Food and Drug Administration
Public Meeting - LPAD Pathway

July 12, 2019

A Matter of Record
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FOOD AND DRUG ADMINISTRATION

Public Meeting

Limited Population Pathway for

Antibacterial and Antifungal Drugs

(LPAD Pathway)

Friday, July 12, 2019

9:01 a.m. to 11:39 a.m.

10903 New Hampshire Avenue

White Oak Campus

Silver Spring, Maryland

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:01 a.m.)

Introductions and Opening Remarks

DR. COX: We're at 9:00, so we'll go ahead and get started. Welcome to everybody who's here joining us in person, and also to all those folks that are joining us via webcast. Welcome to the LPAD Pathway Guidance public meeting.

I think to start out, what we'll do is we'll have the folks on the panel here introduce themselves so you know who's up here, and we'll start with Sarah.

MS. WALINSKY: Hi, everyone. My name is Sarah Walinsky. I am a policy advisor in FDA's CDER and OND.

MS. TIERNEY: Hi there. Julie Tierney, senior policy advisor for strategic planning and legislation in the immediate Office of the Director and Center for Biologics.

DR. ADEBOWALE: Good morning. My name is Abimbola Adebowale. I am the associate director for labeling in the Division of Anti-Infective Drug Products, in the Office of New Drugs.

DR. COX: I'm noticing, too, that to pick up

on the mics, you've got to be pretty close.
DR. ADEBOWALE: Okay. So you couldn't hear me?
DR. COX: Get a little closer.
DR. ADEBOWALE: Closer? Okay. Can you hear me now? Oh, sorry about that.
Good morning. My name is Abimbola Adebowale. I am the associate director for labeling in the Division of Anti-Infective Drug Products, in OND, in CDER.
DR. NAMBIAR: Good morning. Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.
MS. SCHUMANN: Hi. I'm Katie Schumann, policy advisor in the Office of New Drugs, CDER, FDA. Thanks.
DR. COX: Great. Thanks.
Maybe just to start out with a few housekeeping issues, we do ask that folks register at the desk out there. I'm guessing most people got caught before they got in the room. We appreciate your signing in.
For those that are interested in lunch

following the conclusion of the meeting, it will be available at the kiosk around noon, and folks may have seen that or been familiar with it from other advisory committees. It's just over this way. Restrooms are also located over this way. You just go down the hallway, and you make a right, in essence, and then a left, and you'll get to the bank of restrooms.
The workshop website I have on the slide up here. The slides will be uploaded. This meeting is being webcast, just to let folks know, for all of us on the panel and for all the speakers. Typically, the transcripts will be available and posted on the webpage about 30 to 45 days after the meeting.
Our media contact is Alison Hunt. I'm not sure if Alison has joined us yet; maybe not. But she'll serve as our media contact. This meeting is subject to the FDA policy and procedures for electronic media coverage. Representatives of the media are permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public proceedings, including presentations of the speakers today. So if you're a speaker, the media may record

you if they so choose.
As far as the agenda for the day, just to start out, we've got nine speakers registered. Each will have 10 minutes to present. We do ask that each of the speakers try and stick to their allotted time frames. After the 10-minute presentation, there will be a 5-minute time period where folks on the panel are able to ask questions.
If we do see that the presentations are running along quickly or we don't fill the full 5 minutes with regards to the Q&A, we will continue to move along. So it's possible that as a speaker, you may be asked to come to the podium a little bit earlier than your particular listed time. We do ask that the speakers really do try and stick to the timelines. That helps us to manage the time and make sure that everybody gets a fair chance.
There is going to be an open public comment period towards the end. I think it starts at 11:50. If you're interested, for the open public comment period, we're providing 3-minute time slots, and we do ask that you sign up at the registration table out

front. That way we'll know how many people are interested and be able to call people up who are interested.
Just a little bit of background with regards to the LPAD Pathway. Most people are probably familiar, but it was established under the 21st Century Cures Act, which was signed into law in December of 2016. As a part of the requirements under the LPAD legislation, one of the things that we were required to do was to put together a draft guidance describing the LPAD Pathway. Our draft guidance, which published -- help me here, guys. Was it -- June of 2018. Thank you.
So June of 2018 was the date when the draft guidance published and is out there for comment. We got a number of comments. We always appreciate the comments, but one of the things that became apparent as we looked at the comments was there were a lot of requests to have a meeting to talk about this. We thought the best way to do this would actually be to get everybody together, have a public meeting, and that way, you all get to hear each other's comments, in

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essence, and there will be an opportunity for discussion.

It's not surprising that when a new pathway or a new program gets out there, there are some questions as to exactly how it may work and what may actually fit into the program. What we find is that over time, with experience and as examples accrue, there becomes a greater familiarity and a greater knowledge as to how a program may actually function.

As you can see, because this is focused on a particular area, antibacterial and antifungal drugs, it may take a little time to gather that experience and something that's broadly applicable across all therapeutic areas, but we look to the examples to help get a better feel for the community at large as to where the program fits in the overall pathway of approvals.

We do have a website, an LPAD website, and we put this together to try and provide information that we hope will be helpful to you. It has some discussion of the LPAD Pathway and also is intended to list the drugs that are approved under the LPAD Pathway.

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Currently, there is one, but as others are approved under the LPAD Pathway, they will also be listed here, so it can provide you with a resource that we hope will be helpful to you.

Then to sort of cut to the chase on the key requirements of the LPAD Pathway, it's for drugs that are intended to treat serious or life-threatening infections in a limited population of patients with unmet need. We look to the definition of serious or life-threatening and unmet needs as defined in the expedited programs guidance.

One thing you'll see there is that unmet need is, in part, defined by available therapy. The guidance document has a nice discussion of available therapy and recognizes, too, that that's a dynamic issue. We certainly hope that new drugs are approved that address some of the areas of unmet need, and that can gradually change the issue of areas of unmet need.

The LPAD Pathway legislation also specifically states that the standards for approval under 505(c) and (d), or the standards for licensure under 351 of the Public Health Service Act are met. So it still has to

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meet the standards for approval, a drug approved under the LPAD Pathway. The other thing, to trigger the LPAD Pathway as part of this, there needs to be a written request from the sponsor; so the person coming in with the drug application, that the drug be approved as a limited population drug.

You can see one of the issues here is the limited population, who is the limited population. Generally, it's a group of patients that can be limited and described in such a way that is clinically relevant to healthcare providers. A healthcare provider could, in essence, identify a particular patient that was in the limited population.

It may be a defined subset of a broader population of patients for whom the drug could potentially be effective, or in some cases maybe the only population of patients for whom the drug may be effective because of its narrow spectrum of activity. I think we'll hear a little bit more about this as we get to some of the presentations, having had chance to preview some of the slides, and we'll try and bring this issue out a little bit more.

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The standards of approval, inherent in this is the idea of the acceptance of greater uncertainty or higher risk in patients with serious diseases with an unmet need, and really that doing so is an appropriate way to look at risk and benefit.

The interesting thing is you'll notice at the bottom of the slide, we've cited Section 312 Subpart E, which is actually part of the IND regulations, which predates, by many, many years, a lot of the discussion around LPAD. This concept of balancing benefit-risk, degree of unmet need, and seriousness of the condition really has been in the process and in discussion, and in our calculus for a number of years, so I just mention that.

The LPAD Pathway is based on a benefit-risk assessment that more flexibly takes into account the severity, rarity, or prevalence of the infection the drug is intended to treat and the lack of alternatives available for the patient population.

One other thing I'll just mention -- and this is in our draft guidance document -- we are trying to get to this issue of greater flexibility when you've

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got a patient population that has a serious infection and few treatment options available. That's one side of the equation, if you will.

The other side of the equation, I think which is always important to keep in mind -- we talked about how the standards still need to be met -- is there's a line in the draft guidance document that essentially says that the LPAD pathway should also not be used to salvage a trial that fails to demonstrate its objective or an inadequately designed development program. We still need to meet the standard. We're just able to look at the benefit-risk overall and take into consideration the degree of unmet need and how we're evaluating risks and benefits.

Some of the conditions that come along with the LPAD Pathway, if that is the pathway upon which a drug is -- if that's part of the approval of a drug, the labeling has to indicate that the safety and effectiveness has only been demonstrated with respect to the limited population. And again, this gets back to this inherence of how we're weighing the benefits and risks in the setting of an LPAD approval.

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The advertising and labeling will include a limited population in a prominent manner. I'll show you an example of this in just a minute. The prescribed information [inaudible - mic fades] contains the statement, "This drug is indicated for use in the limited and specific population of patients."

So it really is to call to attention where the benefit-risk has been found to be appropriate. The promotional materials, there is a requirement for pre-submission of promotional materials at least 30 days prior to the dissemination of such materials. As far as examples of development program, that may follow a streamlined approach.

A lot of the thinking on streamline approach because of the necessity of getting something out there to address the issue of antimicrobial resistance, patients who have really few treatment options, was captured in our antibacterial therapies for patients with an unmet medical need for the treatment of serious bacterial diseases guidance document.

This document really talks about this key issue of benefit-risk and how to weigh benefit-risk and

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the acceptance of greater degrees of uncertainty in looking at development programs. What we describe in there are clinical trials using noninferiority designs, including a single noninferiority trial at a body site of infection, or use of a wider noninferiority margin than used in a traditional development program.

These by nature would be smaller trials, trials of which there would be greater uncertainty with regards to the overall findings, both efficacy and safety, but recognizing the benefit-risk would be a reasonable tradeoff to allow for availability of a product in a patient population where there may be a particular degree of unmet need.

Other options, clinical trials using superiority design, always a clear demonstration of efficacy; from a practical standpoint, oftentimes very difficult to achieve. Implicit in this is that the arm over which your superior, in most instances, has probably received therapy that may be less than ideal or less than fully effective, a situation that ideally we'd like to avoid.

Nested noninferiority superiority clinical

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trials; this allows you to enroll patients, then based upon their baseline susceptibility characteristics to look at the population of patients with susceptible organisms in a noninferiority approach; to look at those who may have resistant organisms, resistant to the comparator, could be looked at in a superiority design. So it allows you to enroll, essentially, all comers, and then have a prespecified bona fide way to deal with the analysis population, looking at the overall patient population.

The experience, as I mentioned, with the LPAD Pathway to date really is limited. We have one approval today, Arikayce, that used the LPAD Pathway, and I'll mention a little bit more about this in the next slide. We currently receive inquiries on ways to utilize the LPAD Pathway for NDAs.

We recognize that this is an area where there is a thirst for additional information, and we're hoping to give a little more through the talk today and through some of the discussion that happens today. Also, the comments we get today will be helpful as we revise the guidance document to help us to determine

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other issues where additional information could be helpful to developers in the field.

One of the main issues we've seen with sponsors seeking approval under the LPAD Pathway is the issue of the standards. The standards for approval under the LPAD Pathway don't change, Subsection 506(h)(1)(b) of the LPAD provision, and states that the standards for approval under Section 505(c) and 505(d) of the standards of licensure under Section 351 of the Public Health Service Act, as applicable, are met.

So it's important to keep that in mind. We still need to understand that the product works and that the product is safe and effective. If you think about it, it's a pretty reasonable thing to do because these are patient populations with serious infections who need effective therapies that are safe, so it's trying to strike that balance.

A little bit of background information on Arikayce, amikacin liposome inhalation suspension, was approved in September of 2018 in adults who have limited or no alternative treatment options for the

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treatment of MAC lung disease as part of a combination antibacterial drug regimen in patients refractory to other treatment regimens.

You can see from looking at the indication that it's a well-defined limited population. These are patients with MAC lung disease who are refractory to other treatment regimens, so they've essentially not responded to other treatment regimens, clinically definable and limited in a specific group of patients.

There was substantial evidence of effectiveness provided on a surrogate endpoint that led to the approval under accelerated approval. This shows you two things; one, that there was a finding of substantial evidence of effectiveness and also that LPAD can work with the other pathways.

In this case, it was accelerated approval. It went as an LPAD approval, that there was an acceptable level of uncertainty given the seriousness of the condition and the degree of unmet need for patients with refractory MAC who are in need of other effective treatments. This seemed to be an acceptable level of uncertainty.

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Also, too, recognizing that without providing this clarity with regards to the patient population, there was a significant potential for broader use of the indication where benefit-risk had been found to be acceptable and was not clearly described and essentially called to the attention of folks out there.

A couple of other pieces that went into the overall calculus, if you will, there were respiratory adverse events observed in the clinical trials, and then also a relatively limited safety data set. So you can see how this fits pretty well into what we're talking about when we start to look at the provisions of the LPAD legislation.

The risk-benefit was considered favorably only for the limited population of patients as described in the indication. The little blue link there at the bottom provides the link to the summary basis approval on the FDA website. The FOI documents are available, so you can find additional details on the approval there.

I will flip to the labeling, and this is just to give a preview of some of the parts of the label

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where we would include specific labeling. You'll see at the very top, on the left there, under the initial date of approval, the words "LIMITED POPULATION" in all caps, and I think also bolded if my screen is helping me to understand the font there; limited population highlighted in yellow.

In the indication and usage, again in the highlight section, you see limited population again before the indication. The language at the very bottom is, "Only limited clinical safety and effectiveness data for Arikayce are currently available. Reserve Arikayce for use in adults who have limited to no alternative treatment options. This drug is indicated for use in a limited and specific population of patients." So again, in the spirit and providing clarity with regards to the patient population for whom the drug is indicated under the LPAD approval.

Next steps, we're currently working on finalizing the LPAD Pathway draft guidance. The comments that we received to the docket have been helpful to us. We certainly expect that today's meeting will also provide us helpful feedback as we

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work towards finalizing the guidance.
The docket for submitting comments is reopened if there are desires or intentions to submit additional information beyond that which we hear in the meeting today. That will be open to August 12th of this year. We've got the web address for regulations.gov for submitting comments.
With that, I'll say thank you. One other comment, I should say, too, I want to thank in advance all of the speakers who are giving of their time and efforts to come and join us here today. You'll notice that the panel will ask questions, and I would say we're asking questions for clarity, so try not to make judgments on our questions, if you will.
We don't necessarily ask a question because we disagree or we agree. We're just trying to further understand, so I would not overread the questions, which also gives the panel a certain degree of freedom to feel free to ask questions of the speakers without thinking that they'll have tremendous implications.
With that, I will move to our first speaker, who will be a Dr. John Rex, who's the chief medical

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officer at F2G, Limited, and also expert in residence at the Wellcome Trust, and an operating partner for Advent Life Sciences.
John, the podium is yours, and thank you for joining us today.
Presentation - John Rex
DR. REX: Thanks, and thank you to the entire FDA group for organizing this. I think it's a discussion that's been needed. I'm John Rex. Ed has introduced who I am. My location in the electronic universe is on the slide. You know how to find me. I'm happy to share these slides. The title of my talk is Antibiotic R&D 3.0: Taking Full Advantage of the Promising Idea of LPAD.
We've come a long way with antibody development, and I thought it was kind of interesting to realize you could think of it in three steps. Antibiotic R&D 1.0 began at the dawn of the antibiotic era and ran until the middle of the 2000s.
During that time, it was generally quite easy to see the value of new drugs. We had relatively few drugs early on, and they obviously did dramatic things.

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The dead got up out of their bed and walked away, and felt better. It was quite dramatic. But over time, as we began to have more drugs and we began to push into, say, indications that were less life threatening, like upper respiratory infection, it became apparent that the pivotal designs we had been using had flaws.
This was really brought out clearly around the time of the problem with Key Tech, and that led to the beginning of a great rethink that I think of as antibiotic R&D 2.0, which I date from approximately 2007 to today, the 11th or the 12th of July 2019. During this time, we had rapid refinement of our noninferiority designs for major indications. We now have very clear roadmaps for all the big indications, skin, the various UTIs, and so forth.
We have an agreement globally that single pivotal trials could be acceptable for approval, and the EMA and the FDA have worked long and hard to harmonize. The rules aren't exactly the same, but they're close enough that single global trials are entirely possible in the major indications. That's Antibiotic R&D 2.0.

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So it's time for 3.0, and LPAD is our springboard into this. We have several hard problems that we need to solve as we move into 3.0. An important idea is the notion of superiority designs. While you can still do them for certain places, when you can do them, it's bad news, and I want to be able explain that. It's actually effectively a mirage that must be swept away for antimicrobials; 0.4 is arguably the deepest and most important point. This is not just a regulatory problem. The entire community has to collaborate on this for reasons we'll discuss. I'll have some suggestions for next steps, and then some closing thoughts.
As a springboard, LPAD has given us two gifts. First is the very idea of LPAD. As Ed noted, the FDA has always had the ability to consider risk-benefit; every approval does that. But that's not always in the label in a way that anybody else can see. The putting of the word -- as a matter of fact, I counted. There were 5 uses of the word "LPAD" in the first 2 inches of the Arikayce left-hand column.
So by putting it out there in that way, we're

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actually helping everybody else realize this is a place where risk-benefit has really been carefully balanced. Don't do this without understanding the population. Yes, it's always been there, but now we're actually putting a sticker on our forehead that says pay attention to this, and that's different. LPAD also tells us the settings in which this is true, and then it gives us that language. As I said, the limited population. I had to laugh at how many times it said it in the top 2 inches of that document.

If you put that with the other things that are in 21st Century Cures robust stewardship programs and CDC's ongoing surveillance, we can be comfortable that LPAD agents would be used wisely; I will say at least most of the time. There's always somebody who goes off piece, but by and large, this collectively will cause the agent to be used in an appropriate fashion.

What are the problems that antibiotic R&D 3.0 has to solve? Well, it's really about rare situations. It's about rare pathogens, just for resistant pathogens, less common infections, and the issues reduced to study size in how we think about this very

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important phrase, "substantial evidence of efficacy based on adequate and well-controlled trials."

That series of adjectives: substantial, adequate, well controlled, there is nowhere where there's a number attached to that. Nowhere does it say this means an alpha 0.5; this means in a margin of 10 percent; this means a particular endpoint; or this means concurrent randomized controls.

As that as clearly stated, and the FDA has been working for a substantial period of time to talk about ways you use flexibility within those zones, we are permitted, we are encouraged, and we are required to consider risk-benefit. But if you wind it back to the gift of LPAD, we can now say it in a way that's unambiguous. "When we've done this, this drug is not to be used for the ordinary circumstance. Please do not prescribe it from Walgreens."

Ed commented on the different kinds of trial designs that are possible, and let me just say that superiority is an important tool to have available. It's always nice to do it if it's an appropriate setting. But in any infection, superiority is not a

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good answer. Antibiotics do something unusual relative to essentially all the other diseases that we treat. They cure you. If I treat your myocardial infarction, you walk away still having heart disease. If I treat your pneumonia, you walk away without pneumonia, and you live another 60 years.

If it's easy to run a superiority trial -- given the endpoint as curative, if it's easy to run that trial, something terrible has happened in public health. Resistance must be so common that a good choice did not exist because I was able to not -- there was a group who did not get an effective therapy. Except for the mildest of infections, a superiority result in this area, antibiotics and antifungals, means that someone got hurt or may have died who didn't have to have that outcome.

So we want superiority trials to be impossible. We can write them down on paper, but we want them to effectively be impossible. And if superiority is briefly possible due to a gap, the first drug that fills that gap eliminates the possibility of using that pathway again.

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Noninferiority designs have to be our main tool. They work, and they enable drugs to be developed now, and we as a community have to be repeatedly very clear about this in our documents. Yes, we're going to lay out the idea of superiority. No, we don't expect you to do it other than an extremist. Everybody has to be saying that. The regulators, the professional societies, we all have to explain to each other why we're not doing more, because it's not just a regulatory problem. We're all part of this problem. It's easy to be critical and ask for more. Everybody does it.

Agencies are just the first group to ask these questions, but the physicians will say, "I want the guidelines to change." The payers will say, "Where's my superiority data?" See above. Patients will say, "Noninferiority sounds so dodgy. My doctor didn't understand it anyway, so I don't like that."

This is a communication and education problem. There's confusion and debate on the scientific principles, and we must clarify this in public because we have to bring everybody along with us. It's not

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enough to solve the problem in one corner. We have to explain to the entire community why this is the solution that works, not something else. You can't keep wishing for a magic pony to come and carry this problem away. It doesn't exist. We have to work with the existing tools. By the way, in passing, nontraditional agents face the same issues. We have a paper in press on that in Nature Communications.

Here are my suggestions. We're preparing here for the future. When the real crisis emerges, it will be too late. For the agency, convene some working groups. FNIH has been a good mechanism to develop credible pathways for rare infections.

Engage with the tradeoffs to create and publicize feasible pathways. We must use LPAD to expand what is now approvable. The agencies and the professional societies have to spread the word. Noninferiority is not a synonym for worthless, and an infection superiority comes at a huge societal cost.

Professional societies, get with it with the guidelines. It is not acceptable to update them once every 10 years. They need to be updated every year

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electronically online. As an example of this, colistin as a systemic agent needs to cease being used in the United States this afternoon. It doesn't work.

Industry, this is an important message, and it's not about LPAD specifically, but it's saying that you, we in industry, have to be focused on novel agents that really move the needle. There is a need for some other stuff to happen. This LPAD is only one part of the ecosystem fix, but the need for pull incentives is not a discussion for today. This is about FDA and its regulatory powers.

In any future pull mechanism -- and we are going to see them happen, and one is coming in the UK, it's very exciting, and we think one might happen in the U.S. -- not every antibiotic is going to qualify for one of these interesting incentives. It has to be something that really moves the needle. Also, as Ed pointed out, LPAD is not a salvage tool for a drug that almost does nothing. It's for specific settings.

So in close, at heart, I am a doc who moved into industry in 2003 because of the problem of AMR. I once closed an ICU and shut down the upstream ORs

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because of an outbreak of a then untreatable infection. These are big problems. There was a thing yesterday on the radio about some nursing home in the area that had a bunch of people get sick with a respiratory illness, probably some virus.

Infections are scary, and since then, I have had the opportunity to walk all the sides of the challenge of antibiotic R&D. I've done everything from large too small. I have dealt with corporate decision-making, the pressure of time, supply chain, shutting down, lyophilizers. You have to live all sides of this to understand the peace.

Tradeoff-free solutions do not exist. If they did, we would be using them. Since they don't, as a community, we have to find pragmatic solutions to real-world problems, and we need to do that this afternoon. Thank you.

Questions

DR. COX: Great. Thanks, John.

Any questions for Dr. Rex from the panel?

DR. NAMBIAR: It's more than a question; it's just a comment. I think on slide 9, you referred to

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the focus must be novel agents that clearly move the needle. I would like to hear your thoughts on the novelty from a standpoint of seeing a new mechanism of action versus a novelty that should actually translate into a meaningful benefit for patients.

DR. REX: Yes. Novelty here clearly has to be something that's ultimately perceptible in the clinic, and it could be that it's a novel mechanism of action. It wouldn't necessarily have to be, I suppose. This has come up a lot in the discussions of the pipeline reviews.

If you look at the paper from 2018, the third [indiscernible] WHO pipeline review, where we went to a lot of trouble to categorize new agents by the quality of the innovation in them. The need for people developing another same-as has a barely perceptible increment over other things. That's something perhaps we used to do, but that's just not going to work anymore. If we're going to put new incentives in place, they're not going to apply to compounds that don't offer something where we can really see a sharp differentiation.

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I'll also say something that is obvious, which when you think about it, the bigger the impact of the new thing, and the more it moves you from where you were to a new level of efficacy, the easier it is in a small program to demonstrate some of that value; even if what you're doing is a noninferiority comparison. The math all just becomes that much easier and that much stronger if your compound has a strong effect.

DR. NAMBIAR: Thank you.

DR. COX: So maybe I'll ask one. It sounds like, John, you're thinking that noninferiority is still going to be an important staple of drug development. So that overall patient population may include patients who don't necessarily have the degree of unmet need that we're targeting or hoping to be able to address to some extent.

This sounds very much in line with some of the tenets of LPAD, and I just thought it might be good just to talk about this for another minute or two. So you're studying perhaps a patient population that's sick, some of whom have the targeted unmet need, but not necessarily everybody because you need to have a

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patient population who can be treated with a comparator. But at the end of the day, the risk-benefit is being evaluated for that patient population for whom there is unmet need in order to be able to have the more streamlined development program.

Any comments on that? Is that the way you're looking at it, too? It feels like that's the underlying tenet or principle as one of the key components to the LPAD sort of concept, if you will.

DR. REX: It is. And I think, to say it back, you're noting that the data that lead to approval might include people who, after approval, wouldn't be in the limited population, and that's true. I think there you get into the whole ethics of clinical trials.

The Nature Communications paper that's coming out now has a long section. We worked with three ethicists to talk in great length about why it is appropriate to do that sort of thing. All of us are potentially tomorrow's patients. There are lots of reasons for people to be involved in this. There are ways to do these things that are entirely appropriate from an ethical perspective. I think that if we don't

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engage, then you're committing the other sin of waiting until it's really easy to study the bad organism, and then things are even worse, and then it becomes complete chaos.

There's clearly a societal tradeoff to be made. We as a society have agreed that clinical development is an appropriate thing to do. We have mechanisms for enrolling people, for protecting their safety, for being sure that they understand what they're getting into, and we've clearly demonstrated we can do these kinds of studies in a way that makes good sense.

I recognize that tension, and yet it's part of what we have to put out in public because there are people who will not see all the pieces of it. This is part of the conversation here, is to bring all the stakeholders together, and get everybody to, if you will, argue a little bit together and educate across stakeholder communities about why this is the solution, that there isn't some other magic way out. There is not some tradeoff-free solution that makes this all go away.

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DR. COX: Maybe one other area to comment on is that if in fact the patient population in the trial is not exclusively those patients with unmet need, then that gets to the question of what's the scientific relevance of that information to the group of patients with unmet need and in whom the drug would be indicated and used, and bridging that gap scientifically.

I don't know if you wanted to comment on that at all.

DR. REX: I think that group obviously contributes to the safety database for understanding and contributes to the efficacy demonstration as well. We have this funny problem with antibiotics that we define the idea of multidrug resistance, and we say we'd like to know how it works when the pathogen is resistant to these other things. But it's also helpful to know how it works when it's susceptible to this thing.

If you've got a pathogen that's susceptible to this thing, you've actually contributed to an understanding that it will work when the pathogen is susceptible to your test agent, and you can compare

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that to patients who could have been treated another way, which is the population that isn't LPAD, and the patients who could not have been treated another way.

So it really does build your entire data set, but the more you can focus on the people who have the specific requirement, you also prove, by identifying them, that you can identify them. That's the other thing you get out of attempting to do that.

DR. COX: Thank you, Dr. Rex.

DR. REX: Thank you.

DR. COX: Now, we'll move to our next speaker. I want to welcome Dr. Thomas Walsh, professor of medicine and pediatrics, microbiology and immunology at Cornell University, to our podium.

Thank you, Tom, for joining us today, and we look forward to your comments.

Presentation - Thomas Walsh

DR. WALSH: You're most welcome, and thank you so much for joining us all here today. Our mission within our program is very much akin to that of many others, and that is to save lives and advance knowledge in this critical field.

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For the past four decades, my staff and I have cared for -- and we're looking at these recommendations for a perspective of caring -- pediatric and adult patients with invasive mycosis on a daily basis, conducting as well the laboratory and clinical research in invasive mycosis, which has led to our understanding or approval contributing to that of 12 licensed systemic antifungal agents; as well as having studied multiple other investigational agents; and personally serving as PI or associate investigator on more than a hundred clinical protocols.

From that perspective, I am privileged to serve as a Henry Schueler Foundation Scholar in Mucormycosis; working with Save Our Sick Kids Foundation; a perspective of long-standing work with the mycosis study group; representing as well the Medical Mycology Society of the Americas in multiple forums; as well as now working with the European Confederation of Medical Mycology; and most recently serving as the founding director for what we call New York City Cares, which is a New York City collaborative consortium for Candida auris research.

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Fundamentally, why are invasive fungal infections challenging to treat and what are the unmet needs? We've witnessed major advances in antifungal therapy during the past three decades, yet there is a high mortality even when treated with these current agents. We need to ask why; why do we see this? The causes are related, in part, to delayed diagnosis; secondly, to an ever-evolving challenge of immunologically impaired hosts; limited therapeutic options; and increasingly antimicrobial resistance, some of which are intrinsic and some of which are acquired.

Within the unmet needs of antimicrobial resistance -- and I'll introduce a term here of RFIs. We know IFIs, invasive fungal infections, but I think we need to also think through resistant refractory fungal infections. Candida auris, you understand quite well. Aspergillus, trizaole-resistant pathogens, although not so much a threat in North America at this point, it is emerging as a very deadly threat in several countries and now two continents in severely immunocompromised patients.

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Mucormycosis still carries as much as an 80 percent mortality. Fusariam, which we'll come to, is also a deadly lethal pathogen. Scedosporium, lomentospora, virtually nothing available, and other continued emerging hyaline and dematiaceous moulds.

With that, we appreciate there's an urgent need for new antifungal agents similar to that of antibacterial agents with novel mechanisms that will especially hit and circumvent the mechanisms of activity of many of the resistant organisms; improve safety profiles; minimal drug-drug interactions; and predictable pharmacokinetics without the need for therapeutic drug monitoring, which is especially important in our critically ill or complex immunocompromised patients receiving multiple medications and suffering as well from end-organ dysfunction.

Then there's also the element of patient convenience, providing we can see a way to discharge of going from parenteral to oral formulations. And speaking of oral formulations, it's noteworthy that the emergence of resistance or persistence of resistance is

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occurring principally to the antifungal triazole agents, which are our mainstays of oral therapy for most of the deep mycoses.

So it helps us to reflect, which we speak in LPAD, of different populations. From a medical mycological perspective, what are the key resistant fungal pathogens? We need to mention, of course, Candida auris, distinct from other candidia species with a simultaneous expansion, unprecedented across several continents and several clads.

This organism survives in the inanimate environment. Personally, I liken it to the acinetobacter of the medical mycology world. It is extremely tenacious to eliminate, often entailing literally gallons of Clorox in a patient's room.

Persistence of mucocutaneous colonization transcending that of our traditional understanding of gastrointestinal disease, and transmission, well-documented from both environmental and mucocutaneous sources; and intrinsic resistance to two or more antifungal agents, and difficulty in performing randomized trials, even if it's emerging.

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Building upon Dr. Rex's perspective, we want to be ahead of this pathogen. We do not want to have sufficient numbers of Candida auris beleaguering our hospitals to then say, well now we have enough patients in whom we can do a randomized clinical trial. We want to be ahead of this public health threat.

Mucormycosis caries, relentlessly, a lethality of 40 to 80 percent in various studies. In our current protocol-defined therapy, where we're obviously selecting a more enriched population that might have a better prognosis, still demonstrates as much as 60 percent mortality. This organism inflicts painful, devastating, debilitating morbidity for the survivors; yet the estimated number of cases are only 1 to 3 million.

It is indeed a rare disease, and there's no means of a randomized trial. One could look, as we look toward different models, that there is an important model potentially, based on the prior approval that we saw with isavuconazole for a critical option for these and other pathogens.

If we look at fusarium, usually this does not

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rise, but as we look at the breakthrough invasive fungal infections and what is plaguing our patients in the wake of successful treatment of candida and aspergillus, this organism carries lethality varying from 40 to 90 percent, depending upon the host. Strains may be completely resistant to triazole and ampho B.

In our experience, as much as 50 percent may be pan resistant. Other strains may be only susceptible to voriconazole or only susceptible to ampho B, leaving limited options. And again, there's no means of a randomized trial. The prior second-line approval of voriconazole for use of this organism might open up a novel potential pathway. If not exactly that mechanism, then potentially looking toward other ways.

Scedosporium, pseudallescheria, lomentospora, these are resistant to ampho B and echinocandins, and Lomentospora proflificans is completely resistant to all three major classes. Prior to second-line approval for vori, vis-a-vis second scedosporium, again, might offer a potential new pathway, again, targeting these pathogens under the LPAD concept. These are distinct

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pathogens where it's unequivocal in terms of what these patients have.

So what might be possible solutions to study designs beyond randomized trials for resistant refractory fungal infections? One could envision an open-label, non-randomized multicenter phase 2 study of the investigational agent for primary treatment of a pathogen-targeted RFI.

That would be developed in conjunction with a proof-of-concept randomized trial of a more common invasive fungal infection such as candidemia, or one could also develop it with proof of concept in an open-label, non-randomized data with robust enrollment of open label with very difficult to treat infections that could also be used as support of both safety and efficacy data.

The first one might be applicable to Candida auris in that regard. We could have a backup with candidemia if we could show that in an open label, well-conducted study of candida auris, that we were able to impact upon it with proof of concept from the candidemia trial.

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We also have a concept that could apply to a series of moulds. One could say, well, do we need an exact trial for fusarium or an exact trial for scedosporium and lomentospora. You could envision potentially primary treatment of two or more types of these emergent-resistant moulds, both hyaline and dematiaceous, potentially, not the mucorales, which are very different of course, and develop with a proof-of-concept randomized trial, again, backed up, say, a randomized trial for aspergillosis, but enrolling these patients in an a well-conducted, open-label study.

The adaptive designs, which have been invoked as well, are feasible, but they may require relatively larger populations than what these RFIs are able to provide in terms of census. But if we embarked upon one of those two solutions, what are some of the caveats?

Well, if we did an open-label, non-randomized, we need controls that are critical. We need to understand the historical data and prior publications to say these are devastating, life-threatening

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infections, as well as the clinical experience of seasoned investigators. We would need meticulously documented contemporaneous controls, which are obtainable from any one of a number of registries or ongoing during this study in centers not participating.

There's every important burden of supportive data for efficacy, and for that, one could look toward in vitro studies, MICs, time-killed assays, and hollow fibers, but very, very critically are the in vivo studies, and that is well-developed models, what I like to refer to, and doing them under a guidance of what I will call SPARC; that there be several animal model systems and that they be predictive; that the data are aligned; that they're all pointing in the same direction of efficacy; that the data be robust; and that the studies be complementary, not working off just one; for example, one murine system with repetitions.

In that regard, it gives us a foundation. I can assure you when we take informed consent from our patients, we find that very often they will want to know, "Well, what is the background, Dr. Walsh, of this particular compound?" And I say, "It's been studied as

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well in laboratory animal studies, and those with even a modicum of scientific background say it's more reassuring."

So meticulously documented outcomes, with as many as supportive variables as possible, expert review panels; and then again, the regulatory precedent that I mentioned in medical mycology with vori for fusarium, scedosporium and isavuconazole for mucormycosis; not that we have to directly emulate this, but recognizing these are special populations, so potentially building upon this.

We could also think about outside of infectious diseases and think of the review model based upon precedent for rare cancers and other orphan diseases, where we've seen the benefits of single-arm, multicenter studies. These are rare cancers, small cohorts, often less than a hundred, real-world evidence, historical controls, and pooled safety and efficacy results. Although we don't have time to discuss these, this has been especially seen, as depicted here, in many of the signal transduction for tyrosine kinase pathways inhibitors.

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In summary, there's an urgent need for new antifungal agents targeting resistant fungal pathogens; a critical need to meet the public health challenges of resistant fungal infections; and these infections unfortunately occur in our most vulnerable patient populations, resulting in potentially severe morbidity and high mortality.

There are novel regulatory pathways through the LPAD that may be developed and would have an important role in meeting the challenges of resistant fungal infections, and ultimately serving what we all are here to do, is to save lives and improve the outcome of our patients. Thank you.

Questions

DR. COX: Thanks, Tom.

Any questions for Dr. Walsh? Just thinking about Tom, your remarks, it seems like one of the things you're bringing to the fore are some of the examples in the past where an agent has been able to be studied against a fungal pathogen that occurs sufficiently frequently that you can do a randomized trial. Then it sounds like you're describing

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shouldering on an additional study to the randomized trial, with the additional study being focused on the rare fungal pathogens that might be occurring in a low frequency rate, which would make it much more difficult to accrue the usual numbers of patients.

DR. WALSH: Exactly. I think doing that, where one can target the specific pathogen, going to specific centers where one can say we know there's a burden of fusarium here, and we know there's a burden of Candida auris here, you only have to look at the map and target that versus -- although it's an excellent concept of the noninferiority trial nesting in some of the interest populations, it would be too random in that regard to attract them.

So having those parallel studies, and especially focusing on centers with both the population and the expertise, with proper controls and so forth and all the caveats of safety and efficacy, we could understand the efficacy there, bolstered by the preclinical data, and then one has a traditional pathway where one can demonstrate, to the point that we've discussed here, does the drug work in the wider

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range of pathogens, such as candidemia or aspergillosis.

DR. COX: I'm hearing in your comments one other thing that probably also deserves specifically pulling out. You mentioned the idea of if you're interested in studying a particular rare fungal infection, that you might go to the centers where this occurs. So there are certain areas in certain places that we might be able to pre-identify, either based upon epidemiology of the particular pathogen and/or the patient population that might be susceptible, and where they might seek their care.

DR. WALSH: Absolutely. We've undertaken this. In New York, we've actually recruited in, as serving a greater public need, patients that have had, for example, allergic bronchopulmonary asperigillosis, where the expertise may be minimal. We've had a special area of expanding interest in expertise with that, and patients have come in, and we've been able to serve their needs.

Candida auris, it's in the same way. Certainly in the greater metropolitan area, there's a

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burden, but even within that, there are certain institutions that have garnered the expertise in managing these patients.

That's part of New York City Cares, where basically we're harnessing the expertise, as well as bringing in the potential for not only new antifungal agents, but also environmental control, understanding statistical data, a granular database, of what are the outcomes, and how do you manage these infections above and beyond the great forensic work that CDC and New York State Department of Health have done.

DR. COX: Thanks. Yes. So it sounds like that could be an area where setting up or performing a clinical trial could be ideal and have a greater likelihood or chance of enrolling patients and being able to study a drug.

DR. WALSH: Absolutely. And time is not on our side. These are rapidly expanding. Just from Candida auris, it's devastating to see the impact that it's having on lives because we have, really, extremely limited options.

DR. COX: Any other questions from the panel?

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(No response.)

DR. COX: If not, thank you very much, Dr. Walsh.

DR. WALSH: Thank you.

DR. COX: We very much appreciate you joining us and giving us comments today.

Next, I'd like to invite Dr. Mounts to the podium. She's general counsel for CorMedix, and we welcome your comments, Dr. Mounts.

Presentation - Phoebe Mounts

DR. MOUNTS: Thank you everyone, and good morning. I'd especially like to thank Sarah Walinsky and her colleagues at FDA for organizing the LPAD meeting.

CorMedix is very supportive of LPAD, partly because its lead product in the U.S. is the broad spectrum, antimicrobial, taurolidine, that is designed to prevent catheter related bloodstream infections. The first indication for use being developed in the U.S. is for use in central venous catheters in hemodialysis patients.

CorMedix is a small company, and like many

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other small companies, there are limited resources, so any programs from FDA that can help us get these products to market faster and more efficiently is greatly appreciated.

CorMedix believes that preventing catheter related bloodstream infections in hemodialysis patients is an unmet medical need for a limited population. On this slide 3, we present some background information on the limited number of hemodialysis patients, which has been estimated at 420,000 in the U.S., who unfortunately experience life-threatening infections that develop from repeated vascular access through the catheter.

Importantly, the Centers for Disease Control and Prevention have documented many drug-resistant pathogens in this limited population, methicillin-resistant Staph aureus; cephalosporin-resistant E. coli; vancomycin-resistant enterococcus; and carbapenems-resistant enterobacter. This is clearly a limited population in need of new antimicrobial drugs.

Our specific request to FDA with respect to

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the LPAD guidance are summarized on this slide 4. I will cover each of these requests in the following slides. We think LPAD is a very important program, both for industry but also for the public health, and the guidance will be helpful if it elaborates on the agency's current thinking on how to apply and implement the intention of the legislation.

We appreciate the inclusion of products to prevent life-threatening infections and think this is valuable to the public health. The request we feel most strongly about is making an affirmative determination for eligibility for LPAD earlier in product development.

We think that an exclusionary criterion about using the LPAD pathway not being appropriate if criteria for non-LPAD approval are met is not really helpful. We request more information be put in the guidance on the process and timing for review of promotional material if a product is approved under LPAD. And I suspect this final request will be frequently repeated today and is clearly a topic of discussion, which is to clarify the agency's current

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thinking on the streamlined clinical development offered under LPAD.

We are grateful to FDA for issuing the LPAD guidance, which was required under the 21st Century Cures Act, and we think it will be most helpful with some added specificity on how FDA intends to interpret limited population; is there a number limit?

The language in the guidance suggests that a healthcare provider needs to be able to identify appropriate patients in the clinical setting. It seems that as true for most product approvals and can be covered in labeling and the indications for use. For example, hemodialysis patients with a central venous catheter seems to clearly define the limited population.

The guidance seems to suggest that a physician education program may be required. Certainly, physician education should be a focus for antimicrobial drug use, and if this is a reasonable development, it would be helpful for sponsors to be made aware of this so that materials can be developed earlier in the product life cycle.

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Thank you for including prevention in the definition of a drug to treat a serious or life-threatening infection. I have public health roots and training as a microbiologist, and that tells me that we really have to prevent infections. Exposing pathogens to antimicrobials applies a selective force to develop drug resistance, which is really the central issue here.

My strongest plea is to make the determination for at least eligibility for LPAD earlier in drug development. The time of approval is too late. How can sponsors take advantage of a streamlined clinical development program if the decision is not made earlier than after phase 3? Sponsors and FDA need predictability to allocate resources, and again, this is especially important for small, innovative companies with limited resources like CorMedix. More importantly, the eligibility decision needs to be made earlier to expedite the development of new antimicrobial drugs, which is really the goal of the LPAD program.

We respectfully request that FDA does not

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inappropriately limit the LPAD pathway to sponsors. Congress created the pathway, and if a sponsor decides to pursue the pathway and qualifies, it should be made available.

The guidance states that copies of all promotional materials related to the product must be submitted at least 30 calendar days before dissemination. We would appreciate more specificity on the timeline for review and approval. The language presumes feedback before 30 days, but that should be made explicit.

On slide number 10, the heart of LPAD must be the streamlined clinical development, and we will request more specificity on the FDA's current thinking on the available options. Can we use real-world evidence? Are postmarketing registries or other data collection options available to sponsors? The real issue is integrating a phase 3 program with an LPAD decision delayed until product approval. We are not looking for a commitment on approval; just guidance on realistic options during phase 3.

On slide 11 and the next few slides, we have

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some reactions to comments from FDA officials that give us some concern, so we would like to understand the thinking behind these comments. On their surface, the comments suggest a lack of agency enthusiasm for LPAD, which is concerning.

For example, risk evaluation should be no different than any other approval when LPAD requires substantial evidence of safety and effectiveness. Of course, the statute says from clinical trial[s] with an S on the end, and we think the streamlined clinical development in LPAD provides the option for reducing that to a single robust pivotal trial.

The agency has at its disposal existing post-approval authority to monitor and identify risks for any new drug approval, including REMS, adverse event reporting, and the authority to impose postmarketing studies. So it's not clear why this should not be adequate for approval pursuant to LPAD.

On slide 12, agency officials have expressed concerns about off-label use. Again, this is an issue that is not unique to the LPAD Pathway and FDA has as its disposal mechanisms to address off-label use. I

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agree that indiscriminate use of antimicrobials is a major issue in this area, but that needs to be addressed by educating physicians and not restricting use of LPAD to sponsors.

We are also concerned that comments from agency officials may suggest that new antimicrobial drugs cannot be demonstrated to be safe and effective in small trials. The main goal of LPAD, as we see it, is to get antimicrobial drugs on the market as fast as possible to address an unmet medical need, and we think with assistance from FDA, the process can be made more efficient under the LPAD Pathway.

Slide 14 summarizes the requests we are making of FDA. We will certainly file these comments to the docket, but we appreciate the opportunity to discuss them today with you. If I had to prioritize the requests, it would certainly be to make a determination of eligibility for LPAD earlier in product development for predictability for sponsors to maximize resources for both sponsors, as well as FDA.

So in conclusion, CorMedix believes that LPAD should be designed to facilitate antimicrobial drug

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development and should be available to help in the battle to address antimicrobial resistance. This slide just has some citations for information on the slides, and the last slide is to thank FDA, and to thank you, the audience, for your interest in LPAD.

Questions

DR. COX: Thank you, Dr. Mounts. I appreciate your comments.

I'm looking to see if there are any questions from the panel.

MS. WALINSKY: Yes. I have one quick question. You spoke a little bit about prevention, and we've been working on that section in the draft guidance. I would just like to hear a little bit from you about how -- we're trying to craft a limited population. And if the condition is rare, the problem is if you're preventing that condition, it might be indicated for a larger population.

How would you narrow that to a limited population? Could you speak to that?

DR. MOUNTS: Yes. I think that's a particularly challenging problem for our colleagues in

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CBER, where they develop vaccines. And the whole point of vaccine development is, in fact, to broadly use the vaccine to protect the whole population, and you get herd immunity.

I think there's an inherent tension that you've identified in the strategy for products that prevent, but I think you're going to have to develop the flexibility to identify those products and how they can be used to prevent the infection in the targeted population.

So identify those individuals who are susceptible to the respiratory track infections, who have end-stage renal disease, who are going to develop catheter related bloodstream infections when they get infected. Those are the people that you need to target in this study because they are the ones that will be affected.

DR. COX: Great. Thank you, Dr Mounts.

Any other questions for Dr. Mounts?

(No response.)

DR. COX: Thank you, Dr. Mounts. We appreciate your comments.

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Now we'll move to our next speaker, Mr. Colin McGoodwin from the Infectious Diseases Society of America.

Welcome, Colin.

Presentation - Colin McGoodwin

MR. McGOODWIN: Good morning, everyone. My name is Colin McGoodwin with the Infectious Diseases Society of America. I do not have any slides, so unfortunately that means you're all going to have to look at me.

The Infectious Diseases Society of America, thanks to Food and Drug Administration for holding today's meeting to discuss the Limited Population Pathway for Antibacterial and Antifungal Drugs. IDSA represents over 11,000 infectious diseases physicians, scientists, public health practitioners, and other healthcare providers.

Our members care for patients with serious life-threatening infectious diseases, including those caused by multidrug-resistant pathogens with few or no treatment options. Our members also conduct research on antimicrobial resistance in the development of new

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therapeutics and lead antimicrobial stewardship programs.

IDSA first sounded the alarm about the crisis of antimicrobial resistance and the need to invest in new antibiotic research and development in 2004. Since then, IDSA has led efforts to advance policies to stimulate new antibiotic R&D and promote appropriate antibiotic use, including legislation to enact LPAD. Today, IDSA underscores the importance of this pathway, as the state of the antibiotic pipeline has grown even more dire. We are also pleased to offer some recommendations to strengthen the draft LPAD guidance to expand opportunities for antibiotic R&D.

IDSA greatly appreciates the FDA recognizing the gravity of antimicrobial resistance and the fragility of the antibiotic pipeline. Very few large companies remain engaged in antibiotic discovery and development, and the small companies who are driving the vast majority of antibiotic innovation are struggling to stay in business.

Without a robust and renewable antibiotic pipeline, increasing numbers of once treatable

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infections will become deadly, and modern medical advances like chemotherapy, transplants, and other complex surgeries could become too dangerous to perform, undoing decades of progress against disease.

The opioid epidemic is adding further urgency to the crisis of AMR, as injection drug use is causing an increasing number infections caused by resistant pathogens. The CDC reported people who inject drugs are 16 times more likely to develop an invasive MRSA infection.

The Limited Population Pathway is essential to strengthening our antibiotic pipeline because many of the deadliest infections with the fewest treatment options currently occur in a relatively smaller number of people who are often critically ill, which makes traditional large-scale clinical trials infeasible.

Further, new antibiotics with activity against the most difficult to treat pathogens should be used only in the patients who truly need them to protect their utility against the development of resistance. The Limited Population Pathway addresses both of these challenges, and if properly utilized can help bring to

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market some of the most urgently needed new antibiotics and promote their appropriate use.

IDSA supports the policies and processes outlined in the draft guidance. We are pleased to offer some recommendations that we believe will strengthen the ability of the Limited Population Pathway to bring new antibiotics to market with urgently needed indications. To maximize the potential of this new pathway, the use of novel trial designs will be critically important.

Further, while noninferiority trials are often most appropriate for studies of new antibiotics, some of the small studies conducted under this new pathway may not be amenable to noninferiority design. In instances for which superiority designs would be appropriate under the new pathway, the FDA should consider using a p-value of less than 0.1 or another less stringent value for type 1 error control if the risk-benefit ratio is favorable.

In some instances, it may be appropriate to include data from patients in other countries given that certain multidrug-resistant pathogens may be more

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prevalent in other countries than in the United States.

It is important to remember that in addition to new antibiotic approvals, the new pathway also offers important opportunities to promote and monitor appropriate antibiotic use via the statutory requirements that drugs approved under this pathway be clearly labeled as limited population and that their use is monitored. By approving a new antibiotic for a traditional indication and not a limited population indication, the FDA may essentially forfeit these valuable stewardship opportunities.

IDSA understands that approval for limited population indications may not always be feasible or appropriate for a sponsor seeking this route. In such instances, the FDA should utilize other tools at its disposal to incent antibiotic R&D and to provide critically needed new treatment options.

Flexibility in the package insert language for drugs and studies meeting the LPAD criteria but not necessarily meeting FDA indications for approval in that disease syndrome may provide a meaningful incentive to drug sponsors and useful information for

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clinicians.

Package insert language is essential because it informs clinical decision-making and governs sponsor communications regarding its products. Even if a sponsor cannot achieve a limited population indication for a new antibiotic, IDSA recommends the sponsor still be able to share its study data from use of the new drug in patients with resistant infections.

Given our extremely limited antibiotic arsenal and increasing rates of antibiotic resistant infections, clinicians are frequently forced to rely upon treatment options based on extremely limited clinical or even in vitro data. In this environment, additional data that could inform how a new antibiotic may perform in a patient with a difficult to treat infection would be very useful.

Finally, IDSA would like to emphasize that LPAD plays a vital role in the broader national and global fight against antimicrobial resistance, but much more work is needed to foster the antibiotic pipeline necessary to meet current and future threats and to stem the tide of antimicrobial resistance.

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The FDA has an important role as a champion within our government for broader solutions. IDSA calls for antibiotic reimbursement reform and novel pull incentives, such as a market entry reward, for targeted urgently needed new antibiotics that address our greatest unmet needs to ensure fair and reasonable returns on investment for antibiotic R&D. We also support higher investments in AMR research and clinical trials networks.

Equally important, IDSA continues to advocate for a federal requirement for all healthcare facilities to adopt antibiotic stewardship programs that align with CDC recommendations. We also support increased funding for our public health system to address AMR. Lastly, we urge a federal commitment to sustain the expert workforce needed to effectively combat AMR on all fronts, patient care, research, stewardship, infection prevention and control, and public health.

Once again, IDSA thanks FDA for its continued efforts to strengthen the antibiotic pipeline and promote the appropriate use of these precious drugs. Thank you.

Questions

DR. COX: Great. Thanks for your comments, Mr. McGoodwin.

Any questions for Mr. McGoodwin?

(No response.)

DR. COX: So maybe I'll just ask one. We appreciate your comments with regards to LPAD, but the problem that seems that we're facing here is fairly considerable, and you talked about a variety of different strategies to try and address this. Certainly, we at FDA will continue to do all that we can to support antimicrobial drug development.

Any additional thoughts that you have with regards to other levers that could be pulled here that might help out with regards to drugs that are targeting particularly small patient populations? I'll also throw out the idea of clinical trial networks, if that was something you wanted to comment on, too.

MR. McGOODWIN: For more specific comments, I'd want to make sure that I reached out to my members first to make sure that I didn't say anything that didn't align with what they were thinking when we put

this together. But I think we've worked on a ton of different incentives as an organization and different ways to just move. Any type of anything that will strengthen the antibiotic R&D pipeline, we are all for. So anything in that regard, we greatly appreciate. Thank you.

DR. COX: Thanks very much, Mr. McGoodwin. We appreciate your comments.

Now, we'll new move to our next speaker, Mr. Jack Mitchell, who's director of health policy at the National Center for Health Research. Welcome, and the podium is yours.

Presentation - Jack Mitchell

MR. MITCHELL: Good morning. Like Colin, I have no visual aids, so I apologize in advance for that. I'm Jack Mitchell. I'm director of health policy, as Dr. Cox has noted, of the National Center for Health Research. We are a nonprofit think tank that conducts and analyzes research with implications for public health and patient safety. NCHR accepts no money from pharmaceutical and medical device industries, so I have no conflicts of interest to

report.

Unlike our other members of our distinguished panel, I am not a medical or technical expert. My comments reflect the medical and policy expertise of NCHR. I'm probably not in a position to answer a lot of technical questions, but I'd like to give a few comments that we believe reflect the patient perspective from the many patient groups that we routinely interact with.

As your other experts have pointed out, resistance to some antimicrobials has been growing and is recognized as a serious and escalating treatment threat for decades. The CDC has estimated that 23,000 people die annually from drug-resistant infections. Other authoritative estimates have put the number much higher.

As noted by Dr. Cox earlier in his introductory remarks, partially because of this looming health crisis, Congress created a limited population pathway program for FDA as part of the much publicized 21st Century Cures Act, and the agency is required by law to implement it. I think as Dr. Mounts has noted,

however, there may be some confusion or some clarification needed about congressional intent and FDA's intentions in that regard.

FDA, I should say, should be commended for its work in attempting to resolve a long-standing and thorny medical treatment problem. The FDA and the Centers for Medicare and Medicaid are seeking to come to an interagency agreement on the difficult economics of antibiotic and antifungal new product research, which has lagged because of the limited population of patients affected and the enormous expense of getting new drugs approved. Nevertheless, this proposed guidance raises some critical questions, which we believe need to be addressed and which were reflected in the written comments that we've previously submitted to the docket.

A key issue is just having more drug with options on the market does not necessarily always help patients. One analysis of antibiotics approved between 1980 and 2009 found that 42 percent, or 26 drugs out of 61, were taken off the market due to poor sales, or safety, or efficacy problems.

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The best way we feel to make certain that new drugs are safe and effective is by requiring well-designed and valid clinical trials. Relatively few patients, even though some of them may be seriously ill, have an unmet need. That is a situation where none of the drugs available on the market work for their infection. That makes it difficult, more difficult than usual, to study new drugs in the patients most likely to benefit.

For that reason, the guidance suggests that an experimental drug should be tested in a broader population of patients with the intent that if approved, the drug would be indicated for a narrow or limited population of patients who do not have good options. However, if the drug is not tested on the specific population for which it is intended, it would be difficult to determine the efficacy and safety for that particular population.

Drugs approved by testing in a more general population would not necessarily provide patients and their physicians with the evidence needed to necessarily determine the appropriate treatment for the

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patients in this limited population, and therefore it would not be clear if the benefits outweigh the risks for the intended patients, and as Dr. Mounts noted in her comments, Dr. Woodcock of CDER has already noted that the risk profile is different in this limited population category.

If the new drug is expected to be safe and effective for the general population, in other words, the type of patients to be included in the clinical trial, then it would not need to go through the limited pathway. So we would ask how can a doctor justify explaining to clinical trial patients, if they are randomly assigned to receive the experimental drug, the drug might be less effective or less safe than the approved drug that is already known to work for their condition.

The guidance also suggests that patients with serious disease and unmet needs are willing to accept greater uncertainty or greater level of risk. Without doubt, that maybe will be true for many or even the majority of patients. I'd like to note, though, as an organization that routinely works with patients,

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however, we have found that it's not always necessarily the case.

It is our experience that patients who are not faced with chronic or fatal diseases also have expressed the need for FDA to focus on safety. We do not think it is accurate to assume that patients who have an unmet need always have less concerned for safety than risk-to-benefit ratio.

FDA properly recognizes the need to warn patients about different standards for drugs approved for the limited pathway. For that reason, the guidance states that the labeling should include the words "limited population" adjacent to the drug's name, and include a statement about the indication for limited population of patients. That is entirely appropriate, and as noted here, it is repeated in the labeling. However, in and by itself, that seems perhaps inadequate because it does not clearly describe the limited scientific evidence used to support the drug's approval.

Patients and doctors see the FDA approval properly as a gold standard, and they expect

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FDA-approved drugs to meet that high standard. This goes back to Dr. Rex's point that we have a communications and educational problem.

FDA knows what it's doing and knows what they're required to carry out into the 21st Century Cures Act, but that does not mean that patients and their physicians understand these increased risks or different standards, and that needs to be developed much further for the patient's benefit. Again, citing Dr. Mounts' previous concerns, we would endorse the idea of a physician education program towards that goal because this is going to be a very important education and communications problem.

Randomized and double-blind superior trials can be small and provide the best available treatment by comparing to the standard of care plus the new drug as an add-on treatment. This is common for cancer trials we are told by experts. FDA should consider adopting those strategies for antimicrobials rather than solely considering evidence from small trials of patients that are substantially different from the indications that FDA ultimately approves.

Again, as Dr. Cox alluded to earlier, the section of the 21st Century Cures Act, which describes the limited pathway, specifically states that the approval through this pathway still requires the same level of evidence as standard approvals; that is substantial evidence from adequate and well-controlled studies demonstrating efficacy. Again, FDA knows this, but this needs to be better conveyed to patients and their physicians who are not familiar with the FDA approvals and regard it as a gold standard, nonetheless.

This also should include sufficient numbers of participants to conduct appropriate statistical analysis. In addition, the guidance itself states that the pathway does not allow for drugs to be approved without meeting this normal standard.

In conclusion, I thank you for allowing us to express our views in this critically and ongoing topic. Thank you very much.

Questions

DR. COX: Thank you, Mr. Mitchell.

Any questions from the panel for Mr. Mitchell?

(No response.)

DR. COX: Just a few key things that I'm hearing in your comments, the issue of the trial population studied and the relationship to the population in whom the drug would be indicated, and being very mindful of the scientific issues that would need to be carefully addressed with regards to critical factors that would impact the generalizability. That seems to be one theme.

Then I also heard the issue of balancing benefits and risks as we're looking at LPAD drugs to make sure that the benefit-risk is still acceptable. Then you're bringing up the important --

MR. MITCHELL: Most importantly, that it be conveyed to the patients that even though there's the same approval standard, that there could be a different level of risk, and they need to understand that. And I would emphasize that, yes, I agree that most patients who are seriously ill would take a heightened risk, but they need to understand what that risk is, if it can be calculated.

DR. COX: Right. That gets to the issue of

communication, which we recognize there can be challenges as you move from those involved in drug development, those regulating it, the physicians, the patients, and there are multiple different layers there. So you bring up some points that deserve some additional thought, and we appreciate your comments.

MR. MITCHELL: We believe, as I said, that there needs to be some further clarification of congressional intent. There was some controversy involving the language in this regard, as I recall, in the original stages of the 21st Century Cures Act. And from Dr. Mounts' comments, it appears that some of those discrepancies or misunderstandings may not have entirely been resolved.

DR. COX: Would you care to just expand on that a little bit more? I think I'm understanding what you're saying, but it might be helpful if you would just give a little more detail.

(Crosstalk.)

MR. MITCHELL: Well, I would reflect on her comments that there appeared to be not necessarily a common understanding between how FDA may be

implementing this and what congressional intent may be. I think that FDA should take it upon itself to do a little bit more interaction with some of the staff's down on the Hill who wrote this language and who are looking to you to implement a very difficult -- as Dr. Rex has pointed out, a very difficult but important program.

DR. COX: Right. We appreciate that. Just in general, too, we also note that as legislation is going forward, we're often in the situation where we're able to provide technical assistance, too, along the pathway.

I think we have a question. Dr. Adebowale?

DR. ADEBOWALE: Yes. Thank you very much. I really appreciated your presentation. I guess I just wanted some clarification. You did make a statement about the labeling, and it was clear you did say that the limited population information that's included in the labeling is entirely appropriate. However, it's inadequate because it doesn't describe the limited science used to approve the drug to the patient, I guess.

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I guess that was the intent of that comment, because you have many types of labeling. I guess the main concern was in terms of communicating the science to the patient. --

MR. MITCHELL: Yes.

DR. ADEBOWALE: Okay. Thank you. Thank you very much.

MR. MITCHELL: Yes, that was my intent. Thank you.

DR. ADEBOWALE: Okay.

MR. MITCHELL: Thank you very much.

DR. COX: Thank you very much, Mr. Mitchell. We appreciate you joining us here today and giving us your comments.

Now our next speaker is Elizabeth Lovinger, a government relations and policy officer at the Treatment Action Group.

Elizabeth, thank you for joining us today, and we welcome your comments.

Presentation - Elizabeth Lovinger

MS. LOVINGER: Thank you. Like the previous speaker I'm presenting on behalf of the technical

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experts at my organization, so I'll do my best to answer your questions should you have them.

Thank you to the U.S. Food and Drug Administration for this opportunity to offer comment on behalf of Treatment Action Group or TAG. TAG is an independent activist and community-based research and policy think tank, fighting for, among other improvements, better treatments and a cure for HIV and related comorbidities, tuberculosis, and hepatitis C virus.

From our founding over 25 years ago, we have understood that both ambitious research agendas and a flexible but rigorous regulatory authority are necessary for achieving these advances. TAG was instrumental in advocating for the development of accelerated approval and parallel track pathways, which paved the way for earlier but conditional drug approval in response to urgent unmet medical needs, as well as preapproval access under the current expanded access framework. These regulatory flexibilities were vital to progress against the HIV epidemic. We are proud that they have endured and been improved upon to allow

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similar progress in other disease areas.

Since then, other initiatives to stimulate investment in neglected diseases, including orphan drug, priority review, fast track, and breakthrough therapy designations have been introduced. These initiatives have had utility in facilitating product development in at least the disease areas on which TAG works. But we cannot ignore that pivotal to progress on HIV, hepatitis C, and more recently tuberculosis has been investment in rigorous research. We understand the challenges of securing such investments, especially for diseases of little commercial interest or with limited or hard to enroll patient populations.

In our current work on TB, this is a problem we face routinely, and let's not forget that HIV was once a disease that no one paid attention to, especially not pharmaceutical companies or their shareholders. With existing incentives and regulatory flexibilities, we are concerned that already the trade of rigor for speed may compromise the FDA's ability to ensure drug safety and efficacy and undermine equitable access.

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For example, the Orphan Drug Act's exemption for pediatric research means children, the most orphaned of all when it comes to drug development, don't benefit from advances that are made. We are deeply concerned that further lowering the evidentiary bar for regulatory approval will do a disservice rather than a favor to patients.

At the core of FDA's mission is the responsibility for protecting the public health by ensuring the safety, efficacy, and security of drugs. As professor Susan Ellenberg remarked at a recent FDA hearing regarding a new anti-infective drug candidate, people in these desperate situations are every bit as entitled, if not more entitled, to have drugs where there's a definitive evidence that they are going to work.

We support the remarks submitted by the National Center for Health Research and the questioning by survivor Jonathan Furman on safety issues that could come under the Limited Population Pathway for Antibacterial and Antifungal Drugs. If the FDA does decide to go ahead with this pathway despite these

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appeals, we are concerned that the pathway could be applied to tuberculosis, the active infectious form of which, and particularly it's drug-resistant strains, affects a relatively small number of patients in the U.S. However, millions of people are affected by tuberculosis globally.

This creates a risk that drugs approved under lower evidentiary standards given limited patient numbers in the United States could be applied to large patient populations abroad. As such, we ask the FDA to ensure that if this pathway does advance, it makes clear that conditions that affect a large number of patients in other settings outside the U.S. are ineligible.

Further, if this pathway does proceed in some form, we do not agree that compliance with the labeling and promotional material requirements currently in the draft guidance is sufficient to alert patients or providers to the lax evidentiary standards under which benefits and risks were assessed for a drug; and we are alarmed to see comments from pharmaceutical companies asking for even fewer labeling requirements. There is

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also insufficient protection against off-label use, an extremely common practice in the U.S.

Additionally, noting that the LPAD Pathway should not be used to salvage a trial that fails to demonstrate its objective or an inadequately designed development program seems difficult to enforce. We welcome and encourage efforts to attract and appropriately incentivize further research into health areas that have not attracted and are unlikely to attract commercial investment in research, but cutting corners for research is not the way to do this. We need appropriate incentives that facilitate development and promote rigorous science, not merely more incentives. Thank you.

Questions

DR. COX: Great. Thanks for your comments. You covered a wide range of areas in the challenging area of drug development, specifically mostly focused on the areas of TB drug development in this instance.

You mentioned the issue of a drug being studied for patients with more resistant forms of tuberculosis and the challenges there. One of the

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goals of LPAD is to clearly communicate that limited patient population and where the benefit-risk is appropriate.

I heard you mention the idea of ensuring that that information was available to folks. Any thoughts on how to further inform folks, beyond what's in the label, with regards to the population of patients, where the benefit-risk is specifically thought to be a favorable benefit-risk, such as patients with few options and severe disease?

MS. LOVINGER: Yes. I think, from our perspective, we're somewhat concerned that there aren't necessarily circumstances in which labeling would be sufficient, just due to the fact that the majority of the population doesn't have a background in clinical evidence. In my experience, even speaking with government officials who don't have a background in clinical evidence, I think there's a knowledge gap there as well.

So I think from our perspective, we would simply want similar standards to be applied and to not have to communicate that to patients. And if there's a

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need to incentivize further research, then that should be a separate conversation.

DR. COX: Any other questions? Sumathi?

DR. NAMBIAR: Thank you for your comments. I was wondering if you can expand on your comment about limiting access outside of, say, the United States if a product were approved with LPAD labeling. Do you have any thoughts on that?

Particularly for disease conditions, which are not prevalent in the United States, there is truly an unmet medical need for that outside the United States, then imposing some kind of limitations regarding access, which will be interesting hearing your thoughts on that.

MS. LOVINGER: Yes. I think from our perspective, those are circumstances under which a drug should not be eligible for the LPAD pathway because of that risk for application outside the United States.

DR. NAMBIAR: Thank you.

DR. COX: We also heard your comments about the importance of evidence --

MS. LOVINGER: Yes.

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DR. COX: -- and getting quality evidence helps to understand how the product works.

MS. LOVINGER: Yes. I think to clarify from the standpoint of drug-resistant tuberculosis, there are treatments currently that have an efficacy rate of 50 to 60 percent. I think we were particularly concerned when we saw language about widening noninferiority margins.

If for instance there is a wider noninferiority margin of let's say 12 percent, then you could have a new standard of care that has an efficacy rate, from our current standard, say 38 percent. Then if that drug then becomes a new standard of care, there is a risk that you're allowing another drug to enter the market that has an efficacy rate of 26 percent. So I think from the standpoint, particularly of tuberculosis, that's a serious concern that we have.

DR. COX: Great. Any other questions?

(No response.)

DR. COX: Great. We thank you for your comments, and thanks for joining us here today.

MS. LOVINGER: Thank you.

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DR. COX: Our next speaker is David Angulo, who's the chief medical officer at Scynexis, who I believe presenting on behalf of BIO.

Did I get that correct?

MR. ANGULO: That is correct.

DR. COX: Great. Thank you, David.

MR. ANGULO: Thank you.

DR. COX: We appreciate you joining us here today.

Presentation - David Angulo

DR. ANGULO: Thank you. Thank you for the invitation, and thank you for allowing us to present here, and thank you for really organizing this meeting.

I'm David Angulo. I'm the chief medical officer of Scynexis. As a disclosure, we are developing an antifungal agent, so you're going to see my talk really focusing on how LPAD could be applied to antifungal agents and why we believe it's a very important tool that we need to -- it's extremely important to refine as much as we can so that we all can take advantage of that, the public and all the physicians that really need these drugs.

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Why do we believe that LPAD applies fully to antifungal products? And thank you for the previous speakers that really have paved the way for this talk to be relatively easy for me. But certainly, there are serious and life-threatening fungal infections that have very, very high mortality. I don't think that there is a doubt that we check that box. Many fungal infections are serious and life threatening. Examples have been provided, but here are some of them.

Candida, these infections may have mortalities reported up to 60 percent; azole-resistant and invasive aspergillosis with mortalities up to 50 percent. Serious fungal diseases, failing or intolerant to existing therapies, they have mortalities close to 30 percent. Rare fungal infections like scedosporium and fusarium infections, mortalities are higher than 50 percent.

So it's clear that there is, even with current therapies, a very substantial unmet medical need, and this is with current available therapies.

These infections occur in a limited population. They are not very common. They are rare.

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Those patients are easily identified by healthcare providers because typically they are diagnosed via a culture, a biological marker of this particular disease, sometimes histopathology, but you can clearly identify what is the population that you are treating here.

There are substantial unmet medical needs in the antifungal space. The reality is that we have only three main classes of antifungals that really are commonly used to treat invasive fungal diseases: echinocandins, azoles, and polyenes. Only one of them is oral. Treatment for invasive fungal diseases typically takes several weeks to months. So you have only one oral therapy and you have patients who are refractory or resistant to that particular oral therapy, you have very few options.

One of them has significant concerns regarding drug-drug interactions and other classes may not be appropriate for patients with substantial risk for nephrotoxicity. If we take this into consideration, really, the antifungal space has a substantial need for additional options because the physicians right now

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have very few options to play with.
I'm trying to provide here a pragmatic example of how a drug could really be developed or why a drug could be developed in the antifungal space following the LPAD path. We're here expressing that drug X could be indicated in adults who have limited or no alternative treatment options for treatment of a documented invasive fungal infection that is either refractory by one or more treatments, or caused by pathogens known to be resistant to existent therapies, or in whom the treatment is not tolerated.
So all these elements by itself are already limiting substantially the population, and these are the patients that are definitely in a very substantial need to have additional treatment options.
All of them required have some level of consensus regarding refractory, how to define refractory. This is typically defined in clinical trials by an independent committee, and here I'm just providing an example of a fungal infection that could be considered refractory, a patient with candidemia that has the persistent positive cultures and lack of

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clinical response after let's say 5-7 days of the current available therapy. We know that these patients, if nothing is done, may have a very high risk of mortality.
So refractory could be defined based on each one of the indications. Resistant is a little bit easier to define that population because resistant could be based on reported MICs and susceptibility breakpoints. Intolerance is the patients who have developed a toxicity or at risk of developing a toxicity when a product is administered,, particularly for drug-drug interaction reasons.
This particular scenario in our opinion is very consistent with the LPAD Pathway because, by definition, it's a limited population, and they have a lack of alternative therapies. The population is well defined, and it's a subset of potentially a broader population of patients in whom the drug may work.
The labeling, it's very easy for the labeling to define the population in a way that a healthcare provider can identify the patient in a clinical setting in which a particular product, drug X, is indicated

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for, and it's clear that this indication may represent a substantial unmet medical need.
Will a traditional development path work for this work? Randomized-controlled trials, even noninferiority with large margins of noninferiority margins, will it work for this particular type of development path? Of course not. The reality is that we are talking about very, very rare populations, small populations doing randomized-controlled trials versus something that has already failed, or for which the patients are intolerant to, and not having too many options within the antifungal armamentarium to randomize to. These types of purchase of randomized-controlled trials are not likely to work in this case.
Giving an example, for instance, invasive candidiasis, we can still do for all comers for in invasive candidiasis. We can still do randomized-controlled trials. The prevalence estimated in the United States of invasive candidiasis has, I don't know, 25,000 cases a year, and it takes about 2 to 3 years to do a well-controlled,

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randomized-controlled trial.
If you think about a subset of that population, those that are, I'm going to say, candidiasis [indiscernible] cases, or azole-resistant Candida glabrata cases that are only 10 percent or 7 percent of that population, it will be truly impossible to really run a well-controlled, randomized clinical trial.
So here we are claiming that what the LPAD is right now identifying as streamlined approaches needs to be much more open, and needs to be much more creative, and needs to be willing to accept other ways of redeveloping a product and really demonstrating the evidence of effectiveness.
An example here could be a single-arm study in which certainly we explain why a controlled study may not be suitable. The population will be limited, and the sample size of this particular single-arm study will be small. Historical control data or concurrent control data very meticulously collected should be part of the package. However, we have an area in which we're very fortunate that in vitro and in vivo PK/PD

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assessments in studies are typically highly predictable of efficacy in humans. We need to take advantage of these of these particular situations.

In vitro/in vivo PK/PD studies supporting the activity of the drug against the target pathogen could be part of the package supporting this and supporting clinical studies in related pathogens or related indications, even if not for that specific pathogen.

Obviously, the drug should show some clinical evidence of safety in a sufficiently large population that can come from the single-arm study, plus other complementary studies that have been run, and for the limited population, labeling provides adequate controls for use to justify the benefit-risk, in our opinion, in this situation.

Here are other two examples that I'm not entirely sure are clearly defined as a potential option for LPAD, and I think that we should think about them. For instance, novel therapeutic strategies because LPAD is a little bit more tailored to novel drugs, so also novel therapeutic strategies, we should think about them.

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In this particular case for fungal diseases that have very poor outcomes, combination therapy for fungal infections in which a single agent is ineffective or the infections have suboptimal outcomes with very high mortality, we can speak here about invasive aspergillosis, particularly with azole-resistant invasive aspergillosis. With current available therapy options, they still have mortalities of 40 to 50 percent, so combination therapy could be an approach that could use the LPAD Pathway for antifungal development.

Also, we need to think about novel therapeutic strategies for invasive fungal diseases that have other significant unmet needs that will not be suitable for a traditional development path. Here is just an example. If you have an osteo-articular infection due to an azole-resistant candida, let's remember the azoles are the only oral available therapies. These patients are going to receive from 6 months to 1 year of antifungal therapy.

If you have them resistant to the only oral available therapies that are there, they only have the

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opportunity to keep receiving IV therapy for 6 to 9 months or up to one year. So we need to use LPAD to try to help us and provide alternatives in those cases in which the available therapies are not adequate to really meet the needs of the patients and the physicians.

I think that's it for me. Thank you.

Questions

DR. COX: Great. Thank you, Dr. Angulo.

I'll look to the panel for any questions.

(No response.)

DR. COX: I might just ask, you outlined some really difficult conditions to try and study, thinking about patients who might have infrequently occurring fungal infection, some of which might be involving bone and such. There are still some really significant scientific issues to try and work through to gather the evidence to try and understand where a therapeutic might work in understanding its safety and effectiveness.

You mentioned historically controlled trials, which can in the correct circumstances provide valid

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scientific information, but also in other circumstances can be quite challenging to rely upon. So I just reflect those comments back to you. I don't know if you wanted to comment any further.

Historically-controlled trials can be challenging, where the outcome is variable and the treatment effect is not so large. You might look at two control groups from different studies conducted similarly, and there might be a variation in the control group outcome that may actually exceed the size of the treatment effect.

So there are some real challenges here. I just bring them up because I think it's important to continue to keep those in mind. We always look forward to trying to solve these challenging situations.

DR. ANGULO: Absolutely. I am totally in agreement that historically-controlled trials, probably by itself as a single point of evidence or single point of comparison, may not be the solution, but this is kind of a package of weight of evidence, what we are here trying to play with.

Concurrent control patients that have not

participated in the clinical trial with very detailed information collected about them is probably the best alternative, along with historically-controlled trials. It is probably the best alternative that we have to be able to compare the outcomes of these patients that will never be suitable to do a randomized-controlled trial.

So randomized-controlled trials in these very small populations, we're not talking about that. We're talking about also PK/PD parameters that are all pointing in the same direction; in vitro information that is pointing in the same direction; open-label trials that are really pointed in the right direction.

So we're not talking about a single point of evidence; we're talking about collective pieces of information that really will provide enough information to substantiate the effectiveness of the drug, at least for the risk-benefit ratio that these limited populations require.

DR. COX: Certainly, there are conditions where we have enough information about the natural history of disease, treated and untreated, to be able

to use historically-controlled trials, and the outcomes are reliably not good. And if the effect size of the treatment is large enough, you can still make a scientifically valid appraisal.

I'll mention one more thing that came to mind as I heard you describing historically-controlled trials and some of the challenges of doing randomized-controlled trials. One of the other ideas that come up sometimes is disproportionate randomization. If it is possible to do a randomized-controlled trial, maybe you randomized 3 to 1 and gather some information from some randomized controls. Some have even talked about trying to utilize that information along with historical information so that you have some insight into what's going on in the control group.

Any thoughts on that? It's just an idea that's been batted around.

DR. ANGULO: Absolutely. That is another option in which randomized-controlled trials, even when you have very small controls, it's certainly difficult to really plan -- those could be an alternative to also

take into consideration. I'm totally in agreement with that, with the caveat that we need to understand that really doing those studies that are properly powered to really demonstrate a statistical inferiority or superiority is extraordinarily challenging in many of these conditions.

We may have controls there, but with a clear understanding that those are unlikely to be properly powered to really put all the statistical rigor when you make the analysis against the controls.

DR. COX: Thank you, Dr. Angulo.

DR. ANGULO: Thank you.

DR. COX: Any other questions?

(No response.)

DR. COX: We thank you for your comments and for joining us here today.

Our next speaker is Dr. Lisa Wittmer, who is the chief development officer at VenatoRx Pharmaceuticals, and she's also presenting on behalf of the Biotechnology Innovation Organization.

We thank you for joining us here today, Lisa, and the podium is yours.

Presentation - Lisa Wittmer

DR. WITTMER: Good morning. Thank you very much for this opportunity, and thank you so much to FDA, the organizers of the meeting, other speakers, as well as the interest in this meeting. I wanted to present the industry perspective on the guidance and some of the precedents, and that's where I'll focus most of my presentation.

I think what really struck the industry community about the guidance and FDA's direction thus far is that the guidances are really meant to be layered together. There was already an existing guidance on unmet medical needs for antibacterials, which laid out, to some extent, the opportunity for streamlined development. Then the LPAD guidance was issued in addition, and I think the novel aspect of that guidance was really the definition and requirement for use of the LPAD Pathway in a limited population.

FDA has defined and exemplified what that limited population could be. It could be a population that is a subset of a broader population, or it could be an existing small population. But either way, the

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population would need to be clearly identified or identifiable in the clinical setting.

This concept makes sense, and what I'll explore topically in the presentation is whether that backs us into a corner of narrow spectrum therapeutics and more targeted drugs, and leaves out some of the innovative broad spectrum novel agents that still have potential to address unmet medical need.

We understand readily some concepts of streamlined development. This has already been talked about by Dr. Cox's introductory comments on the framework for using a single adequate and well-controlled trial, and we do have a couple of precedents here in the anti-infective space, so that is helpful.

We also see readily in the public domain a number of companies designing trials and advocating for, in special circumstances, wider then established noninferiority margins. These are used sparingly in cases where the unmet medical need is so significant that there is a critical imperative to get a product to the market with the available patients for study in a

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clinical trial. Of course, this does come already with a restricted-use label.

In addition, there's a concept of a nested inferiority, noninferiority design that has been already laid out in the unmet needs guidance and reiterated in the LPAD guidance. Generally, we think of a streamlined development program as being shorter, smaller, and requiring fewer trials. And it's certainly not that we want to cut corners and reduce the amount of evidence, but we all recognize that there are some populations in which the benefit-risk ratio is perhaps a little bit more lenient, such that the same level of evidence in a large number of patients would not be required in order to justify the use of a new product.

One thing that we contemplate is how this new pathway, the LPAD Pathway, is different or similar to existing expedited development pathways. For example, a pathway already allowed under Subpart H regulations, of course that pathway requires use of a surrogate endpoint that's predictive of clinical efficacy, and many of us may look at the anti-infectives space,

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further to the last speaker's comments, and recognize that to some extent, we may already have that structure available to us because of the strength and predictiveness of microbiological data from in vitro and in vivo studies.

So the question is, how is the LPAD approach and streamlined development program really different from the existing expedited pathways? That is something we will very much like for FDA to clarify in the LPAD guidance.

The LPAD guidance lays out a couple of examples for products that would be eligible for this pathway, and the examples include an agent with narrow spectrum activity. In that case, the limited population is necessarily defined. The second example, and I'll focus on the word "only" here, is an antibacterial or antifungal drug based on available therapy that would only have a role in the therapy armamentarium for a select population with no other options.

The requirement that the drug, the novel drug, the investigational drug, have a role only in that

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limited population is perhaps a challenge when we look at the full spectrum of new agents in development. So one of the questions to think about is whether this LPAD guidance is really meant to be predominantly useful for a narrow spectrum and/or targeted antibacterials, and is that the intent of the legislation, and in fact FDA in this guidance.

I wanted to just quickly walk through two examples, and I'll call them a positive and a negative example, to get us thinking a little bit more about the application of the LPAD guidance. Arikayce was mentioned at the outset and is certainly something that we have all gravitated to in order to instruct us specifically how the LPAD guidance is implemented.

Arikayce has a limited population indication. This is the drug that was studied in MAC lung disease. It was approved based upon a Subpart H type pathway. The surrogate endpoint was sputum culture conversion versus any type of clinical endpoint, but it certainly seemed appropriate in this case. A single phase 3 trial using this microbiological endpoint was the basis of approval. Of course, there was some supportive

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evidence from a phase 2 study as well.

The benefit-risk assessment here took into consideration a higher incidence of respiratory AEs in the novel drug treated group versus the control, and still, the benefit-risk was positive because of the critical need for new agents for patients with no other treatment options.

This is an interesting case example, but a little confusing to industry because, based upon Situro and its approval, which is similar to this one, and in that case LPAD was not yet implemented, we wonder whether or not this drug could have used the Subpart H pathway only and not LPAD in order to achieve approval.

Now certainly, we recognize that LPAD is useful because it allows some of the changes to labeling and the additional requirements for promotional material review prior to use in order to ensure, perhaps in a greater way, and have been for Subpart H drugs, that the drug will be used only as intended in the specific population where the unmet need is greatest and that particular benefit-risk profile applies. This in and of itself without other

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examples is quite difficult, then, to use as a roadmap to implement LPAD.

If we look at the Zemdri example -- this is an anti-infective antibiotic, plazomicin -- that was approved for complicated urinary tract infections, because it was approved based upon a single adequate and well-controlled trial, it in fact had a restricted-use label. You can see that in the labeling language it's for patients with limited or no alternative treatment options.

In addition to complicated urinary tract infection, the company embarked upon a study to look at infections caused by resistant pathogens. When they submitted the application to the FDA, they requested approval for bloodstream infections due to CRE, or carbapenem-resistant enterobacteriaceae.

It is very difficult to study these types of infections. In fact, over 2100 patients were screened and 60 to 70 could be enrolled in the trial; very difficult patient populations to study. And I think many of the other speakers made the point that when studying infections due to resistant or rare pathogens,

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the populations are quite small and difficult to access geographically.

There is no approval for bloodstream infections, and in fact there were potentially many critiques that could be made of the data package that was submitted. However, in the context of how difficult it is to study these populations, it is challenging to see if this is a negative case example, how companies can target collecting direct evidence in infections that are rare in order to achieve approval.

Some of the discussion we've had earlier today is really based on studying inaccessible infection, and then shouldering perhaps a small study in resistant infections. That is one concept. Of course, if a product can get to the market with an indication in a more common infection and the requirements for approval of a rare infection indication are unclear, then it's possible industry would be disincentivized from pursuing those indications. Interestingly, in this example, the benefit-risk in the UTI population didn't lend sufficient support, from a safety perspective, to support the bloodstream infection indication.

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While we recognize FDA certainly cannot discuss confidential information relating to this product's review, I raise this as an example just to ask a couple of questions. Does the concept of a limited population truly enable studying of resistant rare infections? Can FDA clarify the context, for example, for CRE infections, of the bar for sufficient evidence of efficacy?

Just to summarize, I would like to give a few industry perspectives. One is the lack of clear precedence, which is certainly not anything that we can directly address. It's just because LPAD is new, and it is quite difficult to identify these limited populations. Is lack of precedent just the observation that this may slow industry in adopting the LPAD Pathway? In addition, it could be very helpful if LPAD could be used for any relevant subpopulation with significant unmet medical need.

There is clarity needed whether LPAD could be granted concurrently with non-LPAD indications. This gets back to the idea that the guidance specifies the goal for the LPAD Pathway is really targeting a very

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limited population.
Then lastly and importantly, and this has been raised by a number of speakers, in addition to the readily recognizable streamlined development plans that we have come to know through other guidances and precedents, it is really important that FDA address some of the less utilized, infrequent approaches that perhaps could be useful here. Maybe these approaches are used in other therapy areas but have not been readily adopted in infectious diseases yet.
Using alternative control groups, alternative statistical approaches, including Bayesian statistics, using microbiological surrogate endpoints, and being able to extrapolate from body sites to other body sites, within reason, when you have evidence that your drug is distributed to those other body sites, that allows extrapolation, to some extent, of efficacy data and a much more pragmatic approach, while scientifically justified, to know a drug's true potential across infections and multiple body sites.
Then lastly, greater reliance perhaps on PK/PD data. Thank you very much for your attention.

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Questions
DR. COX: Great. Thanks Dr. Wittmer.
Any questions for Dr. Wittmer from the panel?
MS. SCHUMANN: Just one question. As we think about the language in the guidance and revising that and going to final, it sounds like one of the areas of confusion might be around the examples that you listed on slide 4. I just want to make sure I understand the concern or the question there is that LPAD would only be available, essentially, or is being targeted for narrow spectrum products, based on the way you read those two examples. I think that's something we could and should look at.
DR. WITTMER: Yes. I think that's the case. Is it really intended to enable fast development of narrow spectrum products? I think narrow spectrum products certainly have tremendous impact and are highly desired in this area. However, a lot of the innovation -- for example, for beta lactamase inhibitors that lead to an improved profile associated with commonly used antibiotics, those are broad spectrum products. And if they're studied in a limited

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population, could they utilize the LPAD Pathway is one of the questions.
MS. SCHUMANN: Great. I think that's incredibly helpful as we move forward with this. I think, as folks know, we've gotten a number of comments on the need for examples and clarity there, so thanks.
DR. COX: Sumathi?
DR. NAMBIAR: I think Katie just asked the question I intended to ask, so we're fine.
DR. COX: Maybe just a couple of thoughts. You talked about the issue of broad spectrum that Katie's brought up. Then it seems like one of the things that you're looking for, if I'm understanding correctly, are the distinguishing features of the LPAD Pathway compared to other pathways --
DR. WITTMER: Yes, correct.
DR. COX: -- if we can provide any additional clarity on that. Then maybe I'll just make one observation or comment, which is you brought up a number of issues, particularly on the last slide, some of which I think are scientific issues that span multiple different areas and could be issues even

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independent of LPAD, and many of them are; alternative control groups and alternative statistical approaches and all.
So there are a number of challenging issues, some of which there is some information out there. Similar to what we talked about with LPAD, it does operate independently, if you will, of many of the other programs that are out there. These scientific issues could certainly be the discussion of any development program, LPAD or otherwise.
So it's certainly worth talking about when those ideas of incorporating -- whether it be alternative control groups or alternate statistical approaches that are brought up, bringing those up during the time that the clinical trials are being designed so that there can be time to work through the scientific issues.
Depending upon the disease that you're studying, the implications may be different; a disease with a reliably bad outcome compared to a disease where there may be an inherent rate of resolution as part of background; and depending upon the severity of the

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condition and such.
So it's definitely worth thinking about and talking about during the drug development phase, and we thank you for your comments, and we look forward to thinking about them more.
Another question, Abi [ph]? Sarah, please.
MS. WALINSKY: I have just one question. Staring at this bullet in front of us about clarity over an LPAD indication with a non-LPAD indication in a broader population, how would you envision that being labeled? I think that's a tough question for us, so I just would love to hear that.
DR. WITTMER: Yes. We recognize that that's a challenge from a labeling perspective, although this was the theme of some of the other presentations today, the concept of studying the accessible population, which has a more common infection, and then using that to bolster the evidence that is achievable by trying to study a more rare infection.
So if that is one of the streamlined development pathways that we see as viable, or more viable, than some of the ones listed on the bottom of

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slide 9, then we would have to solve the problem of how it is labeled.
I think, to some extent, the stewardship practices will kick in with regard to the use of a product in the common infection, and perhaps you will see a product that has utility in a rare infection would become standard of care for the rare infection, but not necessarily standard of care in the common infection because the labeling would specify that it's to be used only in patients with no other treatment alternatives, and you have the antibiotic stewardship practices layered on top of that.
So I don't have a great answer for you, but I certainly recognize the challenge.
DR. COX: Thank you, Dr. Wittmer. We appreciate you joining us and providing your comments to us today.
DR. WITTMER: Thank you.
DR. COX: Our next speaker is Dr. Rienk Pypstra, vice president of anti-infectives, Pfizer, and he's also presenting on behalf of the Biotechnology Innovation Organization.

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Welcome, Dr. Pypstra.
Presentation - Rienk Pypstra
DR. PYPSTRA: Thank you. I want to start by saying first that the LPAD initiative is a very useful initiative, and it's very welcomed because it helps us to make life-saving drugs available. We've discussed today several examples of drugs that cannot be developed in a different way, or that cannot be developed in a traditional way, and in order to make those drugs available, we needed some alternative initiative. This is one of it. Secondly, it also supports the overall anti-infectives R&D ecosystem, and that is also very important, as we've heard before.
My presentation will focus on two aspects. The first one is how can we implement novelty that is occurring into this LPAD pathway, and secondly, some practicalities on how do we fix or clarify exactly postmarketing removal of the LPAD restrictions.
The novel development review initiatives, how can they be applied to LPAD? First of all, there's discussion of smaller, shorter trials, and there are lots of examples there. We have already touched upon

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several of them: boosting controls; having platform trials with continuous controls; and contemporaneous controls.
There is also a discussion that we haven't touched upon yet that's real-world evidence versus randomized-controlled trials, particularly in the context of having clinical trial networks where there is going to be much more evidence available. Maybe these two will start to approach each other in the quality of evidence.
I also briefly want to touch upon tissue agnostic approaches, or at least labeling, and how we can pool pathogen data across different body sites because that is how the drug is going to be used, and the FDA should definitely try to provide guidance in the label of how the drug is intended or going to be used. There is reference to the streamlined clinical development plans, programs that we've discussed before, and I'm not going to dwell on that.
About innovation, there are quite some trends ongoing today, and I would really like to encourage the agency to embrace that innovation. In diagnostics,

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there's a lot going on with genotypical information, and that is being linked to predict susceptibility and large databases are being created. These will be able to be linked as well to patient databases if we do the efforts to do so, which would link genotypical information of pathogens directly to clinical outcomes. That is going to be extremely helpful information.

The electronic patient records are capturing so much information that at ACMED [ph], there was already a presentation where a person who was able to predict the presence of a resistant pathogen without even testing the pathogen, so fascinating stuff is going to be available and possible thanks to artificial intelligence or machine learning.

Clinical trial networks are happening that will probably help us facilitate informed consent, but it will also generate a lot of information. Thanks to international collaborations, we will be able to access also pathogens that are regional and be able to capture that information before it becomes a problem in our home country. It will even allow us to test, empirically, stewardship interventions because you

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could randomize certain sites to do certain stewardship interventions and see what the real outcome is of that, something that we haven't been able to do yet.

Then last but not least, the blurring of the real-world data and randomized control paradigms just because of the sheer volume of evidence. And if we have good harmonized data quality checks in the clinical trial networks, these two types of evidence may approach each other.

So talking about this innovation now, and bringing that, and what does it mean for substantial evidence, we've heard a couple of times about demonstrating noninferiority in a somewhat similar population and then have anecdotal clinical evidence in an open-label trial specifically addressing the question about the MDR pathogen; definitely a very good approach.

We have also heard that PK/PD is a very important part of information, and it can help bridge evidence generated in one body site to another body site in many, many cases. Of course if we have novel mechanisms of actions, it's going to be more difficult,

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but that is certainly an extremely important piece of evidence.

If we have difficulty in recruiting patients because they are so rare and these patients have no other treatment options, very often there are compassionate use programs. Is there something that we can learn from those compassionate use programs, and how can that be included in the substantial evidence?

Then of course, the control arms that we've discussed before, flexibility and endpoints as being applied in cancer trials, going back to microbiological eradication as a surrogate marker may be helpful in certain cases where we just do not have sufficient patient numbers and too much confounding factors because of the complexity of the infection.

Adaptive clinical trial design, there is clear guidance from the agency, and even recently updated, and I would really like to encourage the agency to make best use of all of these options, not to limit ourselves too strictly to the traditional clinical trial design as we've been doing it, but see what is possible to strengthen the power of our small studies.

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This slide here, slide 7, is a very important one. It is about how does these drugs are tested, and Zemdri was one example, tested in a complicated UTI setting, so therefore it gets the label of the drug is indicated in patients with clinical UTI infection. But that's probably not how the drug is going to be used, not necessarily. Particularly if you have drugs addressing AMR, where they're going to be used is most likely in situations with ventilator-associated pneumonia or other infections in an intensive care unit or septicemia.

So is it helpful to indicate a drug for cUTI if you know it's going to be used or be needed in another indication, and under the LPAD umbrella, could the agency not come to a risk-benefit judgment in these not studied indications, based on the available evidence with the appropriate clarifications of course in the labeling, what has been studied, and what is now a possible use of that drug?

Specifically for the labeling, I think the caveats of limited population are very important and very helpful, but what I would like to see is

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something, like here in blue, that a drug for AMR is indicated for the treatment of infections; not a specific type of infection, not a body site, but for the treatment of infections caused by multidrug-resistant Pseudomonas aeruginosa, or acinetobacter, or whatever problem pathogen that we have. I think that would be extremely helpful.

Then the statement that it's based on just limited data is perfectly adequate and is going to be very helpful to limit overuse of the drug. And actually, these types of drugs are going to be controlled very much anyway through stewardship initiatives at the site.

The last slide is about the postmarketing removal of the LPAD restriction. We heard concerns previously that there might be overuse of drugs, and I think we are all in favor of trying to gather all the information that is possible about treatment of a specific indication in a specific setting.

So whilst the drug is approved under a limited population initiative or pathway, I think it is going to be useful to collect further information and make

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sure that we really establish efficacy and safety of that product in that setting.

The question is how do we do that, and is it sufficient to collect safety information? Is it sufficient to collect real-world evidence, or does it really need to be like a supplementary NDA at this moment, a prospective well-controlled clinical trial to come with that evidence? That is a question that would be helpful to be clarified in the guidance.

Another point here is about the Limited Population Pathway. Can you get another claim for another pathogen on the same label, or as the previous speaker asked, can you have a normal claim and then a separate claim that says, well, for this indication there's only limited evidence, and how would you do that? The real-world evidence or the randomized-controlled trial for the initial indication, that is also an important question.

So the point here on this slide is, really, could the agency provide a little bit more practical guidance on the various options on how to address, postmarketing, the LPAD restrictions? That's it.

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Questions

DR. COX: Thank you, Dr. Pypstra.

Any questions? I can start out with one. I'm wondering, you mentioned the issue of tissue agnostics and body sites, and I guess one of the challenges that we've seen is when we look at the many antibacterial drugs, where we've seen trials over the last 10 years or so, we've not infrequently run into circumstances where a drug works in one type of infection, but then at another body site, much to our surprise and not apparent until the clinical trial teaches this, there's a deficit in another site.

When folks look, sometimes they do some very elegant work and can understand this, I'm estimating about half the times, and sometimes the other half the time, we, after looking, can't quite even figure out why, or at least our hypotheses are just speculative as to why a drug worked at one site and not another.

That does raise a real challenging issue for the issue of a drug and looking across body sites. I know it's a tough question. I can't answer it. I'm just curious if you have any thoughts on it.

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DR. PYPSTRA: Well, I think part of the answer is that we should study the drug across indications. Not each of the indications will be adequately powered, I accept that, but at least it will generate some information, and having some information is better than having no information.

The situation that we're facing currently is that drugs are studied primarily in UTI infections, and they're going to be used in other infections for which we have no information whatsoever. So I would rather have a study where it's used in mixed infections, adequately stratified, or using factorial design so that you can compare within the groups and across the different indications, and generating some evidence.

I think the big problems will be identified by that. There may still be some differences between pneumonia and intra-abdominal infections, and they will probably be teased out later onwards through real-world evidence data.

DR. COX: I'm just thinking about your comments, and of brings us back I think to that theme that we've heard through a couple of the presentations.

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And that is, are there ways that could help facilitate the collection of evidence in these very difficult to study infections, whether it be clinical trial networks, centers of excellence and such, so that we might be able to gather more data that is really difficult to gather to help to address some of these questions.

Just a comment, really -- well, two comments maybe. One is that it is true that folks do study indications that are feasible where they can actually gather some data about the efficacy of the drug, which is helpful. It doesn't address all the questions that are out there, all the ways that a drug might be utilized, and certainly we all would want to have that information.

So it does bring us back to this question of are there ways that we can help to gather such information in these more difficult to study infections?

I'll comment, too. I noticed on your slide, you said a randomized-controlled trial, and then some anecdotes. Certainly, we do try and do better than

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anecdotes. We are trying to get to adequate and well-controlled trials. Sometimes in these difficult to study conditions, you can construct an adequate and well-controlled trial. Sometimes it's historically-controlled trial. Sometimes it's a smaller randomized-controlled trial.

But we do try and work with companies throughout the period that they're developing their drug to try and explore what might be possible that might get us to an adequate and well-controlled trial to really help provide the information that will help us to understand how a drug works in treating a particular type of infection, and recognizing that in certain circumstances, the sample sizes might be smaller, the degree of uncertainty might be larger, but still trying to get to that threshold of level of evidence, if you will.

Any other questions for Dr. Pypstra? Sarah?

MS. WALINKSY: You mentioned accelerated approval in two of your slides. I didn't hear you dive deeper in that, and I just wanted to hear a little bit more from you. You mentioned postmarketing removal of

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LPAD restrictions, and again, you mentioned it earlier in the endpoint flexibility as for cancer trials. I just wanted to hear where you're seeing how accelerated approval -- I know with Arikayce, we approved based on both.

DR. PYPSTRA: The principle of accelerated approval that I'm in favor of is that you can make the drug available relatively quickly, based on limited data, and that you have some kind of post-approval commitment to complement the information afterwards, whilst the drug is already available to patients.

We heard from the patient organizations that they want every patient to have access to safe and effective drugs, and we should all endeavor to achieve that. The problem is that in the beginning, we have a drug of which we do not know that information, and what is then better; not to have the drug at all, or to have the drug available under certain restrictions and with adequate labeling? And I think it's the latter.

MS. WALINSKY: Thank you. That's helpful.

Open Public Comments

DR. COX: Thank you, Dr. Pypstra, and we thank

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you for your comments and for joining us here today.

At this point, we've gotten through our scheduled speakers, and now we can move to the open public comments. We have Carrie-Lynn Furr, who is signed up to be our first speaker.

DR. YOUNG: I didn't sign up. I don't know where to sign. I'll follow anywhere. Some of you signed up first.

DR. COX: We'll let our speaker who signed up go first, and then we'll ask you for comments.

DR. YOUNG: Thank you.

DR. FURR: I'm Carrie-Lynn Langlais Furr, CEO of Bacteriophage and Drug Development Consultants. Thank you for the work that FDA has put into implementation of the LPAD Pathway. Like others, I agree that approval under this pathway is very important to increase the arsenal of antibacterial and antifungal products. Thank you also for the opportunity to speak for a moment. I will be brief.

My comment applies broadly but is driven by the development of Bacteriophage based investigational products. Bacteriophage therapeutics are in a novel

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class of biological antibiotics with narrow spectrum activity and reviewed by CBER. Since many small companies are innovating Bacteriophage's and other new antibacterial and antifungal products, I would ask that there be consideration to adding agency discussion of the potential for an investigational product to be approved under LPAD early in development; again, the potential.

For example, at the pre-IND stage, and investigational product with LPAD path potential could be eligible for more frequent interactions with the FDA, similar to what is written in the breakthrough therapy designation guidance. Such interactions in this case would focus on the integrated development plan so that the anticipated need for additional nonclinical data to support the LPAD clinical program is known early on; also to understand if, for example, analytical method validation can be during postmarketing period for certain types of methods.

The implications of shorter development plans or shorter clinical development plans on CMC is often overlooked, and I fear that many small companies with

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great products may fall short of being approved under the LPAD Pathway, or any other pathway, because CMC and other implications that more experienced drug developers would know at the forefront would not be known. Thank you.

DR. COX: Great. Thanks for your comments, Dr. Furr.

MS. WALINSKY: Could I just ask a quick question, just to clarify? Are you suggesting a designation similar to the expedited programs?

DR. FURR: I imagine that in the case of some of these products, they will qualify for orphan drug designation, so there would be some regulatory incentives there once some clinical data is available, perhaps breakthrough therapy designation. So at that point, utilizing the incentives under a breakthrough therapy designation would make similarities under LPAD moot. But maybe all products that could be eligible for approval under the LPAD Pathway wouldn't qualify for all those other incentives.

Like in the case of Arikayce, they qualified for just about all, if I'm forgetting something, of the

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regulatory incentives, so that was great for them. But perhaps having some of the wording specifically for that type of incentive, associated with the pathway in the guidance, would be helpful for publicity; press release purpose, if anything, to perhaps get some investors more interested -- just going on a tangent -- in knowledge of the full drug development process.

MS. WALINSKY: Thank you.

DR. COX: Great. Thanks. And just one other comment, too, that rings true as we've seen it a few times. That is when you're undertaking a more expedited clinical development program, it's really, really important to let the CMC folks know this. The timelines that they'll need to be working under are different, and the stability data that they need to gather and all the other things that need to be in place.

So you don't want to surprise your CMC people. We've seen a few surprised CMC people. So as a public service announcement --

(Laughter.)

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DR. COX: -- I just sort of reiterate that comment.

DR. NAMBIAR: If I can just add to that, actually even in the pre-IND process, we encourage sponsors to come and talk about the CMC aspects of their programs. We're open to the idea of having those discussions very early in the drug development process.

MS. TIERNEY: I guess I also would just put in a plug for a number of CBER-specific programs related to early interactions with sponsors, like our INTERACT program, which is a pre-IND meeting program, as well as we just launched an advanced manufacturing technologies team that might be relevant to some of your clients.

DR. COX: Great. Thanks, Julie.

Our next speaker, since we didn't get you to sign up, if you can state your name and any affiliation you have, we'd appreciate that.

DR. YOUNG: Sure. My name is Lih Young. I'm a PhD in economics by training, and I am a former advocate and activist. I've run for public office since '94, including Rockville city mayor, Maryland State Senate, and several times for U.S. Congress, and

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other several times, U.S. Senate, Congress. House of Representatives and Senate are different.

I'm really concerned about our society and also concerned about the patient and population safety. I have seen very often our government agencies spend a lot of time and effort doing a lot of things for development. That is good, but on the other hand, our society is getting sidetracked and is very dangerous to our consumers and patients.

Even a healthy person can be kidnapped to the hospital for some kind of medication, and there is no way our system is working for those people who are involuntarily admitted to hospital, especially. Some doctors put medication, or injection, or whatever, on the patients, or ask the patient's family to administer something over the counter or whatever. The patient and family do not agree, especially if it's a big jug [indiscernible] or liquid administered by the physician only. But the staff says you must do it, something of this sort.

Involuntary admission to the hospital, the physician would say you have some kind of disease, so

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you have to take this medicine or we'll inject forcefully. It even goes through the core procedure or administrative procedure. The problem, especially, is [indiscernible] will not give the administrative record -- medical record, or will not give the label or the prescription, and will not give maybe the wrapper or something, and a special injection forcefully. They have several people bind together and grab the patient and still injecting something, and in the hospital, sometimes the injection makes you unconscious.

For all these things, they don't do release the instructive wrapper [indiscernible], and the cost is outrageous, obviously, and they charge it to Medicaid, or Medicare, or whatever. That doesn't make sense because they just profit off of people.

There's nowhere to complain and have the agency address these type of issues. I just hope FDA is concerned about our health and about medication. I think it's very important if you can have extra effort in this area. I have been trying this for decades, and it seems to go nowhere. I see a lot of patients, especially the elderly, a happy couple, elderly, or a

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happy family, and they have an outstanding family life, and if you destroy their family life, in society, it is meaningless.

DR. COX: Thank you. I understand your comments and your concerns, and we appreciate them. With regards to clinical trials, all clinical trials need to be ethical. There needs to be informed consent, and the patients enrolled need to be monitored.

DR. YOUNG: I have also a question about data, because all the data I see, it doesn't meet accountability as the first step. The government agency, whatever, there is some kind of conspiracy together. And every time you want to predict something, they have a government attorney and police officer, and there's some kind of conspiracy together. Even in the court, they have social workers as a false witness.

DR. COX: We appreciate your comments. Why don't you and I talk a little bit more after the meeting closes? Okay?

DR. YOUNG: I had something to present to the

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FDA before, but I got an adverse action against me. I'm here again. I'm free of my life. I'm here, really, as a dead man crusading.

So I would like for maybe you give me a website, and I present you something, records, and see if you can work on it.

DR. COX: I'm happy to do so. We'll do so after the meeting.

DR. YOUNG: Thank you.

DR. COX: Thank you for your comments. Katie, did you want to address a question from the Web or how did you want to handle that?

Katie, did you want to address a question from the Web, or how did you want to handle that?

We had one question come in from the Web that I'm aware of, and I think Katie's going to address it for us.

MS. SCHUMANN: Yes, that's fine.

From a Mr. Patrick Sweeney from the Web, we received one question via the webcast. He asked, "If otherwise satisfying all requirements, we'll a currently available antibiotic delivered in a new

unapproved manner for this specific patient population be able to use this pathway?"

I think that question is asking about approved drugs and whether an already approved drug could be eligible for the LPAD Pathway. The answer to that question would be yes. If a drug is already approved, the LPAD Pathway could be used if the drug is studied for a new use that is intended for a limited population.

Obviously, our one example, Arikayce, amikacin, was already approved, so there's nothing that would preclude an already approved drug from seeking approval via this pathway. And that was the only question we received via the webcast. Thanks.

Closing Remarks - Edward Cox

DR. COX: Great. Thanks, Katie.

I want to thank all the folks that joined us here today. I want to thank all of our speakers and for all that joined via the Web, too. We see the folks here. We know there are a number of folks out there who are also listening via the Web.

This is a really challenging and important

area of drug development, so we're grateful every time we see all the folks that are continuing to endeavor to bring new products that are safe and effective out there to patients. The need is there. The challenges are considerable. The economic issues are large. So we really do appreciate all of you continuing to work in this field and continuing to roll your sleeves, working with us to try and advance what really are some challenging development areas.

Just a couple of other things I want to mention, too. We did have up on the slides that the docket is open, and it's available for submitting comments through August 12th. We will certainly take into consideration all the comments that we've received so far submitted to the docket, the comments that we received here at the meeting today, and then also anything additionally that you'd like to submit. We'd like you to get those in prior to August 12th, if you can.

Beyond that, I just want to say thank you to all the folks who made the meeting possible today and all the work that went into bringing folks together,

for all of you all that have traveled here today, too, and taken time out of your busy schedules to join us and provide us with your comments.

We look at this as sort of another piece of the puzzle, if you will, the many pieces that need to come together in order to have a successful development enterprise, and we look forward to working with all of you in the future, and safe travels back home.

So thank you very much for joining us today, and the meeting is adjourned. Thank you.

(Applause.)

(Whereupon, at 11:39 a.m., the meeting was adjourned.)

Okay.

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