIRMAN RELLER: Dr. Archer?

DR. ARCHER: Thank you. I wanted to ask Dr. Rice for the IDSA standpoint: I initially wanted to ask if you had any specific plans whether IDSA could help move along the problem of drug discovery, and I was wondering in specific is there's any thought given to setting up a clinical trials network within the IDSA for identifying patients with these specific problems that might be more easily entered into clinical trials, identified specifically by ID docs. Maybe Don Goldmann would want to comment on that as well.

DR. GOLDMANN: I guess all I can say is the IDSA is here and more than willing to participate in a larger group that could come to those sorts of -- or could develop those sorts of protocols. But right now, to my knowledge, there isn't anything specific that is planned. We are hoping that maybe something like that would come out of this whole process.

CHAIRMAN RELLER: Dr. Rotstein?

DR. ROTSTEIN: Of course, the idea of the

BAMSG, Bacteriology and Mycology Study Group, is to develop a network of intensive care units in hospitals that can identify high risk patients that are suitable for clinical trials. But I have to caution that the very nature of the collaborative is that it tends to focus on intensive care patients who have a lot of the problems that have already been alluded to.

I've been giving some thought to other types of patients who may get, however transiently, into ICUs and, therefore, could be considered high risk, such as cardiovascular surgical patients who develop infections in what I might call a more clean environment in terms of confounders, and they might be a good population in which to study drugs, especially on the Gram positive side, in that they develop wound infections, mediastinitis, bacteremia, endocarditis, other types of infections that are more easily identified in terms of endpoints.

CHAIRMAN RELLER: Dr. Ramirez?

DR. RAMIREZ: Yes. I would like to make a comment, that it was already explained why it is difficult to find resistant organisms in clinical trials, because we don't know the patients with risk factors for resistant organism.

At the same time, it is not as simple as,

well, let's go ahead and change the trial and enroll the patients, because as enroll the patient with multi-resistant -- because when we are doing a clinical trial, usually we are trying to figure out that the patient is going to have an outcome related to the infection, and the antibiotic is going to change the outcome, and most of the time we want to believe that then the outcome was related mostly to this organism causing the infection.

When you get into these patients with multiple medical problems and multiple conditions, the outcome is less and less related to the infection. Since we tend to have an agreement that the only way to enroll these patients in a clinical trial is to really capture is to go to the bone marrow transplant unit and enroll the patient that we don't want to go there, because these patients are going to die of plenty of other problems outside of the VRE or the *pseudomonas*.

The more we are willing to accept a patient with confounding factors, the more we have to be willing to accept that the final clinical outcome is going to be irrelevant, and we definitely have to get surrogate markers for these patients; because the mortality is going to be so high that trying to figure

out -- attribute the mortality to the infection, you need to have a tremendous clinical trial number of patients, and then we are going to go back to the same problem, that we cannot do the trial.

I think it is a good idea, the concept of enrolling patients where we know where the resistant organisms are located, but we have to forget about a clinical outcome -- a valid outcome, and we need to look at surrogate markers.

CHAIRMAN RELLER: Dr. Miller, Shlaes, Goldberger and Chesney. Dr. Miller.

DR. MILLER: Going back to part of what we've been trying to brainstorm on, which is how to stimulate new drug development, I think we need to think about new partners. It's very disturbing the paucity of drugs in the pipeline, and we've heard from Dr. Shlaes that large pharma, you know, is rapidly moving away from anti-infective development.

So following that line of thought, it's really the small pharma and biotechnology companies as well as the Federal government, and specifically the NIAID, I think, that will have to take up the challenge.

This has become much clearer to my institute in the recent times because of the challenge

from bioterrorism agents. So that with the influx of new monies to address coming up with new vaccines and new drugs for those agents, I think we are going to have some opportunities to also broaden the horizon as far as other products for resistant infections as well.

Also, in line with that, I think it's really not compounds that are out already, but there is a tremendous number of compounds and chemicals that have been abandoned by large pharma historically, because they are not the blockbuster drugs, they are not the broad spectrum drugs, that maybe we can think about how to go back to those, license them to the smaller companies, have government support throughout the development process, including conducting clinical trials, and maybe utilizing some of the ideas, the excellent ideas, that FDA has brought to the table to incentivize getting those products developed.

CHAIRMAN RELLER: Dr. Shlaes.

DR. SHLAES: Okay. So, actually, I have two comments. One is I need to ask Dr. Goldberger just for a clarification on his proposal for the small number of well characterized patients. I'm assuming in that case we are using historical controls, and we are not talking about in the context of a comparative

study.

Before you jump to that, let me just respond to Marissa a little bit. Actually, I think most companies have already tried that, in the sense of doing retrospective looks at their prior collections to try and identify compounds that have been discarded.

Certainly, Schering did it. We did it. A number of companies have done it. Cubist actually licensed a compound -- a discarded compound from Lilly, and so did a company called Intermune, oritavancin.

So I think most companies have already done that, to go back through their prior collection to try and identify reasonable candidates to bring forward in today's environment of resistance. So I think what you see in the pipeline now is what companies were able to bring forward from those old collections, which is not much.

DR. GOLDBERGER: To answer your question, yes. In essence, the rationale for having highly characterized patients whose outcome, absent affective antimicrobial therapy, would probably be, in many cases, death or at least serious morbidity would be that there would not have to be in that portion of the

development program a randomized component, although the expectation would be that there would be some other clinical trial or clinical trials to expand the understanding of the drug. But that's right. That would probably not be a randomized study.

CHAIRMAN RELLER: Dr. Chesney and then Dr. Tally.

DR. GOLDBERGER: I didn't get my turn.

CHAIRMAN RELLER: Mark, please finish. Then Dr. Chesney.

DR. GOLDBERGER: I didn't want to take advantage of Dr. Shlaes' remark if he was going to go on a little longer.

First, I wanted to address something that several people have said, including Dr. Ramirez, and that was this issue, you know, about concerns about really understanding the clinical outcome, what it means as you enroll a large number of severely ill patients.

I guess one of the reasons that we've talked about this issue of including a small number of very well characterized patients is, at least from my own experience, physicians are very Bayesian, and they look at new experience based upon what they've seen already.

Looking at a large group of patients with a variety of complex illnesses would look one way without some other good data, but if you had even a couple of dozen patients with one of the organisms in question where you could clearly show therapeutic efficacy, frankly, I think one would look at this larger number of patients in a very different light. That's just sort of my own take on this approach.

I had a couple of questions. One is for Dr. Tally, and it's kind of along the model that you will sometimes see when they are asking you to buy a car, they will say "you be the sales manager; you know, you make an offer." No reasonable offer refused.

You had a slide that was development of drugs for resistant pathogens, and the issue is FDA clearly indicate the number of patients with resistant infections required in efficacy trials, an absolute number, a percentage of the dominant pathogen Ed, MRSA, MSSA, VRE, etcetera.

So my question to you: How much is enough? What's your actual take on that? You are a very reasonable guy. So I think you will give a pretty straightforward answer.

DR. TALLY: We asked that question when we

looked at piperacillin tazobactam, because clearly the mandate for a combination drug had to show -- that FDA had, combination drugs have to show an advantage over the single drug, i.e., piperacillin.

So that was a very clear endpoint. This is from memory now. I think it was about 20 cases with a resistant organism in each system we studied, which would represent about ten to 15 percent of the isolates that were evaluable.

With that, we were able to get approval for, I think, four or five pathogens in two or three different areas. That was a guideline that we had when we went into the studies. So we could go and size our studies to be able to do that and bring in a large clinical program in a reasonable time period.

In that, somebody had asked me about, you know, failing -- not meeting preset endpoints, and indeed two of the eight studies in that study, we didn't meet endpoints. We had to stop on them. Another one, we actually failed two comparative agents.

So I think you can define that. What we don't have as the definition here is how many -- In skin and soft tissue where you are going to have a percentage of MRSA and MSSA -- and I can talk off hard

data now -- Where you have 60 percent of your patients out of 200 bacteriologically evaluable patients have staph, and you have about 15 percent of them resistance, is that enough?

I can say this to you, because we've already asked you that question, and you people have said yes. So if we can get that clarity in different areas, I think that would be helpful to the industry, in answering that. That's why I put it up, because I think we are almost there on that one. So I think we can now start to put that down on paper.

DR. GOLDBERGER: I have one question for Dr. Rice. In the case that you showed which ultimately, I guess, either the final therapy or the final therapy in reserve was quinupristin/dalfopristin for his enterococci, what's your view -- and just using this sort of as a model, your feeling about the fact that, if a product like that, which in this case is the last produce that is currently available that might treat his infection, is out there and widely used for a wide variety of infections where there are many effective alternates, the likelihood that it will be useful in a reserve for patients like this probably goes down substantially. What's your perspective about that?

DR. RICE: I think that's a real risk. I mean, I think that we are seeing right now, John Quinn from Chicago believes that as many as ten percent of his people he treats with linezolid become colonized with a linezolid resistant *Enterococcus faecium*, as one description of a linezolid resistant *Staph. aureus*.

In the Virges study, 21 percent of all the patients who had *Enterococcus faecium* had a reduced susceptibility to quinupristin/dalfopristin, despite the fact that there wasn't even exposure.

So I think that that's a problem, but I think that's a problem we have to deal with. I mean, I guess I'm not a big fan of worrying about how something is going to be marketed when it's truly necessary. I mean, I would rather have it out there and then try to deal with it as best we can and try to set up guidelines for how antibiotics should be used than to depress the development in the first place simply because we are worried about the potential for resistance.

DR. GOLDBERGER: Do you have a program, for instance, in your institution about, you know, that in any way provides guidelines or limits availability of products like that?

DR. RICE: Well, certainly, either quinupristin/dalfopristin or linezolid needs to be approved by the infectious disease consultation service before it is used. Part of that reason is because of expense, but those are -- that's the level of restriction that we have, and actually I have a very active program for educating house staff and attending physicians on issues of resistance, and that has helped us to reduce our use of antimicrobials.

CHAIRMAN RELLER: Dr. Chesney had her hand up earlier, and then Dr. Goldmann and -- Bell and Goldmann.

DR. CHESNEY: I just wanted to remind all of us that we've switched to the highly resistant Gram negatives, which is very, very important. We have all been faced with those kinds of situations. But, you know, we need to remember that the millions and millions of drugs that are being used are being used in the community, and it's much easier for me to get a handle on how to do some of these studies and get some of the numbers in a captive, hospitalized population. But I think we also need to be reminded that, not the bigger problem, but an equal problem is that of controlling it in the community and getting the patients in the community.

CHAIRMAN RELLER: We'll hear from Dr. Bell, then Dr. Goldmann, Dr. Ramirez, and then we will have lunch.

DR. TALLY: You had me in that list, and I didn't get a chance. Early on, just after Dr. Chesney. I'm going to interrupt.

CHAIRMAN RELLER: Oh. So thanks for reminding me. You've been --

DR. TALLY: Because I was answering Mark's questions.

CHAIRMAN RELLER: We have a new tally, and Tally is at the top. Please.

DR. TALLY: I'll direct it to Dr. Wittes. In studying these sick patients in different syndromes and infectious disease, we don't have the advantage of massive numbers to be able to do a simple study to get the numbers. So we have to -- That's why we are thinking of different ways of studying these very sick patients.

About the cost of doing these studies, the high cost is driven by a number of different factors, not the least of which is these diseases have high mortalities, and the ethics committees are demanding more and more safety data so we protect the patient.

We have to get more and more data so we

can, in collaboration with regulatory agencies, come to a reason why the drug did or did not work. So it takes a lot of pharmacological data with it also.

So because of the importance in the health need of getting drugs to treat fatal resistant infections, that's what is driving the cost. If I was doing an outpatient study for bronchitis, the cost is way down, but this is a different patient population.

About the use of controls, historical controls, I shudder with historical controls, because of three factors: The pathogens have changed; the patients have changed with new diseases; and medicine treating them has changed.

So you are fraught with really making bad mistakes using historical controls. I don't think we should go forward, if you have a chance to do a controlled study, to do it somewhere. That's one of the things I struggle with, because you are more likely using historical controls to come up with the wrong answer because of the changes in pathogen, patient and practice.

CHAIRMAN RELLER: Thank you. Dr. Bell.

DR. BELL: I wanted to pick up on this issue of holding antibiotics in reserve. It's come up a couple of times. I think there are two kinds of

antibiotics that could be held in reserve as being "the last resort." One of them is old antibiotics that have -- like vancomycin that have been out for a long time.

They are off patent and are gradually losing their effectiveness, and in that situation where, you know, holding them in reserve really, I would doubt, would be a disincentive to new drug development. It really seems like it makes a lot of good sense.

It's quite a different matter to urge companies to produce a new drug and say, okay, now we are going to hold that one in reserve. I don't necessarily personally view that as a good idea, if it really is a better drug for any number of reasons, and if it really -- that such a policy is a disincentive to new drug development. That's much more difficult issue to navigate through.

When this came up a couple of weeks ago, actually, at Institute of Medicine forum meeting, I posed the question, and biotech people weren't well represented there, but some of the larger pharmaceuticals. I said, well, suppose -- I mean, in essence, what I said was suppose there was no policy of holding in reserve new drugs, and we just said,

okay, you know, use it. Would that be enough financial incentive for the pharmaceutical companies to reliably keep the pipeline flowing again?

The answer I got -- and again, biotech wasn't there. The answer I think I got was no. The answer I think I got was there just aren't enough new ideas or new classes. It's not that simple. It's not a matter anymore -- What I heard a couple of years ago was, if you just relax on the usage controls, that the pipeline will open again.

So I just wanted to mention that. I mean, the idea is certainly on the table, if anybody wants to pick that up. Dr. Tally had mentioned that, you know, this still is a major disincentive to new drug development.

CHAIRMAN RELLER: Dr. Goldmann. Dr. Tally, you want to respond to that?

DR. TALLY: In response to the question, I think -- and having been in big pharma and looking at the reasons for bringing things forward, it's a multifactorial decision on whether or not a company is going to stay in antibacterials. I think David identified several of them.

It's getting harder and harder for an antibiotic that has a final sales of $300 million to

get into the pipeline of a big pharmaceutical company. With all the merging going on, the bar keeps getting higher and higher, because these are for treatment of acute infections, a short period of time, and the economics that David brought out -- This is not statins that you take for the rest of your life.

So that's a problem. Second, pipelines have not been producing molecules to bring forward. They have been producing "me, too" molecules which people are saying we -- You know, it's very hard to bring a "me, too" molecule forward, and it is very hard; because all paradigms have not worked, and you got to have new paradigms work.

Speaking now for biotech, if you take away the constant specter -- and I get pounded on this all the time. If you take away the specter that immediately the new drug is going to be restricted but would take its place, it would take some of the pressure off raising money for biotech to support innovative research where a lot of it is going on.

It would be a partial help to the biotech industry, because as soon -- The question always comes up, is asked, well, you've got a drug that will treat resistant infection. It's going to be restricted, so it's not going to have a market.

So if you take that away and you go back to the drug has to meet criteria to find its place in treatment based on its characteristics, then for biotech it would be easier to raise it, and a $1-$300 million drug is an important drug for biotech companies.

So that's in the future what I think you will see, if the current trend continues, is you will see specialty pharmaceutical companies growing up in areas where the big pharmaceutical companies, for complex financial reasons, have moved out of a particular area.

CHAIRMAN RELLER: Dr. Goldmann.

DR. GOLDMANN: Well, I'm not exactly sure where I'm going with this, but sometimes I think we can learn something from a root cause analysis of case studies. We recently had a young woman with Burkholderia cepacia bacteremic pneumonia with underlying cystic fibrosis.

After thoroughly studying this strain and sending it to Toronto and to Columbia where every conceivable synergy test was done, it was determined that no drug or no combination of drugs were going to be of any use. However, there was a drug that was of conceivable use that is not generally tested in

microlabs, and that's BPI made by Zoma, which has not only activity against that pathogen but permeabalizes it so that other drugs that normally would be ineffective would be effective.

Our efforts to get that drug for any kind of use, compassionate or otherwise, were to no avail. I think it would be useful studying what the barriers were to the availability of that drug for such an indication where it clearly has some potential.

Looking at the history of the compound, I think I'm correct in stating that historical controls were used to power an outcome study for meningococcemia, historical data showing very clear support of evidence that this would be highly efficacious. And of course, meningococcemia, the outcomes are very well delineated. So this seemed reasonable. The pathogen hasn't changed all that much.

Yet when the outcome study was done, the primary outcome was not found to be statistically significant, and so the company, therefore, I think, is understandably cautious about the deployment of that drug.

So it might be worth studying what would have made a different outcome for my 23-year-old

patient who died of Burkholderia bacteremia for which there was a potentially useful agent.

In thinking of cystic fibrosis and all this discussion about surrogate endpoints, I think it would be very interesting to look at the clinical trials that have been done in cystic fibrosis. Certainly, there's no more difficult a population to demonstrate an impact on a primary outcome than that group of patients, given the fact that eradication of the organism is almost never the issue, in the lung at any rate.

I know of no agent that reliably eradicates *Pseudomonas* from the lung of a cystic fibrosis patient, and yet very good clinical trials have been mounted that have actually changed practice, including the use of TOBI, NEBS which demonstrated an impact on quality of life, on hospitalization, on density of bacteria in the sputum, on inflammatory markers, on FEV_1, other surrogate endpoints.

So this might be a good population, not that it applies to patients in an ICU necessarily or a patient with endocarditis, but it's a community that's really thought through the issue of surrogate markers for its clinical trials.

I should also point out that I have been

very instrumental in keeping drugs in reserve for cystic fibrosis patients for these many years, including the quinolones as they came along and others, and I'm not at all convinced that I've done a single cystic fibrosis patient any favor by doing that.

I don't think that we are any better off in terms of the treatment of that disease or the development of resistance than we would have been if we had had an aggressive approach to using these agents as they became available, using appropriate practice guidelines and criteria.

So just some observations about a specific disease that might teach us something that might be applicable to other infections.

CHAIRMAN RELLER: Dr. Shlaes.

DR. SHLAES: Yes. I just want to put one thing in perspective or try and put something in perspective. I mean, I'm a big proponent of the idea that you use it, you lose it is the rule of antibiotics. But the fact is that all politics are local, and there are clear exceptions to this, and there are clear instances where by, in fact, spreading your risks across multiple agents, you don't get resistance.

A good example of that are the studies by John Burke where they have in Salt Lake City a computer based ordering system with immediate feedback to physicians who are ordering antibiotics as to appropriateness of therapy for a given infection and hospital antibiogram. But they have a totally free formulary, and nothing is restricted.

So whatever is on formulary, which is most antibiotics, physicians can use. They show in very long term studies now that they, in fact, have decreased resistance rates and, compared to periods of time where they had a restricted formulary versus this open formulary with physician feedback, they have been able to actually reduce costs.

So I don't think that restriction is always the best way to go. In fact, my experience at the Cleveland VA was that it doesn't work very well, actually even in a single hospital setting.

CHAIRMAN RELLER: I would like to thank everyone for the spirited discussion which will continue after lunch, to Dr. Ramirez for holding his question until after lunch. We will reconvene at ten minutes of one. Thank you.

(Whereupon, the foregoing matter went off the record at 12:11 p.m.)

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

(12:56 p.m.)

CHAIRMAN RELLER: Dr. Schentag will begin the open public hearing.

DR. SCHENTAG: Speaking of rusting out, yes, I am from the Rust Belt. So, hopefully, that won't be perceived as my talk.

Thanks for the opportunity, Dr. Reller, members of the Committee. My privilege today to come and speak about something which is probably titled a bit too long, but you have to be inclusive, after all, and we are talking about development strategies here, and we are trying to both understand and, I think, potentially I'm going to ask that we consider labeling endpoints such as killing rates, resistance failure, dosing types of models, and actually I've got some evidence here that we may be able to think about labeling synergy as well from this kind of study. So I am going to show you both some data and talk about some concepts.

Yesterday, of course, we considered trial design conditions which, you know, might roughly be considered conditions to establish one antibiotic for all, and we are looking at large simple trial type designs.

Today I am going to deal with PK/PD trial design issues, if our goal becomes one antibiotic for each, which, of course, is a much more focused approach, targeted more toward superiority.

Then I think I am going to point out -- and, hopefully, my data as well -- these two approaches are not incompatible, although we certainly take the point that's been made that sometimes you want to use one or the other. But, certainly, they work together well, I think, to answer the questions of antibiotic efficacy for resistant microbes.

Now the first exercise is to sort of drone through something which we think is contributory to the resistance issue, and that is that there is a dose translated AUIC or exposure relationship and time relationship to the development of resistance as it is clinically perceived.

What I mean by that is, if you just take a large number of patients -- there's about 125 patients in this series of clinical trial type of patients, by the way. These data were aggregated from a number of clinical trials -- and plot the probability that the organism will remain susceptible versus time, they separate out into a group that apparently did not develop much resistance, and when you look at those,

the only thing distinguishing is that they have a higher AUIC value of over 100, versus that do start to develop stepwise increases in MIC and then reach the resistance threshold, the points that are shown here on this survival type plot, and those that started out low, less than 100, developed this progressively as you went along.

So time relationships and, most importantly, the message that it doesn't matter what drug you are dealing with here, because there was a fairly large number of different drugs represented here. Time and dose too low together lead to selected resistance, and this is probably an expose, if you will, on selected resistance.

Now it's actually fairly easy to do PK/PD trials of antibiotics. It's not that hard to couple these onto clinical trials, and that's what we have been doing most of ours as over the years. Antibiotics are good models for this, because we have a relatively easy to define and study target.

You could almost look at this as a drug/receptor relationship, and as you know, all pharmacology thrives on the idea of having an easy to quantitate and measure receptor, and the bacteria should be treated that way, because the drug, after

all, affects it directly.

When you do that, you find that small numbers of patients can give you very robust data that you can easily analyze for differences between two different doses even or two different drugs, if you've got this kind of an endpoint.

They also have further power statistically, if you work things through as time considerations, because rates that things happen add even more statistical power to these types of one-time endpoints that sometimes we use when we just look at cure.

Really, the nice thing about PK and PD is the more range you have in your data overall, the easier it is to establish break point and correlations. So the fact that you get a thousandfold range in the AUIC just when you give a fixed dose trial actually helps you pick at what point do you start to see success as the values go higher.

So this is a very useful pharmacologic type of technique, I think, that makes a lot of sense if you develop antibiotics based on a directly measured endpoint. Direct drug effect models and other tools, of course, are the important consideration.

Now resistance problems related to study design: Well, from a study design perspective, PK/PD can probably help us out of our noninferiority complex. I think that's what I got out of yesterday, is a noninferiority complex. People know I probably came in with that, but anyway we have to go for superiority, though.

You can't study resistance in the context of a noninferiority trial, and I think that most people said that today, at least in one form or another. We really have to go for superiority only, because if we define resistance as not responding to the drug, we can't, unless we define superiority as our endpoint, find a drug that will improve out outcome. I mean, we just have no choice here. Resistance forces superiority on us.

The first step in this with PK/PD designs are really conditions where the clinical response and the micro response are closely aligned. If I've learned anything over the years from the folks that see a lot of patients, that are on these committees, they say bring us something where there is a link between your "surrogate" and, you know, what we know is a clinical response in patients.

So, yes, I agree, that's what we need.

The reason for that is it's easier to believe that antibiotic killed the bacteria and cured the disease, if you work in a disease where there's a link. Resistance should provide those opportunities for us, because resistance should equate to failure.

So what I'm going to do for a few minutes now is to talk about a situation where clearly resistance does link closely to failure, and you can show differences between the various approaches, using endpoints like bacterial killing. And eventually, of course, if our populations get large enough, I think we will do it with clinical cure alone as well.

MRSA provides this opportunity, because MRSA is -- Most of you may know this. MRSA is starting to fail vancomycin even when it's sensitive. You know, it's not just the VISA strain anymore, but anecdotal reports from all over the country of patients that have sensitive organisms are not responding to vanco. Their bacteremias aren't clearing. Their pneumonias aren't clearing.

What we decided we would do is we would start to aggregate those cases before it came to the point where it's unethical to do so -- in other words, where it was unethical to use vancomycin, and that's the VRE situation. It's unethical to use vancomycin.

So we were unable to test it against a comparator.

I think with MRSA maybe we can get a handle on that earlier, if we can just find those kinds of patients.

Now what do I mean by that? I want to define that in a PK/PD term for a second. Well, vanco is a fixed dose drug in the sense that we always dose adjust its blood levels to the same thing, peaks at 30s and troughs of around 10, and that always gives you the AUIC for this drug of around 250.

So any variability in this drug's response is going to be due to MIC variability -- in other words, susceptibility. The organism is going to create your range and your PK/PD data, and that's a good model, because a lot of drugs don't get this feature. So only MIC variability is going to show us differences.

The usual MIC for vancomycin -- the MIC_{90}, actually -- has evolved now to the point where it's around 2 mcg/ml. It used to be 1, sometimes even .5 in the older days, but it's bumped up to around 2. If you do the AUIC calculations, that comes out right around 125 at the break point.

Now most of the MRSAs in the United States are probably somewhere around the MIC_{50} of .5, and that

gives you values over 500, and our VISA strain, which, of course, we are all afraid of but it hasn't occurred very often, is up around 8, and that's way low. That's way below 100. So nobody expects vancomycin to work against VISA. In fact, that's how we discovered it. It's failed every time. So there is no doubt that VISA is really VERSA.

The question is are there failures underneath this high bar, and that's what we are finding people from all over the country telling us that they are seeing. So that's what we went out looking for.

Now why is this happening? Well, because the MIC as a .5 to 1 have shifted, we are getting shifts so that a lot of MICs now are 2, which is basically about two to fourfold loss of activity, which doesn't sound like much, but if you are dealing with dosing which was set, you know, ten, 15 years ago for an MIC of .5 and we didn't raise it as the MIC went up, we've lost about four to fourfold activity.

So it should not be expected that it would always work, because we haven't compensated for this with dosing. So now we are seeing these organisms, you can almost predict who is going to have the problem.

You get the additional problem, of course, of having MBCs that are up as well, sometimes, and we may need to do what George McCracken said yesterday, which is we may need to do AUBCs as well to explain this data. But for now MICs seem to work. So I'm going to go with that.

Now a protocol is to look at patients in this situation, because it gives us an opportunity to study resistance which is first defined clinically as clinical failure, not necessarily as a microbial target to begin with, but clinical failure, I think most people would agree, is an interesting way of defining resistance. The clinicians will nod their head anyway.

When you look at those kinds of patients, our first work showed that, sure enough, there is a relationship between how long they stay culture positive and the AUIC, and they are culture positive much longer and much more frequently, 80 percent positive and start out less than 400 which, by definition is kind of the MICs that are in the range of 2 and some ones.

If their AUIC is higher than 400, which is the .5s mostly because of the way we dose vanco, in about three weeks or so they are all culture negative,

with most of them -- half of them or so by ten days, but the other half persist. So this is vancomycin, the reality.

Now you can -- if you want to think about endpoints, if you do free fraction, an AUIC of 400 that's total is free of 140. So we'll have to talk about that, if you are interested in PK/PD break points later, which I don't want to dwell with too much, because the study will define those.

Study design issues: Really dealing with an organism here that's not eradicated quickly. Any improvements in activity could probably first be picked up as faster eradication. So in other words, we could boost the activity of this drug either as a higher dose or adding something to it. You would pick it up first as faster organism killing.

If you don't kill it, of course, it disseminates, and that's what kills you with MRSA, is usually widely disseminated organism in blood and elsewhere. Vanco probably serves the role of keeping the patient from death in most cases, but dissemination continues.

So what we set out to find, again, was MRSA patients who are on vanco -- remember this -- on it for at least five days with continued culture

positivity, the ultimate enriched population. We waited until they had failed vancomycin.

Why did we do that? Because there's no guidelines at this point yet for rejecting vancomycin, because people will tolerate ten days of positive cultures in some cases in the literature. So it's a perfect opportunity to start doing this, but we didn't feel like we should randomize yet.

So we started out with cohort studies. We looked first retrospectively for all the patients we could get that had vanco on its regular regimen, and then there's a large number of people that are already starting to double vancomycin's dosage. So we collected those. We would get higher AUICs, presumably, and we enrolled patients that had vanco continued, but a second antibiotic. We are searching here for synergy, of course.

Now in the vanco failure patient with an MIC of around 2, you really only have those two choices. You can raise your dose and target peaks of around 50 and troughs of around 20, which is what we collected, or we can go for conventional doses with troughs of 10 in combination with something to target synergy, and this is the various array of players that people add at that point.

So we have actually the possibility here of testing combination therapy, the same way we test twice the dose of a single agent. Now twice the dose of the agent is additivity by definition. So if we can get activity beyond what you get from additivity, you should be able to begin to define the edges of synergy.

Of this choice, there isn't really much. Additivity would be expected in most of these cases. The only *in vitro* data that we had for potentially synergistic drug was Synercid. So that's the one we focused on for a while, and it's based mainly on *in vitro* data where it shows that the combination kills faster than either agent alone in a high inoculum situation with some MRSA.

There are animal models as well, endocarditis type models that show that vanco in synergy is active -- synergistic in these definitions that aren't completely definitions from my perspective, but they do show some evidence at least of more activity than you would expect from doubling the vancomycin dose in animals.

I won't belabor that, because it's just a precedent for why we are doing this. The vanco failure study then focused on failures after five days

and collected vanco failures treated with normal troughs, with double the trough, and prospectively we looked at double the trough versus Synercid added to the regular one.

So this stuff is mainly for historical control, and again because we didn't feel comfortable randomizing it at this point, and these two here is mostly investigator taste which regimen they ended up with, but as you will see, they ended up pretty comparable in terms of underlying diseases.

If you do this, of course, you should be able to do serial cultures, and that was our requirement for the study.

Well, here's the outcome. The vanco traditional dose aligned almost exactly with all the single head to head vanco-linezolid studies, vanco-Synercid studies, all the equivalent stuff in around 55 percent, and clinical and micro agreed almost exactly.

Interestingly, five days on vanco 5.5 before they were enrolled. The vanco high dose, a better cure rate, and again close alignment between clinical and micro. So doubling the dose of vanco would show that there is some benefit to additivity in this model, and again this one aligned.

The quinupristin/dalfopristin group reached 83 percent and, interestingly, had been treated for 15 days before they went on this, which reflects most clinicians' desperate effort to find something besides adding one of these two expensive drugs to vanco, I think, and that could be rather interesting.

Now when you look at the mortality -- and I also did attributable mortality, and attributable mortality is patients who remained MRSA positive and symptomatic and died on therapy. So we were pretty rigorous about attributable mortality in this.

The two patients who died on this regimen did not die of continued infection. On the vanco high dose and the vanco traditional dose, they did, you know, show about 16 to 20 percent or so, and 30 percent was the total mortality in this group.

This group did worse overall, but not statistically significant. These numbers are small. The p on a Fischer Exact Test was around .3 or so. So you don't have enough here for statistical significance when you just use your clinical endpoint, even when it aligns to micro, if you are dealing with groups probably less than 20 patients or so.

So what do you do? Well, I could show you

something or you could get statistical significance out of this study easily. This is all three groups plotted as how long it took to clear the organism.

The Synercid plus vanco group had almost all cultures cleared by Day Five after switching. These other two groups, you know, the double dose was better than the single dose, if you will. S

o we did have some evidence of additivity there, but synergy would be defined in this case as action beyond what you would expect from additivity alone. I think that probably this curve, if it holds up, and we are continuing to accrue patients in this study, would probably show very nicely that this is probably the first clinical definition of synergy, and it will most likely hold up long enough, if you accrue enough patients on clinical trials, to do it as a cure as well.

So you have to pick the right organism. You have to pick an organism where nothing works very well, and I think we did that, and then do a superiority trial. In a superiority trial, of course, the greater the real differences, the smaller numbers of patients you need, regardless of your delta.

You can put any delta on this trial that you want, and you will get the same answer. I would

use pretty tight deltas on these types of trials for reasons we have already mentioned.

Some of these endpoints have got a lot of noise in them. Particularly the clinical outcome delta has a lot of noise in it in this situation. So I have no problem with putting tight deltas on clinical cure.

With micro cure, you know, it's pretty clear, I think. Rate of microbial killing or rate of cure alone -- Sometimes all you need is the PD component. You don't even need the PK/PD. You notice I didn't show that to you.

If you are closer to comparator, however, or if you are trying to show two different doses of the same drug different when they are closer together in terms of their response, you might need to convert it to PD and PD.

An example of that that we've done long ago already is this quinolone data where we've shown differences sorted by AUIC with each group P less than 0.01 different from the other, showing faster killing with higher concentrations of the same drug, Ciprofloxacin in this case.

Now with that aside, the choice of this concept of surrogates in superiority trials is

intriguing, and clinical cure is really a soft endpoint. That's why you need tight deltas, I think, if you want meaningful information.

If you choose a disease where clinical cure is closely linked to micro cure, you can get away from that problem somewhat. I do disagree with most people that said nosocomial pneumonia is not one of these diseases, and I think it's mostly because we've been studying it wrong when we study nosocomial pneumonia, and I'd like to show you why I think that.

First of all, I would like to argue that the previous data on the quinolone came from nosocomial pneumonia. Micro cure is better, I think, than clinical cure in these sorts of things, and PK/PD analysis is the key, but regulatory trials of nosocomial pneumonia are structured for equivalence.

Because they are structured for equivalence, they miss all the high information content data that you could get out of them if you wanted to show differences in nosocomial pneumonia, either using a clinical endpoint or a micro endpoint.

Quite simply, they define their endpoint at the end of treatment or ten days after or whatever, some point when all of the change that occurs that you could take advantage of has already come to fruition.

I wish Tom Fleming were here, because he would love this slide. He's always focused on are we doing enough to get this correctly. But the statistical point here is that we need to do better at these things.

As A and B are two different drugs or two different doses of the same drug, with a micro endpoint or a time to cure endpoint of some sort, they differ very much if you look at them at Day Two. They look different at Day Five, but they don't look any different if you wait for B, which works slower, to fully come to its fruition.

All nosocomial pneumonia studies are powered based on a test of cure, ten days or so after the last dose of the antibiotic. So is it surprising we get nothing out of them? Not really, but you got to look here if you do want something out of them.

So it's a superiority component to a noninferiority trial that has to be looked at. Okay? You can build it into a noninferiority trial, but you got to build in the information rich place where you get a superiority component.

If you are faced with this need to demonstrate superiority, yes, as someone said yesterday very well, you could either loosen your

delta and enroll more patients in a cure study versus best available comparator, which is, I think, one of the things people are talking about, or I would argue, I think, that you should tighten the delta requirement and work on endpoints that offer you reasonable opportunity to show you superiority and power it for that.

That in a nutshell is why I think micro cure is so useful in these critical care, multi-resistant type scenarios, and the patients have very little to do with this. I mean, our patients were all sick, and I will tell you the stories, the horror stories of that group if you need it, but they were all sick.

Now here's the thing that I wanted Tom to see, because I know he's a much better statistician than I'll ever be. I took a crack at a dichotomous versus a continuous endpoint trial, just looking at how many patients you would need, and I borrowed this from David Shlaes' letter to the editor in CID.

I tried to take a continuous endpoint study like a time to eradication, and power it equally rigidly, so plus or minus one day here, standard deviation 20 to 40 percent, 80 percent micro rad here at the end, with a target time to eradication of Day

Three.

Any way you look at it, the numbers of patients you need are staggeringly small to show either equivalence of superiority. So we can do this statistically, if you let us work with these endpoints.

Thus, from the front here, from the front lines of digging up resistant patients in multi-center type of arrangements, I think that the data are there. they are obscured in these big NDAs.

There's probably 100 information rich patients in every NDA that will teach you everything that you need that's truly important about the drug. I think you got to be careful to avoid your statistically driven quest for equivalence to silence those little voices.

Most of you know, I only listen to the little voices anyway. So you see why I say these things.

Now recommendations: Primary endpoint of antibiotic action really does need to be looked at as a micro endpoint, whenever superiority trials must be conducted. I think that's the default position. I really do believe it is more important than cure for a lot of reasons, not the least the clinician's obvious

perception that if the bug is dead, the patient gets better.

You still need to deal with safety issues, but equivalence designs can fix that problem. We've already talked about that.

Human superiority trials with micro and PK/PD endpoints must translate into labeling, however. Unless they translate into labeling, this isn't going to happen. I've been told numerous times that, you know, there's still the perception out there that the FDA won't take this data; and if it's true, then this isn't going to happen, and that will become the single biggest impediment to proceeding.

Guidance documents also have to recognize that study designs of both types have value to industry via labeling, and those are the two things that I would argue that we look at.

Everybody has to do a little disclosure. So I did mine here. I would argue that, of course, one other little disclosure I should say is, yes, I do PK/PD studies and, if you all like that, I'm probably going to end up dong more. So that does make me biased toward PK/PD studies, and I apologize in public for that. But I'm going to keep coming at you with this data, whether or not you do this.

So, you know, this is something that we can do out in the clinic. That's why we are going to keep coming at you with this data.

Thank you very much.

CHAIRMAN RELLER: Thank you, Dr. Schentag. We will next hear from Dr. Drusano from the Albany Medical College, and I think it would be best if we took queries for both Dr. Drusano and Dr. Schentag at the same time after George's presentation.

DR. DRUSANO: Thank you, Mr. Chairman. I would like to also thank Dr. Albrecht for recommending that I come down and address you during the public portion of this.

I'm going to talk a little bit about suppression of resistance and to take a pharmacodynamic approach. Dr. Chen?

Now this is a cultural icon test. How many of you actually know who that is? That's the Duke, and he actually said that: "Life is tough. It's tougher if you're stupid." That was when he was in the "Sands of Iwo Jima," Sergeant Striker.

The only reason I show that is because we really are in a real difficult position. We really do need to get new drugs, and to get the ones that are coming into the armamentarium to stay active. It's

really an important issue.

If anybody doubts that, put yourself in the position of an infectious disease consultant who has to go out and tell the family that their love one has died because they had an untreatable organism. That's been happening at our institution on the average of one to three times a month for the last couple of months because of *Acinetobacter* and *Pseudomonas aeruginosa*. Next, please.

So resistance to antimicrobial agents oftentimes, but not always, occurs as a function of single point mutations. Other mechanisms are many, but includes spread of plasmids with multiple resistance determinants.

Horizontal transmission amongst patients also confuses the issue. Now examples of a point mutation providing drug resistance are stable derepression of AMP C type beta lactamases for third generation cephalosporins and target mutations or pump upregulations for fluoroquinolones.

Now as these occur at a frequency of around one per 10^{8} or less frequently, infection site populations exceed the inverse of this number, but often by multiple logs. We can get ten or 11 logs of organisms, not as a concentration but as total

populations, particularly when we talk about nosocomial pneumonia.

Consequently, such total populations do not behave as a single, sensitive population, but rather as a mixture of two populations of differing drug susceptibility. This raises, I think, a very important question.

That is: Can a drug exposure be identified that will prevent the resistant subpopulation from being amplified and take over the total population?

Now before I show you anything, there's a lot of folks that had a lot to do with this. Nelson Jumbe just got his PhD from our lab; Arnold Louie, Mike Miller -- just the most wonderful collaborators a guy could have; Wago Liu is one of our major domos who runs the lab, and Mark Dazelle's name got left off here for which I apologize. Vincent Tam and Tazia Fazili are our fellows, and Bob Leary is our collaborator at USD Supercomputer Center, and Chuck Lowry did a lot of the sequencing.

The first thing I wanted to show you is a mouse thigh infection model, and I wish Bill Craig were here. We took this. We just copied the Craig mouse thigh infection model with one difference.

We left the granulocytes in place for a number of different reasons, because one is for clinical relevance. Two is the simple issue of when you take them away and you want to study something like *Pseudomonas aeruginosa*, you can't get at the resistant mutants because you can never put enough in to get them back, because you killed the animals off so rapidly.

So we have granulocytes in this model, and what we have here is pneumococcus, and you see six and a half logs here, 7.9 logs on this side. Now what one sees is that, if you calculate the AUC to MIC ratio required for stasis, one, two and three log drops from stasis. There is no difference between 6.5 logs and 7.9 logs. So 16.5, 16.1, 37.6, 34.9 -- these are not different. Next, please.

It changes, however, when we look at *Pseudomonas aeruginosa*. Here now as we go from just 7.3 to 7.9 logs, 6/10 of a lot difference, the targets go from 14 AUC/MIC ratio per stasis up to 45. When we get up to 3 log drop, 31 over here -- it's 200 over here. Next, please.

Clearly, *Pseudomonas* and *pneumococcus* differ in their response. *Pneumococcus* has no inoculum effect to treatment, while *Pseudomonas* has a

major inoculum effect. The explanation probably rests in the mutational frequency to resistance.

Pseudomonas has a high frequency, while *Pneumococcus* has a frequency that was not measurable at the bacterial densities used in these experiments with this fluoroquinolone, and we did that experiment six times. We never were able to isolate a primary resistant mutant from the mouse thigh when we started with a wild type isolate.

So what happens with *Pseudomonas* when we look at that? We oftentimes see something that looks like this, if you look at intermediate time, so that you get a major fall-off in the density of organisms at the primary infection site, and then you see regrowth.

Now not always, but sometimes what the explanation behind this is, is you have a sensitive population upon which you have a major effect by the drug exposure that you have given the animal, but then you see the resistant subpopulation which starts out very small, around 1 to 2 logs of organisms, but you have unremitting growth of that resistant population.

So that when you look at the differential effects of the single drug dose on the two different populations, you can put them together, and that is

what one sees when one only looks at the total population.

So we decided to model this. On the lefthand side we just have a simple two-compartment open model to look at how the drug moves about the little mousy body.

On the righthand side one sees the differential equations that look at the effect of the drug exposure on the two populations, the sensitive and the resistant populations.

Now it looks awful, but it's actually really quite straightforward. You have -- On the front part of the equation is the growth side. So you have X_s is the sensitive population. There is a first order growth term that acts on that. L is the logistic growth function. It just makes the organisms bend over into stationary phase so that they don't go off to infinity. That's just the simple growth part.

Then you kill them, and you kill them as a function of concentration of drug. The form of the function is down here. It's a simple sigmoid E_{max} effect function. So what you have here is the maximal kill rate. That maximal kill rate is driven by concentration, and you can see there's a concentration at which the kill rate is half maximal.

So this is very much like a Michaelas Mettin form of a function, and all this is saying is that the more drug you get, the faster you kill the organism up to a specific maximal kill rate.

So you have growth, and you have kill. You have that for the sensitive population, and you have it for the resistant population. Very straightforward.

Here's what we measure, the total population, which is the sum of the sensitive plus the resistant, and then the resistant population. These were all modeled simultaneously in a very large population model that was sent out to UCSD Supercomputer Center where Dr. Leary turned the Blue Horizon machine loose on it. These are the point estimates of the parameters. I just show them out of interest.

Well, how did we do, and how did we fit the model to the data? So this is the total population for *Pseudomonas aeruginosa* with the fluoroquinolone. Here's predicted observed, and this is after the MAP Bayesian step.

So what we see is we did a pretty good job with fitting the model to the data, as the R^2 for the predicted observed plot is .93. Next, please.

For the resistant part of the population, we also did quite reasonably well. Again, this is after the MAP Bayesian step, and the R^2 now is up to .94. So we were able to really quite reasonably describe how different doses of drug were able to have an impact upon both the sensitive and the resistant and, therefore, the total bacterial populations in a mixed population.

But what can we do with this? We were able to use the point estimates of the parameters to calculate an exposure, an AUC/MIC ratio, that would shut off the growth of the resistant mutants.

This is the number of mutants present at the start of therapy, and the rest of them are the number of mutants present 24 hours later in the mouse thigh. What one sees here is that you require an AUC/MIC ratio of 157 of total drug to hold the number of mutants exactly stable from baseline.

So that's nice, but we wanted to see if indeed that was truly correct. Next, please. So we decided to do a prospective validation. We did a validation with two doses of drug, one that was calculated to cause emergence of resistance, outgrowth, amplification of the resistant subpopulation, and one dose that would hold the number

of resistant mutants stable at the primary infection site.

We wanted to do it with drug doses we had never studied before and for a period of time that was further than we had studied before. So what we see here now is the drug dose that would give you a 52 to 1 AUC/MIC ratio.

What one can see is that the dots or the boxes are the actual observed values. These are not -- The continuous line is not the fitted value, but rather the predicted values that we got from the original analysis that we did.

So the original analysis actually predicts quite nicely what happens to both the total and the resistant population over time as we sample, and when we said that that particular dose would cause the amplification of the resistant subpopulation, that is indeed what happened.

When we said it was going to stay steady, it stayed steady for that time frame. So -- next please -- we were able to determine how the overall sensitive plus resistant population responds to pressure from this fluoroquinolone.

More importantly, we were able to model the resistant subpopulation, choose a dose based on

simulation to suppress the resistant mutants. The prospective validation demonstrated that doses chosen to encourage and suppress the mutants did indeed work, and that was the first, as far as I'm aware, prospective validation of such an analysis. Next, please.

Now for the *Pneumococcus*. Now this -- I'm only going to show a couple of slides. This is a very complex topic, and I just don't have time to address it. But it differs by drug. It differs by a lot of different things, and in particular, it differs by whether or not you are dealing with a wild type strain, as I'll show you momentarily.

Now just to throw your mind back to the *Pneumococcal* analysis I showed you previously, we were unable to recover resistant mutants with levofloxacin as the selecting pressure in the mouse thigh infection model, no matter what we did.

No matter how low a dose of drug that we gave, we could not get resistant mutants. However, we then examined ciprofloxacin as the selecting agent, and now selecting mutants was straightforward.

I'll tell you that this may be -- You know, sometimes it is the right thing to take a new drug active against resistant organisms and put it up

onto the shelf, but sometimes -- and I think this is an example -- it's really the absolute wrong thing to do, and I'll show you why. Next, please.

So we take the little mouse and we put the *Pneumococci* in the posterior mouse thigh. We wait two hours. This is the classic Craig model, and it actually goes back to Harry Eagle, for two hours for it to take hold, and then at hour Zero we begin therapy. At 24 hours the animals are sacrificed, and the number of total organisms and resistant mutants are determined from the mouse thigh. Next, please.

So what we did is -- Actually, if you could back up one. I apologize. What we found is that, if we had a plate that had two times the MIC of Cipro in it, we got about 500 mutants per plate.

When we went up to four times the MIC of Cipro, we only had a single organism. So a great difference in the mutational frequency to resistance, and as I'll show you later, differences in the mechanisms of resistance. We were not again able to get anything on a levo plate. Next, please.

When we looked at the one where you had 500 per plate, we looked at the wild type and the resistant to Cipro at two times the MIC, the RC2 mutant. So we looked at the MICs in the presence and

absence of Reserpine for both drugs.

As you can see, for the wild type strain they were essentially identical, and the addition of Reserpine did nothing. But when you go to the RC2 mutant, Cipro now has an MIC of 3.5, and you bring it back down to 1 with the addition of Reserpine. You do nothing to Levo.

We've now done this about ten times for this isolate, and this number actually goes anywhere between .6 to .8, and one time we got 1 by doing arithmetic cuts. But you have very little change in this one, where you have basically a sixfold change with Cipro and then coming back down with the addition of Reserpine.

Now Strain 58, the wild type, the RC2 and the RC4 mutants grew on a plate with four times the MIC of Cipro, were all sequenced through Gyr A, Gyr B, Par C and Par E. Not just QRDR but the entire open reading frame was sequenced for all four target sites.

For RC2 no differences were seen between the parent and RC2 daughter strain. This, coupled with the decrement in ciprofloxacin MIC with reserpine exposure -- I apologize for that -- at 3.5 going back down to 1.0 -- this implies that RC2 is a pump mutant.

For RC4, a mutation was found in parC at

amino acid 79, serine to tyrosine, but this strain also decreased its MIC with the addition of reserpine. So RC2 is a pump mutant. RC4 is a target mutant that also has an upregulated pump.

Now we've examined other new fluoroquinolones in this system or in our hollow fiber PK system, which I'll show you momentarily. All resemble levofloxacin and do not allow emergence of resistance for wild type isolates, but they do, once they get the pump mutant.

Once they have a mutation that upregulates PMRA, we see a thousandfold decrement in the ease with which -- or increase in the ease with which we can pick out a target mutant.

Why is Cipro different for pump upregulation? Likely because it is the most hydrophilic drug and is most efficiently pumped by PMRA. Next, please.

Are there other factors that can alter the probability of resistance? Therapy intensity is one, as we've looked at, but therapy duration should influence the probability of having the resistant population become ascendant.

This is the hollow fiber system that we use. It originally was developed by Jurg Blaser and

Steve Zinner while he was at Brown University. You put the bacteria or viruses -- we've also done HIV. You put the bacteria in the peripheral chamber of the hollow fiber unit.

I should say, since he is in the audience, that Mike Dudley contributed mightily to this system. What you then do is introduce the drug into the central reservoir. If you just circulate it around, you have continuous infusion, but you can dilute into the afferent part of the loop and remove antibiotic containing drug from the efferent part of the loop, and you keep an isovolumetric system so that the ratio of the dilution rate to the total volume of the system gives us the ability to set the half-life to anything that we want. Next, please.

So we did a ten day hollow fiber experiment for two organisms, MSSA and MRSA that was ciprofloxacin sensitive, for six regimens of the Bristol-Myers Squibb desfluoroquinolone compound.

The endpoint was time to complete replacement of the population with resistant organisms. Classification regression tree analysis was employed to look for a breakpoint in the exposure and, as you can see here, -- this is the CART output -- 200/1 AUC/MIC was identified as the breakpoint.

A stratified Kaplan-Meier analysis was performed with this breakpoint being the stratum. The breakpoint was indeed significant, irrespective of how you tested it. So what you can see is, if you were less than 200 to 1, you really got resistant isolates to the fluoroquinolone very rapidly. When you were greater than that, you did ultimately, at least in some of the -- in one of the regimens, but it occurred after day seven.

So to prevent resistance, I think we can hit hard, get more than 200 to one AUC/MIC ratio, at least in the case of these *Staphylococci*, but stop early. That is, stop prior to seven days, because these are drugs that kill very rapidly. So we can get all of the killing effect and minimize the emergence of resistance.

Now the intensity of therapy and duration of therapy both have an impact upon the probability of emergence of resistance. Short duration therapy trials basically should examine an endpoint of frequency of emergence of resistance.

Quickly -- we're almost done -- again go to the hollow fiber approach. Now this is *Pseudomonas aeruginosa*. Vincent Tam presented this at ICAAC. This is the placebo regiment. We start out over eight

logs. It grows up to about 10.5 logs. You can see the number of mutants kind of fluctuates around.

Here's the Cipro control. You see it kill from about 8.5 logs down to 4 logs, very nice log kill, but before the second dose at hour 12 you see the start of emergence of resistance, and after that the 24-hour dose and the 36-hour dose do exactly nothing, because what we are seeing underneath the waves of the total population is now the resistant population is very rapidly growing up.

Remember, this is a system that does not have granulocytes in it. So here is the desfluoroquinolone compound, a very low AUC/MIC ratio. Three does essentially nothing to the total population, but with the resistant population just before the 24-hour dose now, you have caused or allowed, I should say, the amplification of the resistant subpopulation.

As we go to an AUC/MIC of 10, it occurs more rapidly. You get a little bit of a log drop early. That's the sensitive population dying off, and then you see the resistant population basically replacing it.

At 90 to 1, you see a very nice log drop, 3.5 logs, over a thousandfold decrement in the

sensitive population, but you see very rapid emergence of resistance with total replacement of the population.

At 110, you see the same thing. So it's completely replaced by hour 48. Finally, by 200 now we can drop it from 8.5 down to 3 logs, so over a five-log kill, and we can keep the organisms, the resistant mutants, under control.

We modeled this again. The model on this side is a little simpler, because it's an *in vitro* system. Here are the point estimates from the Blue Horizon run at UCSD. Next, please.

Then here's how the model fit to the data. Here is predicted observed. We actually measured the concentrations at all different time points in all of the regimens. As you can see, we did a pretty good job, R^2 to .97.

For the total population, the R^2 is about .94, and so we have a very nice fit of the model to the data. Then finally, for the resistant counts what we see after the MAP Bayesian step is the R^2 is about .8, because we have these down here that were at the detection limit, and we had to plot them somewhere. So it kind of killed off the R^2. Next, please.

So this is what we refer to as the

inverted U phenomenon. Resistant subpopulations, if you have an inadequate exposure, are initially amplified and then decline with increasing drug exposure.

Now this has been postulated actually first in the HIV arena, and this has been talked about a lot there, but to my knowledge at least, nobody has actually been able to demonstrate it with data. This is, I think, again the first demonstration with data of this phenomenon.

So just to show this for *Pseudomonas* plotted, this is again the baseline prior to the introduction of drug, the number of resistant mutants, and here is 10, 40, 90, one more, 100, and then finally 200 that we wind up being able to control the resistant mutants.

If you want to hold them just steady, we can calculate that from the Blue Horizon run, and that cost a lot of money, and somewhere in the neck of the woods of around 270 node hours worth of time on the highly paralleled machine, or you can do this for five cents and draw a line across and drop the vertical.

It was 187 to one out of the Blue Horizon calculation. It's 185 to one out of this calculation. Close enough for government work.

So again, we did a prospective validation placebo, something that was high, 137 to 1 AUC/MIC, and then to bracket that 187. So we did 166 and then 200, and what you see is you got nice, steady numbers of mutants in the placebo group. There's no pressure. That's exactly what you would expect.

Then with 137, yeah, you get a great log kill, but what you see is, boy, you just completely replace it very rapidly by resistant mutants. But when you get up around that break point, you can see this actually is just -- really is on its way up, and if you continue it out, and we did, actually, this actually loses control at hour 96. The 200 does not, and that again is right at where it should be, because we said we were going to hold it exactly steady out to hour 72, and that was our calculation, again a prospective validation of the analysis.

So this was the same *Pseudomonal* strain as in the mouse model, but that was levofloxacin in the mouse model. This is the desfluoroquinolone, but the mouse model contained granulocytes, while the hollow fiber system does not.

The total drug target for the mouse model was 157, which for levo is a free drug target of about 110. The hollow fiber system target is 187, which is

an increase of 1.7 fold. But Bill Craig in his animal model, when he does with and without granulocytes, finds that when you take the granulocytes away, the target goes up by 1.5 to twofold, and these results between the hollow fiber and the mouse are very concordant with the original Craig findings. Next, please.

So the *in vitro* dynamic model investigations frequently -- and also mouse model investigations -- frequently only examine the total bacterial population. The presence of a small preexistent population more resistant to the selecting drug pressure has major implications, particularly as the bacterial population size increases to near clinical infection size.

Here's *Pseudomonas*. Unfortunately, one size does not fit all. There are differences amongst strains. There are differences amongst species. Here's *Pseudomonas*. Target is 187. Next, please.

Klebsiella with the strain that we used, 93. Next, please.

Methicillin sensitive *Staph. aureus*, 66. Next, please.

MRSA-Cipro sensitive, 143. Next, please.

And now this is the daughter strain. This

was derived from that MRSA-Cipro sensitive strain, but now the breakpoint goes up to almost 500. Next, please.

So some drug exposures allow amplification of the resistant subpopulations. Exposures can be identified that will prevent this amplification and functionally suppress the resistant populations. Doses can be calculated to achieve these targets, because that's what we are doing.

We are target setting with these analyses, and doses, particularly of new drugs or of old drugs, can be calculated to achieve these targets using a Monte Carlo simulation approach that I presented to this Committee in 1998.

I think, as my favorite Hollywood movie star once said, "Th-th-th-th-that's all, folks!"

CHAIRMAN RELLER: Comments, questions for Doctors Drusano and Schentag? Dr. Archer and then Dr. Leggett.

DR. ARCHER: That was very nice, George. I have a comment, however, as I'm sure you are well aware.

What you have modeled very nicely is the emergence of resistance during the course of treating an infection, but as we know, the problem with

antibiotics is the unintended effect on the colonizing flora and the generation of a reservoir from colonizing bacteria, which I would -- I mean, you may have a model for that, but I'm not aware yet of any model for the effect of antibiotics on resident flora in terms of numbers of bacteria, the concentrations of antibiotics. But one would assume that the concentrations of antibiotics are much lower at mucosal sites and, therefore, it would be hard to predict what is going to happen to selecting resistant mutants in that circumstance.

DR. DRUSANO: Gordon, as always, a great question, and the answer is -- I wish the statisticians -- I know there's -- Dr. Wittes is here, but I wish all the statisticians were here from yesterday, because my answer immediate to you is something that G.E.P. Box once said, who is a very famous statistician who said all models are wrong, some models are useful.

You are absolutely right. The model that I presented does not have universal applicability. It addresses a specific problem of the suppression of resistance during therapy.

To answer the other question, you could -- Actually, there is a very good model system, at least

for *Staph.* and fluoroquinolones. The reason for that is because the mutational frequency to resistance for *Staph.* to fluoroquinolones is very, very high.

You don't have to have a big population. In the Lancet about four years ago, there was a really neat little study where, I think it was the Finns, actually took a bunch of volunteers and swabbed their arms prior to, and then got the *Staph.* out, sequenced through them, and did all the right stuff, and then gave them a couple of doses of a fluoroquinolone, in this particular instance Ciprofloxacin.

Lo and behold, 48 hours later they reswabbed their arms, and yea, verily, even as you say it is so, Socrates, they had fluoroquinolone resistant *Staph.* in there. So, yes, it's absolutely true that there are certain places where you will get resistance.

Now as you go to other organisms like Gram-negs where the mutational frequencies are going to require denser populations, I think you will see that problem ameliorated quite a bit, but you could also, I suspect, do this same kind of analysis and actually choose an exposure that could possibly -- we haven't done the experiment, but it's a great suggestion, Gordon -- see if you could do that to

prevent that from happening at the primary infection site -- I'm sorry, at the colonizing site, other than the primary infection site.

CHAIRMAN RELLER: Jim?

DR. LEGGETT: A question for you, George, and a question for Jerry and then one for both of you. They are all sort of tied together.

For the *Pseudomonas*, didn't you just show us the optimal AUC to MIC breakpoint cutoff in terms of being 125, that sort of deal? In that regard, what are your thoughts about this sort of mutation prevention concentration or that sort of thing? That's one thing.

DR. DRUSANO: Well, first of all -- Well, let me say that what I showed for basically *Pseudomonas*, for one strain of *Pseudomonas* -- My urging to the Committee and to the FDA is to recognize that -- You know, this represents a couple of years worth of work. So I'm not trying to minimize it.

It, you know, hung up our lab for a couple of years, but it's one strain of *Kleb*. It's one strain of *Pseudomonas*, two strains of *Staph.*, and it's a lot of work. But you know, before you should start drawing hard conclusions about what the right breakpoint, if you wish to use that term, is, you

should probably base that on several tens of organisms at a minimum that are drawn from the clinical circumstance.

What I showed you was implied not -- It was not to be implied to be a one-size-fits-all breakpoint, but actually what I wanted to show you was that it was exactly the opposite of that, because it went as low as 66 and as high as 450. Okay?

So what it really means is that is it possible to gain insight, is it possible to generate a breakpoint that we could shoot for as a target? The answer to that, clearly, I think, is yes. Are those the right numbers with "right" in quotation marks? No, they are not, not because there is anything wrong with the numbers per se. There just aren't enough of the organisms.

Now so if anything, what I would suggest is that we keep on going and that laboratories other than our own kind of get involved in this, and really get some answers, get 20, 30, 40 strains where we can say for *Pseud.*, for *Staph.*, for *Kleb.*, you know, what are the broad breakpoints. And it's not one number. It will be a range.

As to what MPCs are, I think -- Well, I happen to feel strongly. I won't say anything

terribly bad except to say that I think, as a number, it is totally worthless, and the reason for that is very simple. That is you have a static concentration of drug, and that's fine if you have a time above a threshold kind of drug like a beta lactam. Then you can probably draw reasonable implications from that. But if you have an AUC/MIC driven drug like a fluoroquinolone or an aminoglycoside, I would say that how can you draw implications for an MPC where you have a completely static set of concentrations.

So to me, it is a very, very unhelpful type of measurement.

DR. LEGGETT: Where I was headed with that was in terms of this sort of emergence of resistance problem, shouldn't we be reevaluating the so called breakpoints and so, for instance, the argument about levo, a resistant breakpoint of 8 probably really is already way too high, and if we would sort of use the drugs more effectively, could that prevent this?

DR. DRUSANO: I think what you have to say is that -- You have to be clear about what your breakpoint wants to do. Okay? You can make your breakpoint predict clinical success. You can make your breakpoint predict microbiological success. You can use a breakpoint to divide populations of

organisms, which I happen to think is a waste of time, but please don't repeat that to the NCCLS.

Then finally, you can use a breakpoint that will prevent -- Well, I shouldn't say prevent -- suppress the probability of emergence of resistance. So any one of those endpoints, I think, is a worthy endpoint. You just have to define what it is.

Different doses of drug will give you different probabilities of each of those endpoints. So you have to be specific as to endpoint, and you have to be specific as to the dose to which that breakpoint applies.

CHAIRMAN RELLER: Dr. Goldberger, a summary and presentation of issues?

DR. GOLDBERGER: Thank you. In the interest of being brief, I will limit my remarks to 45 minutes or so.

We've had, obviously, a lot of discussion already with regard to some of the questions we are posing for you. So what I'll do is just sort of run through the questions and maybe try to annotate them a little bit as appropriate.

For question 1: What are the barriers/challenges that hinder drug development for resistant pathogens? Again, this is based, obviously,

on a lot of what you've heard today, yesterday, as well as your own experiences.

WE broke this down to some suggested examples that you might want to consider, although, obviously, you are free to consider others.

One: For instance, an out-of-class resistance claim, i.e., fluoroquinolone for PRSP. Here I had made mention, in fact, this morning that there were some patient factors we thought that ought to be taken into account in terms of the kind of questions we might want to accumulate.

The rather interesting issue of an in-class resistance claim, which initially, of course, in this case sounds a little bit like an oxymoron, i.e., how do we get a resistance claim for a penicillin or penicillin-like drug for penicillin resistant *Strep. pneumoniae*? Even though this is a substantial issue, we would be interested in any comments people would like to make about this, including which organisms, for instance, are appropriate, etcetera.

A resistant pathogen with moderate to high prevalence: I think one example we heard about today is how we might try to do trials to get an indication for, say, MRSA where there was a fair amount of bacteremia around.

Then, I think, an emerging resistant pathogen of low prevalence: Although it's not clear to me, in fact, how low the prevalence is, a good example might be potentially VRE or more likely some of the discussions this morning about *Acinetobacter*.

Again, broadly, how do we overcome these challenges and barriers while assuring that the drugs are shown to be safe and effective for their intended use?

Actually, it's probably worth spending a little time as opposed to necessarily getting into enormous detail on the above bullets, in talking about the concepts of what constitutes safety and efficacy in this setting. Again, some of that has already been covered in this morning's session.

Question 2: Based upon the presentation from this morning as well as, obviously, your own experience and observations, please comment on a focused drug development approach for resistant pathogens. Obviously, we would like you to include the following in your discussion:

The likelihood that such a program will provide sufficient data to address safety and efficacy.

We certainly would like you to talk a

little more about the issue of the role of data from sensitive strains of the pathogen to support, for instance, an approval for out-of-class resistance, i.e., if we think, for instance, we have a new drug for VRE, the new drug shows no cross-reactivity in the laboratory with Vancomycin. How much data can we get out of treating susceptible strains of *Enterococci*?

I mean, this has been discussed this morning. We do believe it is potentially quite useful, but it would be helpful just to hear anymore comments, if there are things that were not covered with regard to this.

I think the role of nonclinical data and/or PK/PD data: Obviously, we've just heard two presentations about the latter.

Finally, if anybody has anything they would like to touch on with regard to incentives for developing drugs for resistant pathogens. This may, in fact, ultimately come more from the industry representatives who are here.

One should be aware that, although there are certain types of exclusivity that already exists via existing legislation, as well as some mechanisms we have to expedite drug development, certain other mechanisms that people have talked, i.e., wild card

exclusivity, etcetera, would in fact require additional legislation from Congress.

Finally, two other questions: Basically any other issues, ideas, etcetera, or alternate strategies or approaches you would like to present or discuss regarding the development of drugs for the treatment of resistant pathogens;

And any comments -- question Number 4 -- you would like to make about approaches that might be used to preserve the efficacy of currently marketed antimicrobials and, in fact as well, new antimicrobials that might be developed.

Again, we've had some very good discussion about the pros and cons of restricting availability. obviously, that is not the only approach, and I think one of the goals is, if considerable effort is made to develop new drugs for resistant indications, what can we do to keep the usefulness of those drugs around for a while? Thank you.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: Just to get things started, the barriers challenges that hinder drug development for resistant pathogens -- I think most of them, maybe all of them, have already been mentioned.

I think the issue of a surrogate marker is

so important. I think, for those of us that -- Well, all of us care for these patients all the time. Dr. Schentag's point that the place that we most often see the differences in the first two or three days of therapy based on sterility of the cultures, and this idea of having to wait until ten days to evaluate or compare the patients is not, I think, where the answer is.

Then one of the issues that was brought up this morning, which is that the current drug development is so focused on indication, and I think we have to get away from skin and soft tissue and just go to organism focused studies.

Then, which has also been brought up, the concept that you have to have no preceding antibiotics, when in fact that's the very reason that patients develop resistant organisms, and certainly for children in the otitis media study, the place where we see the most resistant organisms is in the child that's already on antibiotics or was on antibiotics 24 hours ago.

So just to get things started.

CHAIRMAN RELLER: I would like to pick up one theme from yesterday with a question for Dr. Chesney. Doctors Drusano and Schentag suggested there

may be, based on PK/PD data, ways to prevent resistance. Certainly, the task force had much devoted to how we could prevent resistance, in the first place.

I think most people believe that, particularly for resistant *Pneumococci*, the widespread use that 75 percent of antimicrobials for respiratory tract infections, some of which -- we might debate the percentage, but clearly a portion of which is totally uncalled for.

So my question, Dr. Chesney, is are there subsets or trial designs perhaps with CDC or NIH support to delineate those respiratory tract infections where, in fact, therapy may give greater harm than it does benefit, those children with otitis media who do not need antibiotics, for example.

Clearly, as you pointed out yesterday, there are some that every pediatrician would say -- and double tap studies would confirm -- that it's necessary. Those patients with acute exacerbations of chronic bronchitis who do not, where in fact doing placebo controlled trials would help delineate with those subsets those patients with greater certainty for which antibiotics are not necessary and, in fact, there's a downside to using them, that could be the

basis for the promotional efforts that were given in our background documents to decrease the superfluous use of antibiotics that helps to create the very problem that we spent a lot of time addressing.

So this is looking at it in an entirely different light, not the ethical dilemmas of active control versus placebo, but capitalizing on what we do not understand fully for those subsets where, in fact, not only would placebo be an ethical thing to do. It could provide us the very data that we could delineate those patients targeted for non-use as one part of preventing resistance in the future.

DR. CHESNEY: I think I understand what you are asking, and I think, absolutely, we need to delineate the subsets of patients who currently are getting antibiotics who don't need them.

I think that, actually, pediatricians have been very aggressive in this regard, along with the CDC. For example, I think rarely do people use antibiotics now for suppressing recurrent otitis media. I think that's pretty much gone.

Another population that I think is important is the sickle cell population. In spite of the fact that these children are now getting pneumococcal conjugate vaccine, *H. flu-B* conjugate

vaccine and getting the 23-valent vaccine, it is still recommended that they go on prophylactic penicillin.

The problem with that is, until five years of age, they also go to daycare and they have family members, and so transmission of those organisms. And that's a population that I think we could almost -- that we need to look at in addition to the routine respiratory tract populations.

Does that answer the question?

CHAIRMAN RELLER: You've included some groups that I hadn't thought of. But Dr. Shlaes has a comment, and Dr. Archer also.

DR. SHLAES: Actually, I think one of the interesting aspects to the issue that you raise is that it's important not to consider antibacterials in a vacuum in this regard.

For example, I think one of the neglected areas in industry and in human health is acute respiratory viral infections. Now we've had an example in the last few years where we've had a couple of flu drugs come out. I'm not sure that they have -- this experience has encouraged the industry in this regard.

I think this is a mechanism by which one might make a dent in an appropriate antibiotic use by

offering physicians an alternative to treatment of acute respiratory viral infections. How this will play out -- There's a drug, I know, before the agency now from Aventis for rhinovirus.

So how this will play out, I think, in the future is going to depend on how physicians view this -- how one can conduct clinical trials to look at these very short duration, acute illnesses, but which account for a very large percentage of outpatient antimicrobial usage, outpatient antibiotic use.

So I think that is one area where we as a society and the FDA as a regulatory agency and industry are going to have to look very carefully at how we can look at this area of acute respiratory viral infections to get drugs out there, so that drugs are actually used appropriately for those indications as opposed to inappropriately.

One of my, I thought -- I was disillusioned recently when I asked a group of infectious disease physicians at a conference that we were at what they would do when this drug would come out. A pretty uniform response was they would often use both, because they are never sure whether somebody has a bacterial infection or not, which gets to the issue of diagnostics. I think this is something that

we as a society need to think about looking forward.

Then the other comment I'd like to offer is: At the Institute of Medicine meeting which took place a couple of weeks ago on resistance, actually, David Bell was talking about this, and I'll try and paraphrase what he said.

He said a lot of the things we do to prolong the utility of the antibiotics we have now and to kind of prevent emergence of resistance is really like putting your fingers in the dike, and that what we really need is we really need a continuous pipeline of new agents, because these bacteria are going to outsmart us in ways that we haven't thought of yet, just like the case that Lou Rice mentioned where vancomycin came out long before we had MRSA, which is its primary use right now.

So I think that is something that we also have to keep very high on our list. Thanks.

CHAIRMAN RELLER: Dr. Archer, then Dr. Ramirez.

DR. ARCHER: Speaking of diagnostics, I think we haven't spoken about this much, and I think one area where diagnostics would be particular useful, although a huge challenge, would be differentiating colonizing from infecting isolates.

I can think of certainly hospital acquired pneumonia as a huge example of we have abundant bacteria, but we don't know if they are causing infection or not. And then coagulase-negative Staph. in the blood. Just as two examples.

This might be one area where I know the -- Dr. Tally said that kind of dissed genomics earlier as not having done much for drug development, but they might actually help and lead to diagnostics, if we could look at post-genomics, for instance, to look at genes or proteins that are particularly turned on at the site of infection versus colonizing sites.

There might be a way to do some type of RTPCR for diagnosis of these isolates.

I think, if you could differentiate colonizing form infecting isolates at the outset, then you could eliminate a lot of inappropriate drug use. You could eliminate noninfections from trials so that you could follow eradication of two infecting isolates versus those that were only at colonizing sites.

I think there's a lot of other diagnostics that we haven't talked about, but I think those are in many cases just as important as developing new drugs.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: Yes. I would like to make a

negative comment to the area of prevention. Even though -- and we all emphasize prevention, but one of the realities is that if you look at the literature, outside of *Staph. aureus* that was reported as resistant to penicillin in the United States, more than 90 percent of any other organism that had developed resistance to any antibiotics have been generated in a foreign company.

Resistance is an international issue. You can make whatever study you want to. You make all your family medicine doctors not to use antibiotics for acute bronchitis or for viral infection. You still got a resistant organism each year.

This applies for the community acquired organisms that travel back and forth all over the world. Then in our intensive care units, we are generating resistant organisms due to the quality of the patients, and there is no way out. We want to keep using antibiotics.

Then even though as infectious diseases, we always say, well, we look at the industry to get new drugs as the last resort, but this is the only resort that we want to have. I mean, we need new drugs.

I would like to go back to the point why

we are here, is that we are here trying to -- because we know that we need new drugs, and we are here trying to figure out how can we make the approval of the new drugs easier. This is how we have to come out with ideas.

Now I don't want to put my two cents regarding after all this discussion today. When you look at resistant pathogens with moderate to high prevalence or resistant pathogens with low prevalence, and we are talking the VRE, the *Acinetobacter*, the *Pseudomonas*. From the different presentations, I think that we definitely need to define trials in which we enroll the patient with all the risk factors for resistant organisms. I mean, the trial has to be defined in this way.

I like the idea that, if we have the population, we have the patient with risk factors, and even one risk factor will be the patient with the positive culture. Then defining a trial that the entrance to the file is going to be the patient with the positive culture. Then this is going to be the inclusion criteria.

I think that we have to go and eliminate -- This was already discussed -- eliminate this idea that to get an approval you need to show the site of

infection and then the organism. You need to show the skin and soft tissue and then show the organism.

Probably we just need to get approval for the organism, because in reality what's happening in real life is that at this moment, if we get 100 ID physicians, I will say, okay, you have to tell me what is the approval for linezolid for VRE? Who ares? That means you have VRE in the urine, in the blood, in the skin, you just use linezolid.

Then we don't care in reality to see -- I mean, we care about the resistant organism and the drug. Is this -- Now we understand that the organism isn't a CSF. I mean, we may have a different type of dosing, but if the organism is in the blood or is in the lung or is in the urine or is in the soft tissue, it is the same. So we want to use the antibiotic.

Then I think that we need to concentrate probably on developing a trial that you have a positive culture, you enroll the patient, and then because these patients are going to have multiple medical comorbidities, the clinical outcome -- we cannot follow the clinical outcome -- we have to look at bacteriological outcome.

I feel this is almost in agreement, because we are talking of all of these surrogate

markers, but the only one that is clear is bacteriological outcome.

I would probably suggest that -- I was thinking here. If I have to look at bacteriological outcome, we agree that probably the sputum is not a good sample, but I would get a specimen urine, blood and CSF, probably three specimens that if I can repeat a particular time the culture in the same specimen, the MDR organism is not there -- I mean, this would be a good outcome.

I really don't know what happened with the patient, because this patient is very sick, and the patient most likely is going to die of whatever other diseases. But this is going to be the outcome.

This is what I come out with after all these discussions, how to probably decrease the number of patients. I also agree with the idea that this has to be low quantity, high quality. This has to be the specific center, the very good clinical investigator, minimum number of patients, high quality of research.

CHAIRMAN RELLER: Dr. Bell.

DR. BELL: Dr. Ramirez said some of what I was going to say. He said many other wise things, too. But I want to reiterate that, although the approach to dealing with antimicrobial resistance has

to be multi-faceted, we need diagnostics, etcetera, which was laid out in the Public Health Action Plan.

We are only kidding ourselves if we think that we are going to solve the problem by judicious use guidelines and diagnostics and stuff. We need new drugs.

I would encourage the FDA and the drug companies and NIH to be aggressive in making sure that we have the new supply -- we have the constant stream of new drugs, because the trends are all going upward, and it all comes down to that.

I think we should be using these other parameters that have been alluded to here. One question I have for the -- I guess maybe it's for the industry. Are there any lessons that were learned from the recent experience with Synercid and Zyvox that might be instructive retrospectively in terms of -- well, profitability of those drugs or issues regarding clinical trials that, you know, from a retrospective look might be informative in terms of how things could be done differently?

CHAIRMAN RELLER: I want to make sure we get back to Dr. Miller but, Dr. Shlaes, why don't you respond to this, if that's what your hand was up for.

DR. SHLAES: Well, I'm hoping that there

are a lot of people out there in the audience who can help with this. But I think everybody learned a lot of lessons from both of those situations, Synercid and linezolid, and I think actually Dr. Goldberger's idea of less quantity and more quality probably comes from that experience; because I think in the case of Synercid there was a lot of quantity and not much quality in a lot of those cases.

It was very hard to sift through the data to figure out what was what, and I know this Committee struggled with that for a long time. So I think that was one of the lessons that was learned.

Another lesson that was learned was this idea of getting more pathogen specific and looking across clinical indications at efficacy against pathogen and using data from one indication to support efficacy in another indication. I think that was another valuable lessons that we all, I hope, learned from those experiences.

I'm not sure what industry has learned on the commercial side, to be perfectly honest, from those two drugs. Both drugs have serious issues with toxicity, which are impacting their sales.

So I'm honestly not sure what commercial lessons we've learned. Maybe if there's somebody else

around who can speak to that better than me -- Is there somebody who wants to take a stab at that? Okay, they've left me out to dry. Good.

DR. TALLY: We were asked of the impact of this, because with developing a drug it's -- do we learn lessons? I don't think we've had enough time with linezolid on the market. It's the second full year.

I know they are disappointed in the amount of sales they have at this point in time in that flattening off. I know Synercid -- Aventis stopped detailing Synercid this year, and their sales are flat and possibly going down.

I remember Lou Rice telling me at one meeting that the clinicians will figure out which drug to use, and I think what they have done is substituted linezolid for quinupristin/dalfopristin, because it's a safer, easier agent to use and seems to work in those patients. But I think it's finding its place, based upon what David just said, with the recognition that there is some adverse events associated with it. But I don't think we've gotten enough of the data to see the final decision on the commercial, because it takes three to four years, really, to gather all that data, but I know there is disappointment there at this

point in time.

DR. MILLER: I just wanted to take a moment to go back to David Bell's skepticism about prudent drug use. I guess in the immediate time frame I agree with that. However -- and we've said -- A number of people have said this, and we have trouble identifying patients for these trials.

If we had a diagnostic method, we could overcome those limitations. We have difficulty using the drugs, because we don't know enough about the culture and sensitivity of the organisms, because basically on standard of practice right now, we don't do a lot of that. So it's empiric therapy.

So I guess I throw back to FDA: Is there any precedent to ask the pharmaceutical sponsors to come in with diagnostic methods at the time they come in with their drug applications or if there would be any way to leverage that activity or boost the development of diagnostics?

The other statement or the other issue I wanted to return to, and I know that will increase the cost of drug development, so we have to be careful there. But also post-marketing surveillance in terms of assessing whether we are actually using the drugs optimally, monitoring for resistance where we can link

drug use to resistance in the isolates and in specific patients, and then -- I know this will be heresy as well -- using the outcome of resistance as an adverse event to then go back and either change labeling or withdraw drugs or do other actions within purview of FDA. Thank you.

CHAIRMAN RELLER: Doctors Soreth, Ross and Sumaya.

DR. SORETH: To answer your question, Dr. Miller, about using diagnostics as leveraging within a drug development program, I don't think we've done that as such. I know in discussion of enrichment strategies for PRSP, there is utilization of a *pneumococcal* urinary antigen test in such trials, but we certainly didn't use it as leveraging in a company's drug development program. But it's an interesting thought.

To make a comment about something that Dr. Ramirez said with regard to site specific indications or claims versus organism driven claims, I just wanted to make a couple of comments.

Although I think we understand the importance of quality data, data that would perhaps give us an experience of a drug's efficacy in bacteremic patients where we would have some

confidence that the placebo rate or spontaneous rate for cure approaches zero, if not is zero. Nevertheless, I would still make a plug in some scenarios for site specific study of a drug's efficacy, because knowing how the drug performs in patients with bacteremia might be very different from knowing the drug's effectiveness in certain sequestered sites.

You mentioned the CSF. We don't necessarily know how well drugs penetrate bronchial tissue, pulmonary tissue, based solely on experience from bacteremic patients.

So in addition, there is important safety information that comes from easier to study, site specific infections, knowing that the majority of those patients are not going to have resistant organisms, because we are talking about organisms that occur at a low prevalence.

So I think we are trying to look at combinations of the traditional approach that might give us a lot of information about how a drug performs in a certain site and what the safety margin is, in combination with those smaller numbers of patients who have resistant organisms. I think the two taken together will help us work more quickly and get to

where we want to be at the end of the day with a drug development program.

I don't think, particularly in patients with resistant organisms who may, as is the case with VRE, be fundamentally sicker patients, we necessarily well understand a drug's safety profile, because there are so many confounding factors in those patients.

CHAIRMAN RELLER: Dr. Ross.

DR. ROSS: I just wanted to follow on Dr. Soreth's remarks about pathogen specific versus site specific indications. There's, obviously, pros and cons to both approaches.

Historically, if you look at some very old antibiotic labels, they will state that the drug is indicated for treatment of serious infections due to such and such pathogens. Then there's a shift to treatment of, for example, lower respiratory tract infections, and then more recently, much more defined sort of sites of infection.

This becomes problematic with organisms like VRE where you may not really have enough bugs at one particular site to really get a study that has the statistical power that we normally would want.

One of the things to keep in mind, however, about pulling things across different sites

of infection, that with the same pathogen as the natural history and the outcomes can be very different.

Just to take a specific example, for the linezolid application -- I presented this to the Committee in March of 2000. This was just to set the framework. This was a dose response trial comparing a high dose of linezolid versus low dose of linezolid in patients with VRE infection at various sites.

There were differences in outcome in patients with VRE bacteremia at the high dose versus those who had it at the low dose with a higher response rate at the high dose. In contrast, in patients who had urinary tract infections due to VRE, the two arms had outcomes that were much more similar.

This becomes important if you are trying to say, well, what's the benefit, what's the value added of a drug, especially if you are talking about patients with UTI in a nosocomial setting where one major part of the treatment effect is taking out the Foley.

So I think that's one of the reasons that we are interested in looking at the site of infection. The other aspect of it is that, if you start pooling pathogens and pooling infections at different sites,

you are mixing together very different patient populations.

That may be okay, but you need to understand you are doing it, and it can become complicated, especially if you are doing things with historical controls, which is one other thing on the table.

So I just want to make those potential problems and pitfalls -- put those on the table.

CHAIRMAN RELLER: Doctors Chesney, Rotstein and Ramirez to respond to Dr. Soreth. But we need to keep in order, for fairness. Yes, Dr. Chesney?

DR. CHESNEY: Thank you. This is a quick one. But again what are barriers hindering drug development? Getting enough resistant pathogens -- I just wanted to emphasize the concept that -- or the point that Dr. Talbot made, which is developing networks.

Dr. Goldmann mentioned a very resistant Burkholderia, and we had one recently. If we knew through networking that a certain company was looking at that particular drug, then I think that it would be much easier to accumulate some of these very resistant organisms.

CHAIRMAN RELLER: Dr. Rotstein.

DR. ROTSTEIN: I would like to return to the question at hand here and ask if we could possibly liberalize the guidances with regard to resistant organisms. If we don't have proper guidances, maybe that's a thought, that we need new guidances for resistant organisms, something totally different, so to write some regulations in that regard so that we can make progress in this area.

In addition, I would like to just talk about some surrogate markers for MRSA. We've been in the habit of using the MRSA probe, and this has helped us considerably in making the diagnosis of MRSA at an earlier stage.

What often happens with MRSA is you get the organisms. You have to wait at least 48 hours thereafter to confirm that it's MRSA. That is a total of 72 hours. If you could use a probe, we could have the answer within hours.

So you would swab a lesion or sputum, whatever, use the problem, and possibly using an MRSA probe or other probes, PCR probes that we do have. We could get answers faster and then be able to initiate therapy earlier.

The problem with resistant organisms is

you don't know if it's a resistant organism, as people have said before, when you start empiric therapy. You find out about it afterwards. The use of probes that are allowed, because they are not currently allowed in most protocols, would certainly help this issue. Thank you.

CHAIRMAN RELLER: We'll come to the back table. Dr. Sumaya, you still have your query, and Dr. Ramirez. Then we'll get back to Dr. Goldmann and Dr. Talbot and Dr. Rice.

DR. SUMAYA: My comment, I think, relates to what Dr. Bell had said, and you started out with -- also commented on by Dr. Ramirez.

I'm very supportive, because this is a very big issue and will get worse as time goes on, and the need for the pipeline and how we can facilitate the process through FDA and others and potentially use incentives and even marketing support of some type.

We are looking at the eligibility criteria to be able to bring in the appropriate types of subjects in to develop studies, and the surrogate markers, I think, is another very important area, and I would be very supportive of that above the clinical data that would have to be there. But I think surrogate should be the first amongst equals, you

might say. However, in saying that, I think that it's important for this type of national problem that we look at it on a national basis and look it as the population or public health base.

That's where I wear my other hat. So I think it's very important that we look at the genesis of this carefully. I think the genesis principal factors in that relate to the use of antimicrobials, the indiscriminate use, widespread use which may not be best in many cases.

So I think we need to invest some time and some dollars looking at that particular issue and the opportunity here, because we are talking about industry working with FDA and other public health service agencies, networks. This may be the opportunity.

So I was very pleased when I saw Dr. Soreth talk about having education in addition to research and other activities in her presentation, and even in the latter presentation that we had by Dr. -- well, it was the John Wayne presentation -- Drusano. The use of the laboratory in looking again in the genesis of antimicrobial resistance, that development, I think, is also extremely appealing.

So what I would say is this is an

international problem, but in this country we have the widest access to the widest amount of antimicrobials of any other country, and so I think it's a particular problem that we have to be very careful in.

So I would put a lot of money into preventive type measures as well.

CHAIRMAN RELLER: I was curious with Dr. Sumaya's comments and Dr. Bell, and I'll prod him a little bit on the Centers for Disease Control in prevention.

You know, you expressed, David, some skepticism about the ability to affect indiscriminate use.

DR. BELL: No, no, no.

CHAIRMAN RELLER: Our inability to appreciably affect the indiscriminate use of antimicrobials. You didn't say that?

DR. BELL: No.

CHAIRMAN RELLER: That's what I heard. Maybe we just haven't been as innovative or provided conscientious practitioners through rapid diagnostic measures, you know, alternatives like Dr. Shlaes mentioned, appropriate advertising, marketing of appropriate use to prevent some of this, not in any way diminishing the need for new agents. But we also

heard Dr. Shlaes say you go back to the shelves, there's not much there.

Dr. Tally said genomics of the organisms and innovative chemistry has been disappointing to date. So that I don't hear, all incentives to the contrary, that -- and given the time lag and the cost, that there is going to be an immediate solution with new agents.

I mean, it's not -- You know, what we want to avoid is the heresy of the exclusive emphasis. I mean, there isn't one solution to this problem, and we need perhaps a continuing balance and long term approach.

I don't want to take Dr. Ramirez's time, but David, why don't you go ahead and respond, to keep it focused here?

DR. BELL: Well, I think everybody agrees that the way we are going to deal with anti -- Antimicrobial resistance is never going to go away. What we need to do is turn it from an urgent problem into kind of a routine problem.

There are several facets that need to be addressed simultaneously. The Public Health Action Plan to combat antimicrobial resistance, which many folks here provided input on, provides for

surveillance and prevention and control and research and product development. All these are important.

In fact, I might as well just say, the task force is going to have its first annual report coming out this spring to be discussed at an open public meeting in the Washington area June 26th. So we would like to take that opportunity to present what the agencies have done so far and get further input.

There's quite a bit in there under prevention and control that CDC has been doing. I mean, certainly, antibiotics are way overused and misused in this country, and that is a major driver for resistance, and we need to cut back on the overuse and misuse.

There's evidence that we can do that, and CDC and partners have been working with state health departments and medical associations and consumer groups and a variety of other groups in the community and health care settings and in agriculture to try and reduce the overuse and misuse.

I think that, certainly, when no antibiotic is indicated, that's a clear message there for viral infections, when we are to treat colonization, when we know that we are, we can reduce that.

There's less evidence that that actually -- that reducing overuse and misuse actually lowers resistance rates. There's some more reason to believe that it might possibly prolong the inevitable development of resistance, but I don't mean to detract for one minute -- and I'm sorry if my comments were misunderstood, and I want to take -- You know, I want to make this very clear, particularly if there are any journalists in the room or anything.

I mean, it's a major concern. We need to cut -- and we can do this. All I'm saying is that this alone will not work, that it is a matter of putting our finger in the dike, and we do need the new drugs, and this meeting is about how do we get the new drugs. That's all I wanted to say.

CHAIRMAN RELLER: Dr. Ramirez. Then we need to get to the back table here. So let's go. Ramirez, back table, and Dr. O'Fallon. I think that was the order, and Dr. Maxwell.

DR. RAMIREZ: Yes. I totally agree that -- This is why I mentioned that just education alone is not going to work.

It has been mentioned several times -- Two comments -- several times that the new diagnostic methodologies. I can tell you our experience in

Louisville. Gene Summers, the Director of our laboratory -- we've been working with atypical pathogens for years, and he is concentrating developing internal techniques for the diagnosis of atypical pathogens.

For several years probably most of new antibiotics that have been approved by the FDA -- there have been the multi-center studies, all the samples to our reference laboratory, and we have for legionella, mycoplasma, chlamydia, whatever test is there, maybe PCR, every culture, we are doing, and we are getting samples flown all over the world.

Then besides having this reference laboratory, approximately three years ago we said, well, what about we go to the community now, because we are -- You know, we have cultures. We can do Chlamydia culture every day. We can offer -- We are offering this to all the drug companies. We are doing all this multi-center.

So three years ago we decided to go to the Louisville community. I said, listen, guys, you want to make diagnosis of atypical pathogens, we have a state of the art here at home. You don't need to send it to California. You just -- here.

We spent all this money and effort in the

market in our tests. We get one PCR request every two months. Why? Because everybody say why you are going to be asking -- why you are going to spend the money on any of your fancy tests when I just use the fluorospector -- it's going to cover everything.

This is what all the societies are telling us. You just use this antibiotic. That covers the organisms that may cause this. Then the bottom line is that even new diagnostic methodologies is not going to help. Physicians are going to -- they are not going to order the tests. Physicians are going to use the antibiotics that is there that cover the bulk of likely organisms.

Then again, to me, education is not going to work. New diagnostic methodologies are not going to work. And I want to go back then to the process of developing new drugs.

Again, we look at the full population of patients. We've been saying that enrichment of the population -- The problem with the enrichment may work for otitis media, but the problem is that when you get resistant organisms and you start looking at the risk factors for resistant organisms, risk factor for *Pseudomonas*, *Acinetobacter*, the VRE, the MRSA, you keep getting to this tunnel that all the risk factors

are the same.

You need to have the patient with multiple medical comorbidities, immunocompromised as being in the hospital for sometime. Then essentially, if you want to do the trial, your inclusion criteria is going to be these patients with plenty of risk factors. Still, you have to enroll 200 patients to get at the end the four or five patients with MRSA, the four or five patients with *Acinetobacter*.

This is why I think that the inclusion criteria should be the positive culture, not the risk factors, because again we need to try to decrease the number of patients that we evaluate.

The other problem that I see with the site specific -- and I want to again defend my position of why not site specific, because some site specific is very simple to get the organism. The urine is classical one, because part of the clinical diagnosis of UTI is get the 10^3 bacteria. Then you really have the organism as part of the clinical diagnosis.

When you get into a skin and soft tissue infection, you got to enroll a lot of patients to be able to figure out one organism causing the skin and soft tissue infection. The industry already say you have to enroll ten patients to get one organism. You

enroll ten. This is $30-$40,000 for each one of these ten to get one organism.

This is why I think that we need to be more flexible with the site specific approval, if we want to get these drugs quickly for us to be able to use for these multi-resistant organisms.

CHAIRMAN RELLER: Dr. Goldmann.

DR. GOLDMANN: Probably you have all seen Indian Jones and the Temple of Doom where Indian Jones is in the bottom of the tomb, and he is surrounded by snakes with his love interest, and he is trying to figure out a way out. So I would say that he needed some new tricks, just as we need some new antibiotics, because we are surrounded by snakes. But try and imagine an Indiana Jones in which he wasn't surrounded by snakes, and he had weeks and years, if he wanted, to try and figure out the best routes of escape from the tomb.

So we've sort of gotten ourselves in the position where we have no choice but to ask the pharmaceutical industry to come up with new drugs and do it pronto to give us armamentarium to really make some rational decisions about treatment and control.

That said, I think that everyone here would probably benefit from reading the Institute of

Medicine report, "Crossing the Quality Chasm," which has an epilogue written by Paul Plessig on complex systems theory.

I had sworn I was never going to use this jargon in my entire life to a group physicians and scientists, but I've done it now, because if ever there was a complex system to which his thinking applies, it's the problem we have before us.

To get some flavor for what we need to accomplish, I would urge FDA and pharmaceutical industry, in particular, to ask themselves what was it that allowed Ceclor to become the number one drug in terms of dollar sales in oral antibiotic virtually overnight, and even as late as a study -- I think it was in 1998 -- in Colorado Medicaid population, it remained one of the major second line drugs for the treatment of otitis, even though, in my humble view, the drug has no use in the modern therapeutic armamentarium.

What it was that made Cipro become the number one dollar selling oral antibiotic shortly after its introduction, again primarily for the use in respiratory tract infections -- So I think we have to ask ourselves what the regulatory and commercial and market forces were that allowed that paradigm to play

out and continues to play out in other ways in the current day.

I have to agree with David Bell in many respects. I think that the potential for doing better prevention is very real, and we'd best pay attention to how to do this best and invest the resources in it.

There is absolutely no question that outpatient use of antibiotics can be improved. The evidence is becoming very clear that a multifactorial behavioral approach using data feedback, physician reminders, education and other behavioral techniques will have an impact.

There is no question that parental and patient attitudes can be improved. If you take the time to read a paper I just published with mainly a fellow who did most of the work, comparing Germany to the United States published in Lancet and Infectious Diseases a couple of months ago, I was astounded to find the differences in attitudes of patients and parents in Germany versus the U.S.

In Germany, by far the request is for alternative therapies for the treatment of upper respiratory tract infections, not for antibiotics. I think there's a lot we can learn from other cultures about how to change the current perceptions.

In terms of our use in the hospital, I have to thank Dr. Rice for putting up this wonderful slide of what happened in Rahal's institution, and what was the answer to this problem? It says here elimination of imipenem resistance through contact isolation, patient cohorting and local use of polymyxin.

For the elimination of imipenem resistant *Pseudomonas* is just ongoing contact isolation and local polymyxin. So if you look in any intensive care unit in this country, you have to ask yourselves why this is a retroactive -- a totally reactive response to a major problem.

How we can have an environment in our intensive care units where still, to this day, study after study after study shows 35 percent adherence to standard hygienic measures. If you were to go into a computer chip manufacturing plant and somebody a second time didn't grease themselves, cover themselves with a mask, a hat, a gown and gloves to make their computer chips, if they did it twice, they would be fired.

We have this attitude that we are all so busy that somehow we can't do any better than this. And of course, the problem is exacerbated by a public

health system which is supporting to a very -- let me use the word frugal, to be nice about it -- extent the staffing of our intensive care units, in spite of the fact that there is now abundant evidence from epidemiologic studies that overcrowding and understaffing leads directly to increased infection rate with resistant organisms.

So I know that's somewhat of an editorial sort of pent up, but this is not a simple solution. It extends from marketing -- I'm sitting here looking this entire time at my conflict of interest, which is, you'll be happy to know, Zosen pen, subliminally getting the feel and touch and look of Zosan all day long and, yeah, you know, I'm impartial. Sure. I'm not influenced at all by this pen or the biscotti that the Pfizer rep brings me when she comes to see me.

So it extends from the patient and the parent all the way up through the agencies that oversee the behavior of the pharmaceutical companies. It's a complex system, and there are no easy answers.

CHAIRMAN RELLER: Thank you. I think next was Dr. Talbot. Then we will come to Dr. O'Fallon, Maxwell, and then to the table at the back at the right. Dr. Rice, you can sequence in after Dr. Talbot, because those ends got blurred a little bit.

George?

DR. TALBOT: Thank you. We've been advised to think outside the box. So I'd like to do something a little different here, which I would like to actually directly answer Dr. Goldberger's questions.

So number 2/1: Nothing I've heard so far suggests to me that the FDA with its experience and competence and charge could not ensure that a focused development program would provide sufficient data to address safety and efficacy for new antibiotic aimed at a resistant pathogen. So I think that the likelihood is very high that that could be successful.

That's in part because, as Dr. Ramirez has pointed out, those are patients who have a major medical need. So the assessment of the benefit/risk ratio can take that into account.

So how could such a focused development program proceed? We have discussed that. It relates to actually slashes 2 and 3 below, which is use of data on sensitive strains, the use of nonclinical data, the use of PK/PD data. I think all those have to go into making the story that gives you conviction about what is going on.

Another important point here to

reemphasize is the surrogate point. I discussed this yesterday again today, as have other people. I think one key -- The distilled thought I would leave you with is that one person's surrogate is probably another person's endpoint.

If we look at that with relation to the delta issue, we have a choice sometimes of changing the delta, which may or may not work, or we have a choice of changing to an endpoint where you can apply a rigid delta and have confidence in your conclusions. I would suggest that some "surrogate endpoints" actually should be true endpoints that can be studied with statistical certainly and lead to an approval.

My last point relates to the Subpart H and the surrogate endpoint question again. I think one disincentive -- and that's the last slash under number 2. One disincentive is the Subpart H requirement for confirmatory trials.

The problem is that, if you have had to use a "surrogate endpoint" in the beginning to get approval, once you've got that conditional approval, it's not clear that it is going to be any easier afterwards to do a confirmatory study.

So I would much rather -- I would suggest that companies and the agency try to avoid, if at all

possible, that situation where they have to do a confirmatory study in humans, because it may not be anymore possible after the fact than it was before.

So I hope that's helpful, Dr. Goldberger.

CHAIRMAN RELLER: Dr. Rice?

DR. RICE: I just want to again echo the importance of education, and I think in one respect, people have talked about diagnostics. Dr. Ramirez talked about diagnostics being ineffective, because people don't use them.

I would predict that strong education, even if people use them, diagnostics will be a failure. All you need to do is walk around the country and look at the number of people who actually have their broad spectrum antibiotic regimen changed because their blood culture has grown out a susceptible organism. I think you will find that the culture suggests that everybody just continues, because they are more worried about what they don't know about than what they do.

So I think, in conjunction with diagnostics, there has to be a very broad based education program. That should probably be based around not preventing people from starting antibiotics, but probably encouraging people to stop

quickly.

Victor Yu and Nina Sing's study out Pittsburgh, I think, is going to be a landmark study showing that you can treat people unlikely to be infected with very short courses.

The other final point I just wanted to make in response to why the industry may be disappointed with linezolid and Synercid: Synercid had some administration problems, but it's clearly just tossed. Linezolid is not being used, because it is five times as expensive as vancomycin, and 90 percent-plus of the infections you are treating with it can be treated with both.

So if industry isn't going to be realistic about that pricing, then all of these will fail.

CHAIRMAN RELLER: Dr. O'Fallon. Then Dr. Maxwell and then we will come to Dr. Yuh and others.

DR. O'FALLON: We've been -- I'm concerned now to change the direction a little bit here. As not being a physician in the field, I'm more concerned about what are we going to be interested in seeing when we are going to have to judge the approval or not of a new drug for this indication. What kind of evidence do we really want to have?

I have some -- I'm very troubled by what

I'm hearing, the suggestion that it doesn't matter a whole lot what happens to the patient, that the important thing is to show that the bugs are killed. It is very important to show the bugs are killed. No question about that. The PK/PD, cidal, the whole ball of wax are all absolutely important and necessary. Not arguing.

I personally would not want to approve any drug that didn't have any -- appropriate, well designed clinical data, evidence.

Now how much would that have to be? Last year or the last year and a half, we have had two applications for labeling for drug resistant. The first one came in with 14 cases, and we said that wasn't enough. The second one came in with roughly 40 and got approval.

What I am suggesting is this. If there are enough patients out there for a particular indication, organism, however you want to go about that, that there should be a properly controlled study, and I do think it should be a superiority study against a placebo; because, face it, folks, there ain't no history here. We're writing history as we go along. There just is nothing that we can trust in the way of history.

So it's pretty much got to be a placebo controlled study, and it should be, obviously, a superiority. We don't want to prove it's less than a placebo. But we have seen some of them with the -- where the organisms are very rare but potent. They are a potential bad problem.

Then I think that we should be -- What I'm recommending is this. I use the word Phase II in a statistical sense, and that confused you all. There are studies that are used to get preliminary evidence of efficacy. They take 25 to 50 patients. If you define your success variable intelligently, you can at least -- and decide ahead of time what will constitute sufficient success -- I will say 50 percent of the patients succeed would be one possibility -- you can design a study with 25-50 patients that will give you evidence about whether or not the new agent or this agent has that success rate or more in the given population.

I would recommend that they at least give consideration to that sort of thing in cases where everyone says there aren't enough patients to do a true comparative trial.

The final point: The folks over there at that table are saying that the IDSA, I guess it is,

will do anything in their power to help facilitate this. I think one of the things we really need is, as Dr. Chesney said and others have said, a network of, I think, community, community physicians who are going to be willing to participate in well designed studies to establish the efficacy of these patients -- I mean of these treatments in specific diseases.

Are there community physicians, and I'm sure there are, who are more than willing to participate in this? Yes, it takes time. It's much more difficult to put a patient on a study and do all the follow-up that's necessary in order to get the endpoints, but I think that's what is needed, and I would like to see something going along those lines. Perhaps NIAID could be helping with that.

CHAIRMAN RELLER: Thank you, Dr. O'Fallon. Dr. Maxwell, do you still have something you want to say?

DR. MAXWELL: Yes, just briefly. I feel that attacking the problem requires a multi-faceted approach, including many of the comments that have been made, the new drugs in the pipeline, looking at site specific versus bacteriologic measures of efficacy and vice versa, surrogate markers. But I think one important point that has been missed is the

consumer, the patient, as Dr. O'Fallon mentioned.

The education of the consumer is extremely important, because as a practicing clinician still, there are many patients that will come to me who have no indication for an antibiotic. Of course, I won't give it to them, and they will go get it even on the Internet now, and they self-treat themselves.

So I think that it behooves us to look at all of the parameters, including a strong educational effort for the consumer and for the industry as you market drugs to consumers.

I think that it is part of the responsibility of the industry also to get the consumer to understand what role they can play to make sure that they are using these drugs appropriately, because most of the consumers just believe, if it's there, you should be willing to give it to me; and they see it as being somewhat mean spirited if you are unwilling.

The explanations that you would give as a clinician often falls on dead ears and, matter of fact, many of the clinicians buckle, particularly clinicians in the community who depend on the patients coming to them will buckle and give an antibiotic even though they are that it's just a viral infection.

So I would say that education should really not be lost and should probably be a real important component of any strategy that we look to mend this fence.

CHAIRMAN RELLER: Dr. Yuh, and others who had their hands up earlier at the PhRMA table.

DR. YUH: As a statistician by training, I think I learned a lot today. One of my jobs is to summarize information I learn. So I'd like to share.

I think we touched many important issues, in particular, for today's topic. We discussed the pros and cons using the surrogate control. We discussed the PK/PD modeling approach. We discussed the surrogate. We discussed other useful things, enriched design in particular.

Everything we are talking about are some pros and cons. I think we cannot generalize for every approach I have heard today to all indications, all the patient population. Perhaps a lesson here is we need a combination of those things here.

Maybe a working group can examine each approach. As Dr. O'Fallon says, which one is necessary? Which ones are neither necessary nor sufficient? Which one is sufficient? So we can help understand which one we can use for which indication.

In particular, I think I also heard about maybe one trial is more pivotal. We can use all information to support, confirm, the first pivotal trial. I think that is helpful to industry as well.

Another one I was thinking about is the safety. The PK/PD, the surrogate marker and so forth may not give enough safety information where we need sometime to show the advantage of the drug. So how we get that information?

This is an Astra Zeneca philosophy. I am sure many PhRMA companies share the same philosophy. We talk about cost, everything. We believe patients come first, science second. Everything else can go to third or we can talk about a boundary later. Thank you.

CHAIRMAN RELLER: Dr. Drusano, can you come up to one of the microphones, and then Dr. Hardalo, you wanted to say something.

DR. DRUSANO: Thank you, Mr. Chairman. Just a brief comment. I've been hearing a lot about setting up networks, and I think that is really a key issue.

I have also been listening to Dr. Goldberger. There are solutions out there but, unfortunately, many of the high probability solutions

require new enabling language from Congress. So we can set those aside. But I think, really, NIAID may have a key role to play in the solution, not to set up study units per se, but to support the development of exportable assays that are going to be probes for the resistant pathogens that you care about, and they have to be exportable.

So once you have that as an infrastructural support, drug companies could then put monies into a place like the Infectious Diseases Society, because they could actually go around and would know where the high probability units are, and they would be different from pathogen to pathogen.

One unit may have a lot of MRSA. Another unit may have Burkholderia. Another unit may have *Acinetobacter*. So if you have an interest in specific resistant pathogens, these should be funded by the companies, but could be helped out by infrastructure support. And I don't think that would require a lot of other enabling language. Maybe I'm wrong.

CHAIRMAN RELLER: Dr. Hardalo.

DR. HARDALO: I actually wanted to underline what Dr. Drusano is saying. I think that part of the reason why it costs us so much to do these studies is that the infrastructure costs are fixed,

regardless of how big you make the study. If you need to have a certain network in order to capture a certain number of isolates or a certain number of patient cases, it's a fixed cost.

We heard very well form Dr. Tally that, even if you are talking about studying an infection that has between 4,000 and 12,000 patients per year, you can expect to spend anywhere from $180 million to $200 million just to bring a drug to market.

Now if we want to recover the cost of that over five years, you can start doing the math to say what your drug price is going to be. So although we are quite sorry that things like linezolid and Synercid are expensive, it took a lot of work, money, time and resources, and there just simply aren't endless quantities of that.

To reiterate what we have also said in terms of how drug companies make their decisions on what to develop, antibiotics universally have fallen in the lower third to middle third of the portfolio when it comes time to make budget decisions based on what we anticipate will be the net present value.

Adding on these additional things which are nice to have like post-marketing surveillance for safety adverse events, post-marketing surveillance for

antimicrobial susceptibility, all of which are perfectly justifiable but are public health services, not the services of a manufacturer of the drug, will simply increase the cost and decrease the net present value of the antibiotic, making it even less likely that a drug company will choose to develop a new antibiotic and bring it to market, especially for anticipated restricted use.

Diagnostics, very clearly, will help, because when you look at community acquired infections, just as Dr. Ramirez has said, why do clinicians not change their prescribing habits when they are prescribing things like Secor and like Cipro? Because they lack the information to tell them to do something differently, either to say it's wrong, what you are doing has a price, or you should be doing something better.

Again, the only setting for placebo controlled trials would be in those respiratory tract infections where it's a viral etiology. It would be completely useless to talk about placebo controlled trials for MRSA pneumonias or *Acinetobacter* pneumonias in a hospital. Basically, the placebo are the antibiotics we already have, which are useless.

So last but not least, I think what we are

hearing is that each one of us has a responsibility to take a piece of the pie, to work together in a consortium to the best solution, as Dr. Yuh has said, sorting out what's a nice to have from what is a must have, what's possible from what is potentially a need, and working forward toward the shared goal, which is figuring out how we can bring better products to market to put them to the best use.

CHAIRMAN RELLER: Dr. Goldmann, and then I want to ask Dr. Goldberger, because I know many of the members have imminent departures, if there's additional information you would like to be brought out to encourage us to do so swiftly. Dr. Goldmann, Dr. Goldberger.

DR. GOLDMANN: Yes. I just have a question maybe the pharmaceutical representatives can help with.

We've talked a lot about setting up clinical trials groups. I'm in charge of the Risk Group IV of a large clinical trial group in intensive care units. One of the issues that I have already confronted is a tendency of some pharmaceutical companies to want to do their clinical trials of whatever agent in their own units that they are comfortable with or whatever relationship they already

have, as opposed to getting involved de novo with a clinical trials group that may or may not have more rigor or resources to deal with the kinds of questions we are talking about today.

The cystic fibrosis community solved that by essentially creating a network which was so all encompassing and so powerful that you virtually cannot do a study in cystic fibrosis without using that network.

So I just want some dialogue around this issue, whether the pharmaceutical industry sees something that the clinical trial groups were talking about can do that will make it more hospitable or make it conducive for them to participate in those networks.

DR. HARDALO: I guess, you know, one of the things that we've learned in terms of being innovators is that the first decision, is there an upside, yes, and a downside, no. Is there a good reason to go through a network? Well, for certain diseases like infections in cystic fibrosis, especially when you are dealing with an all encompassing network, the upside is, yeah, you better deal with them, because the downside is you don't get your study done.

I think we are rapidly coming to problems like *Acinetobacter* where the cases are so widely dispersed that it would be impossible for one company to do a reasonably sized, robust study in the absence of an effective network. However, until we see that we can use organizations like BAMSG, for example, to study these things, there is an unknown, and that makes most companies quite uncomfortable, not to know will we be able to get a protocol through in a reasonable amount of time that will be robust enough to serve the needs of the FDA? Does the FDA accept this, and would a network like BAMSG be in contact with the FDA or at least in conversation in this type of a workshop, so that whatever came out of such a work group would be acceptable for registration purposes?

Otherwise, the -- If the answer is, no, it wouldn't be, and we would have to go through the same design process twice, then nothing will ever go forward for resistant organisms.

So I think there's a definite willingness to collaborate, but again we all have to be on the same wave length.

CHAIRMAN RELLER: Dr. Rice, yesterday Dr. Andriole, you, Dr. Talbot, Dr. Goldmann have brought

this up. It seems to me like this is a perfect opportunity at the council level at IDSA to put together a resistance trials consortium that could collaborate with those groups that we have heard discussed today to take the first step, so to speak.

If it's not used, then in a way it would be a missed opportunity for industry, FDA, CDC, all of those who are interested in this problem. There may be perhaps seed money from the NIH for infrastructure to the IDSA to set up something like this. What do you think?

DR. RICE: I'll be happy to bring that message back and trumpet it for you.

CHAIRMAN RELLER: And, Dr. Miller, is that an option? I mean, we are talking about infrastructure to meet a national public health need.

DR. MILLER: It's certainly a discussion we can continue to have. I think we feel like we have already broken ground with Risk Group IV, the drug resistant bacterial infections in ICU setting, and we want to forge forward with collaborations with industry and to assure you that we do discuss with FDA, you know, when we are getting the pre-IND packages together and make sure that the clinical trials are robust enough to answer the questions at

hand, and that approvals are imminent then if we follow through and we are successful in the outcomes.

You may not know, but the Division where I am located holds over 400 INDs on a variety of products from, you know, antimicrobials, vaccines, and other novel phage therapies and all kinds of things.

So you know, we are not a pharmaceutical firm, but we really are feeling the necessity to partner both on the resistance issue and addressing other public health needs.

CHAIRMAN RELLER: Dr. Goldberger, set us up for the last word.

DR. GOLDBERGER: Okay. Well, I think actually, looking at the questions, there's been extensive discussion of a lot of the points in question 1. I think there's also been pretty good discussion in question 2, and I want to particularly thank Dr. Talbot for his comments, and I would only add to his one comment with regard to the need for confirmatory trials and the concerns about that.

That could conceivably be a place where the longitudinal epidemiologic studies talked about yesterday might conceivably fit in, rather to provide additional information as opposed to being the primary studies to support a regulatory decision, where I

think there were some more concerns about the conclusions one might draw from them.

I think or I presume that the Committee has pretty much discussed the strategies they think were appropriate and whether or not there were any alternative strategies, and that was question 3.

I think we've sort of covered a lot of these issues. I don't know if we have heard anything dramatically new, but I like to think we've at least had a reasonable discussion.

I think there has been at least some discussion about the preserve the efficacy issue. I think that at subsequent meetings this will probably need a little more discussion in terms of how much value we think these approaches have, which approaches are likely to be more fruitful, and which approaches are likely to have the least negative impact in terms of patient care and, particularly, drug development.

So taking into account the fact that we believe there will be at least one subsequent meeting to continue discussion on this topic, and encouraging everyone who has additional comments to provide them to the docket that has been set up and will be effective right after this meeting, we're probably satisfied with what we have heard.

I know everybody is desperate to leave as opposed to having another two hours of discussion just to polish off the fine points. So from my perspective, I'd be happy to provide thanks to everyone. But of course, as the Chair, you make the final decision.

CHAIRMAN RELLER: I think it's been remarkable that we've kept everyone to the end, and I think the concomitant commitment to that is you stick with us to the end, and we will try to finish at a balanced time that would enable people to do that.

So I would like to close today's -- adjourn today's meeting, and will look forward to the continuation of these important issues in different multiple venues and future meetings. Thank you.

(Whereupon, the foregoing matter went off the record at 3:20 p.m.)