

The Pew Charitable Trusts

**A New Pathway for Antibiotic Innovation
Exploring Drug Development for Limited Populations**

January 31, 2013

The Pew Charitable Trusts
901 E St. NW
Washington, DC 20004

Proceedings Transcript by:

Caset Associates Ltd.
Fairfax, VA 22030
caset@caset.net

CONTENTS

Welcome and Introduction	1
Moderator: Allan Coukell, Deputy Director, Medical Programs, The Pew Charitable Trusts	
Session 1: Defining the Limited Population Regulatory Pathway: What It Is, What It Does, and Why It Is Needed	3
Robert Guidos, JD, Vice President, Public Policy and Government Relations, Infectious Diseases Society of America	
Edward Cox, MD, MPH, Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration	
Nicole Mahoney, PhD, Senior Officer, Antibiotics and Innovation Project, The Pew Charitable Trusts	
John H. Rex, MD, FIDSA, FACP, Infection Clinical Vice President, Infection Therapy Area, AstraZeneca Pharmaceuticals LP	
Michael N. Dudley, PharmD, FIDSA, Senior Vice President, Research and Development and Chief Scientific Officer, Rempex Pharmaceuticals	
Christine Welch, MS, RAC, Vice President, Regulatory Affairs, Achaogen Inc.	
Expert Roundtable Discussion	22
Session 2: Forging a Societal Compact: Perspectives on How to Ensure Antibiotics Approved Under This Pathway Are Used in a Limited Population	39
Part 1: Role of Health Care Providers and Institutions in Use of Limited Population Antibiotics	39
Matthew Bidwell Goetz, MD, Chief of Infectious Diseases, Veterans Affairs, Greater Los Angeles Healthcare System; Professor of Clinical Medicine, David Geffen School of Medicine at UCLA	
Steven C. Ebert, PharmD, FCCP, FIDSA, Clinical Pharmacy Specialist, Clinical Supervisor, Meriter Hospital; Clinical Professor of Pharmacy, University of Wisconsin, Madison	
Pranita Tamma, MD, MHS, Director of Pediatric Antimicrobial Stewardship, Johns Hopkins Hospital	
Kavita K. Trivedi, MD, Medical Epidemiologist and Lead, California Antimicrobial Stewardship Program Initiative, Healthcare Associated Infections Program, California Department of Public Health	
Expert Roundtable Discussion	49
Part 2: Role of Payors in Use of Limited Population Antibiotics	68
Jim Scott, JD, President and CEO, Applied Policy	
Saira A. Jan, MS, PharmD, Director of Clinical Pharmacy Management, Horizon Blue Cross Blue Shield of New Jersey; Clinical Professor, Ernest Mario School of Pharmacy, Rutgers State University of New Jersey	
H. Eric Cannon, PharmD, FAMCP, Chief of Pharmacy, SelectHealth; Director, Academy of Managed Care Pharmacy	
Expert Roundtable Discussion	77
Lessons Learned, Unanswered Questions, and Charting the Path Forward	91
Nicole Mahoney, PhD, Senior Officer, Antibiotics and Innovation Project, The Pew Charitable Trusts	
John Powers, MD, FACP, FIDSA, Associate Clinical Professor of Medicine, George Washington University School of Medicine and University of Maryland School of Medicine	
David M. Shlaes, MD, PhD, Owner, Anti-Infectives Consulting	

TRANSCRIPT

Welcome and Introduction

DR. COUKELL: My name is Allan Coukell. On behalf of The Pew Charitable Trusts, I would like to welcome you to what will be a very interesting daylong discussion about a potential new approach to antibiotic development, a new development and approval pathway for limited populations. I do not have to tell anybody in this room about the emerging problem of resistant infections, the alarmingly few drugs in the antibiotic pipeline. There are multiple factors that have contributed to this. Among the most frequently cited are economic and regulatory challenges. The good news is this has been a very active area of policy development in recent years. There are a lot of ideas. This is far from the first such conversations we have had, and it is exciting.

Pew has been a participant in these conversations in recent years and has worked on a number of things, including the GAIN Act, which adds guaranteed exclusivity for certain new kinds of antibiotics. While that provides some benefits, clearly more needs to be done. Today we are here to talk about proposed new FDA approval pathway for ... patients with serious or life-threatening infections in few or no treatment options.

I will leave our first speakers to talk more about the LPAD proposal in detail. Just briefly ... Conceptually, we see antibiotics come to market based on less data, few or smaller clinical trials, but indicated only for use in a limited population of patients where the benefits exceed the risks that could reduce the cost of development making development cheaper and more feasible. It could also support ... and not used inappropriately where they *were* not indicated through ... Dr. Woodcock actually has talked about as a social ...

In theory then, there are a lot of good things about LPAD pathway, but there are also questions. The goal today is to unpack some of these questions, bring some clarity about what we are talking about when we talk about this pathway so everyone is on the same page and then figure out the feasibility.

The fundamental question I think if you boil it down is how would a limited population antibiotic be different from an antibiotic ... traditional pathway. If we think about it a little more, dove into a little detail, the questions, that sort of top-line questions, are is there a viable business model here for developers and what is the interplay between potentially lower development costs, but also limited populations for the drugs and ... and then how would the drugs be used once they are out and available. How would providers, payors, P&T committees treat them? Would they be used in a way that is consistent with the labeling?

We have a diverse group of ... from both business and public health perspectives. Our format today is a roundtable, and shortly I will get our participants to introduce themselves.

It will be a moderated discussion today. We have asked a couple of people to be

rapporteurs. At the end of the day, we will have a couple of people who have been mostly listening summarize what they have heard and crystallize what seemed to be the areas of consensus or the important outstanding questions.

With that, let me begin by first getting our roundtable participants to introduce themselves. I will start with Chris.

MS. WELCH: Good morning everyone. My name is Christine Welch. I am the vice president of regulatory affairs at Achaogen. Achaogen is a small biotech company located in South San Francisco that is developing new antibacterial agents specifically from multidrug-resistant Gram-negative infections.

DR. DUDLEY: My name is Mike Dudley. I am a senior VP for research and development and chief scientific officer at Rempex Pharmaceuticals in San Diego, California. This sounds like this is the biotech corner over here. We are also involved in discovering and developing new agents primarily focused on Gram-negative infections and have also a product now in commerce for treatment of Acinetobacter and also products in development for resisting Gram-negative bacteria.

DR. REX: I think I am the third of the pharmaceutical trio. John Rex. I am the vice president and head of infection development for AstraZeneca Pharmaceuticals. Like my colleagues to the right, we have products in active development for Gram-positive and Gram-negative infections, including products in all stages of development actually.

MR. GUIDOS: I am Bob Guidos. I am vice president for public policy and government relations with the Infectious Diseases Society of America. IDSA represents more than 10,000 infectious disease physicians and scientists.

DR. COX: Good morning. I am Ed Cox, director of the Office of Antimicrobial Products within the Center for Drug Evaluation and Research at FDA.

DR. MAHONEY: I am Nicole Mahoney, and I lead the Antibiotics and Innovation Project here at Pew, and welcome.

DR. COUKELL: Allan Coukell. I oversee Pew's work on drugs and medical devices.

DR. GOETZ: I am Matt Goetz, professor of clinical medicine at UCLA, chief of the infectious disease program at the VA Greater Los Angeles Healthcare System, and a member of the VA's National Antimicrobial Stewardship Task Force.

DR. EBERT: Good morning. I am Steve Ebert. I am a professor of pharmacy at the University of Wisconsin, Madison, and infectious disease pharmacist at Meriter Hospital in Madison, Wisconsin. I certainly look forward to the introduction of new antibiotics for both Gram-positive and Gram-negative bacteria.

DR. TAMMA: Good morning. My name is Pranita Tamma. I am a pediatric infectious disease physician at Johns Hopkins and a director of Pediatric Antimicrobial Stewardship Program. I am also actively involved in research in improving the use of antibiotics.

MR. SCOTT: Good morning. My name is Jim Scott. I am the president and CEO of Applied Policy. We are a health policy and reimbursement consulting firm that works with pharmaceutical manufacturers on market access and reimbursement primarily through the Centers for Medicare & Medicaid Services. I am a former CMS official, and I am here today to present not an official CMS point of view, but what we understand to be how CMS may approach an issue like this.

DR. JAN: Good morning. I am Saira Jan. I am a professor at Rutgers for pharmacy. I am also a director of pharmacy at Horizon Blue Cross Blue Shield of New Jersey. My responsibilities managing the commercial and Medicare population, drug selection, and developing policies to appropriately use the medications.

DR. CANNON: Good morning. I am Eric Cannon. I am chief of pharmacy with SelectHealth. SelectHealth is the payor arm of Intermountain Healthcare in Salt Lake City. I am also a member of the board of directors for the Academy of Managed Care Pharmacy.

DR. TRIVEDI: Good morning. My name is Kavita Trivedi. I am a public health medical officer with the California Department of Public Health. I lead the Antimicrobial Stewardship Program Initiative in California and also manage outbreaks in all California health care facilities.

Session 1: Defining the Limited Population Regulatory Pathway: What It Is, What It Does, and Why It Is Needed

DR. COUKELL: Thank you. The idea of a limited population antibiotic I think first gained, or this pathway first gained, widespread attention early in 2012 as Congress was considering the reauthorization of the FDA user fees. At that stage, it was talked about both as a more general pathway for many classes of drugs and as specifically as an antibiotic-specific pathway. In terms of moving that idea forward, it was really the Infectious Diseases Society that put forward the first proposal. I think Bob Guidos needs no introduction to most people in the room, nor does Ed Cox from the FDA. FDA, I think, has been proactive in talking about how they see the role of this pathway and how it works. We are really pleased to have them lay out in more detail the thinking on an LPAD pathway. Bob, go ahead.

MR. GUIDOS: Thank you very much. On behalf of IDSA, I want to express our deep gratitude to Pew for all your work in this area and for holding this very important conference today.

As a number of patients succumbing to antibiotic resistant infections continue to rise, the number of new antibiotics and development has plummeted. Over the past two decades, we have witnessed company after company withdrawing from this critical area of medicine while the death toll climbs. Now, there are less than a handful of large, perhaps two dozen small companies still actively engaged in antibiotic R&D, and there are persistent rumors that additional companies could withdraw. To lose another company like AstraZeneca or another set of experts like John Rex and his colleagues

would be a disaster for this country. I say this because it is a real possibility.

As we have seen in the past, when a company gets a new CEO, they come in and do a review with product line, and that is happening now at AstraZeneca. To lose that company and these experts would be unacceptable. In fact, it is such an important thing, and I hate to start this on a downer. Someone from the White House or the secretary of HHS needs to contact the new CEO and make sure that they understand how important this product line is to the United States.

In addition to creating new economic incentives, such as the exclusivity incentive Congress enacted last year, we urgently need feasible FDA approval pathways that advance development of critically needed antibiotics.

The uncertain U.S. regulatory environment is the primary reason that the few pharmaceutical companies still investing in antibiotic R&D report that they plan to focus their future efforts outside the United States.

FDA has an essential role to play in ensuring that Americans have access to safe and effective drugs. But in so doing, the agency must ensure that the risks associated with approving new products are appropriately balanced with the new to provide patients in desperate need with access to beneficial products. To date, when it comes to antibiotics and particularly antibiotics needed to treat patients with the most serious bacterial infections, FDA's risk-benefit equation has been out of balance.

The LPAD approval mechanism is a game changer. It will help to rebalance the risk-benefit equation and save lives. LPAD will provide an important new approval pathway option for companies interested in and able to develop antibacterial drugs to treat the most serious infections. At least 14 companies and 24 medical and public health organizations, including the American Medical Association, have lined up with IDSA in support of LPAD's creation.

Why do we need LPAD? It is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional large-scale clinical trials due to the limited number of patients in which these serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness would be studied in a substantially smaller, more rapid, and less-expensive clinical trials, much like the orphan drug program permits for other rare diseases. LPAD products then would be narrowly indicated to be marketed to and used in small well-defined populations of patients for whom the drug's benefits have been shown to outweigh their risks.

Many bacterial diseases have a broad spectrum of severity. The LPAD mechanism is intended to address the needs of a special population of patients with serious manifestations of such diseases who lack satisfactory treatments.

In caring for such severely ill patients with limited treatment options, the patients, health care providers, regulators, and society can tolerate a greater degree of uncertainty about the overall risk associated with a drug than can be tolerated in

patients with milder manifestations of the disease or those who have more satisfactory therapeutic options.

The LPAD mechanism will not be used to approve antibacterial products that treat less-serious infections or infections where sufficient alternative therapeutic options exist.

If a company chooses to seek an LPAD designation for its antibiotic and FDA approves the designation and ultimately approves the drug, then the drug's label would include the special designation, a description of the indicated population, the rationale for limiting the indication, and a special LPAD logo.

Through this high-profile new label, FDA would provide notice to the health care community, providers, payors, and patients that these products carry greater uncertainty—that is, less-precise estimates of risk. And as a result, the drug marketing and use will be limited to the indicated population. An added benefit, LPAD's products limited marketing and use would help slow the rate at which resistance to these drugs develops, an important goal of the medical public health and patient communities.

Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physician's hands. FDA will have an important role to play in ensuring that appropriate conditions of use are described in a drug's labeling, but will not have a role in authorizing or prohibiting use of approved products within the practice of medicine. However, FDA will be able to monitor LPAD products' safe use through its existing Sentinel system.

Why would companies pursue a product that would have more limited use? Currently, antibiotics are typically priced far below their true value to society. As with orphan drug designations, an LPAD designation is expected to increase the price of these drugs markedly compared with traditionally approved antibiotics, making investment in LPAD antibiotics more attractive to companies.

The drug's higher price in turn will encourage payors, the health care community, and providers to play a more active role in ensuring LPADs are used narrowly, as indicated, which will also help preserve the drug's effectiveness over time. Pricing LPAD drugs at a premium is easily justified based on the severity of the targeted disease, the limited availability of alternative therapies, and by granting the patient potentially decades more of quality life due to the effective therapy. In addition, because multidrug resistant infections are more expensive to take care of than susceptible infections, LPAD's premium cost will be offset by reducing excess health care costs due to resistance.

I want to address two misperceptions that I recently read about in various media reports about LPAD. Over the past year, I have heard nothing in my discussions with FDA that would signal the agency has any interest or plans to take actions to penalize physicians who might prescribe LPAD drugs off-label or to otherwise implement restrictions on off-label use. From the ID physician perspective, this would not be supportable.

It is a fact that the vast majority of inappropriate antibiotic use that has occurred, and is

occurring, is actually use that is on-label. Because FDA's traditionally labeled indications for antibiotics are very broad and allow companies to market these drugs widely to physicians across the country, examples of these indications include treatment for respiratory infections, many of which might be caused by a virus or skin infections. Not surprisingly, marketing works. And the drugs are then prescribed widely in ways that are not prudent.

Some of these widely marketed drugs might be extremely useful for treating very serious infections. But instead, they are being used to treat more common infections or infections where alternative treatments exist. All of this is in compliance with the broad existing label. This broader use prompts the development of resistance and is problematic. LPAD drugs would include narrow indications that are more consistent with antibiotic stewardship principles.

There are also built-in protections that would further limit off-label use. First is the premium pricing expected for LPAD products. The marked cost difference versus other agents will reduce LPAD off-label use, particularly if premium reimbursement models restrict reimbursement to on-label uses only.

Second, medical liability concerns will deter physicians from using these less well-studied drugs off-label. Third, most of these agents will be parenteral—that is, not pill form. There will be no opportunity to use them for more common outpatient infections.

The final point is it is absolutely critical that we not ban off-label use of LPAD drugs. Off-label use of antibiotics typically occurs when physicians are confronted by problems that on-label drugs are not equipped to handle. Patients will be harmed if off-label use is banned. For example, let's say an antibiotic that treats KPC *Klebsiella* in the lung and blood is approved via LPAD. A patient develops KPC *Klebsiella* infection in the brain. His or her physician should not be banned from using the potentially lifesaving drug for the brain infection. The patient will have a much higher chance of dying if that off-label use is banned.

If we want to reduce inappropriate antibiotic use, the key is not to create enforcement mechanisms that target off-label use. It is to control the label as LPAD does to ensure that on-label marketing is more narrowly targeted.

In summary, the adoption of the LPAD mechanism will create a new anti-infective drug approval pathway that permits a more appropriate risk-benefit ratio for serious infections and will bring lifesaving medicines to those patients most serious in need of them. It will empower FDA to innovate the antibiotic pipeline by providing them flexibility to more rapidly approve urgently needed medicines. It will rightly leave in physicians' hands the power to oversee the use of approved products within the practice of medicine. It will provide a streamlined approval pathway that will enable pharmaceutical companies to study LPAD drugs in far fewer patients than currently is required, more rapidly, and at significantly less cost. It will place a higher evaluation on these precious drugs among payors, providers, patients, and society in general. It will ensure the burden of protecting these drugs is on those stakeholders best positioned to

ensure their appropriate use that is health care providers, health care systems, payors, patients. And finally, it will create an even great incentive to establish critically needed antimicrobial stewardship programs in health care facilities across the United States. Thank you.

DR. COUKELL: Thanks, Bob. Dr. Cox.

DR. COX: Thank you, Allan and Nicole, and the folks at Pew for having me here today. I appreciate the opportunity. Thanks, Bob, for describing LPAD. We greatly appreciate all the important work that folks at IDSA are doing in this field.

You will hear, as I go through this, some common themes to some of the stuff that Bob has just talked about. We did not get a chance to share beforehand, but I almost put that out there as valuable to the group here. My hypothesis will be interesting for you all to hear what I say, having heard what he just said. And next time as we plan for the conference, when asked who should go first, I will make a note here.

Let's first take a step back in time and see what has gotten us in the current situation that we are in. If we think back into the 1990s, the early 2000 time period, development of antibacterial drugs typically involve broad development for a wide range of infections. Oftentimes the severity of infections in a program range from mild to moderate if it was an oral drug and may actually go to severe if an intravenous form was available. But typical, multiple-indication NDAs were commonly what we saw for development of new antibacterial drugs, these broad programs.

Beyond that, too broad use really seemed to be the goal of these broad development programs. The risk-benefit for these drugs needed to be appropriate for this full range of infections from mild to moderate, and severe if included. This led to large development programs to study all these indications and also to accrue a large enough safety database to support the range of severity of infections that drugs resulting from these programs were developed for. No question, a number of these drugs remain on the market as important drugs that we rely upon today to treat patients. Unfortunately, some in the post-marketing setting were found to have infrequent serious adverse events that have led to the products no longer being marketed.

If we look at the last five to 10 years, the number of antibacterial drugs reaching approval has decreased significantly. The degree of innovation in the field has not kept pace with resistance and patient needs. All the while, resistance and new resistance mechanisms have been churning along and eroding away at our therapeutic armamentarium. That is leaving some patients without treatment options for the infections that they have.

The antibacterial pipeline had already been faltering in the late 1990s and 2000 and then the events around Ketek, a broad-use oral drug targeting indications in the respiratory tract, among other things. Further increased uncertainty led to controversy in the field.

Examining what has happened over the last decade, the degree of development and

innovation to antibacterial drugs has not been at a level that has been sufficient to be able to meet patient needs.

And no question that all would like to see precise characterization of safety and efficacy that was very precise, but the last five to 10 years have also reminded us of practical feasibility and patient needs that are out there that need to be met.

It seems clear from experiences over the last decade that the practical reality of antibacterial drug development based on large development programs that we have seen in the recent past are simply not a sustainable model for antibacterial drug development. Even beyond the broad development of the past, the more recent later stage traditional development that we have seen has been fairly limited and predominately in the area of skin infections.

The scientific challenges and economic realities make the current situation not a feasible model for antibacterial drug development in order to be able to meet patient needs.

Where are we now? What we are seeing now are some patients with infections for which we have few or no available antibacterial drug treatment options. We need new options to treat these patients. We need to take steps to avoid in some cases, in essence returning to what would be a situation similar to the pre-antibiotic area.

We also can predict, from what we know about resistance, that selected pressure from antibacterial drug use ... we all recognize, too, that even appropriate antibacterial drug use provides selected pressure, that resistance will continue to be a problem.

How do we get to a model for development, to new antibacterial drugs that will allow for the development of new antibacterial drugs for patients, to meet patient needs, expedite the availability of new, safe, and effective antibacterial drugs for patients with the greatest need, and provide information to practitioners so that they are aware of the risks, the benefits, level of uncertainty for new antibacterial drugs, focusing on drugs that are approved based on more-streamlined development programs focused on areas where patients have limited therapeutic options where unmet need exists?

Over the last year, there have been discussions about more streamlined and expedited development programs. We have seen some early signs of renewed interest in antibacterial drug development focusing on patients with serious infections, where the use of the product would be for patients with serious infections with few therapeutic options.

The programs that we have been discussing are smaller development programs that will provide evidence of safety and efficacy for the intended population of patients for whom we lack treatment options. These programs are at very early stages of development and even with an expedited approach to development, it will still likely take several years to get a new product to market. And we also have to keep in mind that only some development programs are successful.

If you think about development focused on patients with unmet need, you can see that

the risk-benefit and the ability to tolerate uncertainty is much different when focusing on the use of the drug for patients with serious infections with few or no available therapeutic options. This is a very different risk-benefit consideration in an antibacterial drug intended for broad use and broad range of severity, and patients who have other treatment options.

If a development program that targets a more limited patient population, patients with unmet need, are successful, the labeling would describe the drug, its indicated use for use in patients with limited or no alternative therapies. It would also provide a description for the basis of the approval so that the risks, benefits, and uncertainties for this drug are available to the health care community in order to facilitate appropriate prescribing choices.

The more limited development program holds promise as a pathway for the development of new drugs for those patients for whom there is a critical need for new antibacterial drugs. This is a different approach from antibacterial drug development of the past, which often targeted broad use.

This focused development approach in areas of unmet need also presents practical challenges in the antibacterial field because of the wide spectrum of severity for bacterial infections. You have mild, moderate, and severe infections. And then, added on top of that, is the other dimension of unmet need, in the setting of serious infections.

If one thinks of the spectrum of severity for infectious diseases, you can think of mild, moderate, and then go out to severe and then add another category or out in the severe of the area of unmet need. Past programs would develop safety databases to provide risk-benefit across this whole range. Now, what we are focusing on is the area of serious infections, so this pole and adding that additional dimension of areas of unmet need.

For many patients, though, as we think about the other end of the spectrum here, the mild/moderate, the patients who have existing options, will provide appropriate therapies and choices for those patients. But in the setting where there is serious infection and unmet need a greater degree of uncertainty is appropriate given the greater benefit that will be provided to those patients who do not have options.

Another challenging factor in the area of selecting antibacterial drug therapy, or deciding to initiate antibacterial therapy, is the issue of diagnostic uncertainty. It poses an additional challenge in this area. It is critically important that appropriate use of these drugs by the health care community is really a very critical component of this overall approach to developing antibacterial drugs for more limited patient populations with serious infections and unmet need.

The approach of focused development should lead to a focused indication for patients with serious infection and unmet need, should facilitate the earlier availability of new antibacterial drugs for those who need them most, will lead to risk-benefit assessments that are appropriate for those with serious infection who need these drugs most and should help a faltering antibacterial drug development pipeline that was providing only a few options and not keeping up with patient needs.

Now with this approach, how do we make this a successful, durable, and sustainable pathway for the development of new antibacterial drugs to meet patient needs? We talked about the streamlined, more-focused development programs and the risk-benefit for a more focused development patient population with serious infection and unmet need. We need to think about how to achieve appropriate use of these products. A lot of this will be dependent upon the engagement of the health care community to facilitate appropriate use of these products. It was great to see as we went around the panel and looking at the agenda that we have providers, we have payors, we have folks from the health departments. They will play a critical role in the appropriate use of these products.

Critical components to achieve success, durability and sustainability of this approach in order to be able to meet patient needs are a clear way to let the health care community know that the database and the risk-benefit and uncertainty for a streamlined development program is different from what folks are accustomed to in the past. Provide the health care community a signal or a quick and easy way to identify such drugs. Then also, to provide the health care community information on the risks, benefits, and uncertainty based on the current knowledge base for the products so that they and their prescribing choices can use the drugs appropriately.

Success is necessary first and foremost so that the drugs are used appropriately for the treatment of patients with infections where the risks and benefits are appropriate. And second for the continued durability and sustainability of such an approach for future patients because we know unmet need will continue on into the future. I think this is in part what is meant by the term "social compact" in essence is being a key component of this approach.

A few summary points in closing. The need for new antibacterial drugs is urgent. We have patients now with infections who need new treatment options now. We are seeing some early interest from pharmaceutical companies in more streamlined development programs targeting serious infections in areas of unmet need, but we have to recognize that even the early interest in streamlined development programs will take time to get a new product to market to be able to treat patients. And some of these development programs, as we know, will not be successful.

It will be very important for the health care community to understand the risks, benefits and uncertainty for a more streamlined development program and to use a drug that is a product of a more streamlined development pathway appropriately as they make their prescribing choices. Engagement of the health care community will be important for drugs developed in using such a pathway and will be critical to their appropriate use. I thank you for your attention.

DR. COUKELL: Thank both of you for really laying out a nice description of LPAD to get us started. I know that both of your presentations probably raised a lot of questions, which we will get into.

Before we move on with that, I want to introduce or reintroduce my colleague Nicole

Mahoney. One of the things we want to try to do today is make the conversation as concrete and real world or specific as we can. Nicole has spent some time working with our panelists, working with some of you in the audience, to develop some hypothetical drugs. They are really straw-man scenarios that we think help crystallize what we may be looking at here.

DR. MAHONEY: As Allan mentioned, we wanted to make this conversation a little bit more concrete, and we constructed these hypothetical drug models to do that, to suggest the types of antibiotics that may be tested under a limited population program. This information can be found in your binder. I am not going to go through it in excruciating detail. I just want to familiarize everybody with it.

These drugs are made up. They are not based on any specific investigational drugs. And they are intended simply as a frame of reference and a discussion tool for this meeting.

The models that we constructed are based on a recently published regulatory framework proposed by members of the pharmaceutical industry, and they were fine based on our conversations with various groups. And that paper that describes that regulatory pathway is actually also in your folder.

The framework that we base this on outlines four levels of evidence that could be sufficient to support FDA approval as just a proposal. The different levels are called Tiers A through D, and each one matches the level and types of safety and efficacy data with the magnitude of unmet need. In other words, less evidence might be used to support the most-needed antibiotics.

At one end of the spectrum is Tier A. That is the traditional drug development pathway with two large trials. At the other end is Tier D, the animal rule. Tiers B and C provide a middle ground and a potential development path for limited population antibiotics. That is where our drugs that we made up land.

Today, we do not want to get bogged down in a very detailed discussion about clinical trial design or the evidence required for FDA approval, although we understand that is going to be part of the conversation. We just feel that those issues are being addressed at length by several other groups, and we want to focus on some of the questions that are not being tackled yet.

Instead we want to convey the types of antibiotics that might be approved under the proposal and get your feedback on that. If we are off base, please tell us. We want to give you an idea of the estimated number of patients that might benefit from limited population drugs to give you an idea of a potential market and the price that these drugs might command because we have already heard that they will probably be priced at a premium and perhaps even oncology pricing.

I want to emphasize that we realize the limitation of our methods. We use public data sources. And it is particularly true, the limitations are particularly true around the market estimates. But we still hope that the following information will serve as a useful discussion tool for this meeting.

We came up with two hypothetical drugs. The first drug is hypothetical drug B, and that is because its development program is based on the B model in the paper I described. This would be a broad-spectrum IV drug initially developed for a limited population of patients with infections caused by multidrug-resistant strains of *Klebsiella*, *E. coli*, and *Pseudomonas*.

We do agree that most of these drugs for serious and life-threatening infections are going to be administered in the hospital and will be IV drugs. But we want to keep in mind that that may not always be the case. For one, we know of some development programs where drugs are being developed in IV and oral formulation. And secondly, some IV drugs are administered in places other than the hospital setting. We have to keep that in mind because different reimbursement strategies apply, for example.

We estimated a potential market for a drug like this to be about 75,000 multidrug-resistant hospital infections out of about 500,000 total, again made up based on available data.

And the clinical trial development program would consist of one standard Phase 3 trial in a particular type of infection. In this case, we chose complicated intra-abdominal infections. And small prospective studies of multidrug-resistant organisms at various infection sites. This would all be underpinned and supported by Phase 1 trials, microbiology, animal safety data, and animal infection models for efficacy exposure.

In total, the analyses would include for more estimated about 500 patients treated with drug B and a safety database of about 700 across all the studies I described.

We think the projected R&D budget will be less than \$150,000 for the preclinical through Phase 3 program. Projected pricing...again, this is made up and tough for us to figure out—but we assume it would be from about \$2,000 to possibly \$10,000 per course.

As mentioned, these types of drugs will have very different labels from what we are currently used to. I put up a hypothetical drug label. The label will highlight the data that was used in support of approval of the drug and point out its limitations. It will also specifically state that drug B is only indicated in situations where other therapy is not available or inappropriate.

The second model is hypothetical drug C. That is based on the Tier C development program described in the paper in your folder. That consists of a little bit less evidence, and presumably, this would be used in cases where there is a big unmet need and severe infections.

It is a narrow-spectrum IV drug with activity limited to *Pseudomonas*. Just one organism. We estimated the potential market could range from 20,000 to about 55,000 multidrug-resistant *Pseudomonas* infections out of anywhere from 140,000 to 540,000 or so cases total.

In this case, the clinical trials are going to be smaller prospective studies and descriptive

data based on *Pseudomonas* infections at various infection sites. And, again, that will be underpinned by some Phase 1 trials, microbiology, animal safety data, and animal infection models.

In this case, the analyses would include about 300 patients total treated with drug C and a safety database of maybe 400 across all studies. The projected budget on that would be less than \$100 million. And our projected pricing based on discussions we have had would be anywhere from \$15,000 to \$30,000 for a course. Significantly more than what we are used to.

Again, the label would be restrictive, talking about the limited data used to underpin the approval and it would also explicitly state that the drug should only be used if other alternatives are known or suspected to be less suitable.

Like I said, we are hoping that this gives some context, particularly if people who have not necessarily thought about it in concrete terms, and we are looking forward to a discussion on what we have presented and how it might fit into what other people are thinking about LPAD. Thank you.

DR. COUKELL: Thanks, Nicole. Let me move to the remainder of the speakers on our first panel. I am just going to go in the order that they are on the agenda. John Rex from AstraZeneca.

DR. REX: Thank you. Thanks, Allan and Nicole, for organizing this. This is a really important day, and I am glad all of you also have chosen to spend your time here, because we all choose everyday what we get up and do. You do not have to do this. There are many other things in life. I am grateful that there are this many people interested in this area.

I am going to respond quickly to Bob, who has asked a question about AstraZeneca. AstraZeneca is very definitely in the anti-infective game. But your notion that it would be nice to have all of the CEOs who choose to have their company spend time in this area be thanked for choosing to spend their time that way is an outstanding one. This community needs a diverse vibrant pipeline of drugs. Mike and Christine, to my right, are my competitors, but they are also my dear colleagues, and I want them to succeed because we need all of these drugs. Diversity is the key. Thank you.

From our standpoint, we are delighted to hear the discussion we have had so far. We have been particularly delighted to see the progress on the regulatory environment. I really do want everybody to take a look at this paper, and not just because I am the first author, but because it actually represents the detailed work of a significant community of people. Everybody listed on there worked very hard over a period of 18 months to develop these ideas. They have been hammered out in multiple public conversations. The key is the figure on Page 3. That is the heart of this, and Nicole has sketched it very nicely.

For us, the real value of this is twofold. One, it gives you a language. We now have a way to talk without spending an hour figuring out how we are going to talk so we can now

talk about Tier B and Tier C. And it addresses the notion of pathogen-focused drug approvals. Tier C is very much about a pathogen-focused drug.

The EMA has recently proposed guidance and had a workshop on that guidance that reflects these concepts. And the FDA has also likewise clearly signaled an intent to develop a similar work. The GAIN Act embedded in FDASIA requested them to do this. And there is a workshop on Monday about this general topic. Very good things.

But the path forward is still challenging. I would like to put my comments on three things. The first is that approvals via this tiered approach will require resolution of the problem of small data sets. The size and scope of statistical inferential testing, which is near and dear to the heart of drug approval, will be very much reduced if present at all, relative to traditional approvals. And as a consequence, both sponsors and regulatory agencies would find value in having new ways to describe the risks and benefits. I think that is what today's conversation is about, is how to clearly signal that we are doing more with less.

To this end, we think that a special mark or category for new antibiotics would be a useful tool. Is it absolutely, 100 percent necessary? No. The regulatory tools exist to permit it to be done. Look at the orphan drug legislation for ideas that are very much along these lines. But on the other hand, we really do see that this tool could be very helpful to both regulatory agencies and to sponsors.

As we approach the question of doing it, I have two concerns to raise about doing this. The first is that if we undertake it, we would want it to happen quickly. I would not want to see this be a process that took three or four or five years, during which time we are all saying, "Can we approve an antibiotic or not?" If we are going to do it, let's do it.

The second thing is something that Bob talked about at length, which is to say that the labeling language associated with this category must recognize the distinctive nature of antibiotics and the fact that while traditionally labeling for antibiotic studies, everybody's site, we study the lung, we study the sinuses, we study the skin, we study the urine, we study the belly. Many of the patients that I have taken care of in my lifetime have either not read the textbook, so they will have an infection in a site that is less clearly defined than one of those; or they will have an infection in a site that is not easily studied in anything less than a geologic timeframe. When I have to treat somebody with a brain abscess, they are not interested in me saying, "Come back in five years, please." I need an answer right now.

It is important to recognize that physicians have long utilized the powerful ability of preclinical testing to tell you how much drug it takes in your blood, in your plasma, or in your tissue to treat an infection. That kind of scientifically appropriate guided thinking is a lot about the way antibiotics are used. And what I would say to you is that sort of scientifically appropriate guided thinking is what the label should describe. You need to describe what has been done: We studied this site. We studied that site. And you need to describe what else is known: What is the blood level here? What is the blood level there? And then say, "We have never studied the brain. That is a data free zone."

But if you get in trouble and you have no other choices, here is the information that we think is most reliable in making up your mind. The label can definitely do that. It can provide the best data so that a learned intermediary, a phrase I learned recently, a skilled practitioner, a pharmacist who knows his or her PK/PD can think it through really carefully and say, "Yes. That makes sense to me."

The other thing that I would raise as a concern is I want to draw a line between two words that is very easy to get confused about. The words are serious and severe. This is a really important idea that I have to bring up, because I actually heard them being tangled up a little bit already this morning.

It is important to recognize that ... I am going to define them carefully. Serious is the threat to your life that an infection provides. An infection is serious if it could kill you. It sounds reasonable to me. Serious if it could kill you. An infection is severe if at that moment you are hypotensive and in my ICU. Got the idea? Severity is how sick you look. Serious is how sick you could get.

Let me tell you a story. When I was a medical student, I admitted a 20-year-old young man who about two hours before had acutely developed what turned out to be pneumococcal pneumonia. He had an absolutely classic bacterial pneumonia, *Streptococcus pneumoniae*. He had spiked a fever. He had started to cough up sputum that had blood in it. He had a shaking chill, and he was scared. However, he was sitting up on the gurney in the emergency room. He was absolutely talking to me. Was he hypotensive? No. Was he severely ill? No. Actually, the young man's physiology was just fine. However, was he seriously ill? That is the interesting question.

Without antibiotics what is the mortality rate of a 20-year-old man with pneumococcal pneumonia? If you are the heroine of Jane Austin's "Sense and Sensibility," you develop pneumococcal pneumonia, and you lay down in the bed. What is your mortality rate if you are 20 years old? It is one in six. What is your mortality rate if you are in the over-50 club? It is two out of three. Whether or not you are hypotensive in the ICU, if you have bacterial pneumonia, you have a serious, life-threatening infection. And indeed, if you survive without antibiotics, you are in a recuperative phase for six months. Look it up. It is extraordinary.

There is no such thing as a nonserious bacterial infection. Every one of them can kill you. The real question is how severe are you at the time. Please be careful with the words, because it is easy to get tangled up in the themes. And we can develop our best data in people who have more severe manifestations of serious infections if you now follow the logic. But if you insist on only people in the ICU, that actually becomes a smaller and smaller subset. There is a bell-shaped curve. Most people are in the middle of severity. You have to focus it in a place where I can do enough work in a reasonable period of time to be able to study the patients. That is my plea.

In summary, AZ would welcome work on a special mark or category. LPAD is a great abbreviation. Such work should not delay the progression of current pipeline antibiotics. Resulting labeling should recognize that appropriate use encompasses scientifically

informed use of an antibiotic to treat an infection at body sites not yet formally studied. When pharmacokinetics and pharmacodynamics are brought together, a scientifically informed physician can make a sound decision about using an antibiotic in such circumstances. And finally, be careful with the ideas of serious and severe. Thank you.

DR. COUKELL: Thanks John. Let me pass the clicker down to Mike. If we could get Mike Dudley's slides up please. Mike, as you have heard, is with Rempex Pharmaceuticals.

DR. DUDLEY: Thanks Allan. I, too, would like to echo the remarks earlier about thanking Pew for organizing this. This is an important conversation to have. We are grateful as a small company to begin to give you a perspective of how we view this world and bring things forward. But I think as John said, we are all in the same very small lifeboat right now, in terms of developing these agents together, and it is very helpful to actually talk about this in this way.

What I would like to do is ... I was anticipating that a lot of the issues that you have already heard would hopefully be discussed before I had a chance to speak. I want to address a few other things that I think that are very important and probably will not necessarily get discussed in this panel, but will be important, I think, for the ensuing sessions that come on this afternoon. And they talk about things in antibiotic R&D that actually go beyond clinical trials with respect to making sure that we can get these drugs available into the hands of clinicians and appropriate use in patients. Those issues are related to drug development that are going to be important to identifying those patients and supporting what we would view as very important efforts in stewardship as well.

Secondly, the issue of how do we financially bear the types of costs in our health care system that are going to be needed to bring forward agents such as a Tier B or Tier C. We would like to talk to you about some concrete ideas about that, as well.

I think you have heard about the fact that of all the challenges that have been brought forth both from a regulatory as well as from a clinical use and industrial standpoint as well and there has been a massive exit from this field, certainly from the large pharmaceutical companies and have left really small biotechs or small companies to really fill this void and undertake actually the very risky, early stage discovery and development activities that are important to bringing these drugs forward. We view LPAD and other proposed pathways that Ed alluded to here are important ways to rapidly advance these things and to certainly enable companies then and investors to attain the successes for innovation and risk taking that is really part of that early process as well.

As I have mentioned, there are other issues besides clinical trials that have been left unsaid. I would like to cover some of those in some of my comments. But some of those involve simple things, rather dry, things like manufacturing or CMC and also susceptibility test development. We talk about resistance, and we talk about sensitive, but where does that come from? How do we know that? And that is a step that is going to be critical not only to identifying patients who should receive these drugs, but also for supporting stewardship activities and ensure their appropriate use. If we do not address

those, it is my fear, and I think those of others, that the benefits and the risks that we take with uncertainty without LPAD-like programs could be lost.

Finally, it is important to address the pricing issues I have talked about as well, because small companies like mine and Christine's are dependent upon raising capital from the investor markets, from venture capital markets. There are small companies that are in this area as well. It is important for us to have a clear pathway as well as for large pharma to be incentivized to get back into this space. That helps both of us. That helps large pharma and small pharma alike in moving forward.

I have summarized here just to give you a picture of where our baby is coming from. Where are they actually, the drugs that are in the pipeline or recently approved? What you will notice here is what I think many know, but perhaps have not appreciated, in terms of the debt that the drugs that we have in development now or that have been recently approved that address some of the critical issues particularly in the Gram-negative spaces you have heard are from small companies. They come from small companies that raise capital from private investor market pools to undertake some of the most risky steps that take place in the drug discovery and development process. That is, finding a drug that actually should go into people and getting that drug into to the people for the first time and figuring out what the dose needs to be to be studied in a larger group of patients.

You can see there that these are originating from small companies. And, in many cases but not all, being passed on to larger pharmaceutical companies, which in the past, have put their shoulder to the plow in terms of doing the more-expensive, large trials across different populations as you have heard about earlier as well.

While large pharma, though, has traditionally carried these agents into the later stages of development, because of the exit of these companies is that smaller companies now are having to raise the capital to take these things farther into the development process and even, for example, in the case of Telavancin, to approval.

What are some of the other areas that I think that we need to be thinking critically about in terms of bringing drugs forward here and that we need to solve? There are more issues, as I said, than just clinical trials. Susceptibility testing. We oftentimes, as John appropriated, we are oftentimes loose in our terminology here. What do we really mean by that? What are we talking about in terms of susceptibility testing? Infectious diseases and antibacterials is actually the foundation of what everyone calls personalized medicine. It has just been going on for 30 or 40 years now because we have actually been able to study a patient's disease agent in the absence of a host. You can take the bacteria into the clinical laboratory or the hospital and find out what drug is appropriate for that patient. This is foundational in terms of actually identifying patients who should receive this drug, yet we do not talk about how this is done in many cases. It identifies the drug as being active or the organism is sensitive to the drug or resistant.

This is a key tool in patient care. It is also a key tool in stewardship, in terms of getting the right drug to the right patient as well. In fact, this has been recognized. In fact, in FDAAA in 2007 written into the law, and IDSA and some of us were part of that discussion of actually having up-to-date criteria definitions for existing drugs is extremely important because the reliance of clinicians and others to do that.

Now anybody who has ever taken a freshman microbiology class or even in high school microbiology has actually probably dropped a disk on a lawn of bacteria and looked at the zones and said that is how I tell that an antibiotic is active against that pathogen. That indeed is how it is. This is technology that goes back to the '40s in terms of developing or even longer than that. But that is cumbersome, and most hospitals do not do that anymore for obvious reasons, because it takes a lot of time to do that.

In fact, there are automated susceptibility testing devices. Many of the technologies were actually developed for moon shots. We could actually find out if there were nasty bacteria on the moon that astronauts would not bring back to them that fit in a box, as you can see on the bottom of this slide here. Those testing devices are used in hospitals to actually identify whether the drugs are active, and they are regulated by FDA's devices.

The problem with these is that the regulatory pathways for approval of these devices for new drugs often lags one to two years after the approval of the drug. Clinicians do not have a routine way of knowing whether these new drugs are going to work in the patients and the organisms within their own institution. That needs to get fixed. That needs to get fixed for these drugs to be used in the right patients, and it needs to get fixed in order for stewardship processes to take place for that.

Clinical microbiology can still do this. They can do what is known as offline manual testing, which is like the high school student in a microbiology lab. They can do that. It is slow and laborious. Or even some hospitals and formularies will not accept a drug unless there actually is one of these tests available. We could work real hard and get these drugs available, and nobody is going to be able to test them and use them routinely in that as well. We need to address that to really support these efforts.

The second area that I want to cover is manufacturing and cost of goods. That is going to figure into some of the discussion about how these things are going to be priced as well. Antimicrobials, as has been pointed out by many, is, they are given relatively large doses. We are talking about not microgram or milligram doses, but we are talking oftentimes in gram doses of these drugs. When you are developing these drugs under accelerated paradigms, you have to solve problems very quickly in terms of how you make grams of these things very quickly to support even the most moderately sized clinical trials.

For some classes of drugs, the number of manufacturing sites is very limited for data facilities. For example, you cannot be manufacturing a beta-lactam antibiotic alongside a tetracycline antibiotic. They have to be dedicated facilities because of concerns about allergenicity and cross-contamination, and it even goes further because there is a

difference between a penicillin and a carbapenem. We have a very small, shallow pool in which we can go and get that done.

The limited development programs that we are talking about, in terms of clinical development, place manufacturing activities squarely on the critical path. We could take the pathways that we are talking about now and doing more-efficient trials and answer the questions about the focus, the risk-benefit, but then we may not be able to manufacture those drugs quickly enough. You can throw money at the problem in some cases, but sometimes it just takes time.

We need to be thinking about whether or not we have appropriately balanced the risk just like we are doing on the clinical setting and with experience in patients with the appropriate uncertainties that we have in terms of having a perfected manufacturing process when a drug is being launched into commerce as well.

When you are at the early stages, you are not making things at the metric-ton scale. You are making it in kilogram quantities and therefore it is very expensive. Again, pricing now enters into this discussion because we are not now just talking about covering the cost of the investment of developing the drug through the clinical and preclinical spaces.

But Rob and I were just talking about just covering the cost just to make it. The cost becomes a very important part of this equation, not only for that return on investment for taking all the risk of the early stage development, but also just to pay to make the drug to get it into the pharmacy or the hospital. Sure, we can charge higher prices for this, \$10,000 to \$30,000 a course, as Nicole has showed you. But there is a shifting cost in already strapped hospital budgets going to solve the problem. We need a better model for financing these LPADs as well, because we are going to accelerate. We are hoping to get there sooner, as others have pointed out here as well.

The problem is that the incentive has been in the past for an innovator company to sell as much drug as possible to try to get your return on investment to try to cover those costs. That is at odds. What we all know is good for society. The reserve is important antibiotics to patients with limited treatment options. We have to disrupt that cycle. We cannot do that anymore.

This is a classic example of a market failure where it requires an intervention and a new financing model to protect the nation's long-term health. There are government programs that are already in place that could be modified to do this and address an LPAD-like antibiotic. We will look forward to talking about this and introducing some of these ideas in a later session in an acronym known there as RADARS, which would reward antibiotic development and responsible stewardship for developing these agents. Thanks.

DR. COUKELL: Thanks, Mike. Chris Welch from Achaogen.

MS. WELCH: Hello. Again, I would like to thank Pew, Nicole, and Allan for the opportunity to speak today. It is a very important discussion and one that Achaogen, a small company, is very appreciative to be involved with.

We have two molecules in clinical development. One molecule that is ... in Phase 2 study and moving into Phase 3. And a second program in early Phase 1 clinical development. Of course, for a small company at standpoint, any new regulatory mechanism that provides or supports feasible time-efficient and less-costly development plans would significantly improve our ability to bring new antibiotics to patients who need them.

But also forefront in our minds is the need to have a clear regulatory mechanism, a high probability of regulatory success, and then thirdly and ultimately present a compelling return for investment to our investors. These are very important concerns for us and I also acknowledge they are for all drug developers. But for a small company like Achaogen, our development plans will stop if we cannot continue to maintain the support from our investors.

And for Achaogen, the funding for our programs comes from both private investors, but also from government funding. I would like to acknowledge and express our appreciation for that aspect of our funding, and particularly and specifically BARDA, NIAID, and the Department of Defense, for enabling our development plans to move forward, and this is a very important point. But with respect to that point, we have to be able to communicate robust development plans to our investors to continue to get that support.

Going to LPAD, we have appreciated the opportunity since the early draft of the legislative language to provide input into that. We have worked closely with Bob and have been very interested in how this can support our development plans.

On a somewhat separate track and parallel track, we have been designing an innovative pathogen-focused Phase 3 development plan for our lead molecule, plazomicin. In terms of talking about concrete examples, I would just like to share with this group today just a few facts about that program because I think it is very relevant to this discussion today.

I think most importantly this program is designed to address a significant unmet need in patients with serious infections due to Carbapenem-resistant *Enterobacteriaceae*. The program is built on a single Phase 3 registration study, a superiority study. Plazomicin was the standard of care of best available therapy with an all-cause mortality endpoint.

Importantly, we believe that this study as designed will satisfy the regulatory basis for approval. And by that I mean it will provide substantial evidence of efficacy and safety that is required as a current regulatory standard.

For plazomicin, we have designed a registration program that is focused on a small population, a multidrug-resistant population. And it is based on a relatively small clinical program. We have been able to do that in a sense without LPAD. I think it is important to understand that we can actually do that today and obtain regulatory support for that program.

I would just like to say a few words about the Phase 3 study itself. This study will enroll approximately 350 subjects. It will cost approximately \$35 million. It will take

approximately or a minimum two years to enroll and will include 60 to 70 sites worldwide. It is a very significant undertaking.

The good news for this study is that we have conducted a very robust feasibility study, and we have had very encouraging data from that feasibility study. The target population is available for us to study. And investigators clearly see the need. I am very encouraged and very positive about engaging in this study. The important point is while we can meet the objectives and I think it is exactly the right program for plazomicin in addressing a significant and met need.

One thing is clear to us, is that it is not necessarily going to bring plazomicin to market more rapidly. And I think this is a really important point. In other words, a small clinical superiority study in an MDR population does not necessarily mean a more rapid study.

We have asked ourselves as we have contemplated LPAD, how does LPAD help us? Will it bring plazomicin to market more quickly if it was available today? And our answer is that we are not actually sure. And the main reason we are not sure is because we do not fully understand the regulatory basis for approval that LPAD would allow and specifically the scope of the data and the nature of these small clinical trials that will support approval.

I would find it very difficult today and challenging to persuade investors that we can obtain regulatory approval with small descriptive studies. It is being challenging and I have been to many meetings where I have explained our analytic development pathway and that it has been challenging. But there is clearly a changing external regulatory environment. For example, the GAIN Act is a very concrete example that we can reference and also the expected pathogen-focused guidance that we expect in 2013. These are very concrete examples that we can use when we are persuading investors to continue to support our programs.

In summary, on our part in getting products to market more quickly, what we believe is we truly continue to support new regulatory mechanisms that will bring lifesaving antibiotics to patients more quickly through streamlined and efficient programs.

But we believe is needed are more rapid approval mechanisms, for example, that would leverage mechanisms through accelerated approval in terms of actually getting products to patients more quickly.

And while the treatment of acute infections presents a different scenario to the treatment of chronic HIV infection or the treatment of cancer, we do believe that PK and PD target attainment analysis and objective clinical and microbiological endpoints are worthy candidates where we can set as a predictiveness of a clinical benefit.

The other concern on our minds as we contemplate this novel, innovative program is pricing and reimbursement. Clearly, a small population means a small opportunity for return on investment. We feel strongly that LPAD really needs to provide or allow for conditions that will allow for premium pricing. In fact, this is where LPAD might be very influential in ensuring that that is an outcome of such a designation.

In summary, we believe LPAD will be helpful. LPAD will help us to have a concrete regulatory mechanism that we can follow and we can use as a reference point with our investors.

But we also believe that more rapid approval mechanisms really need to be looked at if we are going to get new antibiotics to patients more quickly. And in terms of our driving our internal business decisions, that clearly would be a very useful aspect to be able to communicate less time. It means less money. It also means patients will get new therapies more quickly.

In summary, the questions on our mind around data, the regulatory basis for approval, and then how does LPAD provide an opportunity for premium pricing products with an LPAD designation. Thank you.

Expert Roundtable Discussion

DR. COUKELL: Thank you. I want to open it to discussion now. We will take some questions from the audience, too, but let me start with the roundtable. Let me take the prerogative to ask the first few questions.

Bob, as IDSA thinks about how the label will translate into use, you were very clear that this is not a prohibition. To be very clear, it is not a new indication that has particular teeth as it applies to the prescriber. You talk about having an LPAD symbol on the label. Distinguish between people actually reading the label and seeing the symbol versus ... What is your conceptual model on how this different data set translates out into the user community?

MR. GUIDOS: I guess I would say ... obviously, there are folks who are never going to see that label of patients, etc., especially if they are parenteral and something that maybe physicians themselves do not see very often. But there is going to have to be an educational program about what these products are, how they are different, why they needed to be treated differently, that the risks are less well-characterized. I think IDSA is very committed to that. What I envision is that FDA, CDC, public health folks, the American Medical Association, which is already committed in its resolution to be part of the educational program as LPAD would be rolled out, and IDSA in particular, but others would have to be working to educate physicians and health care systems about why these products are different.

We would not rely totally on the label, although what is on the label is very important. I think the label, as I mentioned, will have to be, I would say, include the designation, include the indication, and describe sufficiently why that indication is more limited than traditional labels have been in the past.

DR. COUKELL: Thanks. Dr. Cox, one of the things that sometimes comes up in discussion is whether or not legislation is needed to establish the pathway. FDA in previous comments has been quite clear in having a strong preference for legislation. Would you talk about how FDA sees that fitting with the development of the overall pathway?

DR. COX: The question about the role of legislation, the need for legislation, is a more complex legal question that really would be in the province of the lawyers. As we think about the scientific issues that we face here though, the need for new therapies for patients really is urgent. Something that is available quickly and can be in place could be very important to the field.

It really is a critical need that we face now so there really is a real urgency here. Folks have talked some about rule-making. Rule-making is a longer process just by its nature, comment and rule-making. While I cannot answer specifically the legal question about the particular role of legislation, as that would fall more in the province of lawyers. The needs here are urgent and having something in place quickly could certainly help to address the patient needs that are out there for folks who have serious infections who do not have options now.

DR. COUKELL: I am just going to push you on that a bit. I think what I just heard is legislation may be faster. But in testimony last year when Dr. Woodcock talked about it, she also talked about sending a signal that part of this was a social compact and the legislation was an important signal to the wider medical community that this was something different. Is that also part of your thinking?

DR. COX: It really is an important point if we think about it. Bob has touched on this some in his comments. The label is an important way for us to provide information about the product, its risks, its benefits, and its uncertainty. And the idea of signaling to the community that this product is different, and you really need to think about it and need to think about scenarios where use is appropriate, is a key component to this.

And also, and this was mentioned in Bob's comments too, it is not just the label, but it is education. It is involving the payor and provider community. That sort of comprehensive look and clarity of an approach, that will provide clear signaling about such agents and then the role and the important role that groups beyond FDA will play in the appropriate use of these products is really a key component to the success of such an approach.

What I mean by success is getting essentially the right drug to the right group of patients. We do not want drugs being used, and I think this is probably universally true, where the risks outweigh the benefits. We want to move to the use of the drug where in fact the benefits would outweigh the risks. That is going to take not just the labeling, not just the information, but the engagement of the health care community to achieve that.

DR. COUKELL: Mike, I see your card up. Let me finish asking some questions and then we will go to you and anyone who has questions or comments. But let me go back to the three of you from companies who you each spent a slightly different amount of time focusing on regulatory implications versus the business implications. Let me ask you so that our health care providers and our payors really know what they may be dealing with here. Talk as concretely as you can about how you conceive pricing for these drugs. How are these drugs going to be different from what people have experienced in the past as you think about them? And then also, when you think about an LPAD indication,

is that a first step towards a more traditional, broader indication? Or is that the end of the road for these drugs?

DR. REX: Everybody is nodding in this direction. Two questions. Pricing and would the first indication, the first approval be the end of the road. Pricing. I think that it is entirely logical that if you are willing to spend \$15,000 for an antineoplastic that would prolong your life 15 months that you would spend \$15,000 for an anti-infective that would give you back 60 years of life. Remember my young man on the gurney. I gave him back 60 years of life, at least a one out of six chance of dying, with a drug at that time that is quite inexpensive. I think it is entirely reasonable.

And if you look at the limited amount of use that we would anticipate, if you want to have the drug available ... Mike pointed it out about some of these classes of drugs. You have to have a separate building in which to manufacture some of these drugs. You do not just set up shop next to the place where you make any other class of drugs. You have to have another building for them. It is expensive. You want to have the drug available. You want to have it available in a global supply chain so that you can have it within some reasonable number of minutes or hours around the world. You have to think about what it costs to do this. I think it is entirely reasonable. The prices Nicole suggested, I think you are in a ballpark that would make good financial sense.

The second question. Is LPAD the end of the line? I would say no. All antibiotic labels develop over time. But I would think that a drug that starts off in this category would tend to stay in that category because the cost of adding a whole bunch of other indications is enormous. In round figures, a standard Phase 3 trial ... it is useful to know this number ... a standard about a thousand-patient Phase 3 trial: Think of it as costing \$70 million roughly and taking a couple of years to do. It can go up and down a little bit from that, but it is in the range. And actually, that is about double Christine's figure. It is in that range.

It gets more expensive the more special the kind of patients you want to find. It takes longer to find people with certain special diseases. You want to find somebody with KPC-producing *Pseudomonas aeruginosa*. That would take a while. But if that was your goal. That is expensive as well. Those would be my two answers.

DR. DUDLEY: I do not have too much to add to John's statement there about pricing. I think we all recognize that they are going to be more expensive. I think how we concretely approach that I think is the elephant in the room. I think that is where we have to solve the problem. We just cannot say, "Well hospitals, if you want it, you are going to have to pay for it." That is something that certainly we grapple with in terms of thinking about these programs. I think just in the large pharma boardroom, as well as in an investor discussion, you have to begin to answer those questions as well.

I think Ed said it really nice. Clearly, where the risk-benefit analysis now is focused on that special population. I think that is a good way to think about this in terms of how these drugs will get their so-called first approval in a limited program is that you have to think about it in the context of that specific population.

But then as we certainly would expect multidrug resistance to begin to spread into other populations, we are going to need to address risk-benefit questions in those other populations as well. For example, NDM-1 beta-lactamase, carbapenemase broad-spectrum beta-lactamase may only be occurring in some limited hospitals in this country. But if you go to India or Pakistan, they are in the outpatients. They are coming in with urinary tract infections. That is a completely different patient population. We might anticipate that we may see that here soon too as well. That is going to be a different risk-benefit analysis and that is going to be then another population that we would anticipate studying then if that type of resistance were to take off.

We do see that as a pathway that to get the drugs available for the indications and the pathogens that we are dealing with now, but we are constantly looking forward in terms of what other populations which one would need to study that and in the post-marketing scenario as we gain more experience by confirming what we already know is a good place to do that.

MS. WELCH: I concur with my fellow industry representatives. From a pricing standpoint, I think the figures that you put up, Nicole, are definitely in the ballpark and certainly the type of figures that we discuss. I know I mentioned for the Phase 3 study that that would cost approximately \$35 million, but that is only one piece. We are really talking about probably in the region of about \$150 million overall to develop plazomicin on a limited program. I think that it's really important to consider that.

I then I think in terms of LPAD first step, it is always going to be on a case-by-case basis and how companies approach this will depend upon the molecule itself and spectrum of activity, its risk-benefit profile, its safety profile, etc. When I think about our two molecules, we will be looking at them differently. And in one case, it might be yes that is where it will stay. In other case, we might consider other indications. But then the funding aspect would be very important in that regard.

DR. COUKELL: Can I ask you a quick follow-up, Christine? When you talked about your Phase 3 study for KPC with an all-cause mortality, it is an exciting study. One of the points you made is that LPAD is not necessarily faster. You talked about the time required to conduct that study. Is that why LPAD is not faster or is it the regulatory piece that gives you pause?

MS. WELCH: I need to clarify. We are not progressing this development plan as an LPAD with an LPAD designation.

DR. COUKELL: But you are making the point about the time it takes to conduct the study.

MS. WELCH: The point is, based on our understanding of the regulatory environment today and where the pathogen-focused guidance will allow ... how that will allow us to develop an antibacterial as opposed to LPAD. And what we do not understand on LPAD is the nature of the small clinical trials. Small clinical trials can be small descriptive studies and LPAD in the Q&A refer to 30 to 100 clinical studies. But on that basis, you are not going to be able to get an inferential outcome on that study, whereas with our

approach we are progressing that inferential outcome. And I think that is the difference. Because of where we are today and our understanding of the regulatory environment, we have to have a study that involves 350 subjects, and it is going to take several years.

Now if LPAD is going to take a longer path and it is consistently with Tier C that allows for that descriptive approach, but then I do not understand what the regulatory basis of approval is, because we have to demonstrate substantial efficacy and safety. That is the standard of approval.

In the PCAST report, I was looking at the three approval mechanisms that were laid out. The standard for approval did not change across those mechanisms, and that is really key to this discussion. When we think about the plazomicin program, it is pathogen-focused, but we are still focusing on leading that regulatory basis for approval. Does LPAD change that? I do not know. Does that answer your question?

DR. COUKELL: It does. Let me go to Kavita, Eric, and John. Mike, did you want to—

Dr. Dudley: It is off point. We may come back to it.

DR. CANNON: I think real quick ... Dr. Rex mentioned that because of the expense of adding indications that we would not see a lot of broadening of the use of these products, but early on in this discussion we heard about the need for us to allow for a lot of off-label use of these products. If we allow for off-label use, do we not naturally broaden the use of the products? I guess I would like some perspective on that in that I understand the need for off-label use. And I think as a payer, we would be willing to accept that. But our fear has always been this broad use or this overuse, and does that naturally progress towards an expansion of the use of the products?

DR. REX: Let me flip it around and say that ... first, be careful with the words “a lot of.” How many brain abscesses are there a year? Not an enormous number that I need to treat. How many cases of KPC *Klebsiella osteomyelitis*? Some. And I think the focus here really is on the notion that on-label means the pathogen. There may be settings where for a day or two you do not know for sure what it is and you are hedging your bets because the last three patients in your unit had this bug and this person might or might not have it. And you are waiting definitive information. There might be some empiric use. But most of the time this agent should be very quickly focused in on people where you have a clear indication that this is what you are stuck with. This is the corner you are in. You are out of other choices.

I think there would be some use ... say it differently. A Tier C label is going to say we did 50 people with nosocomial pneumonia. We did 50 people with intra-abdominal infection. We did 48 with UTIs. That is what we have. And everything is pharmacokinetically-based. My belief is that an effective mechanism is the stewardship programs are increasingly in place. Everybody who uses one of these drugs is going to perhaps talk to a pharmacist about using it. It is parenteral. It makes it more trouble to use in general. Price will discourage inappropriate use. I think the community will—I certainly hope to see them rally around and focus in on the correct use.

And actually, I would like to point out that the FDA did something really interesting recently. I want to tie it to this issue of what the community of use. The FDA approved a new drug for TB. This drug, called Sirturo or bedaquiline, let me read you one sentence out of the label: Reserve Sirturo for use when an affected treatment regimen cannot otherwise be provided. Let me read you another sentence out of the label: An increased risk of death was seen in the Sirturo treatment group compared to the placebo treatment group.

The FDA had to draw a very careful line here about this drug. What I will tell you is this drug was studied in ... not a large number. It is only several hundred subjects. But they were clearly human beings who had TB that had previously failed everything, who got better when they took this drug. It was clear it was needed.

What I am tying this to is the community of practice. How many people treat TB? I am a board-certified ID doc. I will treat ordinary TB. But if you give me somebody with one of these complex cases, I am going to find an expert and very quickly get that patient being managed either directly or indirectly via that expert. There is a community of practice for TB that I think really controls this.

I think we would be looking for the same sort of attitude about the community of practice around antibiotics at the upper end, and LPAD could help create that.

DR. COX: I just wanted to follow up too on John's comment too about Sirturo. It does create ... it is interesting to look at that and the study that led to the information in the box warning about increased mortality. The patients in the comparative arm for the study from which that is derived, it was still possible to construct a regimen of other drugs to treat these patients with MDR-TB. But we all know that there are patients with MDR-TB, the subset of XDR-TB in whom that would not be the case. We also know too that untreated tuberculosis is bad.

You can see how the label got to where it is, which is ... and it is very similar to what we are talking about today in some ways, which is if you move to the patient population who have TB for whom you cannot construct a viable regimen in order to treat their tuberculosis. Then in essence, the risk-benefit changes considerably. It is different than those patients that have MDR-TB who you can construct a regimen. The indication moves towards those for whom you need this drug in order to be able to construct a regimen to treat their TB because you do not want to leave their tuberculosis untreated. You can see how the benefit-risk changes substantially as you move to that group of patients.

And then also the other goal of the label too was to provide the information from the clinical trials so folks were aware of the information that is in the box warning about the increased mortality from that study. I just wanted to provide that additional comment and information on the example you were mentioning.

DR. REX: I will come back to a point earlier. To maybe be a little provocative, I want to raise the point that prescribing on-label does not necessarily ensure that the use is appropriate. That is different. The label and we need to disambiguate this. We talk

about labels as stickers on vials like the one describing ... I will call that a sticker. But the label in terms of what John just read is what we are talking about here. Prescribing on-label does not necessarily mean that it is appropriate. For example, prescribing an aminoglycoside that is indicated in complicated urinary tract infections in a renal transplant of patient when a cephalosporin will do. Is that appropriate? Prescribing Colistin for a patient with renal transplant or treatment of Acinetobacter infections, which is not indicated for it, is that appropriate? Maybe.

I think what I have a lot of confidence in is this community of users that John referred to. And the community of users that are out there have experience in managing these patients. And the community of users are sitting on the other side of the table over there that run stewardship programs that have been in place in many hospitals for decades now. This is not something new. The terminology is new. When I was in the clinic, we were far more draconian, and we called it antibiotic management or the antibiotic police.

But antibiotic stewardship, as many can talk about this better than I can, has a much more humanistic, much more global look at this, not only dealing with appropriate use, but also making sure that these drugs will be used over a long period of time. That is the system that we have in place now to help us determine how these drugs should be used and what constitutes appropriate use within the hospital. We cannot necessarily rely upon the label to tell us what those guidelines or what the appropriate patients are going to be in perpetuity.

DR. COUKELL: If I heard the question correctly, it may have been going more to the idea that we would experience de facto indication creep over time without the new data, but we will come back to that. I want to go to Kavita.

DR. TRIVEDI: I have just a couple of quick questions. One, how does the LPAD mechanism ... how is it different from the orphan drug program and why do we need to go to something like the LPAD mechanism at all? And secondly, what are the unintended consequences? In the public health world, we are really worried about unintended consequences of putting this mechanism out there and does this encourage pharmaceutical companies to then develop other drugs in a more rigorous streamlined fashion so that we are actually hurting public health in the end? Just two quick questions.

MR. GUIDOS: Let me just start with the orphan drug program. Obviously, Ed is going to be able to add a lot to this. I will just talk about IDSA's own experience. We had pursued the orphan drug program for many years as one potential option for this. And in fact, we had several meetings in 2008 with the heads of the orphan drug program and exchange of letters, that are on IDSA's website, with the FDA.

Basically, it came down to the orphan drug program, according to the FDA folks, is not possible with these drugs because they approve it based on limited population, under 200,000 people. They do not split it by pneumonia caught by a certain strain of Acinetobacter. It is pneumonia. Therefore, any drug for pneumonia would not qualify.

That was our experience. There were other reasons why, but it is very complex. And this in fact is the orphan drug substitute for antibiotics, is how I view it.

As far as questions that Christine has raised about the standard for approving antibiotics under LPAD, the question to FDA is, what is the current standard you use to approve a drug for cystic fibrosis or otherwise based on 10 patients, 50 patients?

DR. COX: There are probably several questions here. I will try and step through a few of them. The question about the standards. The standard is in essence the same as you move across these different areas whether it be orphan or whether it be a non-orphan condition. Substantial evidence of effectiveness and end with a satisfactory safety profile.

What changes though is again it comes to risk-benefit. As you move to patients who have serious diseases and you move to areas where there is unmet need, the risk-benefit changes. The risk-benefit calculus is always key here.

To your question too about LPAD versus orphan. Based on Bob's description of LPAD and what we know about bacterial diseases, one of the things that is trying to be captured or achieved is the issue of providing information and then having that information affect appropriate use. One of the things that really is particular, unique, or to bacterial diseases is the spectrum of severity that we have for bacterial diseases, a spectrum of disease where you have other options and then you have diseases that are more severe, where you do not have options. There are different elements that Bob is mentioning in LPAD, compared to some of the things that are in the orphan drug program.

DR. JAN: Thank you. I think this is a great discussion. I would like to just backtrack a little bit and try to bring a payor's perspective. In terms of a perspective, one thing I would want to really emphasize is that when we talk about off-label use, this off-label use is very different than an off-label use you are talking about antipsychotic drugs or talking about even oncology products. Here you are talking about life and death. And the way we are perceiving this product to be is you do not have any choices and this is the last choice and we would use it.

But I think one thing that Dr. Rex actually really brought up, and I do not want to lose that in the rest of the day discussion, is two kinds of infections: serious and severe. Yes, we are pursuing the severe infections, and that is the thought process initially when we are starting to say nothing else is available. There is a lot of resistance. This is the high-profile population we need to address. But I think we need to expand that a little bit and see the role of these products in less serious-infections. You gave a perfect example.

When we are spending health care dollars, we need to also understand we are addressing this issue when it becomes serious. Is there a role of this product in patients who are less severe? But if you do not provide this product, it may progress to a serious state and may suck up more health care dollars. We are still thinking about ... I am coming from an outpatient perspective. But when we review drugs, these are important things that we look at. This patient -- if we do not treat them with a high-cost product,

make progress to a stage where you would have a patient on ventilators, maybe in ICU for 20 days. We actually just had an incident in a family two weeks ago when the patient died because of this condition. But he was in an ICU for a month taking all these resources.

I would like to really have pharmaceutical companies think about this as a bigger aspect of it, to say we think about the cost like we treat a disease state management. Treat patient when he is end-stage renal disease. Have you started doing interventions earlier on in life? An antibiotic plays a very important role.

The other thing I would like to say is like I said here, the outcomes are very quick. You are not going to have ... like we talk about oncology products. Yes, you are prolonging life. We spend millions of dollars in the last two weeks in patients who basically die. The cost is not an issue. I think what is critical is that what you addressed, Mike, I think, is the fact that are we using the right drugs currently. We do not use first-line agents and antibiotics because broader antibiotics are available. The problem of inappropriate uses are already there. We have to fix that. That will not be addressed by just doing labeling changes or educating physicians on the labels. But look at the common scenario when the patient is in the hospital. Nobody is reading the label.

What we need is medical policies and guidelines, which most of the hospitals have, and outpatients have to make sure and ensure a proper utilization. It benefits the patient. It benefits the pharma. It benefits the employer group who is paying the bill, not the insurer. The thing is a proper utilization instituting guidelines and making sure it happens.

The other thing is it differs from I would think the orphan drug, and the expectation of orphan drug is that you need to have tracking mechanisms for the utilization post-marketing. Once the drug is administered, there has to be either a form of registry or a tracking process to make sure. To your point, yes. The patient who has this kind of infection has been studied in lung infection, but now ends up with an infection in the brain. You have nothing else. You will try that. But what we need to do is track that to say was the outcome appropriate. And that would be all population management to make that determination, because the approval is based on 50 patients most probably. But if that tracking is lost and we rely on total label-based education, we are not going to achieve the results.

DR. COUKELL: Thank you. Let me keep going and go to Matt.

DR. GOETZ: A number of comments. The need is obvious. We have patients with multidrug-resistant infections for whom we are using antimicrobials of limited data for their efficacy and much data oftentimes for their toxicity, a very troubling space to be in. There are all kinds of things he said about trial design. I do not want to get that in detail. The notions that we can use concurrent or quasi-concurrent, historical controls I think have tremendous benefit as was outlined in the paper recently in *Lancet Infectious Diseases*. It is troubling that we oftentimes now rely upon studies which are 70 years old

to conduct non-inferiority margins, which is certainly fraught with another kind of historical problem.

We need not underestimate the difficulty of the path forward. I think about this from the perspective of antimicrobial stewardship and formulary committees that will need to wrestle with many of the issues.

The point is very well said about the value for the dollar for the 20-year-old who has a serious infection, which will quickly become a severe infection with physiological instability where the investment in that patient is of tremendous value even when therapy is given empirically. No doubt. No question about that. And were I that patient, I would want the ...

Then there is the other end of the spectrum. The patient who is somewhat more in the oncology model, perhaps the older patient with multiple comorbidities where the use becomes more challenging in many regards and oftentimes there are parallel discussions occurring with palliative care at the same time that we are using tremendous medical resources and that every shade of gray in between. No doubt, guidelines will be developed. Criteria for use will be spoken about. Stewardship committees will come up with their recommendations. Where the rubber hits the road, the guidelines break down often. There are clean ... as John said, patients do not always follow the textbook rules.

What I am fond of saying to people who want a clear description, I say I can give you an index card with a guideline or I can give you the encyclopedia, which tells you everything. The encyclopedia is not very user-friendly. The index card is incomplete. Use your judgment as to where you go between there. But different people have different judgments.

I also want to come back in part in this discursive comment to what Bob said about the AMA buying into this. IDSA has certainly done tremendous good work. But one of the things we need to recognize is that it is not only well-trained infectious diseases specialists who are on the front line employing the use of these agents. We also have the critical care physicians. We have the hospitalists. We have the people in the emergency department who first see these people when they come in and give them their empiric, antimicrobial therapy. Their discernment and my discernment as well are imperfect. I am not going to identify that patient who has a one in six chance of dying. And I say well this person might be a patient who has a one in six chance of dying. If you will, the value for the dollar spent decreases, but it certainly alleviates the physician's anxiety on the broader spectrum drug is used.

We need to reach out to those other groups as well and make sure that we have their conceptual buy-in and that they reach out to the physicians within their domain. The Surviving Sepsis Campaign did tremendous good for many people with sepsis. No doubt. But at times it also may have overreached, and we want to be concerned. We need to be concerned about those unintended consequences about the overreaching, which will occur in certain quarters. And then the point is well-made. Therapy will be given

empirically and then the concept of ... antibiotic time out ... concept of the CDC, the Infectious Diseases Society ... talking about can be employed.

But also, there is a challenge in that microbiology is very good, but it is not perfect. There are the arguments in physiologically unstable person who has an anatomic site of infection, which is difficult to sample. The questions oftentimes remain as how do you know that that pathogen is not there. Shall we continue? We cannot solve that here, but we have to recognize that it is a problem and a challenge. This is also a plea for the people in the room that we need better diagnostic tools to know who has the pathogen. We need better diagnostic tools that are timely, that are specific for the specific pathogen, and Lord help us, we need better biomarkers to determine who has infection and who does not have infection. I will stop there.

DR. COUKELL: Thank you. And you can see how some of these points and questions shade into the next part of our discussion. Let me bring Steven in. I want to make sure we get to a couple of the questions that we have on our agenda and also make sure there is time for audience questions before we break. Steve, please go ahead.

DR. EBERT: Thanks, Allan. I agree that a lot of the topics that are coming up more recently are going to be things we are going to be covering later. Let me keep my questions or comments fairly short because I think this has been addressed as well. Some of this issue with regards to labeling really to me seems to be based on three pillars, if you will. The antimicrobial-resistant organism being a target for the labeling, the types of infections whether you are talking about the seriousness of the infection or the severity of the infection seem to be another pillar. And then the third one, which I think personally has a really slippery slope, is where other antibiotic options are not available. That can mean a lot of different things. Clearly, it could be patients who have antibiotic-resistant organisms, but it could also be a patient who has multiple contraindications to conventional agents. How do we prioritize these three things when we look at labeling? Are they all of equal footing? Do we just ignore them or do we handle all of those individually?

DR. COX: If we think about the patient and the patient who has a serious infection who does not have an option, the reason that the patient does not have an option can be essentially any of those causes. Given the seriousness of the infection, successfully treating that infection with another option can provide tremendous benefit. Whether it be that the patient has a resistant organism and available therapies do not cover this resistant organism, that may lead you to another choice. If there is a contraindication against using a particular drug in a patient, that may be another justifiable reason for using a drug.

And similarly, if the patient is allergic to available therapies, that may be another reason to seek an alternative agent for a patient who needs treatment for a serious disease. I think Dr. Ebert is making an important point, which is there can be reasons beyond just resistance that patients may in essence need other options to treat their infections.

DR. COUKELL: Thank you. Let me do what you should not do in science or when you are moderating, which is ask two questions at once. I want to ask a couple of the questions that are on the agenda to the folks from companies in particular. One is, as you think about a limited population indication, does that change what you would do around marketing promotion or education around the drug? Secondly, is there a role for companies in monitoring the extent to which the drugs are used on-label and off-label?

DR. REX: I will play. First question. Does LPAD change how we talk about the drug? I am going to say no, but I am going to say it for a very specific reason, which is to say that we were already going to talk about it in this way. That is part of the matter. Stewardship is absolutely required. We cannot go backwards on that. Every one of these drugs creates a precious jewel and we cannot run it into the ground. I would say that it does not really ... it would help in the sense that it actually ... it gives a conversation starter. You now have an acronym and that is actually very powerful because now you can get into the conversation without many pages of explanation. You actually have a starting point. I like that aspect of it. That would definitely change.

It is hard to speak for industry as a whole because there is no such thing as one single industry neuron to which you can go for advice or an opinion. But everybody who is in this game chooses to be here because they have seen the consequences of untreatable infections. That is the behavior pattern that we need to encourage.

Your second question. I am sorry. I blanked out.

DR. COUKELL: One question is as drugs go on to the market with limited population indication we'll naturally want to know: Are they being used consistent with that indication? I think it is an open question whether we will actually know that. And is there a role for companies?

DR. REX: Let me pick that up with two levels. The first one is I want to ... the way you stated it was as drug, not the plural. I want to point out the special problem of drug number two or number three. Let us imagine that today there is a burning need for a new drug for *Pseudomonas*. Somebody puts one drug on the market that is good for *Pseudomonas*, a new one. Do we now not need drug Number 2 or Number 3? The answer is we absolutely need drug Number 2 and Number 3 because the lesson of history is that drug Number 1 will wear out. Whatever we do around this notion of what does it mean when there are no other choices, we need to be careful about the wording so that we keep in mind the absolute requirement for diversity in antibiotics. It is really important that we permit drug Number 2, Number 3, and Number 4 to get invented, because without that diverse vibrant pipeline, we will never make it.

And then as to monitoring, I have to say that ID doctors are really good at writing up case series. I think there would be a tremendous appetite for data on my three cases of whatever. It has been done for years. It is a very concrete approach to providing this sort of information. A registry is expensive and everything you do here that adds to it is a cost to somebody and it is probably a cost to the pharmaceutical firm. I cannot bear a lot more cost.

DR. DUDLEY: I think the only thing I would add to that is I think that there are mechanisms in place for looking in the post-marketing setting for these. I think we would be interested in understanding how these drugs are used. Again, appropriate use goes beyond what the labeled indications are going to be. There are systems I know that CDC is working on to try to understand how antibiotics are used within hospitals. These are ways that they are going to be able to hardwire into some of that information that is going to be helpful. But we are going to be interested in understanding what appropriate use is and by understanding the consequences of discordant therapy. So not starting therapy with an appropriate antibiotic soon as I think it was mentioned earlier in terms of the consequences that take place in that setting as well. We will.

MS. WELCH: I entirely agree that LPAD does not change how we would talk about this drug based on in terms of how we are thinking when we think about plazomicin and how we would market that. We recognize our responsibilities. From a targeting standpoint, we are talking premium pricing. We have to be consistent with the labeling and therefore our marketing strategy would be reflective of that. There is clear responsibility and accountability I think for companies in terms of how we would approach marketing of LPAD-type products.

I think then in terms of post-marketing surveillance, I definitely agree with John that we would be concerned about any burdensome requirements through registries. Anything REMS-like like would be obviously of concern, not just for industry, but for health care use as well. If there was any formal reporting requirements, that would be really very difficult to manage. But of course as the usual post-marketing surveillance mechanisms and tools, which would of course flag inappropriate use and are effective today in identifying that.

MR. GUIDOS: Of course, there are no LPADs available to date to know how they would be marketed. But based on drugs that are currently available through traditional methods, I would have to take some issue because I know, hearing from my doctors, about how some even more recently approved products are being marketed. My doctor would say that those products are not being marketed following stewardship practices. This is why it is very critical that we talk about reimbursement models that delink the use or sales from return on investment. I hope we will get into that this afternoon.

DR. DUDLEY: Let me just follow up too because again sort of the M word here, marketing, what are we really talking about? I think there is marketing from the standpoint of having the drug available. I think that is what we want to talk about. Now, capital-M marketing, which means the sales rep or the traditional models that we are thinking about. I know we are not interested in that. We are not interested in the traditional sales rep model of having sales reps going out and doing it. They are hard to control in the field. It will cost you money. Then you get your CEO in trouble, as we have seen from that. And hospitals do not want them. Do we need to provide information? Do we need to assist an interpretation of what the trial showed and what the safety profile is and what is that population? Absolutely. But it is not the guy bringing pizza to the residents anymore. A lot of companies do that well now, and that is the model that will not go forward with antibiotics.

DR. COUKELL: We have floor microphones. Is there anyone ... that is John Powers.

DR. POWERS: Ed, can I ask you this one about in terms of labeling? One of the things that has not been discussed yet today is that the label was really not intended to be a mechanism to instruct physicians on how to practice medicine. And FDA has always said that they do not regulate the practice of medicine. What it ends up being is a mechanism and agreement on what a drug company can actually market for. We use drugs for brain abscesses, many of which do not have indications for that. But the drug company is not authorized to sell the drug for that, nor do I need a drug company to tell me how to practice medicine. If we are saying FDA is not going to do it, I do not need a drug company to do that either.

It sounds like in your description of the TB drug, though, that what happened is that FDA dictum of you get what you study in the clinical trials is starting to get a little tilted in that we are saying we studied one population, but then we are going to infer benefits to another. That may be tricky if we look at drugs like Tigecycline where we took that same approach and said it was approved through a standard pathway. Maybe it will be better for people with resistance. And in fact, it looks like, the accumulating data looks like it actually may have higher mortality in that setting.

I guess what I am asking is the question about if we are going to pursue this kind of a pathway, wouldn't it be best for people to actually study the population they are interested in rather than leave us having to extrapolate from some other population to a different one.

DR. COX: It does get to this question of risk and benefit. It depends on how you frame it. If you look at the trials within the bedaquiline program and you look at the demonstration of efficacy in CT08 is demonstration of effectiveness of an anti-tuberculosis drug for treatment of patients with pulmonary TB with MDR-TB. If you look at it that way, I think you can conclude that the drug is an effective drug for treatment of patients with tuberculosis. And now we are faced with the question of how do we position that drug from a benefit-risk standpoint to be able to meet the patient needs that are out there for patients who do not have options.

In the overall program, there was an additional study, the CT09 study, that also included patients that were not eligible for the CT08 study because of the resistance patterns of the drugs. There is some experience with patients with more resistant organisms.

And the other thing, too, to recognize is that was an accelerated approval, too. As an accelerated approval, additional data will be accrued and required confirmatory clinical trial that will also help to further inform on the drug.

One thing I did not mention, and it is worthwhile to read this label. There is a lot of good information in there. If you look at the description about the mortality finding, you will find a couple of things that are interesting. If my memory serves me correctly, the median time to death after bedaquiline therapy was completed was ... I think it was 326 days. The deaths were happening pretty far out, which raises questions. I think the real

answer to this question is going to come from the confirmatory clinical trial as to what actually is going on here.

The drug, through an accelerated approval, is available now or will be available. It is approved. The benefit-risk is trying to get at the patient populations who really do have a desperate need for new therapies. And the reason is that we have shown it is an effective anti-tuberculosis drug. We have some data from CT09, and we are moving it to a benefit-risk situation where patients have desperate needs.

DR. POWERS: I was not asking about that approval in particular. I was talking about going forward to this mechanism. Wouldn't it be best to really focus on the population that really needs it, not have to extrapolate from something else?

DR. COX: In those circumstances where you can gather data on the broader population of patients, I think that is always informative. I think there are always a variety of options as to how you approach this and to the extent that you can study broader populations, to study sickest patients, that can always be informative. A very reasonable point, John.

DR. COUKELL: Let me say a couple of things here. One is I am going to go to John Rex, who wanted to respond to that. I appreciate the exchange we have just had. I think there is always a line to walk here between delving into the specifics and then talking about the generalities. We will walk back and forth. Thank you for bringing that back to the more general question.

The other thing I forgot to say this morning, and it is important at this point, is to say it is an open meeting. It is being webcast. It is being transcribed. I should say that just for transparency. But also, as you ask questions, we will make sure that you have a microphone and please identify yourself for the transcript. John Rex wanted to respond to that, and then I want to go to whoever has the microphone on this side.

DR. REX: John Powers has asked a really good question about data in the patient population you really want. I just wanted to give you a sense of how difficult it is to focus in on just that subset and get an adequate number of cases. By the time somebody has a highly resistant organism, it is not random. These are people who have had a lot of other health care exposures. Why did they have other health care system exposures? Because they have been sick. They have a list of other illnesses that is quite lengthy. They are very complex. You get down to this smaller and smaller pool of people, at least today, who have the organisms of interest.

I say "at least today" because part of the notion here is that it will be easy to study a new drug for metallo-beta-lactamase-producing organisms in about 15 years. When the organisms are common in the community and they are just ordinary, when it is possible to enroll several thousand patients in a Phase 3 trial, it would be easy then. The epidemic will be upon us. And a lot of what we are trying to do here is to solve for ways to develop a drug before the epidemic is upon us. Remember the mortality of these infections. It is not acceptable to somebody to say, "You have metallo-beta-lactamase-

producing *E. coli* in your bloodstream. Don't die. I will be back in five years." That does not work.

DR. COUKELL: We had a question on this side.

DR. BAINE: First, I am Bill Baine with the Agency for Healthcare Research Quality. My opinions are my own. I want to stipulate that if we ever come to success, a lot of the credit will go to Bob Guidos for years and years of hard work on this. But why don't we already have plenty of drugs to treat these organisms? Because, as was already said, we have a market failure. I think that has to be addressed, and in two aspects. One is that even under an LPAD system, it would be important for a manufacturer to sell one more dose of drugs. The manufacturer makes more money if some guy out there in the community who prescribes a drug for acute exacerbation of chronic bronchitis, which was really meant for ICU sepsis.

We need to get away, I am afraid, from the market system, just as when I ... if I move to Oregon and I have to start worrying about the missiles coming from North Korea, I am not going to go in the market for B-1 bombers. The government is supposed to take care of it. I think at some point we are going to have to have a North Atlantic therapeutic alliance in which governments will say how much will you want me to pay this country to have a year's worth of coverage for *Acinetobacter* ... and then that is off ... we do not have people detailing it anymore.

DR. COUKELL: Thank you for that comment. We are going to come back this afternoon briefly to the idea of delinking volume and revenue. I want to, until we get there, try to keep us mostly focused on what is the LPAD proposal and how would it work in practice. Do we have a question on this side? Who has the microphone?

DR. TOMAYKO: John Tomayko with GlaxoSmithKline. I first just want to say that I share John Rex's point that I am glad to see everybody here and that I also want everybody to succeed my competitors. But what I wanted to talk about was that we need other incentives and I know we will get to that this afternoon and it goes to what John Powers said. We need other incentives besides LPADs because we are going to be competing for these patients that we have to study.

I was delighted to hear your great study plan, but I was sitting here thinking: They are going to be doing this when I am doing it. And will we all be able to do this? And Ed said earlier that not all of us are going to succeed, and this is not going to happen quickly. We might fail because of our molecules' intrinsic properties, and that is part of drug development. But if we fail because we cannot get investment into our compounds or we cannot find the patients that have the diseases we want to demonstrate a benefit in because there is so few of them at this point in the emerging epidemic that has been discussed, then we have another problem to talk about. It is just important for everybody to realize that there is a lot of moving parts here.

DR. COUKELL: Would you pass the microphone forward to David Shlaes?

DR. SHLAES: Thank you. I wanted to get back to this question of why we need new legislation, which I do not think was really answered. I will tell you why I think it might be needed. I think it might be needed to avoid Ketek for an LPAD drug. The gorilla in the room is Congress and Congress' supervisory relationship, if you would like, to FDA. And the issue is what happens when one of these drugs hits a safety wall, which I guarantee will happen. This will happen because we are not studying it in a very large number of patients, and the risk is high. That is the question.

I think if Congress has signed off on this, it will make everybody more comfortable. But I think that is the reason why legislation is needed, and it is less to do with the actual legal aspects of regulation.

DR. COUKELL: Thanks for that. Do we have a question on this side?

MR. BARRETT: Hi. My name is Lew Barrett. I spent my last seven years of my career at Wyeth being the commercial head of infectious diseases. I am expressing my own personal opinion. I have been a consultant since 2010. But I do have a commercial point of view that I wanted to put out. And I have a couple of comments, but I will be brief. The first is the title of the program is New Pathway for Antibiotic Innovation. My only comment to the group is there are a lot of companies looking at proteins for the treatment of infectious diseases, including multidrug-resistant bacteria. I would like to at least put on the table: Is there a role for changing the word antibiotic to anti-infective? That is comment number one.

Secondly, Mike, I appreciate you bringing up CMC and diagnostics because, David, you brought up a gorilla in a room. I think they are a gorilla in actually having commercial success. What really is going to happen is you are still going to have companies making a determination of where they are going to make their investments as they are developing drugs, and that is the development cost plus commercialization costs and may the best products win when you put them in a risk-adjusted ROI modeling. There is still that issue.

I think my personal opinion is that LPAD will make anti-infectives an area where small companies, whether public or private, have perhaps an opportunity to re-access capital, which I think is critical for the small companies to develop these antibiotics. Whether a big pharma decides to get back into, and I underline back into, discovery of anti-infectives, I am not sure that LPAD will make a difference. However, it may increase their interest in licensing or acquiring to get back into the commercial side of this space.

And then my last comment. Nicole, I appreciated watching your forecast model. I just wanted to address another item that is especially challenging as one tries to develop forecast models, and that is the paucity of good national or worldwide data. I know, Nicole, you had a lot of difficulty coming up with numbers, and I actually wrote an article on this subject. It was extremely challenging to try to put a scope on how many multidrug-resistant *Acinetobacter baumannii* there are or *Pseudomonas* or NDM *Klebsiella* or KPCs. It is an especially difficult challenge. I will stop there. Thank you.

DR. COUKELL: Thank you. Let me first of all acknowledge that the forecast data in Nicole's hypothetical drugs do rely heavily on the numbers that you have published. Nicole would absolutely agree with the difficulty of finding robust forecast numbers.

Let me take your other point and just go back first to Bob Guidos and add: As you think about this, does this apply to small-molecule antibacterial drugs? Does it apply to proteins for bacterial illness? Does it apply to antifungals? Does it apply to antivirals? What are we talking about, as you can see?

MR. GUIDOS: I would just say as we first started thinking about this, we were thinking more broadly that it actually has an application and would be beneficial in these other areas for our perspective at the moment. This is such a high priority. We would like to start with the antibacterials and potentially think about broadening up after we have that structure already laid out.

DR. COX: And not speaking specifically to legislation, but just thinking about therapies for patients who have infections, we, in our group, deal both with small-molecule traditional antibacterial drugs and then also therapeutic proteins, including monoclonal antibodies. They are both therapeutic options that could provide benefits to patients. And they are depending upon the scenario for which they are developed. The particular type of infection they are intended for may actually also be important options for patients who have serious infections. I take your point about the scope of the wording as we were talking about these things.

The other point, too, you raised was the issue of diagnostic tests. A drug development program may also provide an opportunity for a development of a diagnostic test to gather information and could be very important in how these drugs are used out there in post-approval. Having a diagnostic test that allows you to select the appropriate patient for a use of the drug could be something that is very valuable. It could help to get to appropriate use. It could help to reduce inappropriate use and slow the rate in which resistance develops, another good point. Thank you.

Session 2: Forging a Societal Compact: Perspectives on How to Ensure Antibiotics Approved Under This Pathway Are Used in a Limited Population

Part 1: Role of Health Care Providers and Institutions in Use of Limited Population Antibiotics

DR. COUKELL: Our second panel is to think about: Were an antibiotic to receive an LPAD indication, how would it be used in the health care setting? How would an LPAD antibiotic be different from an antibiotic approved through the conventional pathway? How would providers and formulary committees or P&T committees and clinicians look at the evidence? How would the price influence its use? How would the drugs be monitored? How would they fit with stewardship programs and prescribing guidelines?

Let me go first to Matt Goetz who, as we have heard, is chief of infectious diseases at the Veterans Affairs in Los Angeles.

DR. GOETZ: Thank you. I am pleased to have the opportunity to speak. I am going to try to keep my prepared comments to a short duration. I really think that it is the Q&A and the interchange that is probably most informative. And many things that I would say in a stump speech kind of format you would all well know.

I am going to really think here about where the rubber hits the road, which I think is what we are talking about now as to how formulary committees would decide how to place these agents, set up structures for their use; how stewardship committees will interact with physicians; how approvals will be under authority, authorization to use the drugs that will be granted or not granted on a class basis or provider basis; and then the types of discussions that I will have in some period of time I hope because I hope we have the new drugs to talk about with my colleagues in emergency departments and hospital wards and ICUs, talking about the uncertainties that they face with physiologically unstable patients. And whether these drugs are the appropriate agents to use or not. It will be easy to approve the use of drugs for the person with a KPC-producing microorganism demonstrated in the bloodstream who is doing poorly for whom this is the only choice. That part will be straightforward.

All the ambiguities come in what is sometimes the father of clinical medicine, where we have to make critical decisions in a dearth of information or when we need to extrapolate to circumstances where the pathogen may be present, but its clinical significance may be uncertain. At some level, for example, we have very good data. We should not treat patients who are colonized. All in favor, say, "Yes." And we all say, "Yes." We should not treat patients who are colonized. We should treat patients who are infected. Yes, we all recognize that.

The boundary between one zone and the other is well described on the macro sense, but not particularly in the micro sense. And at some fundamental level of truth, when I am honest with people, with my trainees, I say that colonization is what I say it is and infection is what I say it is. Then I refer back to the Supreme Court that said that they know what obscenity and pornography are, but they just cannot define it. I think at some fundamental level we deal with that and that is truly where the rubber hits the road for the stewards. The rubber hits the road perhaps where the payor is as well when they try to adjudicate decisions. And we simply have to accept that we cannot, though, and will not ever get to the perfect. We cannot define it, so we certainly cannot get there.

Formulary committees will face challenges and craft and criteria regulating the use of the agents. The groups have to balance approving use only in patients to satisfy the entry criteria of pivotal studies or exactly what is in the packaged label with the needs of individual patients who are exceedingly diverse. Legal constraints, which were talked about somewhere, would be entirely the wrong way of going at this because there is no set of rules or guidance that can be given that is going to cover all clinical circumstances, and that constraint in the practice of clinical medicine certainly would not work.

Formulary committees nonetheless will try to establish where the guidance is and to the degree to which the FDA can be clear in the package label and to the degree to which our professional societies, IDSA, certainly taking a leadership role. But as I emphasized before, we have to recognize that it is not just infectious disease providers who write for these antibiotics or who are responsible for the care of the patients—that oftentimes the stewards are the outsiders coming in to meddle is the interpretation that is given.

The stewards, by definition, have a responsibility to society and for future patients and, at some level, to the institution, a need that has to be balanced with the perspective of the provider who is responsible for that patient right here, right now, who oftentimes has a time frame that extends to 12 to 24 hours and is wrestling with many other uncertainties in that critical care patients. And the antibiotic is a priority number 17 sometimes once they have the antibody that they need.

This will lead to all kinds of issues with empiric therapy. In thinking about the payment scheme for these antibiotics, the antibiotics—again, echo what I said before the break—certainly have tremendous value, unquestioned value in the right patients. Of course, if you use anything in the wrong patient, it has no value whatsoever.

The oncology-pricing model has a lot of appeal. I can see where that comes from, and it gets us the antibiotic we need. Wonderful. But it is a little bit different model. We think about how the antibiotic is approved from the oncology model. The oncology model, we at least know the person has the malignancy at hand at the time the decision is made to use the antibody with the chemotherapeutic agent. With the antibiotic and the critically ill patient, there is a lot more empiric use that will be occurring. This will lead to a lot of struggle, if you will, at the ground-floor level.

The other thing that I think that we need to think about is—I talked about diagnostic tools before—but are really the educational needs and informatics needs that we have. There are many hospitals, many programs, systems with outstanding stewardship programs without outstanding teams. It really is a team effort. The team requires fundamentally an outstanding clinical pharmacist who is generally the front-line person for our stewardship programs, and it requires strong medical directors in an involvement by infectious diseases clinicians. But it also requires teamwork with engagement and buy-in, not only from hospital administration, which is utterly crucial, but from other clinical stakeholders within the organization—again, emergency department stats, hospital stats, critical care who represent other important constituencies because of their responsibilities within the institution. Not all of these other groups have the same fine-grained understanding that the people sitting in this room do about the appropriate use of the antibiotics that we are talking about. We need to reach out to those people and treat them really as partners.

The partnership aspect, I think, is really key because oftentimes the benefit and the glory for the stewardship program go to people like me. When things go wrong, it is the provider's fault who is taking care of the patient. We have to really find ways of sharing and bring them in if we are going to be successful. We have some programs that are

excellent. Those programs need support. And then we have a lack of personnel if we think about this on a national basis.

NDM-1s do not only exist in our academic medical centers. They do exist and they will exist more in sites that do not have all the resources. We need to come up with schemes that reward institutions for having the programs in place and giving them the financial support that they need to be successful or we'll have overuse.

We also have a crying need to train the people, and we have a crying need for informatics so that the stewards actually know who their patients are, that they need intervening, and that they can provide feedback reports within their institutions as to what they are doing. The tools exist in theory. They do not necessarily exist in practice. Institutions certainly have not uniformly bought into them.

And then we need national roll-up systems as well. Yes, providers will write the case reports about their successes and sometimes about their failures as well with these drugs. And those data can be powerful in helping to modify how we use these agents. But I think in the era of the electronic medical health care record we also need nationwide data mining to look at the consequences, the pros and the cons of the use of these drugs, and to better understand the clinical epidemiology of the highly resistant organisms and the needs that those patients face.

We will get, I think, in the long term a lot more outcomes data by looking at the ecology of actual clinical use by mining electronic medical records than we ever will from registries, which are not scalable, and there are costs for everybody in registries. I think that post-marketing surveillance we currently do does not go deep enough. I will stop there.

DR. COUKELL: Thank you. Let me go next to Steve Ebert from Meriter Hospital in Wisconsin.

DR. EBERT: Thank you very much, Allan. It is a pleasure to be here and to be able to have the opportunity to speak to all of you. I am going to expand a little bit on some of the things that Matt said, and I think you will see a common theme through all of the providers here. My roles include management of our antibiotic stewardship program at our hospital and also serving as a member of our antibiotic subcommittee, which determines, among other things, the formulary role for our antibiotics.

Formularies in and of themselves are more than a list of drugs. They are also a list of treatment guidelines or protocols that we expect to see followed with the appropriate use of antibiotics. Along with that needs to be the daily assessment and monitoring of patients to try to see whether we can to the best of our abilities keep those patients within the framework of the guidelines that we are using.

With regards to antibiotic selection for formulary, again, I think a lot of this is fairly common sense. But it is an individualized decision for hospitals or for health care systems based on their susceptibility patterns and the spectrum of activity for drugs.

With regards to clinical activity or clinical efficacy and the FDA approvals, I think in general, as has already been discussed today, the relative number of indications is really, I think, of minor importance when one looks at adding drugs to formulary, more so how you would incorporate those particular antibiotics into your treatment pathways and where do they sit with regards to the ranking.

Many of these things are obvious with regards to drug categories or classifications, including interactions or contraindications, but also some things that I think Mike alluded to earlier—drug incompatibilities. Frequently in the ICU, you are trying to run numerous number of antibiotics or other medications into the patient simultaneously with the roles of extended infusions, now that we see how inconvenient is it going to be for nurses to administer those medications.

Issues of drug stability. Are we able to send patients home with medications that are infused? Is there going to be a problem with reconstitution or compounding of those medications?

As Mike mentioned, does a reliable susceptibility test method exist? Many providers are uncomfortable extrapolating susceptibilities from other drug classes to their particular drug without clearly knowing in the medical record that that drug is in fact active.

When one looks at incorporating your drug into the treatment pathway, all of these things are important, of course—but a few other issues. One is, again, the pharmacokinetics and the pharmacodynamics of the drug. When the initial dosing regimen was chosen, whether it is for an LPAD drug or for other drugs, did the manufacturers get the dose right the first time? How often do we see where the selection in the regimens that are used are for minimally effective doses, only to find out later that the doses need to be increased because of an emerging issue with resistance likely due to lower exposures.

Along with that is the pharmacokinetic testing of drugs in select patient populations. The one that is near and dear to my heart right now, in particular, are the pharmacokinetics of antibiotics in the morbidly obese population. We find that very limited clinical research data exist for those, yet we daily are treating 150 to 200 kilo patient,s not really knowing what we are doing with regards to selecting the appropriate dose and potentially underdosing those patients and setting them up for underdosing and the emergence of resistance.

Also, it was mentioned—drug penetration to relevant sites of infection. You are not going to see clinical trials for all areas for all infections, but if we can infer in some cases that the drug gets to the site of infection, that is a useful feature.

Most drugs are going to have some type of a restriction, especially newer agents in a particular formulary whether it is provider or organism or as I mentioned before.

One of the things I try to emphasize with our group is that in many cases antibiotics come out as either in our world a target drug or a stewardship drug. By a target drug, I mean again what was mentioned in here that the drug was approved for an indication

where it really is not needed, where the skin soft tissue infection in an area where you have myriad other agents available. Unfortunately, when marketing sometimes has to push that as the first line agent, we on the stewardship end are forced to target that drug and say it is being used unnecessarily, as opposed to a stewardship drug, where later we use it as a tool to de-escalate our antibiotic therapy to what is more appropriate in those particular patients.

As I said, the challenge with restrictions are really do you restrict agents at the get-go or do you do so at a later point, when, hopefully, you have some microbiological data to base your decisions for de-escalation and potentially can remove the agent. And clearly as has been mentioned here, the empiric therapy is going to be a big part of all of these particular agents and whether that is going to be “permissible” or if we are going to try to drill down to a deeper level with how the drug is used and where do we decide that enough is enough with that particular therapy.

In particular, with these high-cost antibiotics, I think there is going to be an enhanced need to require some type of documentation of the need to initiate or to continue those particular agents. The better job we can do of identifying those criteria—of course, trying to get adherence to the criteria is another thing—but if we can identify those, I think it is very important.

I try to brainstorm as far as what I thought might be a continuum. Clearly, documented infection with a multidrug-resistant organism is going to be on one end of the spectrum. But does it go to the other extreme of patients with now an ongoing infection with prior colonization with multidrug-resistant organisms? Patients with prior infection with not resistant organisms, but organisms such as *Pseudomonas*, which may evolve into multidrug-resistant organisms?

Patients who are residents in an intensive care unit, where the prevalence of multidrug-resistant organisms, is common. Where do we slice the appropriate versus inappropriate with those individuals all overlaid by the issue of, as I mentioned earlier, are other drugs available for use because of contraindication, because of allergy, or, in this era, because of drug shortage that we simply do not have the available agents no longer used for us?

I think with regards to economics, the more effective antibiotics, hopefully, will result in some cost savings, whether, of course, mortality, antibiotic-free days, reduced length of stay, and reduce length of ICU stay. Ventilator days are, of course, what we are all worried about now, re-admissions to the hospitals. Certainly, those are all, I think, tangible issues. And if these drugs can serve to reduce those costs, certainly the higher costs of the drug may be justifiable.

But if not and/or, the economic outcome is extended medical care. Again, there was the mention of the 20 year old with pneumococcal pneumonia where it is very easy to justify it. But how about the 89 year old with end-stage COPD who has *Acinetobacter* pneumonia? Do you weigh those two patients the same way, and are they going to have

different impacts on overall cost of care? If that is not the case, we may need to go to other means of support.

The NTAP programs, for example, that have been advocated now by CMS, where an overpayment, if you will, into DRGs with select drugs meeting certain criteria, seems like it might be a reasonable area to explore with these new agents. With that, thanks.

DR. COUKELL: Thank you. Let me go next to Pranita Tamma, director of Pediatric Antimicrobial Stewardship at Johns Hopkins Hospital.

DR. TAMMA: Thank you, Allan and Nicole, for all your hard work in organizing this event. I agree with the other panelists in that the limited population pathway is definitely needed. We are at risk of a post-antibiotic period in the near future for a portion of the population. It is a small portion, but it is growing. And the idea of allowing for smaller sample sizes in clinical trials, which are less costly to conduct, focusing on antibiotics for high-risk populations, is certainly a step in the right direction. However, special labeling for antibiotics dictating the populations they should be reserved for and making the costs prohibitive for routine use is not enough to ensure that these agents are actually used judiciously.

With the first point regarding labels, the truth is most physicians do not read labels. They generally never even see the drug labels. For most physicians, the involvement is limited to having a rough idea of what organisms the antibodies cover, the types of infections they may work for, ordering the drug, and then observing the patient afterwards. And, really, that is the extent of the involvement.

Physicians are generally not aware of the actual indications that antibiotics are approved for regarding things like age restrictions, body size for intended use, etc. In pediatrics where I work, about 80 percent of our drug use is used off-label. There is really even less of a drive for physicians, particularly those taking care of children, for example, to read labels.

Regarding costs, it is quite similar. Most physicians are unaware of the cost of drugs. Particularly this is true for drugs that are being prescribed on an inpatient basis, where costs do not interfere with the ability of the patient who received the drug. Insurance companies do not have a say in what drugs are being prescribed. Patients do not have enormous copayments to worry about that might make them less likely to pick up and use the drug that was prescribed.

Although patients, administrators, insurance providers see the hospital bill, physicians generally do not. They really have no idea what these agents are costing. I do not think making the drug very pricey is going to limit its use by physicians.

But I do not think it is a completely dismal picture because I really do think that supplementing some of these practices with antibiotic stewardship could make a huge difference.

For those of you who are not familiar with what antibiotic stewardship really is, it involves someone or a group of people, often pharmacists and physicians, working together closely with clinicians to optimize the selection, the dose, the route, and duration of antibiotics as well as being cognizant of adverse drug events that can occur with antibiotics.

In the institution I work, as an example for certain antibiotics and we ... I hate using the word “broad spectrum” because most antibiotics probably really are. But for certain broad spectrum drugs, the ordering physician discusses the case with me or with an ID pharmacist before ordering the drug, and we decide if it seems appropriate or not. Obviously, there are exceptions for emergencies. And then about 48 hours or 72 hours after we know more about the microbiology data, the clinical course of the patient, a better sense of if this is truly an infection or not, we discuss with the ordering physician the need to continue the drug. Maybe it needs to be narrowed. Maybe it can be stopped. Maybe we can convert it to an oral agent.

But unfortunately, such programs are resource-intensive and available in a minority of hospitals. There is a lot of data in the literature showing that such programs are effective. In our experience, it is as well. You take an agent like daptomycin—which, for those of you who are not so familiar, it is a broad-spectrum agent that works well against Gram-positive organisms. For us, we really do want to preserve its use. It is a good drug. It can treat infections that a lot of other agents cannot treat. We would like to preserve its use for when it is necessary and to keep it effective as long as possible for the future.

But when we compare our institution where there is, I guess, a gatekeeper to make sure this drug is being used only when absolutely indicated, our use of this agent daptomycin is minuscule next to other institutions in our region, where there is not someone keeping track of it. It is not because our patients are not as sick or because they do not have equally resistant organisms. I really do think stewardship is effective.

Obviously, most institutions are not capable of having a formal stewardship program because, like I said, it is resource-intensive. But even if there is a single pharmacist with some sort of medical director as backup to make sure that if LPAD drugs are being prescribed, that it is being used appropriately, I really do think it could make a huge difference to ensure that these drugs are being used for the right population. Thank you.

DR. COUKELL: Thank you. And now Kavita Trivedi, who is a medical epidemiologist with the California Antimicrobial Stewardship Program with the California Department of Public Health.

DR. TRIVEDI: I would be remiss not to say, go 49ers! My 4 1/2-year-old son was like, “Mom, aren’t you going to wear a 49ers T-shirt at your meeting?” I almost did that.

My background is, again, coming from public health. I am just going to put some ideas out there that I think are useful to discuss, but I am by no means saying this is absolutely the way I think that this mechanism should move forward.

But I think it is really important to remember that about 50 percent of antibiotics used in the acute care settings are considered inappropriate and unnecessary. The antibiotics we have out there right now are not being used appropriately, so why should we believe that any new antibiotics that come out on the market, even with special labeling, would be used any differently? I just want to comment on what Pranita said about the labeling. We have ample evidence that physicians do not read labels, have no idea what the labels actually say.

I just want to make one comment about an outbreak we had recently about fungal endophthalmitis. We investigated a dye called brilliant blue G dye that is actually used by retinal surgeons very commonly throughout this country to identify the membrane that is pulled away before they do retinal procedures. We found out about a brilliant blue G dye batch coming from a compounding pharmacy—I am sure you all have heard of those places—which was contaminated by a fungi. This actually occurred before the big fungal meningitis outbreak. This batch of dye was used in many patients throughout the country, unfortunately, many in California. And about 45 patients ended up with terrible fungal endophthalmitis, many of whom had to be enucleated and lost vision out of that eye. Very serious outcome.

The irony about this investigation was that we learned once we talked to retinal surgeons, because we did not really know about this dye or that it was even on the market, is that there is no labeling for this dye out there. It is not an off-label use. There is no label use for this dye on the market. And none of the retinal surgeons knew that. They had no idea that this was just a drug that was actually approved in animals, not at all approved in this country whatsoever.

I just want to note that it is not only about off-label use. It is about no-label use, that if the culture, the practice of medicine, if the people that you learned medicine from use a particular antibiotic or drug or a dye in a certain manner, you are going to end up doing the same thing, and you are not necessarily going to do the research to make sure that that drug is actually even approved in this country whatsoever. I just want to comment on unfortunate physician practices.

The other thing I want to mention is about diagnostics. This gets a little bit into the nitty-gritty. I would hope that formularies, institutions, or maybe even at the national level will ... when these LPAD drugs are put on the market, we will ensure that cultures show that these are multidrug-resistant organisms. Now the problem with that is, it seems very simple, is that we have lots of different breakpoints. We have, especially for carbapenems and enterobacteriaceae, we have the Clinical and Laboratory Standards Institute telling us what breakpoints to use, and then we have FDA breakpoints. I know we are trying to harmonize them, but it is not happening as quickly as we would like. We have data in California that 30 percent of our hospitals are using the CLSI breakpoints. If we want to ensure that these organisms are multidrug resistant, we need to make sure we are using the same susceptibility testing methods.

I will also note that in California we have carbapenem-resistant enterobacteriaceae is less common on the West Coast as it is on the East Coast. We have a lot of laboratories

that are seeing these for the first time and that are then wanting confirmation of the susceptibility testing. What they are doing is then sending it to the state laboratories, and then in turn, we send it to CDC. And then there is confirmation that occurs at that level.

One idea, again—this is just an idea—a consideration would be, maybe, we send these isolates, these organisms that we are concerned that LPAD drug may be useful for to be used on, send them to some place where there is a centralized laboratory methodology that is occurring. We know that they are actually testing all of these drugs, all of these organisms in the exact same way, to ensure that they truly are multidrug resistant and then that the LPAD drug could be used on those patients. That is one idea. A mechanism that is actually already in place if that is what state health departments use is again using the CDC laboratory as a gold standard.

You may think, “Well, why get public health involved? We have no resources.” I am probably less paid than all of my colleagues at this table. But I do think that there is a precedent for using the public health structure. For botulism antitoxin, for example, CDC—I used to hold the bot beeper—we would release botulism antitoxin to any clinician in the country that felt that they needed it for their patient. Clinicians would call us, clinicians at the CDC, and then we would assess the patients whether or not we thought the antitoxin should be released, and then we would call the quarantine stations, and they would release the antitoxin. It is a little bit more oversight.

But I never felt and I do not think the physicians that we were talking to on the other line felt that we were inhibiting their practice of medicine. It was just another consultation about their case. Most oftentimes, we would release the antitoxin because they would only call us. How do you get CDC’s phone number anyway? I do not know how that happens. You really have to go through a lot of loopholes to get to the right person to talk to about releasing the antitoxin. Again, there is precedence for doing something of that nature.

And then lastly, I want to mention long-term care facilities. I hear about antimicrobial stewardship issues in all health care settings in the state of California—of course, community hospitals, acute care hospitals, and then our long-term care facilities. We have over 1,100 in California. The type of antibiotic prescribing that occurs in long-term care facilities is absolutely egregious in many situations. I just got an email about a physician in a long-term care facility who had a positive MRSA in the nares for a patient, and the patient is on Linezolid for an entire course.

As much as we would like to believe that our colleagues and physicians and health care providers are using antibiotics appropriately, we know that is not happening. We know that a lot of our ID physicians are not using these antibiotics appropriately. I am really concerned, especially in the long-term care setting, how these LPAD drugs are going to be used.

Again, one idea I had for all health care settings is perhaps we could develop a consent form, where the prescribing physician, the pharmacist involved, as well as the resident

or the patient that is being given the drug has to acknowledge both the benefits and the risks of having an LPAD drug administered to them, and that again provides another loophole that the physician has to consider. None of us likes to do paperwork. Do you want to do the paperwork to then release the drug appropriately to the patient? Maybe another way to ensure that we are prescribing drugs appropriately, especially, like I said, in the long-term care setting. Thanks.

Expert Roundtable Discussion

DR. COUKELL: Thank you for a very interesting sets of remarks.

Let me start quickly by going back through. Matt, would you just say a bit more, specifically, as you assess how to use an agent in the hospital, the extent to which the actual FDA label influences decisions that get made?

DR. GOETZ: We can talk about it at the formulary level, where the guidance at the formulary level will say that the drug should be used according to the FDA label. If we think about how documents have evolved in my institution or in my health care system, if you will, for antibiotics in particular, there is always a section for items for consideration where there will be language which will say something akin to the fact where this agent can also be used in the following circumstances where there is no other appropriate therapy. And the drug should only be used by an infectious diseases expert or someone within the facility who is designated as having that expertise because, quite frankly, if you look at ... to talk specifically about the VA, 150 some facilities, which range in complexity clearly, but some have more and some have less infectious diseases expertise.

The other aspect is that, again, the people using the drugs, the people at the front line, is seeing the patient when they are critically ill or severely ill, to use John Rex's phrase, are not necessarily infectious diseases doctors.

I think in some of the documents that were distributed and saying why is the LPAD program necessary. Why do we need these new drugs? Because for every hour that is delayed for the person who is septic shock, the mortality rate increases 5 percent. We will take those data at their value. It would indicate then that the whole approval process makes the botulism model not work. Certainly, and we compound that by 75,000 uses per year, not really feasible.

It also makes the ... it is 2 o'clock in the morning. I am going to pick the phone up. I am going to call the steward and get permission for this drug model not work particularly well either. There was a fascinating study from the University of Pennsylvania some years back showing what happens with antibiotic approval at night. The quality of the approval at night when my fellow holds the pager is not quite as good as the quality of approval during the day. Any systems, my own included, gave up on the system having the fellow hold the pager at night because the quickest way to go back to sleep is to say yes. And if they are saying yes ... it is a little bit cynical. There are fellows who say no. They are a little sleep deprived the next morning. And the patient does not necessarily benefit either. Let's talk about the reality of the circumstance.

Think about the formulary and the label. Drugs will be used by individuals who are going beyond the label. We need to authorize people to use those drugs. There is going to be a trust, but verify approach that is taken. The labels will never be all inclusive. The patients need to use the drug. If we can get to something better than 50 percent—I accept 50 percent of inappropriate antibiotics. It is in the literature. We can fuss about the number whether it is 50, 60, or some other number. It is beside the point. We are doing well if we can get to 80 to 90 percent of all drug use being appropriate. That would be really a spectacular undertaking.

DR. COUKELL: Thank you. If I am hearing you correctly, at least at the formulary level, the FDA label is going to be influential.

DR. GOETZ: No question, but at the formulary level. But allowances for exceptions need to be in place.

DR. COUKELL: Steve, you talked about looking for reduced length of stay or ventilator days or re-admissions to justify the higher cost. In practice, are you going to be looking for data from what source to justify that cost and how will that play out? If you have a very high-cost antibiotic, how will the institution address that? What data would justify that in your mind?

DR. EBERT: One of the advantages of the electronic health record is it has been very useful to rapidly generate that type of information. With the bundles now, for example, ventilators-associated pneumonia were tracking issues such as ventilator-associated days and, quite frankly, antibiotic days in patients. But what would need to happen would be the development of a pharmacoeconomic model that would infer that if you had a patient with a ventilator-associated pneumonia with a multidrug-resistant organism, and in fact the patient had pneumonia as opposed to just tracheal colonization, that by using an appropriate agent one would be able to, A, reduce the length of antibiotic therapy. And if the ventilation was associated with the pneumonia, per se, or the inability to wean the patient from the ventilator was associated with the pneumonia, that one would then secondarily be able to wean the patient off more quickly.

The converse, of course, then is that we would ... again, because ventilator days are clearly related to ICU days is that one could also reduce their ICU stay overall.

DR. COUKELL: Thanks. Pranita, I asked Matt Goetz what influenced the approved label had on a formulary decision. You point out that in the pediatric setting, 80 percent of drug use is off-label. In the pediatric setting, do you see an LPAD antibiotic any differently from one that comes through the traditional antibiotic approval pathway?

DR. TAMMA: That is a good question. I work at a hospital where we have a ... we are not an independent children's hospital. I am part of the P&T committee and the antibiotic subcommittee for both children and adults. I have a good sense of the practices on both sides. Even though what I said is true that most drugs in pediatrics are used off-label or, as Kavita pointed out, there is no label for them, I do not think that it is that different

from adults. Part of the reason with the adult colleagues is that more of the medications that actually have been tested in their population, if that makes sense.

One thing I wanted to go into a little more about the formulary question is that I do agree. When we bring drugs onto our formulary, we have indications that we would like them to be used for. But physicians are not privy to what is ... they know what drugs are on the formulary, but they are not privy to the indications what we would advocate them to be used for. You take a drug like Imipenem. There are certain reasons ... it is a broad spectrum antibiotic. There are certain indications we would like it to be used for when we introduce it on our formulary. But once it is there, it is in the door, and physicians can start using it for what they want unless we keep track and call them. And obviously that involves stewardship.

I would imagine it is the same for any hospital formulary where there are indications for what drugs should be used for, but who is actually overseeing that that is happening is a very different story. I do not think that that is any different in pediatrics or adult medicine.

DR. COUKELL: Thank you. Kavita, you propose a couple of centralized approaches to guiding the use of the drugs—pre-approval consent forms, centralized labs. Matt questions whether this can be fast enough and work at the volumes we are likely talking about for antibiotics. Can it?

DR. TRIVEDI: I think in California based on the number of these isolates that come through the state health department. Absolutely. I think it can. But I really feel like the diagnostic question, which has already been brought up by multiple people, is a real issue. Some facilities, based on the breakpoints, they are going to see resistance to all of the usual antibiotics, and that same isolate in another facility that is using a different breakpoint, they are going to see something very different. The LPAD drug may actually be relevant in both facilities, and maybe both facilities do not know that.

But I just want to mention again the long-term care setting. I think in that setting there usually is no formularies. The issue of the formulary, whether or not it is restricted, is off the table in long-term care settings completely. In addition, multidrug-resistant organisms are very rampant. Basically, we find that if you look for multidrug-resistant organisms in long-term care facility patients, you find them. And then the question is, what do you do about that? We often have families and patients, residents, that will demand treatment because they have a positive culture and not understanding the difference between colonization and infection.

I do not know if you can put these drugs out and have different regulations for where they are used in the long term. I think it is a really difficult thing to tease out, but I think it is something that is so important because 75 percent of antibiotics are used inappropriately in long-term care facilities. We have a huge problem there. A lot of people like to point the finger at long-term facilities and say that is where multidrug-resistant organisms are starting. I do not care where they are starting. If they are

occurring there, then LPAD drugs are going to be asked to be used in those settings. We absolutely have to think about the mechanism by which they are used in those settings.

DR. COUKELL: Do you want to respond?

DR. GOETZ: I was going to amplify this. Are you suggesting perhaps that we need to prequalify institutions to use the drugs? Are you suggesting that we need to have some sort of data-gathering system? I know you have been very interested in this in California to look at the magnitude of antimicrobial use, and the relationship between antimicrobial use and resistance provides some feedback, or dare I use the word scoring, which is not quite what I want to say.

DR. TRIVEDI: Right now, for example, our NDM-1s since we see a lot of those in California from patients that are directly coming from India and go straight to one of our hospitals. Those isolates, again, go straight to CDC for confirmation. And we know all the epi data behind those patients because we are waiting for that one that gets transferred between one patient to another in a facility. I think that level of intimate knowledge of these patients is going to be hard to do.

I just want to point out that there is a mechanism by which we are able to get that information, send these isolates to CDC for confirmation, and then we go back and are able to appropriately treat the patients if they end up having one of those resistant phenotypes. You could implement the LPAD drugs within that mechanism somehow. Again, it is just an idea. Or you could have a consent form that is built at the institutional level where the P&T committee sits down and talks about when do we want these drugs to be used, how do we want these drugs to be used. That is another idea.

DR. COUKELL: Thank you. If I got them in order, it was John Rex, Steve Ebert, and Pranita.

DR. REX: Thanks. I want to weave together a couple of the themes that I have been hearing and speak from the standpoint of being the doc in the ICU. I will make it clear. I used to do this for 15 years. I was that doc. There is something here about ... I want to raise an issue and be sure that it is on the table as we think about how to construct this notion. That is really the point of my comment.

The idea of the 2 a.m. antibiotic beeper is a really hard one. I have both been that person and have been the person who had to call that person. It really does not work very well for lots of reasons. But let me emphasize the importance of speed with antimicrobial therapy. Anand Kumar is a critical care guy who has been studying this for a period of time. For a while, there was an idea ... in medicine, there has long been an idea called the golden hour. That was an idea that came out of the cardiac care and the trauma literature. The trauma surgeon said you have an hour. If you can get people's blood pressure up in an hour, you can get them better.

And there was a paper, probably seven or eight years ago, that actually for antibiotics said it looks like a golden six hours, in fact, for antibiotics. If you get the antibiotic right within six hours, you are doing better.

And then a series of people, particularly Anand Kumar, have explored that. Well, maybe it is really only a golden an hour. And then their most recent paper was it is about a golden 15 minutes. What he is really saying is that every second that ticks by, your morbidity, your mortality, goes up. Somebody needs to plug their computer in if your battery is low, 7 percent. You have a very short window here.

In the debates that I have heard, it has felt like there were two possible approaches to this. One was to say that you permit the use acutely. It can be prescribed. Also, remember, how long does it take from the moment that I say I want this drug in my patient's blood stream, not even written the order? I have punched it into a computer screen at a hospital, and the pharmacist in the room can tell me. If it is an hour, that is really good, quite frankly. I can get the time way down if I grab my medical student and say, "You go to the pharmacy, get the drug, and bring it back and put it into the patient." I can probably get it into 20 minutes if I do that. But the truth is that does not happen very often, and not everybody has the luxury of a medical student to do that.

The idea that you are going to call somebody and introduce another time lag is a hard one. And then comes in the idea of diagnostics. I want to bring that in as well. We actually have a great diagnostics called a culture. It just takes way too long.

What about rapid diagnostics? How long does a rapid diagnostic actually take? What is rapid? I am at the bedside. I look at the patient, and I say, "I think you might have." I want to send the test. I am going to collect some sputum. I put it in a cup. I hand it to the runner who takes it to the lab because the runner is standing right there next to me. And they take it, and they roar it down to the lab. The lab says I have this great PCR test and it takes four hours, but actually, we just turned the machine on 20 minutes ago. In four hours and 20 minutes, I can get your sample in. I will give you an answer in eight hours. That does not do it. What if the test was actually a one-hour PCR and the machine is available? Well, it is an hour, and now they have to come back with the result, and now I have to prescribe the antibiotic. Now it is two hours out.

The only thing that really works, ultimately, is at the bedside I need a stick that turns blue or green based on something I do in 90 seconds at the bedside. Other than that, I have to think, and I have to guess.

My point of all this long tirade, if you will, is that I think there is a real need to focus on perhaps catching it a little ways down the road. There may need to be a post-utilization review. That is something I do that I have often seen. Rapid diagnostics would help a lot, but you have to understand what rapid really feels like to the doc. It is not rapid from the microbiologist standpoint. It is rapid from the doc's standpoint or from the patient's standpoint because you do not have an hour. You do not have 30 minutes. You do not even have 15 minutes. You have to go quickly. I think that is what I wanted to say. Thank you.

DR. COUKELL: To boil that down with today's technology, an antibiotic approved through the LPAD pathway will be used empirically.

DR. REX: At least maybe a dose. If you can give me even eight hours, I can be a lot smarter eight hours from now. It might be that 36 hours is what I have to have. At least a brief window can make a big difference.

DR. EBERT: A couple of things that I think really expand on that whole electronic health record. One is that we now have the ability, if you will, when physicians prescribe antibiotics, to mandate that electronically. They include an indication for that. I think as to what Matt mentioned earlier, they simply make up the answer electronically as opposed to doing it on paper so that there is not necessarily the credibility with regards to the indication. It does allow for a quicker highlighting of those patients maybe 24 hours later to make sure that they are using the antibiotics appropriately.

But as Dr. Rex mentioned, I really agree that what is appropriate for an antibiotic is a moving target. From the time that the patient initially started on the therapy until the time that the microbiology tests are available is clearly a moving target. As I mentioned earlier, that is why there may be different criteria for use as we move from a suspect infection to a documented infection.

The other challenge, again, with current tests is that we see really four different results from a microbiology test. One is that the patient in fact does have the organism that we are concerned about and we continue the antibiotic therapy.

The second would be that they have an organism, which is susceptible to more conventional agents. Hopefully, we can convince the clinician to de-escalate therapy, but not always.

Third is where our cultures are negative, which in many cases is more than half the time. Now what do we do? Again, can we de-escalate therapy in the patient with a negative culture assuming that they had a severe infection to begin with?

And the final one that we really wrangle with is where the cultures were never obtained in the first place. How do we ever justify the de-escalation of therapy in those patients?

DR. TAMMA: I just wanted to make two points. One with regard to this comment about the 2 a.m. patient, the emergency. I think most of us would agree that is the minority of antibiotics that are prescribed for critically ill patients. I still do think that ensuring the first dose of antibiotics is appropriate for these agents is necessary. However, for our program and for most stewardship programs, certainly for ICU patients, patients in the ER where we do think there could be an emergency, we do allow the first dose of antibiotics, no matter how broad it is to be administered, without going through the stewardship system. And after the first dose, when they are asking for a second dose, we discuss it with the team.

I think we can decide for these agents, depending on if they are being used empirically or not, what the most appropriate mechanism would be. I just wanted you to be aware of that. For stewardship programs, we definitely do take into account critically ill patients. We are never interested in delaying therapy.

The second issue was related to something Kavita brought up about the breakpoint changes. I know there are people in this room who are involved with the CLSI, the agency that gives us recommendations on breakpoints. This is something that John Powers and I have been discussing.

In 2010, the breakpoints for third-generation cephalosporins against enterobacteriaceae decreased from less than or equal to eight to less than or equal to one, so a threefold decline. With that change in our institution, we calculated that there would be over 300 percent increase in the use of broader-spectrum beta-lactams, which is in conflict with that idea we have of trying to preserve these broad-spectrum agents for when we truly need them.

The big issue is most of the data that guides these changes is limited to PK/PD data, which is basically in vitro data, not data from actual patients. The very limited clinical studies basically show that as the MIC increases, patient outcomes worsen. But existing studies do not take into account patient factors. They do not adjust for severity of illness or other factors that might confound this relationship.

One thing that I think would be very helpful from the CLSI is to definitely encourage more of these clinical studies, these well-designed studies to determine if these breakpoint changes are truly necessary because they are resulting in use of broader agents. But until we know that it is really improving patient care, it could be quite dangerous.

DR. DUDLEY: I wanted to pick up also on a couple of themes. First, on a statement about prequalification, I think, as Dr. Goetz mentioned, I actually find that very intriguing. I think the idea here is that what we are saying is that there is some process by which you make an assessment whether these drugs could be appropriate in your institution, whether it has the right patient population, whether the epidemiology is supporting that as well. I think that is certainly from a drug developer's standpoint that makes a lot of sense. To a certain extent, that is happening at your formulary committee, I am sure.

But I think from a program that might be administered on a larger basis in terms of availability of these drugs, some process by we understand or it could prequalify institutions for that would really help.

You might need the drug in Lexington, KY, but you do not need it in Laramie, WY, because you do not have those types of epidemiology or the patient population that you have that is important.

I think the other part of this which is important, and it speaks a bit to the breakpoint discussion that was mentioned earlier, is that, I think it was Kavita, you, mentioned that 30 percent of California hospitals are not using the new breakpoints for carbapenemase. They are. Thirty percent are, and 70 percent are not. That is a little disturbing because of the fact that the new breakpoints do a very good job of detecting carbapenemase-producing organisms.

We know from Ron Jones' data. He has gone back and looked at the epidemiology that KPC-producing *Klebsiella* were circulating at hospitals for several years before the first report from North Carolina at all.

In order for us to prequalify an institution, we have to use the tools that are available now. That is disturbing, but that could be part of that process of prequalifying that you are using the right consensus, best tools available to understand whether the drug should really work for you or not.

DR. COUKELL: Mike, one way you could imagine a prequalification working in a REMS-like system.

DR. DUDLEY: Not so much a REMS-like system, but it could be a payor system that could basically say that you need certain qualifications at your institutions. In California, I believe now you have to have a stewardship program, and I am sure those come in all sorts of flavors and expertise, but you have to have that. You have to have some evidence that you are using up-to-date criteria to define resistance in your institutions. You better be using those criteria.

Ron Jones made a point at the CLSI meeting just a few weeks ago that many hospitals still cannot identify KPC-producing organisms because they are using the wrong instruments or they are not using the right guidelines. That is very disturbing if we are not doing that.

You have to prequalify yourselves by meeting those types of criteria and having a stewardship program that would make essentially a request or say that this is a drug that makes sense in our patient population given our epidemiology and given our use patterns.

DR. COUKELL: Just to push that a bit further so I am really clear of what you are saying. Obviously, the institutions that are committed to stewardship and doing it right are perfectly capable of prequalifying themselves. Those probably are not the ones we are worried about here. It is interesting that you are interested in prequalification. You see it as payor mediated?

DR. DUDLEY: It certainly could be. I think it certainly could be part of that in terms of saying that you may not be able to get this drug unless you have met certain prequalifications that are based upon what the payor may say that you have to be able to demonstrate. Of course, working in concert with the stewardship folks. We do not want to pit the stewardship folks against the payor, but I think in working with them and saying this is what makes sense for our institution based upon the following, I think that could certainly help.

DR. GOETZ: I think the point is that these drugs work best when they are used ... will likely work best in the context of a program. As a stand-alone item, they do not work. We have all been saying that in different ways, and how to get there is perhaps the question.

I want to comment on a couple of things. The microbiology issues are really fraught with concern because there are physicians who go back and forth between institutions. The breakpoints mean different ... susceptibility and resistance means different things depending on where your patient is ... considerable confusion. And the microbiology laboratories have really had problems implementing, not because of sloth. It is not because of being unaware. It is, on one hand, lack of resource support because there are many new methods that they can apply. But where are the microbiology technologists to do the work? And the automated systems we run into other regulatory issues with the FDA approval of the automated devices. It is not a rapid process. There are many other scope issues and regulatory issues that are brought to bear.

But without support for our microbiology laboratories and without the rapidity of implementation of automated testing to implementing the new guidelines, we are going to be stuck in this issue for some time to come. We likely have not seen the end of changes in breakpoints. This will only continue.

DR. COUKELL: Before you move on, let me ask about that. That is a generalized issue. Does it have any implications that are specific to an LPAD drug, or is that a generalized issue for antibiotics?

DR. GOETZ: It is a generalized issue for the misuse of antibiotics.

We talked about cultures and the importance of the microbiology laboratory. If we are honest with ourselves, in what proportion of patients with hospital-associated pneumonia who are not intubated do we have a microbiological diagnosis because of our ability or inability to get a sputum specimen from a 75-year-old person from the nursing home who does not have good cough? I have seen a good culture obtained. It does not happen often. There is going to be that level of empiric therapy that our current microbiological techniques will not help us with. I pose that as a problem. I do not have the solution, but it is something that we do need to think about carefully.

And then I am going to go back to thinking about informatics again. I think that that is a key point. Again, coming back to what do we do when I hope these programs are successful because I want another tool in my toolbox for our patients? Despite all the problems we can describe, I want the other tools. Our patients need the other tool. But then we need to provide monitoring. We need the investment in the informatics tools, in the electronic health care records so that we can actually measure what we are doing, so our stewards know what is being done in a timely fashion, so that we can roll up reports, provide data to our providers as to what they are doing, as to how, in some general sense, they compare to other providers with similar patients, recognizing that we will never have perfect risk adjustment.

The extreme outliers are extreme outliers so that we can look at international basis as to what the levels of use are, identify hot spots where there are trouble. And then also look at outcomes data. Again, I said it before, but I think it is really critical to recognize that we have such a complex domain where we are treating, where we have the patient, the anatomic site, and the pathogen all at once influencing our outcomes. The

permutations are near infinite when we think about it. We have so many small data sets. The person with the prosthetic device with the completely resistant *Acinetobacter*. The person with the brain abscess. The person who is immunocompromised one way or another. Look at outcomes across all those spaces. No clinical trial is going to capture that. We have to use our natural world experience. As I said, if Google knows what I am thinking right now, why can't we ... we need to work towards the world where we can mine the electronic health care record.

DR. REX: Two themes to pick up. One to echo Matt. A lot of medicine is not just off-label. It is off-textbook. What you are treating is some vague mixture of a variety of things. It is not that physicians are lazy and did not want to get the culture. You tried to get the culture. Well, they did get the culture. They got it about two days after the antibiotic got started because you were not able to collect the specimen. We have all seen this. The specimen got lost on the way to the lab. It is not for the lack wish or lack of desire to do it. Everybody will say please start X and also draw two blood cultures, sputum culture, and a urine culture. They do not always get done. Sometimes, it is after the antibiotic gets started because the nurse has to make a choice about what he or she can do for the patient in a timely fashion.

We all wish for Dr. Crusher's scanner from "Star Trek," where she waves it over the patient and says, "You have Arcturian fever, and your therapy will come out of this machine to my left in 30 seconds."

The other comment I want to make is about breakpoints of about PK/PD. The breakpoints are going to be changing, and they are often going to be changed and set in the future, I hope, based heavily PK/PD. It is important to realize what that means now as opposed to what it meant 15 years ago. When we were discovering in the '90s how to link plasma concentrations to the likelihood of response, there was a lot we did not know.

Fast-forward to today and Paul Ambrose who is in the room today have recently have shown a slide in which he demonstrates startlingly well that if you get PK/PD right by modern standards, standards of the past few years, then the likelihood of having an efficacy failure in a phase 3 registration trial is 0 out of 14. It is very good. You can still fail for other reasons. You can have a safety signal crop up. You can fail to run the trial effectively. You can still fail. PK/PD is very powerful.

And the reason to understand this is to come to the question of how can we get more data about treatment at the edge? You asked about breakpoints and can you ask for more clinical data. I want to say the answer to that is actually no. What modern PK/PD means is the following. And the answer is going to be 1 percent. I am going to multiply 10 percent times 10 percent. Is that going to get down to 1 percent?

You set your exposure, your blood, the dose I am going to give you such that 90 percent of the population is guaranteed to get a blood level that meets or exceeds a target threshold. Ninety percent. And that target threshold is chosen such that it covers 90 percent or more of the isolates now in circulation. You take the other side of the 90

percent in both cases—the 10 percent who are a little low, and the 10 percent who have an isolate with a very high MIC—and you get a number that is 1 percent or less. That is the boundary.

DR. COUKELL: Let me jump in there. I think we can safely leave the detailed discussion of how far we can extrapolate PK and PD data for another conversation. But point taken.

On your first point, you eloquently make the case that the clinical environment is complicated and so on. In your mind, the LPAD indication ... the implications for the development program are fairly clear. In your mind, what does the LPAD indication mean to how the drugs will be used?

DR. REX: I think what we have heard from everybody is that it will clearly identify to the user community which drugs have less data behind them and require more attention. The debate now is, how do you apply that more attention? How much of a screen is the screen with the first dose, is the screen with the third dose, is the screen at the level of an institution? You need to factor that into the need at times to start fairly quickly. I think there is never going to be a perfect answer. But the LPAD we would hope would move use closer to correct. If we make the perfect enemy of the good, we may not be able to go anywhere.

DR. EBERT: Actually, Dr. Rex mentioned most of my comments, and the issues are primarily with PK/PD, so I am going to pass.

MR. SCOTT: I had a question for the hospitals. Medicare has conditions of participation. Under Medicare, some of those conditions of participation subject to survey and certification are things like infection control programs. I was wondering if you saw a role for that in the antibiotic stewardship and if you give a high-level overview of how that may apply to LPAD.

DR. COUKELL: Who wants to jump in on that?

DR. TRIVEDI: I can jump in. Right now, on the infection control worksheet as you probably know, there are five questions that we ask hospitals on whether or not they have stewardship programs and what they are doing in terms of quality of use and oversight. I have it somewhere here, all the specific questions. But they are not required right now of hospitals. I think they are called quality improvement measures. But typically what CMS usually does is years down the line once hospitals are used to answering these questions and they get put into mandatory requirements. But right now, I think they just came out with them recently as five quality improvement measures that include stewardship issues. I guess the question would be, could we include the LPAD antibiotics in those quality improvement measures? I think that would be a really good way of having some sort of oversight occurring at the institutional level. I think that would be fabulous.

We do not really know that much since we just started these questions. CMS just started these questions. We do not know that much about how hospitals are doing in relation to the questions. As someone mentioned in California, stewardship is

mandatory. We still seem to have a lot of hospitals that do not have good stewardship programs, even though it is mandatory from the state perspective. I do not know how hospitals are doing across the country with these quality improvement measures, but I think it is a great point.

DR. GOETZ: Things are a little bit different in the Department of Veterans Affairs where I spend all my time, but I can certainly foresee systems that could be set up that would link stewardship, infection control, and utilization or access to medications.

I wonder about two things though. First of all, how will we address the long-term care facility issue, which is yet another concern? I raise that as a question. I do not have a clear answer.

The other thing that I wonder about, is there a role of how my joint commission interacts with hospitals on these issues as well as a quality control issue? It would seem to me that a joint commission is moving towards looking at antimicrobial stewardship very clearly. Infection control has obviously been a very important topic for a number of years. I am always wary of asking a regulator to regulate me more, but unintended consequences. But from a societal perspective, attention to these programs from a number of different perspectives will improve the quality and the conscientious diligence to which they are undertaken. And joint commission I think can play a role there.

DR. DUDLEY: I know Steve Solomon is in the audience here as well and certainly can comment more on CDC than somebody from industry here. I know that CDC has taken antibiotic stewardship very seriously and has a lot of programs right now that are beginning to develop and assist those efforts measuring antibiotic use within hospitals, projects. You are all familiar about the programs that they have sponsored about getting smart about antibiotics, which have been largely focused on the community practice. But I think CDC to me is well equipped and has already made great strides in terms of helping hospitals to get stewardship activities off the ground and giving direction. That could be part of this process in terms of this prequalification or setting forth what are the elements of a stewardship program that really meets certain criteria that allow you to get access to these types of antibiotics where there is limited clinical data.

DR. COUKELL: Steve, do you want to jump in at this point since you have been singled out? We can come back to you if you would like.

DR. SOLOMON: Come back to me.

DR. COUKELL: Kavita had a question.

DR. TRIVEDI: My question is we talked a little bit about monitoring, if there is a way to monitor this. I was thinking about the vaccine-adverse events reporting system and how people voluntarily can report to CDC what they are seeing in terms of vaccines. I think Bob had mentioned the FDA Sentinel system. Could you talk a little bit about, I guess, what the thoughts are about how we would monitor the use of these LPAD drugs with that system?

DR. COX: As you have mentioned, there are post-marketing adverse event reports on the drug side in essence that are similar to the vaccine-adverse event reporting system to be able to track what is going on with the drug once it is out there and being used in practice. The challenging situation we face with that data is that oftentimes we have to just try and estimate what the denominator might be. For infrequently occurring, serious adverse events, it is an important way to follow a drug once it is out there and marketed.

There is also the Sentinel system, which is being developed and is currently being used ... I am not exactly sure the scale at this point, but it is available. I know there is additional work going on. As a matter of fact, I think there is a meeting today on this very topic. If I were there, I would be able to tell you more.

That provides a way to essentially use the administrative databases that are out there and to do queries to be able to look at particular drugs and adverse effects that may be associated with those drugs through queries through the Sentinel system. That provides another mechanism, a tool that exists now and then is still being further developed. That is another way.

And then the other thing we heard mentioned a little bit earlier, too, is also either a registry or other ways to in essence try and understand prescribing and then being able to understand either outcomes or adverse effects. There are ways to try and understand what is going on with the drug once it is out there and being used in the practice setting.

DR. COUKELL: I want to ask one more question of our second panel and then go to the audience.

When I was a hospital pharmacist, if you had told me that a category of commonly used drugs might be about to increase in price by tenfold, I would have been pretty worried. Several of you referenced comments in your opening remarks, some to say clinicians are not that aware. That was certainly true. But talk about the role of price here and how the hospitals and other care institutions are going to treat these drugs. Whoever wants to jump in.

DR. GOETZ: It will certainly be eye-opening to our formulary committees as to how the drugs are used. If you will, formulary committees are swallowing these costs when it comes to high-priced cancer drugs, when it comes to the cost ... I am thinking about my own facility when it comes to antivirals for hepatitis C, when it comes to the treatments for people with other biological agents. Multiple sclerosis drugs would be one example, but there are a number of others.

In so doing, the formulary committees had been very cautious to be sure that the right patients are getting these agents and that have set up carefully constructed criteria for use in guideline documents. Prior approval is necessary. This is where the heartburn really comes with these drugs because they need to be used empirically as we spend some time talking about.

And there will be incredible pressures I foresee to get people off therapy if they do not meet the criteria for use, and that is where there will be ... between the hammer and the anvil will be the stewardship personnel. The formulary committees ... we are saying get the people off it. They do not need it. And the prescribing physicians who will say I do not have enough information to say my patient does not have this infection. They are critically ill. And the stewards will be caught in the middle of that.

DR. EBERT: I agree. One of the good or bad things about not having a lot of antibiotics that have come into the pipeline has been that the vast majority of the antibiotics we have now are generic. The cost has actually gone down for many of those classes of drugs. Adding a new, very expensive class of drugs clearly will be culture shock for institutions. But I agree with what Matt said. If we can try to streamline the conversion of these agents to a narrower spectrum of agents whenever possible, I think that will be an easier pill to swallow.

I think this may tie into one of the other questions that you have on your list, Allan, which is the whole idea of remedies to the institution to curtail inappropriate use. In thinking about that, I see that as a very important component of this risk assessment model, the risk-benefit model, and try to clearly delineate the fact that these drugs do not come without potentially some unforeseen risk. Physicians like to use antibiotics. They also generally perceive them as fairly safe agents. If we can somehow through a communication to physicians from an institution say you have been using these LPAD agents when they really are not needed and that you are unnecessarily putting the patient at risk are potentially either known or unknown type of a risk, that may have some influence on their overall practice.

DR. TAMMA: One other idea with the cost that you are saying is pharmacists routinely in our institution, they always have printouts of the medicines patients are on and the actual cost next to that. One possibility could be on the physician order entry to actually have the price appear when they order these agents so they can be little astounded by how much they actually cost.

DR. COUKELL: Let's go to the floor for questions.

DR. SOLOMON: I will respond to that.

DR. COUKELL: Introduce yourself if you would.

DR. SOLOMON: This is Steve Solomon from CDC. Thanks to Mike for that shout-out. One of the reasons that this is a terrific panel is that we are working at CDC with so many of the folks who are represented on this panel. The California State Health Department, the Johns Hopkins Stewardship Program, the VA, not to mention our colleagues from industry and, of course, from IDSA and, of course, Ed Cox at FDA.

I will not go back around to all the different things that have been said other than to indicate that as Mike indicates, this is a time for a tremendous amount of activity and increasing assertiveness, I think, throughout both public health and the clinical sector on the question of stewardship and improving antimicrobial use.

There are a number of things in the pipeline right now, and we are talking literally the next 12 to 18 months to begin to figure out how to get better data, what to do with that data. The GAIN Act has been mentioned here several times. What has not been mentioned yet, I do not think that as part of the GAIN Act the federal government is required to report back to the secretary, HHS, FDA, and CDC on the success of stewardship programs and how well stewardship programs are being adopted across the United States. As Ed indicated about some other things in real time there were discussions going on today and next week about how to begin to do that. There is a tremendous amount of activity.

We are getting great support from our federal advisory committee. Both Mike is on that. Kevin Outterson is on that. There are, I think, half of the Interagency Task Force on Antimicrobial Resistance is somewhere in this room. The ITAFR was also taking that up. Just to validate the point, there is a tremendous amount going on around stewardship and measuring antimicrobial use. It is throughout government and private sector in the clinical arena. There are a lot of people working on it. I am very optimistic that within 12 to 18 months we are going to see, really, a great leap forward, if I can use that term. It is not going to solve all the problems. It is going to be a long time before we get where we all want to be, but I think it is going to be a tremendous advance. I think you will see that over the next 12 to 18 to 24 months.

MR. CRAIG: I am Michael Craig with CDC. I just want to add a little more granularity to what Steve mentioned and appreciate the comments from both Pranita and Kavita and Matthew. The system about measuring antibiotic use and resistance is one we are piloting right now. We already have a system that the National Healthcare Safety Network that reports infections from over 10,000 health care facilities nationwide, and we are trying to build out the functionality within that safety, where not only antibiotic data use can be reported through that system and resistance patterns, but you can have the benchmarking that has been talked about, where you can compare across facilities, across regions, about not only what antibiotics are being used, but resistance patterns you are seeing.

I think that that really is a win-win to everyone in this room because I think it is a win-win to the physicians to see how their practice is comparative to other physicians with similar patients who are risk adjusted to hospitals, to see how that they compare to the companies that are producing these drugs, to see where some of these patients are at. What are the patterns across the country in terms of what is being used and what resistance patterns are there? And I think to the rest of us because the system that this is being based on is already tied to CMS reimbursements. This is something that CMS can easily require once it is mature and once it is at a place where everyone agrees with it. Public reporting of the data, transparency of the data, and potentially tie it to reimbursement and some quality improvement projects that CMS has.

DR. COUKELL: Let me go to our next question. If anyone has a question particularly of our panelists from the hospital clinical care panel.

DR. BAINE: I am really addressing ... my question is a question that you presented, Mr. Moderator. First, I would like to make a suggestion that we distinguish between cost and price. And the reason we do not have a drug right now to treat resistant Acinetobacter is because it is a rare event, and so the price has to be very high. The way to lower the price would be to use it inappropriately so you would have more sales and you get ...

You asked about the hospital. Could the pharmacy justify using an expensive drug? You spoke in terms of fewer re-admissions and so on. I think it is important to keep in mind whose perspective we are taking. That is the hospital's perspective. We are also supposed to be taking care of the patient, and the patient has a life expectancy so that the cost-effectiveness of the drug would be very much dependent on the individual patient. Are you treating a 90-year-old guy who you would never give cancer chemotherapy to, or are you treating the 20 year old who was in the emergency room that was saved who we heard about earlier.

And my question has to do with the issue of empirical use. When you have the model for drug B and drug C and you say we need 500 patients, we need 300 patients, are those people who actually have the resistant Acinetobacter, or are those the number of blood cultures you draw, the number of septic patients ... looking for the one in five or the one in 10 or the one in 20 who actually have the bug you are interested in ...

DR. COUKELL: Thank you. Bill, just for the sake of the transcription, would you just say your name and your affiliation?

DR. BAINE: William Baine, AHRQ.

DR. COUKELL: Do you want to speak to that? Let me come back to you. Do any of our developers want to talk to the question of, if you are looking at a total population of 500 patients, how many of them actually have the resistant ... we touched on it this morning.

DR. DUDLEY: I think we did touch on it this morning. A frequent exercise of the people in the room who do this more often than I do of trying to say how many patients with MDR organisms are there out there and how do you square that with antibiotic sales making assumptions about doses. And the answer is you can never make those numbers work. It is because of presumptive therapy. It is because you are in situations where those organisms are suspected. There are few alternatives. And for the scenario that John talked about, you have to institute appropriate antibiotic therapy quickly. Therefore, sometimes just number of infections, body counts of bacteria, is not going to get you necessarily to where the appropriate use is or the number of doses.

DR. COUKELL: So our hypothetical scenario is probably underestimate revenues for the companies, underestimate cost for the hospitals and payors.

DR. DUDLEY: Yes. There are different ways that you can shockingly enough use Monte Carlo simulation to actually help you understand that those kinds of scenarios based

upon assumptions. But that is the way antibiotics are used, and they are appropriately used that way.

DR. COUKELL: Thank you for that. Do you want to jump in, Dr. Cox?

DR. COX: I will add right on to that and say that you do not know which way it is going to go in terms of the numbers. IDSA has a vignette or used to have a vignette on your website about a hypothetical salmonella outbreak. You may not realize it, but food-borne outbreaks occur reasonably frequently. And the one on IDSA's website was drawn from an actual episode that occurred 10 or 15 years ago, where there were tens of thousands of cases, as I recall. It was a big number. That organism in the modern era could tomorrow be a metallo-beta-lactamase-producing organism for which the therapies are fairly expensive. We hope that that does not occur.

I just wanted to emphasize the unpredictability of this. In part, what we are saying is we have to develop them against the curve. We have to develop in advance of the epidemic. You need to find something that is at least a breakeven so that there is the ability as a discoverer to say to an investor, "I think that bringing this forward would make some sense." Remember, it starts way back at the beginning, a glimmer in somebody's eye that I am willing to invest in a discovery program that will not produce a molecule for 15 years.

DR. COUKELL: Go ahead.

MS. WELCH: Just to finish the industry comment on this and to address the question in terms of studying these patients from a clinical trial standpoint, that is obviously going to vary with regard to the pathogen, but we have heard this morning how difficult it is to identify patients and, therefore, the effect that has on the actual duration of the trial. My understanding from the models that were shared, which were represented of a Tier B and Tier C, they would probably represent a mixed population of patients with both susceptible and multidrug-resistant pathogens in those specific examples. John can confirm whether that is correct or not.

DR. DUDLEY: Mine is more just of a general comment. I want to thank all the speakers. The comments, I thought, were very helpful. It brought to light some of the real-world challenges faced in stewardships and formulary committees and the practice of medicine, and those challenges are real. I found it encouraging to hear about some of the possible ways to use the formulary committee to think about how either the infection control or the stewardship program might be able to interface with appropriate use. It sounds like it is essentially all antibiotics. It is not just any one particular group from what I am hearing from folks.

Just end my comment with I think the problem that we face here now with patients not having options essentially is calling us to meet this challenge. And the problem is one that is significant enough and deserves our attention to be able to try and overcome some of these challenges that do seem to be present and probably even somewhat inherent to this field. It is more of a comment and welcome any reactions, but just wanted to throw that out there for people's thoughts.

DR. COUKELL: Reactions to that?

DR. GOETZ: Essentially agreement.

DR. SHLAES: Actually, I wanted to get back to a question that Dr. Ebert raised or a comment, which was around use of pharmacoeconomic data to justify the price. I actually think for the Tier C drugs that we are talking about I do not think that is happening unless you have a very extrapolated pathway to get to a pharmacoeconomic justification. I wonder if maybe one of the developers could comment on whether in a Tier C drug program you would actually be able to produce pharmacoeconomic data to justify the high price and whether there is even a relationship between the price and the pharmacoeconomic data that you might be able to achieve.

MS. WELCH: I can just add a brief comment on that based on very limited experience with this one particular study that we are looking at. We do intend to collect some pharmacoeconomic data. We are a little unsure at this time exactly what that will look like, and it will be descriptive in nature. But we certainly do intend to look at days in the ICU, days on ventilator, etc., and hopefully be able to weave that into our pricing and reimbursement case as we conclude that study.

DR. EBERT: I think it would be difficult. I tend to think of whether it is Tier B or Tier C maybe more a function of how you are going to execute the development program and do-ability of the trials as opposed to that.

I think that pharmacoeconomic issues here ... you are dealing with pathogens for which there are limited choices. Pharmacoeconomics is a very helpful tool for cost-effectiveness analyses, but our assumption here is that where there are limited choices or where there is multidrug resistance, we do not have appropriate choices. If you are going to do a cost-benefit analysis, then you have to ask ... the cost-benefit analysis says, is it worth treating this patient's infection at all, which I do not think we want to go to that question. That is a separate question.

A classic pharmacoeconomic analysis where you have several paths to get to the same outcome is appropriate, but in a situation of MDR resistance or limited choices, you are probably not able to really use that.

DR. COUKELL: Thanks. I want to take a last question from John Powers.

DR. POWERS: This is just more of a comment. One of the things in reading through the Federal Register notice for LPAD. If you compare it to other regulatory initiatives like Ed mentioned earlier, accelerated approval, or subpart E for INDs, there really is a lack of clarity on some of the definitions and the processes, and that is OK because we are at this point of just discussing the whole theory behind it. But one of the things that comes up in this process is, how would the information on these drugs get to hospital formularies and practitioners? That seems to be a real missing link in this.

The other thing that probably bears discussion as well is the issue that, if you look under things like subpart H, there are things in there ... FDA regulates drug companies, not the

practice of medicine. They are informing the practice of medicine. What happens when somebody goes out and does off-label? We always used to joke, regulation is not there for the guys that are doing everything right—it is there for the few that do not. What happens when somebody does off-label market one these drugs inappropriately?

And we can all talk about how that won't happen except when you start to count up the number of companies that have been fined recently for off-label marketing, some of which are for antibiotics. In subpart H, for instance, it outlines some of the issues of that so companies would send in their advertising information ahead of time, etc. That is really not in this proposal yet, but maybe were some discussions of how would that actually work out. I think there is some level of detail here that probably needs some more discussion.

DR. COUKELL: Thanks for raising those points, and I think they open up a whole other area of discussion. Rather than go to that now, I am going to suggest ... we have a lot of time for discussion this afternoon. We will come back to that among other things.

AFTERNOON SESSION

Part 2: Role of Payors in Use of Limited Population Antibiotics

DR. COUKELL: It was a stimulating discussion this morning, and I am looking forward to this afternoon. Just to give the running order of the afternoon, our next panel includes payors to give us a payor perspective on that. We will follow that with some more of the roundtable discussion that we have had, and then we will bring up to the roundtable three people who have been in the audience. Nicole will stay here, and we will bring up two others who have been in the audience and taking notes for our final panel—both crystallize what they have heard, what they think the outstanding questions are around this pathway, and then we will have some final discussion on that.

As I have said, the third panel today is on payors and we are very pleased to have payors representing different sectors here. We do not have someone from CMS. We tried very hard to get someone from CMS. But I am delighted to have Jim Scott here, who, as he described this morning, is someone with that background and is a reimbursement consultant in terms of full disclosure. Jim has also been and will be in the future a consultant to Pew. Jim, would you start and give us your thinking about how CMS may approach limited population drugs?

I guess I should just say in terms of stage setting, obviously the questions we have on the agenda are around, is there a role for payors in treating these drugs different from antibiotics approved through the existing pathway? What approach would they take to on- and off-label use? How does pricing factor in? Does it make a difference if these are premium-priced products the way we have been talking today?

MR. SCOTT: Thanks, Allan and Nicole, for putting this panel together today. It is so rare that we have an opportunity, and it is so necessary in considering a proposal like the LPAD to have payors, providers, and the government and public health officials all at the same table discussing this at the beginning of the process instead of waiting until an FDA pathway has been established and then turning over and talking about payment at that point.

A lot of the discussion earlier this morning focused on, of course, how do you get this through the FDA. From our perspective, we think about what would the payor perspective be as far as reimbursement for the products. While it might be nice to have subjective determinations and everybody judge appropriate use, if you want to have a payment component, payment always comes down to determination—that is really a bright line, determination. Pay or don't pay. And then within that, if you do pay, what are the strings that are attached and how much do you pay? That is a gross oversimplification, but it does ultimately payors have to decide whether or not to pay the bill.

One of the things I would like to address first is why Medicare. The exchanges that are coming up—the Medicaid, the VA, the DOD are all important—but Medicare's older population, with 50 million beneficiaries and centralized decision-making, make it a

government payor that manufacturers, providers, and private payors really look to as a baseline.

For Medicare, the way I see it, the limited-use antibiotic policy proposal would have two key parts. The first part would be, how do you limit reimbursement to the appropriate use? We have heard a lot of discussion earlier today about how would you define that appropriate use. Whatever it is, whether it is on-label or off-label, but used appropriately or on label and some subset of that, how could payors limit it to that?

And then the other part of it is, could payors provide an enhanced payment amount to recognize the additional cost for the smaller population?

CMS looks at these two issues. The first is more related to coverage, and then the second is more related to payment policy. At CMS, coverage and payment policy are two totally separate things. Coverage is handled by the Center for Clinical Standards and Quality, and payment is handled by the Center for Medicare. They are two separate groups and two totally independent determinations.

Let me talk about coverage policy first. Under current law, I believe CMS has multiple authorities that could limit antibiotic use in accordance with an LPAD policy, but I will focus on three of them here today. The first is national coverage determinations. The second is conditions of participation. And the third is quality measurement programs.

With respect to national coverage determinations, that is what I hear talked about a lot, and it may come to mind first. I actually think this is the least likely tool that CMS would use, but I also think it is important to discuss it.

In making national coverage policy, CMS thinks about what the statutory directive is and that is this reasonable and necessary to treat illness or to diagnose or treat an illness or injury. Pretty clearly, antibiotics fall in there. But the subset of the way CMS thinks about that is, does this new product improve health outcomes, and is that improvement in health outcomes generalizable to the Medicare population?

One of the things that we have seen in the past is that the FDA clinical data will apply to adults or maybe stratified in cohorts of age brackets, but it does not specifically address how this new product is going to work in the Medicare population. As a payor, CMS wants to know, how is this product going to work in its particular population that tends to be older and sicker? In the beginning of the process to the extent that that data can be collected and made available, I think it will be valuable in the end of the process. And then, really, how does that data show that it improved health outcomes?

For the national coverage determinations, CMS has rarely done one with respect to drugs, and those drugs have usually been pretty limited. You can think of erythropoietin-stimulating agents in dialysis facilities have been a subject of that.

The antibiotics ... the way they are proposed to be used here largely in inpatient settings is something that at first blush CMS would probably not want to embrace and bark on the national coverage determination process. That being said, you do not necessarily

want a national coverage determination, because at CMS, the default position is that they pay unless they say they are not going to pay. You start off with the broadest possible coverage, and a national coverage determination on a newly FDA-approved product is likely to limit use, which may be desirable here. But it is unusual for CMS to be approached with a request like that.

The conditions of participation we touched on briefly in the last question and answer session. Hospitals are required to meet certain standards and have policies. One of those is accreditation, and most hospitals are accredited by the Joint Commission. They can have policies in place regarding antibiotic stewardship. Also, to participate in Medicare, you have to meet state law requirements. That can also require antibiotic stewardship. And then also they have the infection control programs that we briefly mentioned. While not mandatory, it could ultimately become mandatory.

The weakness in those is that CMS usually enforces, do you have a standard or did you ask the questions, and does not go much beyond that. And they rely on external validation like the Joint Commission to demonstrate that they met that. Is that good enough for a limited-use antibiotic program or not? It may be. Maybe not.

The next item I would like to address is the quality measurement programs. The one that I would like to focus on here is—CMS has a number of quality reporting programs, one in virtually every setting of care—one of them relevant here is the hospital inpatient quality-reporting program. It has a number of quality measures that are developed outside in the private sector, usually by specialty societies or the AMA physician consortium for performance improvement. And then they go through an endorsement process and are ultimately adopted by CMS. CMS has already used that process to limit the use of antibiotics. There are several measures, but, for example, one is called measure PN6, which is the initial selection of appropriate antibiotic in community-acquired pneumonia.

What happens with these quality-reporting programs is they are technically voluntary. But their voluntary in a way that makes them practically mandatory, because if hospitals do not comply with and report the quality measures, they get 2 percent payment reduction across all their Medicare payments. No hospital wants to risk a 2 percent cut to all its Medicare payments. They all follow the quality-reporting programs.

And then the other part of it is that Medicare maintains a website where they publicly report this information, and generally people that go into the medical fields are really good students and like to get As. They publicly report how the hospitals are doing relative to other hospitals. You would not be surprised to see that the compliance with the quality measures reported is in the really high 90s. They have the payment policy on one side to participate in the first place, and then they have the competitive side on the other where they post it on the website, and every hospital wants to do better than the others do, and that is the way they encourage adherence there. That could clearly be broadened here. That is the coverage side, and that is how I view whether Medicare would pay or not pay.

The next question is how much to pay. And the thing to remember here is that CMS pays providers. They do not pay drug companies directly. The payment goes to the provider for providing the service or using the product. But the provider actually has to acquire the product in the first place.

An infused antibiotic, an IV antibiotic could reimburse under several different ways under Medicare, and it really depends on where it is used. Medicare Part A covers inpatient hospital services, and that is reimbursed one way. Medicare Part B covers hospital outpatient use and physician office use. Medicare Part D would cover home infusion and other sites of care not covered under Parts A and B. And then the other way Medicare pays is about 25 percent of its patients are enrolled in Medicare Advantage, which is a health plan, and the health plan could either pay under its medical benefit side or under its pharmacy side, depending on its own policies.

I am going to focus on for the sake of time the inpatient settings. The way Medicare pays hospitals is based on diagnosis-related groups. The patients are essentially classified at discharge, and the hospital is paid a lump sum based on their diagnosis. Medicare adjust the diagnosis-related groups by severity. They call them Medicare severity adjusted diagnosis related groups, or MSDRGs.

The MSDRGs are calculated based on the resources the hospitals presumed to have used to treat a patient of that type. They do not apply to a particular patient. It is by design an average of all of these kinds of patients. Your actual cost per patient, some are going to be higher, and some are going to be lower.

It also affects because of the time until discharge ... because the payment is not determined until discharge, the payment policy is not immediate. You make the decision whether or not to use the drug before the payment is actually ever made.

CMS only recalibrates the diagnosis-related groups once a year, and they use the data that is two to three years old because of the time it takes the regulatory process and to clean and validate the previous data. The current year's payments are not based on the current year actual cost. And this poses a barrier to new technologies. To address that, CMS has a new technology add-on payment program. Then that new technology add-on payment program has three criteria. It requires a substantial improvement. It requires you to show that it would be inadequately paid under the current diagnosis-related groups. And that your product is actually new—it has not been used around long enough that it could be captured in the existing CMS data.

If CMS awards you the new technology add-on payment, you can get 50 percent of the amount by the cost of the product, or if it is lower, 50 percent of the amount of the cost, by which the case exceeds the expected payment for that diagnosis-related group. You only get 50 percent of the actual cost of the product. In the LPAD discussion, is that 50 percent enough or not enough? That is something to be worked out in the policy.

I have talked more than enough but give you an overview there. I would like to turn it back to Allan.

DR. COUKELL: Jim, thanks for that. It is a complicated thing to summarize, and you did it well. Let's keep moving, and let me go to Saira Jan, who is the director of clinical pharmacy management at Horizon Blue Cross Blue Shield of New Jersey.

DR. JAN: Thank you, Allan. I think the perspective that I am going to give you is more of an outpatient setting. The product that we are discussing today is more inpatient. But I do not think it is going to be limited to inpatient as it progresses and the options that are out there. Just to give you a brief overview of the formulary process, it is kind of similar to what happens in the P&T in a hospital setting, and I am not going to repeat.

The only thing that will be different in a managed care environment are a payor perspective. When I talk about payor, I do not isolate insurance companies. I think payors are the CMS, the federal government. And the biggest payor of all that we neglect to see is the employer groups. These are the people actually who are funding for the products that we pay. Insurers are intermediaries that are managing inappropriate utilization.

When we look at a drug that is introduced into the market, it is not only based on the FDA-approved studies or the studies that have been presented to FDA for approval, but also the in-house data. The access of claims data and the utilization information that an insurance company has is critical in analyzing the outcomes. We try to match the outcomes. Remember, they are claim-based outcomes, so they are not going to be as clinically rigorous as it is going to be from a claims data, but something that kind of gives us indication of what we need to look in deeper. The difference is looking at the compliance, adherence, and the outcomes.

From a payor perspective, I think, when a drug gets introduced into the market, it is just not the efficacy of the drug, but effectiveness of the drug. The hospital setting is going to totally mirror or at least be very close to the clinical endpoints that you are going to see in a very well-designed controlled study. What you are going to see in an inpatient setting may somewhat differ, and that is where the outcomes kind of ties in.

What payors are struggling with and are trying to achieve is the integration of pharmacy and medical claims data to get rid of the silos, to drop the barriers of looking at the cost and confusing it with the price. When I am talking about a cost, I am talking about the overall picture of how this condition is treated. That goes beyond the therapeutic classes. From a physician's perspective, if a condition has to be treated, he is not going to say, "I am going to use penicillin versus cephalosporin.: He is going to see what is the first-line agent. It is cross-therapeutic. That goes very directly into the formulary decision-making process.

What the formulary group also works on is developing criteria, and that applies for the drug, how it is going to be used. They are not going to be developed on the basis of random things. It is going to be totally based on FDA label indication. What is the indication for? What are the exclusion and inclusion criteria in the studies that that drug has been studied?

But at the same time, it will also have a policy, and every plan, I am sure, has a policy for off-label use. Off-label use is reviewed, and usually the payors are going to pay for the off-label use where there is evidence behind it, a little bit of evidence. Where there is negative evidence or where there is evidence that it could be detrimental, then you would have issues in terms of the approval or the payment.

Now the way the hospital drugs are reviewed is the fact that a payor is going to pay what the hospital bills them. They are going to have the information. What would drive more rigorous management of these conditions is the site of delivery. If there is an antibiotic that is given IV in a hospital and the patient is hospitalized, then it comes in as aggregated, and you know what the drug was given in, and you pay based on the contract with the hospital, whatever the billing was.

If the patient goes in and walks out the next day and the hospital is a venue of just the delivery and the patient is outpatient, then we will have more criteria and more management. And they are not restrictive criteria. I just want to make that very clear. It is more around appropriateness of therapy.

I think the stakeholder that benefits the most is the managed care and employer based where you give the right treatment to the right patient. Targeted therapy, I think, is a gold standard that everybody is wanting to do. If this drug is targeted and is given to the right population, I do not think anybody is going to have any issues about it. As far as the pricing is concerned, I think we have discussed it a lot in the morning. There are a lot of drugs that are much more expensive. Where that becomes an issue is the fact that is it going to be limited to restrictive indication or it is going to be approved with a limited indication. And then as the years go by, that indication gets expanded, and then how do you manage because there are negative consequences of inappropriate use, which is resistance?

I know payors are usually labeled with the fact that because it is high cost, it is going to be restrictive. It is not only high cost. Here is the safety concern. And payors do look at a lot of drugs that pose safety concerns, which pose issues. And that is why the clinical studies that, when they are looked at, you look and review not only the data that is submitted to FDA, but also the in-house data and then coupled with the utilization. We do have access to claims data. We have access to pharmacy claims data, and we have access to medical claims data. And that is why I think I had tried to bring to the attention to this group it is really very important that there is some thought of outcome management.

There is no way you can create a pharmacoeconomic model for justification of this product based on what you are going to do the clinical trial on because it is going to expand. You have real-life situations where it is going to be used. Where it is going to make use is to tie in the actual utilization data and the mortality data and the hospital days data, and look at the big picture and justify for the consequences. What is happening? Are you preventing deaths?

From a managed care perspective, one critical thing that would be important for us is to understand, what is the rate of re-admission with the same organism? The patient got this. They were fine. But within a month, they were re-admitted with the same organism. What happened when a patient is discharged and then has some other consequences?

We are working on a project with ... and that ties in with the label aspect. I am working on a project with FDA on mitoxantrone, where the label clearly indicates that you have to monitor it for the rest of your life. That does not happen. Are the agents that are going to be approved that may require lifelong monitoring, and what does that entail?

Those are the kinds of things that I think we need to look at. I am not very familiar with the molecules that are being studied right now. It is not just the immediate reimbursement or immediate monitoring of the product when the drug is administered, but what is happening after the fact.

I know it is costly to have the REMS program, but are there other opportunities to make sure that the drug is given appropriately whether documentation where the capturing of the data post-infusion to look at the outcomes and the consequences? Yes, it is costly, but that is also going to safeguard your product. If it is not given to the appropriate population or its expanded use whether appropriate or inappropriate where other alternatives are available is going to jeopardize the product. I think that is the key thing.

I think most of the drugs that have been withdrawn from the market, I would say, is not mostly the drug, but it is the wrong population. That is why when manage care is looking at the population, we definitely look at the inclusion criteria and exclusion criteria to say what are the populations in the real life that can be affected because some of the comorbidities may not be captured in there.

But with your population ... I am hoping that this pathway would be limited. I think we need this pathway for these drug classes, where you have nothing else to offer and you are giving this product, at least initially, until we get a good handle on this versus this is a good antibiotic and has different indications and just going by the organism, because tying in with the severity and the seriousness of the condition with the organism is going to be critical.

And then we have to look at the bigger picture of where does it play a role in preventing to go to the seriousness.

DR. COUKELL: Thank you. Let me go now to Eric Cannon, chief of pharmacy with SelectHealth, which is part of Intermountain Healthcare. It is a pharmacy benefits management group.

DR. CANNON: Great. Thank you. I had put together a list of thoughts here, and I thought they were fairly concise and organized, and I have made additional notes throughout the morning. If you actually looked at my notes, you would think I had not taken my medication this morning.

A couple of things come to mind, though. As we talk about limited population antibiotics, they have been compared somewhat to orphan drugs. I think there is some similarity there in that I think most health plans or most health systems across the country provide payment for orphan drugs. And likewise, I think most plans will provide payment and coverage for this class of antibiotics. That is where the similarity, I think, ends.

Orphan drugs, I think, as we look at there is a very clear definition of where you will use it. You look at Cerezyme in Gaucher's disease. It is very black and white. And this morning as we have had the discussions about empiric use, which is not going to be black and white in this situation. I think that will cause payors to struggle a little bit.

And as a health plan, and Saira hit on this, we have a fiduciary responsibility to our clients, who in most instances are employer groups, although we have a significant number of our clients who are also individuals, and they are purchasing individual plans.

I think the thing that has changed and is changing more and more is that design of the benefits. If you go back 10, 15 years ago, I had a fixed copay or I had a fixed coinsurance. I may have had a small deductible, \$100, \$250. But I think we are seeing now high-deductible health plans, and they are combined with federally qualified health savings account. If you look at the benefits I have now for my employer for my family, we have a \$3,000 deductible. Once we hit that \$3,000 deductible, we then pay 20 percent of the cost up until we hit an out-of-pocket maximum, which could be \$6,000 to \$10,000, and then at that point, then we do not pay anything.

In the past, a member or a patient may have had an out-of-pocket maximum. They may have paid 20 percent up to \$3,000. The employer is putting a lot of that responsibility to make health care decisions back on the patient. In the past, providers in a hospital would think, "I am going to give this drug, and it will be covered." In the new world, yes, it will be covered, but the patient may have a \$6,000 or \$10,000 responsibility that they have to pay.

Now coming from Intermountain Healthcare, one of the things that we are dealing with more and more is, as these deductibles increase, the bad debt for us and our facilities is also increasing. I think that increases the scrutiny both on the payor side and on the hospital side.

How would it look, and I think for us as an integrated delivery system, I think there is some advantages to that integration. We do a lot of what are called clinical programs where we really integrate. And I have clinical pharmacists on my team that sit down with clinicians, whether they are in the hospitals or the clinics. We also integrate that with administrative staff.

One of the things we have found is that it is very difficult to implement pathways and guidelines if we are not bringing in the back-office staff. They are very much a part of that process. Those teams will sit together, and they will discuss how things are used.

A great example is Synagis for RSV prophylaxis. Where there are clear guidelines for its use ... one of the things that we did early on when the drug came out was we sat down with neonatologists. We sat down with OB/GYNs that may be in that prenatal care. We sat down with pediatricians that may be caring for these infants after they are born and really developed guidelines.

One of the things we came to an agreement on was, if you give the drug per the guidelines and you start it while this baby is in the NICU, we as a payor commit that we will continue to pay for that drug and cover it once that baby is discharged from the NICU into the outpatient setting. As we look at these drugs, it is a very viable option, where as a payor and as an institution and clinicians, we can agree where the product will be used. And the idea and the goal here, if I am understanding things right, would be to get people out of hospitals as quickly as we can, and they would maybe have to continue these products into the outpatient, and that provides an opportunity, I think, for us to do that.

The other piece of those clinical programs that I think is important here is this concept of you cannot manage something if you do not measure it. I think that would be an inherent requirement in all of this whether it is a registry from the manufacturer or within our own system. I think, unlike our managing and measuring diabetes or asthma, we are not going to have the volumes of patients that we may need within our own little health system to actually manage and measure those things. This is going to have to be a much bigger effort if we are going to track the outcomes and really understand where the drug ought to be used and where it should not be used.

If you look at the Intermountain system, a lot of this information gets built into the electronic medical record. The physician order entry system within the hospital has antibiotic-assistant-type programs that are combined into that.

As far as formulary goes for us, we combine our formulary process between the outpatient and the inpatient. We have two separate committees, but we really coordinate those two efforts. This is a drug where I think on the institution side we would probably review it and would look at all of the typical formulary things.

I think where this is going to be a little bit different is some of the typical formulary review process, where we look at the rigor of the study, we look at the size of the population. There are some of those things that we have set as standards as we do P&T processes, and as we do formulary reviews that, I think, given how the drugs will be approved in the limited populations in which they will have been tested, we will need to modify that approach somewhat. We cannot expect to have the same level of rigor that we may on other outpatient drugs. That will be a mind shift, I think, for both P&T committees within health plans and P&T committees within facilities.

I guess my final point would be the only way this will work and the only way we will maintain some consistency is really through partnerships, and that is partnerships between the manufacturers, the institutions, and the payors where we are in agreement on where the products would be used. We are in agreement on what the

measurement will be and that process for following up and disseminating the information as we find it and learn more.

Expert Roundtable Discussion

DR. COUKELL: Thank you. Let's open it up to discussion. Let me start with a couple of quick questions. Jim, if I understood you correctly, a most likely scenario here for inpatient intravenous antibiotics used as part of a DRG is that, eventually, the DRG will catch up and incorporate the premium pricing, but absent an NTAP-type supplement, at least initially and then certainly once the NTAP expires, it is the hospital that essentially bears the cost of the supplementary cost for a patient that is using that high-cost drug. That is the most likely scenario.

DR. CANNON: That is right, Allan. If you take, for example, Dificid—that is the example everybody is excited about because it is a pill that got a new technology add-on payment for C. diff. It demonstrated that it made a substantial clinical improvement because they compared it to vancomycin. It demonstrated that there was an insufficient DRG payment because the average cost of a case if you use Dificid is \$55,130 compared to the comparator case of \$43,673. The DRG payment was inadequate. Then CMS calculated that, based on \$2,800 and 6.2 days of Dificid, that it would cost \$1,736 over a usual case, and they chopped that number in half and get the add-on payment of \$868. That started on October 1 of last year in 2012. They call that fiscal year 2013. And that continues for two to three years. It will be definitely for this, definitely for next year, and maybe for the third year.

Optimer is likely to view it as a crisis when this ends because, all of a sudden, after the payment ends, the DRG is going to drop, and the hospital gets the same payment whether they use ... that it will incorporate. It should have caught up and maybe slightly increase the DRG payment, but they get paid the same amount whether they use vancomycin or continue to use Dificid. It will appear to take a loss per case for every case they use Dificid because it is likely to be ... it definitely will not be as high as the add-on payment was. It is unclear whether that is a sustainable program in the long term.

DR. COUKELL: Thanks. Saira, you talked about the need for outcomes data, and you said there is no way to do the pharmaco-economic model based on the clinical programs that we are talking about. Who will collect that outcomes data? Where will that come from?

DR. JAN: There are different opportunities. Depending on where the drug is administered, I think that would be an opportunity for collaboration with the hospital to say ... because that would have an important component of identification—identification of the population and then who the drug was administered.

But I think another interesting thing would be to say this patient and the hospital days. There could be a collaboration between a hospital and a payor to say, did that decrease the hospital days? Did that decrease the ICU days between the hospital and then outpatient? And then whether it was a re-admission and what that cost. That is a big outcome analysis.

I think the key drivers would be where the drug is infused, and if it just stays limited in a hospital setting, then that would be the site where the data will have to be collected from. I think it will also have to be looked at the off-label use. If a drug is being administered in a setting where it is outside the scope of what it was approved for, you want to measure their outcomes also to say, yes, it was totally infused. It made sense, but it was for another indication, but did that translate into a positive outcome or the patient died? Those are the kinds of things.

I think that would be critical because you are dealing with not long-term trials. You are dealing with short-term trials. You are dealing with minimum exposure to the patients in terms of side effect profiles. You want to understand whether the side effect is immediate or the side effect is delayed.

There are now hospital systems that are collaborating, but the systems like VA, where you have integration of hospital and outpatient with systems, like what Eric is saying, where are the Kaisers of the world where they own the hospitals. I think that would be a great opportunity. It may not necessarily be the most expensive venue like a REMS program, but in a more aspect of data collection and involving the informatics to really analyze the data. I think it would be a great opportunity for a pharmaceutical company to collaborate because I think the role of pharmaceutical companies have evolved over the years. It is just not identifying a product and launching the product, but also managing the life cycle of the product and seeing how it is being used in order to ensure that the product survives the lifespan.

DR. COUKELL: Thank you. Eric, did I understand correctly that patients are increasingly responsible for a 20 percent copay, even on inpatient drugs? As you think about an LPAD drug that may come to market with a different level of evidence, do you foresee this being part of a conversation with the patient? Does the fact that they have some cost sharing here change the extent to which they are consulted on the treatment choice, I guess?

DR. CANNON: I think the concept behind the high-deductible health plans and the health savings account was really coming from employers looking at their employees and saying, "I am paying this amount of money and really shifting." With my employer in my health savings account, they will match me dollar for dollar up to ... the first year they did it, it was \$2,000. This year, they decreased it. It was down to \$1,500. But still I have a \$3,000 deductible. I put in \$1,500. They put in \$1,500. I also have lower premiums taken out of my check. In the end, as I sit down and work the numbers, I actually come out ahead.

And the concept was that you would really sit down with your physician and talk about those treatments and things. And I think from the standpoint of if I have high blood pressure and I want to use a branded drug versus a generic drug, which is a conversation that can happen.

I think as we get more into certain things ... if I go to my orthopedic surgeon, he tells me I need an MRI. I do not know what the conversation is going to be. I am not going to

have a conversation. Likewise, in this situation here, I do not know that there is a lot of conversation to be had other than this is the appropriate treatment for you based on either your symptomatology in the case of empiric use or based on the microbiology at that point in time that we have it. I think that is one of those things where I think it is important from a company standpoint or manufacturer standpoint that we really work to disseminate this information.

No one is opposed, I do not think, to having a high-priced drug so long as it is sensibly priced. If it is absurdly priced, then people will have issues. But along with that, there needs to be some clear education about the benefits of the drug. A, there is no alternatives. B, we think we can get you out of the hospital quicker. C, the likelihood that it is going to come back is greatly reduced. Having that information available.

And that is one of the things that is always hard for me in my position—is as I sit down within an employer and we are seeing it more and more in the case of oncolytics where a drug could be \$100,000. It could be \$150,000. We see progression-free survival at six weeks, eight weeks. If we are lucky, eight months. And really trying to sit in front of someone who is a very well-educated person who more than likely has grown a very large business and help them understand why that makes sense. I think this is a situation where I think it is more clear-cut, but I think having that data available and that documentation in such a way that can be disseminated to the public will be important.

DR. COUKELL: What is the distinction between high priced and absurdly priced for an LPAD drug? You do not have to give us a specific number.

DR. CANNON: Let me give you an example. I get in trouble all the time, so I guess this does not matter. If you look at 17-OHP that was years ago available only through compounding to prevent preterm labor. We compounded the product within our pharmacies to get someone through a pregnancy. I think we had the cost. We thought it was expensive. It was about \$79. Suddenly, the product becomes available commercially, and the manufacturer is charging us \$30,000. That is absurd.

The other piece of this is it is very hard right now for employers if you look at MS drugs. MS drugs when they first came out ... I was working in a retail pharmacy. We thought it was crazy. They were about \$10,000 a year. Fifteen years later, we are at \$70,000 a year. That is absurd.

Those are the types of things that I think ... it is easy in my mind, I guess, to justify \$15,000. It is the only choice. It is the only treatment. We know it will work. One hundred thousand dollars. That is going to be absurd.

DR. JAN: I just want to add one thing to it. We have to think about the Medicare population also. When you introduce this drug and it is going to be administered in the hospital. But if the plan is that the patient will be discharged and they walk out of the hospital, which is the coinsurance, there is no copay. Then there is a coinsurance. So 35 percent, 25 percent coinsurance of that amount will be a big value for the Medicare population.

Those are the kinds of things we have to think, and it will all depend on the scope of your indication and how it would be. If somebody has this multiple-drug resistance and they are going to be infused in the hospital, but then they will be discharged and they should be on it for a month, how is this patient going to afford this from a coinsurance perspective?

I think the pricing would make sense to say where it is being given for what condition whether it is immediate, whether it is a maintenance, and then maybe the pricing should be considered when you are talking about maintenance.

MR. SCOTT: Just to build on that, under Medicare part D, which is what would cover outpatient if the patient walks out of the hospital and is a Medicare beneficiary, copay assistance and cost-sharing assistance is generally prohibited. It is allowed in limited circumstances. But if LPAD pathway is to be established and it carries all the way through to patient access, that may be one area you want to look into as to whether or not ... what are the costs to the patient in the outpatient setting, and is there ability to help with that copay or cost sharing that would otherwise be prohibited under current law?

DR. COUKELL: I want to go to John and then to Steve.

DR. REX: Thanks. I want to ask Saira and Eric in particular to talk a little bit more about the notion of outcomes that you are interested in. As I was listening to you, I had this reaction. When I think of outcome data, I think of formal comparisons in a randomized setting. And then I think that is really hard work.

As you talked about it, you talked about some things that I admit I had not really thought about using, but that struck me as very interesting, like the frequency with which you are rehospitalized for that pathogen. That was an interesting measure. But it would still be context-free. Whatever measure I come up with, it feels like I am in danger of having a context-free outcome measure.

Talk a little bit about how you think about that problem because, intrinsically, we can get some outcomes. What is the context? And if you try to create a context, how do you know that the comparison group is the right comparison?

I guess I would flip in an additional fact that the patients with MDR pathogens tend not to be your normal folks. You can on occasion run into a bad bug just by accident. But at least initially, currently it is going to tend to be a marker of a lot of exposure to the health care system, and that is a marker for comorbidity, and that is marker for not having a typical pattern of disease progression.

The real question is outcomes and how you use them in a data set that is intrinsically not directly comparative.

DR. CANNON: Here is my fear. I will tell you what outcomes I think you ought to measure. I have 10 colleagues across the country that will tell you you measured the wrong outcomes. I may tell you what outcome I am interested in, and six weeks from

now, I will tell you that was the wrong outcome, just given the schizophrenic nature of sometimes, I think, of what we do.

I think when we talk about outcomes—and we probably use that term too loosely—I liked when Christine said that they were building into the trial basically some observational type measures. Clearly, I do not think we expect these drugs to be cost saving. But I think there should be some level of cost-effectiveness, and that could be the typical course for this patient is—I do not know—18, 20, 22 days in the hospital. And with the drug, we were able to discharge in seven days, six days, and five days. Those types of things. In a patient with this type of infection, we would have anticipated seeing these complications that cost X based on the fact that we were able to treat the patient. We avoided those complications.

The piece of this that I think is hard, and is very hard for me as a payor is the time sensitivity of all of this. As you talked earlier today about the golden hour or the golden minute, there really needs to be this ability for clinicians within a facility to give the drug to the patient right away. From the standpoint of my being a payor, I do not think we want to be in the way of that. But I think we feel a need to be able, given the fiduciary responsibilities, that we have for our clients, we feel a need to be able to in some way justify that. There are people a lot smarter than I am probably that can come up with ways to create that justification.

DR. JAN: The only thing I am going to add on that is that I am talking about outcomes. If you have a choice, yes, you are going to do a well-designed controlled study in a clinical setting. But we have all the time seen and many times observed that what you see in well-designed controlled studies do not really translate into real life. For real life, there are a lot of different things that are going on, and that has to be taken into account.

What I think as a country we have not leveraged is the fact that we do not really utilize the observational data quite a bit. I am referring to outcomes data from a managed care perspective—is to say these are high-risk patients, and we are looking at the scenario where nothing has worked ... one of those scenarios where nothing has worked, and this is the last resort. You have a control group of patients who, with the standard treatment, what the mortality outcome would have been versus when this drug was given what the mortality was. Did they survive? Did they not survive? We have the stats now to say a significant amount of individuals die because of the hospital-acquired conditions with the resistant organisms. We have those stats. We have in the hospital communities where standard treatment would be used versus this product. What did it translate into? Did we save lives, or did we go the other route? That is one observational study.

The second could be, yes, you treated them. They were fine, but then the group that got the traditional therapy came back to the hospital again with the same cohort of the patient population that has all the multiple comorbidities. Within a month, they were back, and, by the way, they stayed in ICU for a month, and that is where the cost component comes in versus this treatment population that went in and was given this

product, and they came out, and then they were fine. They were never re-admitted in the hospital.

Those are small, simple observations and aspects, which may not be very costly, but could supplement the well-designed clinical trials because that is reality. We all know. The oncology clinical endpoints are never seen in real life. The survival rates and all the things that ... because they are very well designed within an exclusive population. But this condition that you guys are pursuing is going to have different things happening. I think the observational studies will be very critical in terms of not only the cost savings, but survival data. I think that is going to be very critical.

DR. EBERT: Two questions. One should be a fairly quick one. Eric, have any antibiotics gone through the Synagis process that you talked about, where you start them in the hospital and then continue them in the outpatient area, and they are covered as well?

DR. CANNON: We are doing some of that with Zyvox.

DR. EBERT: The other question really ties in what has already been discussed a little bit with regards to re-admissions. I am kind of intrigued with that from a provider standpoint. It is my impression that more likely with a private pay or PBM those patients that are re-admitted, the hospital is probably going to still receive some sort of payment for that re-admission. It is really contingent on you to reward, if you will, that reduction in re-admissions.

But from a CMS perspective, at least from certain hospitalizations or indications, there may not be payment for that re-admission process. It is a subtle difference there. On one hand, it is more in the seat of the provider, per se. And the other, it is more in the seat of the payor.

DR. JAN: I think you bring out a good point, but there is another twist to that also. Yes, you are right from the CMS perspective. But there are a lot of quality measures that are being introduced. Hospital-acquired infections, and beyond that now, there will be a lot more transparencies where it will be open to the public. Which hospital is associated with re-admissions? Which hospital is associated with infections? A common individual who is going to go and get an elective procedure in a hospital can preview everything that is going on.

I think from a provider's perspective that is also going to be very important to understand the consequences of utilization of certain antibiotics and what they translate into because that would be public domain.

Now already we have a reporting system available where different hospitals are listed. And the admissions rate and re-admissions and infection rates, the different procedures, are available for individuals to select that hospital.

DR. COUKELL: Jim, I think you want to add to the responses.

MR. SCOTT: Just a couple of things that I thought might be a little shocking about how CMS differs from commercial plans. Eric pointed out that they think about cost-

effectiveness. Typically, under current law, CMS does not consider cost in determining whether or not a particular treatment is medically necessary. They may be moving away from that and towards more value-based purchasing programs, but as traditionally and currently, cost is not really what they want to hear data about. What they really want to hear data about is improved health outcomes. And like you heard from Saira and Eric, there is a range of what the health outcomes are. And CMS does not require clinical trials to demonstrate that to them. But then once you get to CMS, they ask you where is the data.

What we recommend generally is that you start talking to CMS early in the process, and get their views on what health outcomes are, and see how if you can build observational aspects into your trials or do things like that so that you can generate some data to have to present to them when they ask you the question later.

DR. COUKELL: I want to go Matt.

DR. GOETZ: There are a couple of themes I wanted to explore a little bit that relate to some things that Saira said and John Rex's questions about outcomes data. You had some questions about how you would approve off-label use. And there is a concept that I know that some formulary groups used of coverage with evidence development that we use this in the VA sometimes that we have ... for a use of an agent on an off-label indication where there is some preliminary data, but the data are incomplete, shall we say, where the responsibility for the provider or group of providers then is to report back to the formulary group as to what the outcomes were in that patient in a formal way. We get a gradually accreting body of data.

Some individuals have proposed, and to limited degrees, if you will, institutionalize that process by going into databases looking at broad ranges of outcomes in patients to help augment the necessarily incomplete datasets that come with any drug development program. The smaller the drug development program, the more incomplete the data, of course ... full range of potential uses of any drug, particularly antimicrobial, studied because of all the complexities we talked about today.

That is another reason to look at outcomes, is they develop the evidence that looks for the indications that were not explicitly studied during the limited drug development program, which then gives the formulary committees the confidence to expand or not expand the range of patients who get the medication. And doing that in a formal way really helps. I do not think we will have randomized controlled trials to address all those outcomes data.

But as we think about the use of concurrent controls, patients, who for whatever reason do not have access to the medications where we do the best we can, propensity-adjusted analyses to look at outcomes, or cross-patients who do or do not get agents, that can be helpful.

And then there are also issues, I think, that will be important as we think about the role or lack of role of empiric therapy, the need for immediate therapy, perhaps, to look at where the timing of therapy comes versus the clinical acuity of the patient and the

development of definitive microbiological data supporting the use of these agents just to augment some of that discussion about outcomes.

Finally, one comment about the transition from inpatient to outpatient. It can be very troubling, and payors are the last resort oftentimes find themselves in awkward positions. Right now, one of the issues that we have with our outpatient parenteral antimicrobial therapy program in a VA facility ... people discharged from private facilities who have VA benefits who are being discharged on the intravenous drug they simply cannot afford. Then the cost winds up being absorbed to the patient's benefit by our facilities.

DR. COUKELL: Mike, let me go to you quickly. We are going to hear from Rempex shortly.

DR. DUDLEY: Thanks, Allan. Just a couple of last gasps on this issue, and if I maybe can state what has been said, and maybe a different way is what you are looking for is sort of some of this pharmacoeconomic analysis or some of these outcome measures is a better way. You are looking, one, for the sponsor to provide something that you can benchmark, something that you can use to help benchmark your institution. Something about utilization data in the trial. Something about length of stay, mortality. Because you are right. Oftentimes the definitions and even the outcome measures that are used in a pivotal clinical trial are not something that your clinicians are used to doing. In cystic fibrosis, you may not ever use a CFQ-R to actually assess your patients, for example.

You are looking for something that can help benchmark what was done in the development program, particularly in a smaller type of LPAD development program that helps you understand where am I.

Then the second thing is that you also want to have something, which you then can use in the post-marketing setting because you have the benefit of larger databases that might have been derived in a drug development program to actually measure outcomes that you care about or measure other things that you have.

This fits to me much more like with the learn-confirm models for drug development that had been discussed. They were discussed by Dr. Shiner a couple of decades ago and then reintroduced recently by Chuck Knirsch and colleagues at Pfizer about how we actually learn more about how these drugs are used in the post-marketing setting and answer those questions that cannot be derived in the premarket setting, particularly in our limited program. I think those are helpful feedback in terms of things that are important to include in the trials, not so much that they are the basis for an approval decision, but they can help you benchmark things going forward.

DR. JAN: The only thing I am going to add on that is just not to look at how they are utilized, but what the outcomes are. If you have seen increase survival, have you seen that in the bigger populations?

DR. COUKELL: Let me go back quickly to each of our three panelists. It strikes me that a lot of the things you are talking about apply regardless of whether a drug has come

through an LPAD pathway. As you think about these drugs, there are at least three things that may factor into how you think about drugs. One is the FDA has said it is not indicated for a population beyond the limited population. The second is there has been a more limited development program, and regardless of what the FDA says, fewer patients have been exposed, and you know less. And thirdly, there is premium pricing.

When the payors think about are they going to treat these drugs differently, which of those things, all of them or none of them, distinguishes LPAD drugs from antibiotics that come through the traditional approval pathway.

MR. SCOTT: I will go first. What I think is that generally CMS would need some kind of legislative direction because there is no landing place for this at CMS currently. Using that tool, you have a broader brush to make up the rules. But if you are going to try to fit it into something now, the limited population and the short time of the trials would really impact the ability if you were to, say, ask CMS for a national coverage determination to be able to say that we should improved health outcomes, and there is sufficient evidence to generalize this for the whole Medicare population, and, therefore, you should do a national coverage determination that prohibits inappropriate use, but encourages appropriate use. That would be a limitation of that kind of drug.

It would not have any effect on the payment side except that if you want to get your new technology out on payment, you are going to have to show that it is better than what is out there. It is a substantial improvement. Is there going to be enough information, and did you use the FDA ... when you did your FDA trial and did a comparator for noninferiority, was that comparator the same comparator CMS is going to view as what the standard of care in the Medicare population is to demonstrate it is a substantial improvement?

DR. JAN: I think if you look at those three points, I think I would put the cost at the bottom. I think what would be the most important thing is if it is a limited population and it is something then, I think, the payors would be concerned on narrowing it for the FDA-approved indication. But the real-life situation would not be that, like what you have painted initially in the morning that is going to happen. People are going to use off-label. That will be a struggle.

I think that is why it is very critical for this part, if possible, to have comparative-effectiveness data and not noninferiority trials, but a superiority trial. I think many drugs get approved, especially if it is a short term. It has to be a superiority and some active comparator that makes sense in this scenario in order for anybody, including CMS, to pay for that prize.

But I think if the product is going that route and if it is a superior product and it has that profile, that should not be a challenge. But I think, initially, it may be the fact that it would be approved for FDA. Again, I do not think the payors would be affected or can manage the approval process upfront because it will be administered in the hospital setting. But if it is outpatient, that is where more management can come into place.

DR. CANNON: A couple of quick thoughts. My gut wants to say cost is not much of an issue. Here is the reality. All of health care is becoming very expensive. Regardless of the disease state, we are adding more and more cost. As these products come out, cost will be a very big issue, even though I said, yes, I think we will pay for it. The reality is, at some point, we are going to run out of money. Cost factors into this somehow. I am not quite sure where.

The limited population piece of it, I think, is very appealing to most payors in that it is a limited population. It is easily defined or more easily defined than some of the traditional small-molecule drugs we may deal with where you can see this indication creep, that you cannot even really comprehend where it is going to go.

The limited-approval process, I think too many times, I think, we see manufacturers, and they will come to us and will say, "Help me understand the benefit of your drug." Did you decrease? Were you able to get the patient out of the hospital faster? Whatever it may be. And the response we get too many times is, "I was not required to look at that by the FDA." I know you were not required to look at it by the FDA. At the same time, I need that information to justify to my constituents why we are going to spend this amount of money for it.

DR. COUKELL: Thanks. We are going to break on time, and I want to do two things. I want to make sure that folks from the floor have a chance to get in, and also Rempex has a proposal that is somewhat related to LPAD today. We want to squeeze that in. Let me go to Kevin. I saw you had a question. If we could get a microphone up here, and then we will go to Rempex. If you would just introduce yourself.

DR. OUTTERSON: Kevin Outterson from Boston University. A whole panel of reimbursement warms my heart. I have a question for Jim—Medicare, what a Rube Goldberg complex and how we pay for drugs under Medicare. It was just tacked and bolted. Year after year, we keep adding something else. I do not get the sense that you are actually asking for us to bolt another piece under Medicare. It seems like it is going to be hard to fit into the existing structure.

We do have some other models in Medicare, the way we pay for DSH, the way we pay for GME, graduate medical education. If you had your druthers, how would you approach it with Medicare?

MR. SCOTT: As far as how the LPAD proposal would actually work, I think it depends on a lot of different things. What I have thought about so far is what framework should you consider. I have not really settled on a recommendation as to what the best path is. But I think even under a legislative approach, you would want to consider Medicare's current tools because you are going to be asked to explain why those are insufficient, and if you can just tweak them instead of making a whole new system that might be more appetizing to Congress. The more innovative the idea, the heavier lift, I think, it is going to be. I think there is a whole range of ways to pay for these. Rempex is going to have a presentation. I think this discussion is moving that along.

One of the things to think about is that at CMS, if you use the current systems and, rightly or wrongly, cost does not really matter. If you do not need legislation, then CMS can pay. If you do need legislation, the whole discussion is about cost because we are in the budget austerity climate, and it sounds like it is not going to save money, and then how do you get additional funds made available for something like this in the midst of the fiscal cliff?

DR. YTTTRI: Jennifer Yttri from the National Research Center for Women and Families. I would like to comment that in hearing from the payor's side and the physician's side earlier, one population that I think would really benefit in addition to the payors and the physicians from all of this evidence-based outcomes data are the patients. They are the ones that will need this information on survival, on time in the hospital. All these outcomes that we are talking about to really understand whether or not an LPAD-approved antibiotic is a good choice for them where there are in this severe population or not.

Since it is very difficult to define this patient population, as we have discussed extensively, I think that there should be a bit more concrete discussion amongst the panelists here in terms of who is going to be providing that kind of information, that kind of data. If you are putting it all on the post-marketing end, well, you are relying on the patients to actually provide that data, and, unfortunately, we do not know if they will benefit partially because they are hard to determine. Putting all the emphasis on them, how are they going to benefit from these limited population studies?

DR. COUKELL: It is an important question. We have touched on a couple of points today, and I think we are going to hear more about it, I predict, in our third panel. Thank you. Let me invite Dan Burgess from Rempex to come up now. Dan has a couple of slides if we could bring them up.

MR. BURGESS: Thanks very much, Allan and Nicole, for giving me a chance to spend a couple of minutes talking about a way we thought might make some sense to think about this in a broader context. I guess I am coming at it -- I am CEO of Rempex, and I have been trying to raise money to fund antibiotic development now for about six years and have a pretty good sense for what some of the challenges are.

The practical reality, particularly as it relates to this last panel, we have three big issues we have been dealing with. One has been clinical path uncertainty. I think this group has done a great job working with the FDA of really starting to address that issue.

The other issue is certainly how many patients are we talking about here. I think, as John did a nice job of pointing out earlier today, we are trying to guess five, 10, 15 years in advance what the real resistance problems are going to be and develop drugs for that. It may be that NDM-1 becomes a huge issue, or it may be that NMD-1 is not really much of an issue at all. We do not know yet. We are trying to throw \$150 million hoping we are right.

Now, the only way you are going to be able to make those two things work is if somewhere along the way, if in fact you get the product approved, there is a pot of

something that looks like gold at the end of the rainbow. The more reimbursement hurdles we put up here, the more challenging it is to get folks to fund this, whether it be big pharma allocating resources away from one disease into this set of diseases or investors putting money into biotech companies.

What we have tried to do is come up with at least a straw man that we can put out that we call Rewarding Antibiotic Development and Responsible Stewardship or RADARS, that try to stay encompassed a lot of what we have heard today. Again, I would like to quote something else John said today, which was the perfect is the enemy of the good here. This is not a perfect plan by any stretch. As we have heard, there are all sorts of ways that we can probably pick this apart. By the same token, we are all here for a reason, which is we have a major problem. If we do not start moving forward with something, the problem is just going to get worse.

The idea is to create an economic platform to incentivize innovators to develop antibiotics to combat resistant pathogens, as we have talked about. But equally important, we want to preserve the usefulness of these antibiotics for as long as possible, as we have talked about, and do so without bankrupting our hospital system. I think we have heard all of those issues talked about today. How can we potentially do that?

We have tried to design a program that would work hand in hand with the LPAD discussion we have had today as well as some of the QIDP and GAIN work that has been done earlier last year. The first part of this is that we would actually guarantee innovators like the industry folks you see here today a minimum revenue level for five years at attractive pricing. And the idea here, again, is to hit on something else that was discussed earlier of decoupling the marketing aspects of this, if you will, from successful product development for something that everybody agrees is important.

It will also allow the hospitals to be reimbursed above DRG for on-label use with a caveat that that is guided by the stewardship programs in all the ways we talked about today. And the government only ends up paying for successes and does not have to pick winners prior to approval, which has been a challenge with dealing with some programs like Project Bioshield, which the government was trying to incentivize industry to deal with here a number of years ago.

Basic concepts. HHS, as I say, would guarantee the innovator a certain minimum revenue stream at fixed prices for a period of five years. And, again, that would be somewhat akin to Project Bioshield.

The per-patient pricing would be high in the first year in the order of \$1,000 a day to compensate for the low initial volumes and the correspondingly high production costs that Mike was referring to earlier here because cost of goods, particularly in the early years, will be very high, but would decline over five years to something more like \$500 a day. The key piece here is this guaranteed minimum revenue. It would \$100 million in the first year and rise to \$350 million in the fifth year, irrespective of how much product gets used. At those prices you see there, there are not enough patients here to hit those

numbers. HHS would essentially cut the innovator a check for the difference. We will talk about what industry is giving up in exchange for that.

As part of the NTAP-type payments would be set up here and would continue for 10 years. Again, these payments would be designed not to cover half the cost, but to actually bring the cost down to whatever current standard of care order of magnitude is to that. Let's say that is \$100 a day that one is akin to paying for antibiotics in the ICU setting. It may be that there would be \$900 check cut to that hospital that would then deal with that. That would then decline over those five years as we got down to that \$500 price point. In year six to 10, that would fall to \$400. And the guaranteed minimum would go away in year six through 10.

In exchange for that, the innovator agrees we are not going to market the product at all. We are trying to actually preserve this product for a reasonable period of time. If in reality at the end of five years NDM has not taken off, we are probably not going to see much in year six through 10, but will have made enough in years one through five to justify going through the exercise.

At the same time, hopefully, the payors become less concerned about the fact that big pharma is out there marketing these things in a way that is going to push the volumes up to much higher levels than folks thought. We are not going to be marketing these at all. We will have MSLs out there. It will be educating folks on what the appropriate plans are and go from that perspective.

The other aspect of this would be HHS and FDA would use either the QIDP or the LPAD designation to define eligibility. There is no application process here. We think if you put up barslike superiority trials, you will not get new drugs unfortunately. We understand that is the desire. Over time, hopefully, that information will be developed, but we have a crisis right now, which is a lack of antibiotics. The more hurdles we put on the development side, the fewer antibiotics we are going to have. The idea is you have to create something that allows you to get five or 10 new antibiotics out there. Then we can start addressing superiority questions and things like that. But you actually have to get enough of these things out there because some of them are going to fail and for all the reasons we have heard about all day today.

What is the net benefit of all this at the end of day? You already have an NTAP-type mechanism in place. It is going to have to be adjusted. You already have a Bioshield program that is in place. Again, it is going to have to be adjusted and refunded to some degree. Overall, your out-of-pocket costs to the system are likely to be lower because you are not going to be using ... it is a way of hopefully making these LPAD-type antibiotics. You are giving everyone an incentive to use them in the way you are talking about, which is you only get paid if you are the hospital if you in fact have hit the criteria that were talked about in your approved antibiotic stewardship program.

If you are looking to having to write a \$900 out-of-pocket check for inappropriate use, that is not something you are probably going to want to do. We, as the pharma company, cannot promote you to do that or urge you to do that. A lot of those pressure

points are not going to be there that are in the existing system. Again, this is not going to be perfect, but it is a starting point to think about how we may be able to contain the cost here, get the drugs where they need to be, and create an incentive system that puts everybody, hopefully, on the same page.

Lastly, as an add-on benefit, if you will, a lot of these antibiotics we are developing are going to be dual-use with some of the bioterror pathogens that we have been concerned about in theory now for some number of years. You are probably going to get some added benefit from that as well. I know that a number of the programs that ... is working on that we are working on have real benefits in that area as well. And now you would actually get some clinical advocacy data on those programs as well.

That was the quick concept. I will throw it out there for folks. If there is interest, I would be happy to answer any questions on that.

DR. COUKELL: Dan, thanks for that. And obviously, the idea of de-linking the volume and revenue is one that is of interest to a lot of people, and there are a lot of conversations going on. We very much appreciate you putting forward a concrete proposal and recognize the caveats that came with it.

I want to get a quick reaction from our panel, the payors in particular, to the ... a lot of technical questions here, but to the top-line idea of a guaranteed revenue. First, I just want to ask a small question. In your mind, what is the impact of removing the sales rep and stopping the promotion?

MR. BURGESS: Again, I think the idea is, one, it makes those guaranteed minimum numbers more attractive because we have less money to put against that. The number you have to guarantee, if you will, becomes lower because our expenses become lower.

Two, we do think the MSLs need to be out there doing the true education process to let folks know that these products are out there. But, again, if there is no sales-based incentive for folks, we think that that is going to preserve these antibiotics for a longer period of time and not get into a lot of the initial issues that we talked about earlier this morning that people are concerned about.

DR. COUKELL: Does anyone have an initial response to the guaranteed revenue model?

MR. SCOTT: I admire your courage for putting a proposal out there first. I think this is the right place to start because somebody has to put something down on paper so we can have a concrete discussion and move it forward.

I like how it builds on the NTAP model and kind of takes into account some current programs. It fits well in there.

My questions were, would the new technology add-on payment-type program ... would this only be for Medicare patients, or would this be for all patients?

MR. BURGESS: I think that is something that can be discussed as to whether or not we would expect private payors to follow along with that or if this is something that HHS

says we have a market failure here. For the next 10 years, or whatever it may be, we will pick up the NTAP payments for society, if you will. I think you could debate that either direction.

MR. SCOTT: Then the other point that I alluded to earlier is it sounds expensive. I do not know how to ... if there is any number ...

MR. BURGESS: We looked at that a little bit. And, again, if you look at what is that \$1,000 a day versus the guaranteed minimum we are talking about, it is exactly in line with the kinds of numbers that Nicole put up earlier today in terms that would allow you to treat on the order by your five of 50,000 patients with resistant organisms for that \$350 million.

DR. COUKELL: Thank you for that. This discussion may lead over into our third session. I think, as you have seen the back and forth between the payors and the manufacturers, I think we have only scratched the surface, but it is a very interesting and important conversation.

Session 3: Lessons Learned, Unanswered Questions, and Charting the Path Forward

DR. COUKELL: Let's get our final session of the day underway. We have invited John Powers and David Shlaes and Nicole Mahoney, who you all met earlier as rapporteurs. The charge to them to kick off this third session is to summarize what they have heard today because I think we started the day with open questions about what is the LPAD pathway and how it works. We want to know from three different perspectives. Is it now clear what LPAD is, how it would work? Are there areas where you think everyone is on the same page? And then equally important, are there important questions that have to be resolved? I am going to ask Nicole to kick us off.

DR. MAHONEY: Thanks, Allan. I am going to try to give what is probably the most vanilla overview of the three because writing up my thoughts in 10 minutes is not my strong suit, but I will try to give it a go and just give a broad overview of what we have heard.

From our purposes, we were interested in exploring LPAD from a business and a public health perspective, that is, does it make sense from a business perspective. Is it feasible? And then the trade-off of these small development programs is that you would have the drug actually being used in limited populations or in limited ways. We are interested in knowing is that possible. Is that what is really going to happen? And if so, where are the pressure points where you might actually intervene and ensure that the drugs are being appropriately.

From the business point of view, we heard a couple of concerns. We heard that, however this goes forward or if it goes forward, we need to be careful about definitions, and that means definitions of disease—"serious," "severe"—throwing those terms around. We have to know what they mean.

We have to be clear on what unmet need is and what it means, and actually that is not necessarily clear to everyone across different conditions.

And we have to be careful about how we define population. Who are these subpopulations, or what subpopulations are going to be studied? Those things are very important to consider.

It was very clear from everyone on the panel that there is a huge need for new antibiotics. I have the overall impression that people think there is value in LPAD, but there is also a concern from the business perspective on how much time would it take to implement something like this. That should be a consideration moving forward. Regulatory means, legislative means—what takes longer? What is the most practical? And what we do not want to do is interfere with new antibiotics getting to market.

And for LPAD or an approach like this to be successful, we definitely heard that businesses need clarity on the regulatory pathway. For small businesses, that might mean giving the investors the confidence that they need to invest in their development programs. That is something that we have to consider going forward. How clear do we make the LPAD pathway, and how well defined is it?

And then they also have issues with pricing and reimbursement. There has to be more clarity, obviously, around those things, to know how much return on investment they might have and if it is practical for them to move forward.

And then another thing that I thought was very refreshing that we heard were practical considerations, for example, chemistry and manufacturing issues at FDA and the approval of diagnostics. Because if those things are not in place or if those things are not going along at the same speed at the regulatory process, then you are going to have a disconnect between getting these drugs to market and then being able to use them. That is a big issue. I was glad to hear those practical considerations coming up because you often do not.

And then, as I mentioned, there is a trade-off for the expedited pathway, and that is that drug would not be used broadly. We started discussing in the second panel how we might limit the use.

One thing that came across loud and clear is that penalties for off-label use is probably not a decent solution and that there has to be some flexibility in rational use of limited pathway antibiotics.

And stewardship programs are going to play a very important role in limiting the use of these drugs, but they can vary widely between settings, and that is a big concern. For example, long-term care facilities may be especially difficult places to monitor the use of these drugs and use them appropriately. That is a big consideration.

And we heard from some of the health care providers that labeling and cost might not be enough to ensure that these drugs are used properly.

We also heard, though, that prior approval might not be a practical solution either. My take-home from this was that, at least in the beginning, the therapy is going to be empirical therapy. But we may be able to or the health care providers may be able to step in at an intermediary point and modify the use of the drug and ask the question after a dose or a couple of doses were given once you have microbiology data—should we be curtailing the use of this drug? That is a point where they might be able to intervene, but these drugs might be used as first-line therapies. I think it was helpful to get that across today.

Across the board, it seems that everyone agrees from health care providers the companies and the payors that we need to monitor the use of these drugs and we need some kind of tracking system. But we also heard that registries and data collection are expensive. We have some hope that electronic health records will help, but it was not entirely clear to me how data collection would occur. Just that it needs to be done.

And then an interesting concept that we heard during the health care provider session was that perhaps a precertification program could be put in place, and we heard this again from Rempex at the end of our last discussion. Precertification could be put in place before LPAD drugs could be used in particular settings.

From the reimbursement angle, it seems that payors have few means of influencing the use of limited population drugs in the hospital setting because payments are bundled, and they are based on discharge claims, and there is more of an opportunity for doing so for management in an outpatient setting.

However, bundled payments may not cover the drug cost, and that will get shifted to the hospital or potentially the patient. That is something really important to consider. And that also is a distinct possible and something to consider in the cases where therapy is going to move from the inpatient to outpatient setting. How do you maintain continuity, and how do you consider cost to the patient when they move from the hospital to the outpatient setting?

And then finally, payors made it very clear, and I believe companies need this, too, that people need more data on value and outcomes. I cannot say that we know what that data is or how it would be collected, but we have to figure out how to do that, and we also have to define what outcomes mean and what important outcomes are for antibiotics. Those were my take-aways. I am looking forward to hearing from John and David next.

DR. COUKELL: Thanks, Nicole. I flipped a coin, and you have elected to go first. John Powers and David Shlaes are both well known probably to most of our audience. They need little introduction. John is currently an associate clinical professor of medicine at George Washington University.

DR. POWERS: I am going to reinforce some of the things that Nicole said and try to amplify some of them. Since we started at the beginning about some regulatory issues, one of the outstanding questions here is it sounds like some companies are already proceeding with these kinds of programs without this being in place. The question is,

what is actually different about this than the other accelerated-approval mechanisms that FDA already has? Even if this kind of a pathway is developed, the next question comes in. How does it interact with the other pathways? How does it have to do with REMS? How does it have to do with accelerated approval, etc.? And knowing how those things fit together would be very helpful.

The next thing in that regard is that many of those, when you read them, for instance, the accelerated approval regulations have a lot of detail about the things that Nicole already outlined. For instance, they define what a serious and a life-threatening illness is. They talk about that if you have a surrogate endpoint, that it should be a replacement for irreversible morbidity or mortality. Some of those things are already outlined that do not seem to be included yet in this proposal. Again, I would not expect it to be at this point, but there are things that really need to be discussed.

A lot of this discussion seems to revolve around stating and restating and restating again the problem, which is about need. But what we are trying to get to here is how to find something that is a solution for that need. It seems to me pretty inherently logical that one cannot have a life-saving drug if the drug is not demonstrated to save lives. And also in relation to what the payors are saying in terms of what they want in terms of outcome information, it seems that if we are going to accept less information, then what we would really want to see is some information that conforms to FDA's adequate and well-controlled study standard that the drug actually does something for decreasing irreversible morbidity or mortality.

When we talk about risk, we do not seem to define what we are talking about risk of. Are we just talking of risk of adverse events related to the drug, or are we talking about risk that the drug is not even effective in the setting we think it is? The latter is unacceptable. And that is that the entire 1962 amendments are about the idea that any harm from a drug is only justified by the fact that it actually has the benefits for the patient, which in this case we are talking about are irreversible morbidity and mortality.

If you are designing a study like the one Christine outlined for us earlier this morning, where your outcome is improving all-cause mortality, it does not matter much whether your LFTs go up, whether you have renal insufficiency or those things because there are certainly drugs out there right now. Amphotericin B and fungal infections, colistin, aminoglycosides, and the past that all have substantial toxicities associated with them, but were marketed because of their ability to impact substantially morbidity, mortality in patients. I think it gets lost in terms of ... on the flip side of that, if your benefit is a change in a lab test or a symptom, and then the problem is we do not know what the adverse events of that drug are. This is not a situation where what you do not know is not going to hurt you. It could end up being problematic in the long run if we do not have that information.

It seems that having decreases in irreversible morbidity or mortality really justifies going down this pathway in the first place, and that defines the benefit that the payors are looking for in terms of what would justify a cost.

The other issue is that in a number of these meetings that we have all been in, there has been this issue brought up that people are dying of lots of other things other than their infection. And if that is the case, then that makes it very challenging for observational studies to parse this all out. It needs some kind of control group to compare to to actually figure out whether the new drug really is decreasing morbidity and mortality.

The other issue that was already brought up earlier is this really gets the issue of superiority. We are talking about people that do not have any other options, and you have to be better than what they would have gotten otherwise. That is really challenging to fit that into a noninferiority paradigm.

We have had a lot of discussions about yes, but we need drugs for the next 15 years. And there are some logical inconsistencies in this argument. One, any drug that gets put out today, resistance is going to develop to it over the next 15 years if it is going to be used at all. And in fact, several of the new drugs had resistance before they were even put out there just because of what is out there in the community.

The other issue is, and this relates to the patient, we talked a lot about organisms, but this relates to the patients who are both in these studies and future patients. Someone in a noninferiority trial already has an option. They have a drug, that control drug that could actually be beneficial for them right now. And they are signing up for a study where the new thing might be 10, 15, and 20 percent worse than what they could have gotten any Monday through Sunday day of the week. There are some ethical implications to that in terms of, first of all, do people really know that is what they are signing up for in these trials? And secondly, we have an ethical obligation not to expose them to that kind of risk. That is why I asked you the question earlier about really exposing the patients who are really going to benefit.

And Christine brought up earlier, in the long run since those people are harder to find that may not make this faster, it may make it more narrowed and focused, but it may not make it faster. But that is still okay because at least then we will still be able to focus down.

The other issue is “diagnostics” has become a dirty word at these conferences. We all agree that they are needed, but after decades of discussion, I cannot even point to really anything. That is not true. There are some people using them for *Staph aureus* bacterium in their trials. But still without those diagnostics, it is going to become very hard to, A, find the population to put into studies, B, to actually use that in practice to focus it, C, to actually tell whether reimbursement is actually going to be focused or not.

That gets us to the issue of we are talking about limited approvals and limited usage in a specialty that talks about empiric coverage. Those two things do not go together. And the solution to that is diagnostics. And the other thing is you can make the argument that perhaps there is not much of an incentive for a company to develop diagnostics if people are using empirical coverage. And the only thing that it is going to do is narrow their market down, which hopefully some of the things that we heard about different

reimbursement strategies might be able to overcome that kind of stuff that might make a diagnostic much more useful for people to be able to develop.

The other thing that came up in the discussions that I have always been interested in is defining what resistance really means. Plenty of people in our hospital die of susceptible infections. And, in fact, in our hospital we had an outbreak of the KPC-producing *Klebsiella*. Most of those people had two to three drugs to which they were still susceptible. They got them. They died.

The implication there is that the patient population here is really important. And it is not just about MIC, and it is not just about organism. It is about the disease and the host. And therefore, that makes it really challenging to try to make any sense out of a case series in people who are older and critically ill.

John brought up this issue of a 20 year old that he took care of. We do not see 20 year olds in the ICU with resistant pathogens because the data shows that the people who these kinds of diseases are older, sicker, have more comorbidities, have other diseases, and plenty of other drugs on board. Yes, we do see 20 year olds, but they are on their third bone marrow transplant. They are not exactly like guys walking down the street. And in fact, even if those organisms outside of community MRSA really have not spread out to cause much disease in the average health population. The one good news about this is that itself will limit the distribution of these drugs. We are talking about sick ICU patients.

But the flip side of that is interpreting case series out of that kind of population is exceedingly difficult. FDA has tried to do it before in the late '90s with some drugs that Ed will remember. We are looking at literally hundreds of case reports, and it is very challenging to pick out the effect of the drug versus the effect of anything else that is going on either placebo-biased observations or natural history of the disease.

One way to help with this will also be to develop these external concurrent controls, as Matt said, that are not 75 years old with enough granularity and patient characteristics that will allow any sponsor to then use that control group compare their drug to it. That is also going to take a clinical trial's infrastructure that I know Bob has talked about a lot that just does not exist at this point. One of the things that this is going to need that we did not develop is the infrastructure to be able to do it.

The ICU guys have an ARDS network, those kinds of things that have been stood up. Can we either piggyback on those things or develop something new based on what NIAID is trying to do now where there are six different research areas, one of which is going to be devoted to antibiotic resistance as well?

But getting to resistance now, we have had a lot of discussions about how resistance is defined by putting drug in a test tube with some organisms. But that definition of resistance, as Pranita brought up, sort of ignores the patient-centered issues and that those outcomes are very different, depending upon who you are talking about in those settings. In the work she and I are doing together, we have seen that some of the changes in breakpoints are absolutely dead-on. If you look at people based on the

breakpoints, if they are higher than that, comparable patients suggested by propensity scoring do worse.

On the other hand, we looked at other drugs that she mentioned earlier where we looked at that and it is wrong. People are now being defined as resistant when in fact they do fine. And we already saw the penicillin breakpoints get changed to make it more relevant to that people who actually were called resistant were doing fine. But as Pranita brought up, that drove quinolone resistance way higher. As she said, in their institution, it would result in a 300 percent increase in usage of other drugs.

That does two things that are very important. One, it limits choices for patient populations that are already really limited. Secondly, it may drive them to either less-effective or more-toxic drugs than they would otherwise get. Coming up with this definition is really important as well.

The other thing is that this obviously is ... we have had a lot of talk about drug labeling. When we talk about drug labeling, it is important to realize that that is used as a communication tool for FDA to communicate with the practicing community. And as we have all said, it fails at that. We know it has.

I was remembering this morning about the rosiglitazone advisory committee back in the '90s where ... I was trying to find it on the Web. That FDA presented a labeling study where they changed the label for rosiglitazone and then went out and actually evaluated whether it changed practice. Not one bit.

Ed and I put in 201.24 into labeling, which for 669 drugs back ... 2004. It is not clear at all that that had any impact on how people practice medicine.

But I think it has had an unfortunate side effect in that 201.24 has in it the wording that clinicians should strongly suspect an infection. And what I heard this morning relates to the issue that the label really is for. It regulates what drug companies can sell their products for.

And then having the wording strongly suspect in there essentially allows companies to sell the drug to anybody. I am going to propose that ought to be taken out. Since we are going through the rule-making process that we can just put in this drug is safe and effective for people due to infection X, due to bug Y, and leave it at that. And let clinicians decide about the strongly suspected or anything else and not get into the issue of allowing people to potentially market drugs for things where people do not really have the infection because it does not comport with the idea of limited pathway. In our hospital, everybody could be strongly suspected of these organisms. It does not narrow it down at all in that tier.

The other thing is, and I did not get a chance to ask this question, but the different reimbursement model absolutely has to happen. It has to disconnect whether a hospital uses or patients in the hospital use the drug versus the ability of some place to use it. I think the idea of buying a license to use the drug, the company makes a commitment to have that available and manufacture it so we do not run into drug shortages. But the

company gets paid whether or not the drug gets used. That disconnect has to happen because right now there is a perverse incentive to drive usage as the way for companies to make more money in a setting where they are telling us they do not make enough money on these drugs. The proposal we heard today sounds like at least a good start to start that conversation forward.

The last thing I wanted to finish up with is saying all this stuff says one thing to me overall. We need better tools to do this. We need better diagnostics. We need better communication in terms of how to get the information out to practitioners. We need a better infrastructure. And we need a different reimbursement policy. This is not going to be a quick fix. And even if we get these drugs to people, we want to make sure also that the goal here is not just approving more drugs and counting up the number. It is getting more safe and effective drugs to people so we can actually solve that problem of unmet medical need. I will stop at that point. Thanks.

DR. COUKELL: Thank you. David Shlaes has a long background in drug development and is currently the owner of Anti-Infectives Consulting.

DR. SHLAES: First of all, I want to thank Pew and Allan and Nicole for putting this together. I think you guys did a spectacular job. Thank you. I am going to try not to respond to a lot of the things that John just said and stick with where I was going to go to begin with.

I think one of the things that was clearly highlighted here is that there is a disconnect between a limited antibiotic development label and pathway and empiric use. But the fact is that this is true for all antibiotics. There is nothing new or different about empiric use and LPAD and LPAD product because 80 percent of use in the hospital, as John so eloquently described, is empiric. A patient strikes a fever. They look sick. You are going to give them an antibiotic. If you have a reason to suspect because of your local epidemiology or some other reason that the antibiotics you have available to you are not going to be efficacious except for the new LPAD product, that is what you are going to use.

The fit between an LPAD product and the basic tenets of antimicrobial stewardship is much better than it is in the case of any other antibiotic for several reasons. One is the price is going to be high. I think, no matter how you cut it, that high price is going to discourage use. I heard all the payors say we will pay. But there still is going to be greater supervision and surveillance over the use of these drugs than over the use of other drugs just because of the price.

And I think a really good concrete example, if you want to actually look at it and if Mike Dunn is still here, we can ask him to tell us about it is Zyvox. The price of Zyvox is high. The prescription volume for Zyvox compared to many other drugs, many other antibiotics, is very low. Not very many people actually get treated even though the dollar volume is high because the price is high. I do not think there is a whole lot of inappropriate use of Zyvox in spite of one or two examples. I think there is just not because the price is high. It is much better controlled than antibiotics for which the price

is low. The price is going to be a self-policing policy. And actually, I know Mike did and Pfizer did a very careful price point study to look at what the prescription volume would be under various pricing scenarios, which is how they ended up where they are. And actually, just parenthetically, I will mention that Zyvox is going to go generic in another two years, and it is going to be very interesting to see what happens to Zyvox resistance at that point.

The other thing I wanted to explore a little bit was this whole idea of empiric therapy since 80 percent of use in hospitals is empiric. I think that the idea of suspicion is still an important idea because that is basically how physicians use antibiotics. If your particular epidemiologic situation in your institution or in the particular patient population in which your patient finds themselves is consistent with a highly resistant pathogen and there is this drug available that would be effective against that pathogen, you cannot deny them that drug. You simply cannot. I think that there is a very strong motivation for using suspicion.

On the other hand, there is also a strong motivation to follow that up with appropriate stewardship and ask, was your suspicion justified at the end of the day? And actually, I bet at least 50 percent of the time you never know. You are going to pay for these drugs regardless.

If you want a paradox or a disconnect between limited use and empiric use, but I do not think it is such a bad a paradox, and it is the way physicians use antibiotics now.

The other thing I wanted to get into with a little bit more granularity is the desire of payors to have more information around outcomes before a drug like this would be marketed. And the fact is that for some of these drugs who go through very limited patient population development pathway where there may be no active control, as a matter of fact, I can almost guarantee you that for a lot of these drugs there will be no active controls in the trials. I can guarantee it. How will you get that information?

The suggestion I am going to make is that we use the same kind of very reliable modeling, predictive modeling, that we have used for years and years in the antibiotic era to try and provide this kind of outcome information. I believe that this is perfectly feasible. It is scientifically justified, and, at least at the beginning, it provides you a hypothesis that you can then later test once the drug is out there doing more data mining and things like that. But at least it gives you a start or a hypothesis, if you would like, about what the effectiveness might be based on modeling, PK/PD modeling in pharmacometrics. I think that is one area that could be explored.

And then the other thing that one could do now, and I am not actually sure how much of infrastructure this would require, but I think one could do this with existing databases before ... becomes available is to essentially do the prospective observational study using database mining. Is there some reason that somebody knows of why we cannot do that now other than somebody has to pay for the study? I think that is another area that we ought to think about as an underpinning to not only clinically, but I think more importantly in a way for the payors to get an appreciation of the potential benefit of

these sorts of antibiotics. I guess I will stop there. But those were the highlights I wanted to go through.

DR. COUKELL: Thank you, David. Let me invite questions and comments from our panel. Let me first go to both of you. There is a lot in what you both said, but a couple of specific questions. John, you say that labeling fails to communicate effectively with providers. Granted, you make a small change in the labeling for a drug that has been out there for a while. That is pretty clear. How sweeping do you want to be here? The initial FDA labeling fails to influence how the drug is used. Does it make any difference, do you think, if we have this new category of drugs called a limited population?

DR. POWERS: I am not sure. Once you tell people that a drug is safe and effective, I think they do not look much into the details of what went into that at that point in time. There are some things in changes to labels that do seem to have an effect like black box warnings, which are often used for drugs that have been out there for a while, but nobody has made that kind of suggestion for this.

The ability to interpret that kind of information—a friend of mine I had the chief residency with, the best doctor I know, smart guy—and he always says to me, “John, I let you tell me whether that stuff works or not.” The willingness to get down to that granularity and that data in average practice, it is going to get lost in the mist of we really do not know as much about this drug as that last one you were using. The question is how do you communicate that. Even though the labeling format has been changed now, it is still pretty dense to go through. I am not saying that that is not a good thing to pursue. I guess what I am suggesting is perhaps there needs to be additional communication beyond that.

This is not novel either. One of the issues that came up earlier was communicating to the patients about this as well. Now the problem with that is we have medication guides and things like that. But we are not talking about outpatient drugs here. We are talking about people that are critically ill. The question is, how are patients going to make a decision when they are in that situation when they are critically ill?

That is why I think a lot of this information ... this gets mitigated by the fact that if you have clear evidence that the drug actually has an impact on irreversible morbidity and mortality, then a lot of those concerns go away because you have a clear benefit, and those toxicities are justifiable in that setting. I am not saying the label is worthless. I am just saying there could be probably other things we could do in addition.

DR. COUKELL: And David, to you. Eighty percent of antibiotic therapy is empiric. The point has been well made today. But I think the underlying premise of LPAD is FDA is saying this one ought not to be your first choice for empiric therapy. Do you see that this indication has any impact on people choosing an LPAD drug for empiric therapy?

DR. SHLAES: Yes, I do. I think a big part of this impact is going to be the price. But I think the way it is going to work is people are going to look, and people do this now and look at their own local epidemiologic situation in terms of their resistance levels, and they make a judgment, and physicians do this every day. It is part of their job. They say, what

is the likelihood that my patient has an infection at this site? What is the likelihood that my patient has an infection with this bacterium, and what is the likelihood that that pathogen is resistant to most other things in that setting? Then they make a prescription decision about how they are going to treat that patient. There is nothing, I think, particularly different about the way people decide about empiric therapy for an LPAD drug versus something else.

I think what is different and what will be different is going to be the follow-up because I do not think that people are going to allow patients to stay on a very high-priced drug for very long without more than the usual justification. I think that is going to be a big part of it.

DR. COUKELL: John, we will come back to you. But I want to bring in the rest of the panel if they want. I would invite you in particular in the vein of summing up to say what have you heard today. Have you heard clarity on what LPAD is and how it works? Are there in your mind outstanding questions that need to be addressed before this goes forward? Summary thoughts.

DR. GOETZ: I will be bold and start. This may or may not be the summary thoughts that you are looking for. It comes back again to, in a sense, how do we enforce, how do we promote, how do we encourage, promulgate use of the drug as close as possible to the package, recognizing that we are somewhere between knowledge that a person has an infection by a highly resistant organism and highly suspicious.

In thinking about physician behavior, we are also creatures of habits as well as creatures of thought across the broad range of physicians. I do not think that we should underestimate the role of the champions and opinion leaders of setting the stage for what is normative behavior within our organizations where they are across our different groups of providers.

On the one hand, there is a new antibiotic that is released, which is the drug that solves all problems. You never need to think that your patient might have a resistant infection again because no matter where the patient came from that problem is solved. Our junior trainees, if you will, oftentimes buy into that. Sometimes people with greater seniority in different realms encourage that behavior advertently or inadvertently by what they say by the morning report phenomenon of did you think about their patient could have had this infection. We think we are encouraging thinking, but sometimes we are encouraging defensive behaviors.

It is crucial that our societies—and again, as I said this morning—multiple societies, critical care groups, emergency groups, and others really emphasize that, yes, there are ... while there may be times that these drugs need to be used empiric, stop and think critically. Engage in what some people call systems-two-type thinking rather than reflexive-system-one thinking before turning to this agent.

DR. TAMMA: I just wanted to say one thing about your comment, David, about empiric use of these agents. I really do think that these agents should be used as a last resort. We have seen studies where even one day, two days, three days is enough for a

resistance to emerge. And when you think of the amount of patients started on empiric therapy, it is not going to be a small population that would be receiving these drugs. Then you think of the patients who received some drugs at the time they were getting diuretics and all sorts of things at the same time, and their picture improves at two days. And the physicians say, "We think the antibiotics are helping. We want to continue this new drug for another seven days." I think that it is a very slippery slope. I would really be in favor of not using them empirically.

DR. COUKELL: Before you respond, can I get anyone who has a stewardship perspective? Do you have a perspective on David's suggestion that the pricing of Zyvox has minimized inappropriate use? Have we seen that?

DR. CANNON: I think it has to some degree. I think it has been from a health systems standpoint, it has been very challenging for us. I think when it first came out that was not the case. Some of it, I think, has been that we have more robust stewardship programs within our hospitals. We have more agreement on how we will use it. I do not think cost is a complete barrier. I do not disagree that cost can be a barrier and that it does cause people to reflect on what they are going to do. But I do not know that it is a complete inhibitor of inappropriate utilization.

DR. POWERS: I can tell you. We always try to find simple answers for these things. But just in our hospital, we take care of a lot of neutropenic cancer patients. It is not used because of the adverse event profile of that drug. I could not tell you how much it cost because we do not use it for other reasons. It is probably not as simple as a single reason of how much it cost. There are other things that go into it, too.

DR. JAN: The only thing I am going to add is that we did have a prior-authorization program for Zyvox. If you had looked at the denial reasons, you would be very surprised, the patients that were denied who would have otherwise received the product. Yes, I think cost is maybe the reason, but it is not all the time the reason because otherwise you would not have had any denials. It was a lot of inappropriate requests that were denied and controlled.

DR. COUKELL: But would you have had a prior-authorization program without the cost?

DR. JAN: Because of the cost, no, but we may have prior-authorization programs for drugs that have narrow therapeutic index or safety concerns. It is not always driven by cost. That is the perception. It is sometimes true because the new drugs that come into the market are expensive, especially the specialty drugs, and require a lot of monitoring. But prior authorization is done because drugs are either expensive or require monitoring or have safety concerns.

MR. SCOTT: Medicare does not have prior authorization, and they do not have formularies for hospitals or for hospital outpatient departments. However, they do set the payment amount, and depending on whether the provider being paid thinks that is a sufficient amount, they may have their own utilization policies through the hospital formulary committees and rules that they use to do it. But Medicare is not the one limiting the use.

DR. REX: I will take you up, Allan, on your request for a summary review. I first want to say it has been a really good day. My comment is around the choice between the sin of omission versus the sin of commission. A lot of our debate this afternoon has been about how to make this perfect. We can strive for perfection. I love that motto. Relentless pursuit of perfection. But I do not know that we can achieve it. If our goal is a diverse, vibrant pipeline, we need to find a balance here. You realize right now that there are no remaining reliable oral therapies for *Neisseria gonorrhoeae*. There are actually strains of *Neisseria gonorrhoeae* that are effectively untreatable, and they are going to spread. It is unacceptable circumstance.

We have made a lot of baby steps. The progress in the regulatory environment is very exciting. I think LPAD is potentially a simple idea. I have actually gone back to look at the text with the idea say description of the notion. And it is really about we are doing one thing, which is marking a drug that was approved with a smaller data set.

The other stuff we have been debating today, in a sense, is the same kind of secondary problem that you have with every drug that we use. It is not unique to antibiotics. How do you get people to use it correctly? How do you get people to stop it when it is inappropriate? It comes up all the time.

I guess my wish is for this conversation, the national conversation about LPAD, is I do not want us to get hung up on this. I think I said that at the beginning of the day. We think LPAD ... we can see how it can be useful. But if we make it so complex that we spend three years arguing about it, and we are unable to move forward because we are spending three years arguing about it, we have really hurt ourselves. That is the sin of omission versus commission.

DR. COUKELL: Thanks for that. I think the reason for the discussion is if we are looking at a different approval standard from what we have had historically, it is reasonable to want to think through, "OK we have created a new category of drugs with a different approval standard. How will they then be used in the real world?" Not to make it overly complex. John, you were trying to get in earlier, and I cut you off.

DR. POWERS: I wanted to bring up the issue of how we got here in the first place. We are complaining a lot about the issue of resistance, and yet empiric usage is in part driving that problem both on the outpatient and the inpatient setting. To say that that is OK because that is how docs practice medicine is ignoring the fact that that is how we got here, and we want to do better than that in the future, and developing diagnostics would help us with that.

The other thing is ... the flip side of it is getting to the omission/commission piece of this. We often forget that if you give somebody treatment they do not need, you are not giving them the one that they do. If you are treating somebody for pneumonia when they have heart failure, you are not giving them the right thing. If you treat somebody for MRSA pneumonia when they have *E. coli* pneumonia because you cannot make a diagnosis, you are still not giving them the right thing.

The interesting thing is when you look at, for instance, the hospital-acquired pneumonia applications that are submitted to FDA that allow investigators to prescribe a second Gram-negative drug at their investigator's discretion. You will actually see that the doctors are wrong 50 percent of the time in both directions. They prescribe two drugs when the person does not have a Gram-negative infection or they do not give it when in fact the person did. There are two sides to that coin here. It is not just about giving everything to everybody and hope we are getting it right. There is an overlapping Venn diagram of people that we are actually missing as well. That really gets to the point again of getting back to diagnosing people and the right population.

DR. COUKELL: Connect that to LPAD for me.

DR. POWERS: The issue is the empirical usage may be given this big blanket of people. Here are the people who really need it. Here are the people that are going to get it. For LPAD to work, we need to get those people as well as avoid the ones who got it. We have talked a lot about avoiding not giving it to people who do not need it. But we also have to talk about getting it to the people who do.

DR. REX: Thanks for bringing up the diagnostic thing again. I want to make it really clear that everybody in the industry thinks good diagnostics would be glorious. It would solve so many problems to have simple tools that you could use.

There was a nice workshop put on about 18 months ago, a joint U.S.-EU workshop on this. It would really help with the risk-benefit. We would know who needed it. We have a lot of clarity. There actually is progress being made. There are a number of vendors that are bringing things along. There are drug companies that are collaborating with vendors because, as you are doing a development program, you can actually help a diagnostic company validate their tools.

Have no one leave with the thought that diagnostics are not being developed and are not being developed aggressively. They are being developed aggressively. It is hard, but there is serious work going on. And that is the kind of thing that makes this kind of discussion feasible, that you can imagine then that you would have the tool that you compare with something approved under a pathway and a label like this.

MS. WELCH: To Allan's request to provide some summary points, not necessarily in any order of priority, but a few things that come to my mind having listened to all this discussion. It has been incredibly useful, particularly, to hear the payor side and the health care user side. I think for me, certainly, it has filled in some information gaps, and it has given me a lot to go away and think about and share with my company. I really applaud all the organizers for this and the contributors because I think it has all helped and put us all on a level playing field, and I think that is really great in terms of a knowledge standpoint.

Two points that I clearly heard that LPAD really fits well with antimicrobial stewardship. I think that really makes so much sense. I think that is a clear point that comes out of that. And also, that it can be linked to a premium price, a higher price. And, again, that

makes a lot of sense. I am really confident that those points can be taken forward as something that is really tangible to LPAD.

But I am going to go back to one of the questions that we were given in our list. One of them was how would antibiotics ... how might this pathway impact business decisions and investments in antibiotic development? This is very close to my heart and my daily business life. And I still have a number of questions around that because I will get asked. If I say to investors we can apply for an LPAD designation. We are going to go the LPAD route. What does that mean? What does it mean in terms of the program, the type of studies, superiority, and descriptive data? I do not have that clarity today, nor from a pricing standpoint does it give it the other end clarity. There is a lot to be worked through, and I acknowledge that. I cannot answer that question today with clarity certainly to my business partners.

And then the second question was, how would antibiotics approved into this pathway to be priced to make this a viable business model? I think we have really identified the challenges, the gaps there, really, in terms of what we would have to do on the development side to get back to that type of pricing. And they still stand out for me as issues and questions that need to be addressed as we move forward with progressing this initiative.

DR. COUKELL: Thank you. We deliberately did not spend a lot of time today on precisely what the regulatory path would be. But I think both you and John Powers next to you would say clarity on that is essential before you decide either as a company or from your perspective, whether this is a viable or necessary tool. Is that fair to say?

MS. WELCH: Yes, certainly from my standpoint. Maybe just on the health economics, I just thought it was very helpful to get those very simple examples of the type of data that would be helpful. I previously have been involved in designing a REMS program and have a lot of concerns. That would be ... a lot of challenges if we ended up in that type of scenario. But I think the very simple examples of how outcomes data could help the life cycle management makes complete sense and really is the current paradigm that we work with today as drug developers. We get it that we do not stop when we get approval. It is the continual process of generating information and managing that life cycle. I appreciate that feedback.

DR. COUKELL: I am going to go to Jim Scott, and I will give the last word to Bob Guidos.

MR. SCOTT: In the spirit of final thoughts, I wanted to make it clear that there is a pathway through CMS to limit use and provide enhanced payment for limited use of antibiotic drugs. However, those policies would touch multiple parts of the agency. It would raise many issues of first impression for the agency. The agency has multiple priorities. Devoting time and resources to this in the face of trying to get the health insurance marketplace set up by October 1 would definitely be a challenge. Also, you are trying to hit a moving target. CMS is moving towards value-based purchasing and bundled payments. Even as we speak, CMS made an announcement that it has 500 providers participating in a new bundled payment initiative.

To provide the certainty that I think the manufacturers are asking for and then embodied in the idea of limiting use and providing payment, it seems to me that a legislative pathway is needed to make sure that that can happen and that CMS can give this the time and attention it deserves.

MR. GUIDOS: I actually want to talk about legislative pathways as well. Unfortunately, for most of the people in the room probably do not know this, but we are actually talking about two legislative pathways. What Jim is talking about is legislation that affects CMS. It is a different committee on the Hill. It is a whole different group of folks. It makes this very much more complex. What I am talking about is legislation specifically on creating an LPAD.

I want to just follow up on the points that were made about the standard and the need for clarity about the regulatory framework for moving forward and how those questions are going to be answered.

But I also understood and heard earlier today that we are talking about not changing the standard. That it is the same evidentiary standard that exists for orphan drugs, but it is risk-benefit that is different here. I think that John would agree with that. That is what we need to have.

I just want to make a point that I think legislation can move forward now to create this pathway, and those answers about how to make that happen and bring clarity can be worked out by the agency following that legislation. I just do not want us to have to worry about answering that before we can actually move forward with the legislation. I do not think we have to do that, and I think that moving forward with the legislation is so critical at this time that we should not wait.

DR. COUKELL: Thank you for that.

Let me just finish by thanking a few people. First of all, all our panelists for what I think was a really interesting and constructive discussion. And secondly, I would like to thank Nicole who has done a super job arranging this meeting and doing all the advanced work as well as a bunch of people who I will not get all their names, but who have supported her on logistics and planning. Rachel -- from our antibiotics and innovation team, but also our ... from our conference center. Thank you.