

*Food and Drug Administration
Public Meeting - LPAD Pathway*

July 12, 2019

*A Matter of Record
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12 Friday, July 12, 2019	12 Public Presentation
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1 C O N T E N T S	1 P R O C E E D I N G S
2 AGENDA ITEM PAGE	2 (9:01 a.m.)
3 Introductions and Opening Remarks	3 Introductions and Opening Remarks
4 Edward Cox, MD, MPH 4	4 DR. COX: We're at 9:00, so we'll go ahead and
5 Public Presentation	5 get started. Welcome to everybody who's here joining
6 John Rex, MD 22	6 us in person, and also to all those folks that are
7 Questions 31	7 joining us via webcast. Welcome to the LPAD Pathway
8 Public Presentation	8 Guidance public meeting.
9 Thomas Walsh, MD, PhD 37	9 I think to start out, what we'll do is we'll
10 Questions 48	10 have the folks on the panel here introduce themselves
11 Public Presentation	11 so you know who's up here, and we'll start with Sarah.
12 Phoebe Mounts, PhD 52	12 MS. WALINSKY: Hi, everyone. My name is Sarah
13 Questions 60	13 Walinsky. I am a policy advisor in FDA's CDER and OND.
14 Public Presentation	14 MS. TIERNEY: Hi there. Julie Tierney, senior
15 Colin McGoodwin 62	15 policy advisor for strategic planning and legislation
16 Questions 69	16 in the immediate Office of the Director and Center for
17 Public Presentation	17 Biologics.
18 Jack Mitchell 70	18 DR. ADEBOWALE: Good morning. My name is
19 Questions 77	19 Abimbola Adebowale. I am the associate director for
20	20 labeling in the Division of Anti-Infective Drug
21	21 Products, in the Office of New Drugs.
22	22 DR. COX: I'm noticing, too, that to pick up

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

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

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

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1 front. That way we'll know how many people are
2 interested and be able to call people up who are
3 interested.
4 Just a little bit of background with regards
5 to the LPAD Pathway. Most people are probably
6 familiar, but it was established under the 21st Century
7 Cures Act, which was signed into law in December of
8 2016. As a part of the requirements under the LPAD
9 legislation, one of the things that we were required to
10 do was to put together a draft guidance describing the
11 LPAD Pathway. Our draft guidance, which
12 published -- help me here, guys. Was it -- June of
13 2018. Thank you.
14 So June of 2018 was the date when the draft
15 guidance published and is out there for comment. We
16 got a number of comments. We always appreciate the
17 comments, but one of the things that became apparent as
18 we looked at the comments was there were a lot of
19 requests to have a meeting to talk about this. We
20 thought the best way to do this would actually be to
21 get everybody together, have a public meeting, and that
22 way, you all get to hear each other's comments, in

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1 essence, and there will be an opportunity for
2 discussion.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 got a patient population that has a serious infection
2 and few treatment options available. That's one side
3 of the equation, if you will.
4 The other side of the equation, I think which
5 is always important to keep in mind -- we talked about
6 how the standards still need to be met -- is there's a
7 line in the draft guidance document that essentially
8 says that the LPAD pathway should also not be used to
9 salvage a trial that fails to demonstrate its objective
10 or an inadequately designed development program. We
11 still need to meet the standard. We're just able to
12 look at the benefit-risk overall and take into
13 consideration the degree of unmet need and how we're
14 evaluating risks and benefits.
15 Some of the conditions that come along with
16 the LPAD Pathway, if that is the pathway upon which a
17 drug is -- if that's part of the approval of a drug,
18 the labeling has to indicate that the safety and
19 effectiveness has only been demonstrated with respect
20 to the limited population. And again, this gets back
21 to this inherence of how we're weighing the benefits
22 and risks in the setting of an LPAD approval.

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1 The advertising and labeling will include a
2 limited population in a prominent manner. I'll show
3 you an example of this in just a minute. The
4 prescribed information [inaudible - mic fades] contains
5 the statement, "This drug is indicated for use in the
6 limited and specific population of patients."
7 So it really is to call to attention where the
8 benefit-risk has been found to be appropriate. The
9 promotional materials, there is a requirement for
10 pre-submission of promotional materials at least 30
11 days prior to the dissemination of such materials. As
12 far as examples of development program, that may follow
13 a streamlined approach.
14 A lot of the thinking on streamline approach
15 because of the necessity of getting something out there
16 to address the issue of antimicrobial resistance,
17 patients who have really few treatment options, was
18 captured in our antibacterial therapies for patients
19 with an unmet medical need for the treatment of serious
20 bacterial diseases guidance document.
21 This document really talks about this key
22 issue of benefit-risk and how to weigh benefit-risk and

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1 the acceptance of greater degrees of uncertainty in
2 looking at development programs. What we describe in
3 there are clinical trials using noninferiority designs,
4 including a single noninferiority trial at a body site
5 of infection, or use of a wider noninferiority margin
6 than used in a traditional development program.
7 These by nature would be smaller trials,
8 trials of which there would be greater uncertainty with
9 regards to the overall findings, both efficacy and
10 safety, but recognizing the benefit-risk would be a
11 reasonable tradeoff to allow for availability of a
12 product in a patient population where there may be a
13 particular degree of unmet need.
14 Other options, clinical trials using
15 superiority design, always a clear demonstration of
16 efficacy; from a practical standpoint, oftentimes very
17 difficult to achieve. Implicit in this is that the arm
18 over which your superior, in most instances, has
19 probably received therapy that may be less than ideal
20 or less than fully effective, a situation that ideally
21 we'd like to avoid.
22 Nested noninferiority superiority clinical

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1 trials; this allows you to enroll patients, then based
2 upon their baseline susceptibility characteristics to
3 look at the population of patients with susceptible
4 organisms in a noninferiority approach; to look at
5 those who may have resistant organisms, resistant to
6 the comparator, could be looked at in a superiority
7 design. So it allows you to enroll, essentially,
8 all comers, and then have a prespecified bona fide way
9 to deal with the analysis population, looking at the
10 overall patient population.
11 The experience, as I mentioned, with the LPAD
12 Pathway to date really is limited. We have one
13 approval today, Arikayce, that used the LPAD Pathway,
14 and I'll mention a little bit more about this in the
15 next slide. We currently receive inquiries on ways to
16 utilize the LPAD Pathway for NDAs.
17 We recognize that this is an area where there
18 is a thirst for additional information, and we're
19 hoping to give a little more through the talk today and
20 through some of the discussion that happens today.
21 Also, the comments we get today will be helpful as we
22 revise the guidance document to help us to determine

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1 other issues where additional information could be
2 helpful to developers in the field.
3 One of the main issues we've seen with
4 sponsors seeking approval under the LPAD Pathway is the
5 issue of the standards. The standards for approval
6 under the LPAD Pathway don't change,
7 Subsection 506(h)(1)(b) of the LPAD provision, and
8 states that the standards for approval under Section
9 505(c) and 505(d) of the standards of licensure under
10 Section 351 of the Public Health Service Act, as
11 applicable, are met.
12 So it's important to keep that in mind. We
13 still need to understand that the product works and
14 that the product is safe and effective. If you think
15 about it, it's a pretty reasonable thing to do because
16 these are patient populations with serious infections
17 who need effective therapies that are safe, so it's
18 trying to strike that balance.
19 A little bit of background information on
20 Arikayce, amikacin liposome inhalation suspension, was
21 approved in September of 2018 in adults who have
22 limited or no alternative treatment options for the

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1 treatment of MAC lung disease as part of a combination
2 antibacterial drug regimen in patients refractory to
3 other treatment regimens.
4 You can see from looking at the indication
5 that it's a well-defined limited population. These are
6 patients with MAC lung disease who are refractory to
7 other treatment regimens, so they've essentially not
8 responded to other treatment regimens, clinically
9 definable and limited in a specific group of patients.
10 There was substantial evidence of
11 effectiveness provided on a surrogate endpoint that led
12 to the approval under accelerated approval. This shows
13 you two things; one, that there was a finding of
14 substantial evidence of effectiveness and also that
15 LPAD can work with the other pathways.
16 In this case, it was accelerated approval. It
17 went as an LPAD approval, that there was an acceptable
18 level of uncertainty given the seriousness of the
19 condition and the degree of unmet need for patients
20 with refractory MAC who are in need of other effective
21 treatments. This seemed to be an acceptable level of
22 uncertainty.

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1 Also, too, recognizing that without providing
2 this clarity with regards to the patient population,
3 there was a significant potential for broader use of
4 the indication where benefit-risk had been found to be
5 acceptable and was not clearly described and
6 essentially called to the attention of folks out there.
7 A couple of other pieces that went into the
8 overall calculus, if you will, there were respiratory
9 adverse events observed in the clinical trials, and
10 then also a relatively limited safety data set. So you
11 can see how this fits pretty well into what we're
12 talking about when we start to look at the provisions
13 of the LPAD legislation.
14 The risk-benefit was considered favorably only
15 for the limited population of patients as described in
16 the indication. The little blue link there at the
17 bottom provides the link to the summary basis approval
18 on the FDA website. The FOI documents are available,
19 so you can find additional details on the approval
20 there.
21 I will flip to the labeling, and this is just
22 to give a preview of some of the parts of the label

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1 where we would include specific labeling. You'll see
2 at the very top, on the left there, under the initial
3 date of approval, the words "LIMITED POPULATION" in all
4 caps, and I think also bolded if my screen is helping
5 me to understand the font there; limited population
6 highlighted in yellow.
7 In the indication and usage, again in the
8 highlight section, you see limited population again
9 before the indication. The language at the very bottom
10 is, "Only limited clinical safety and effectiveness
11 data for Arikayce are currently available. Reserve
12 Arikayce for use in adults who have limited to no
13 alternative treatment options. This drug is indicated
14 for use in a limited and specific population of
15 patients." So again, in the spirit and providing
16 clarity with regards to the patient population for whom
17 the drug is indicated under the LPAD approval.
18 Next steps, we're currently working on
19 finalizing the LPAD Pathway draft guidance. The
20 comments that we received to the docket have been
21 helpful to us. We certainly expect that today's
22 meeting will also provide us helpful feedback as we

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

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

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

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

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1 actually helping everybody else realize this is a place
2 where risk-benefit has really been carefully balanced.
3 Don't do this without understanding the population.
4 Yes, it's always been there, but now we're actually
5 putting a sticker on our forehead that says pay
6 attention to this, and that's different. LPAD also
7 tells us the settings in which this is true, and then
8 it gives us that language. As I said, the limited
9 population. I had to laugh at how many times it said
10 it in the top 2 inches of that document.
11 If you put that with the other things that are
12 in 21st Century Cures robust stewardship programs and
13 CDC's ongoing surveillance, we can be comfortable that
14 LPAD agents would be used wisely; I will say at least
15 most of the time. There's always somebody who goes off
16 piece, but by and large, this collectively will cause
17 the agent to be used in an appropriate fashion.
18 What are the problems that antibiotic R&D 3.0
19 has to solve? Well, it's really about rare situations.
20 It's about rare pathogens, just for resistant
21 pathogens, less common infections, and the issues
22 reduced to study size in how we think about this very

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1 important phrase, "substantial evidence of efficacy
2 based on adequate and well-controlled trials."
3 That series of adjectives: substantial,
4 adequate, well controlled, there is nowhere where
5 there's a number attached to that. Nowhere does it say
6 this means an alpha 0.5; this means in a margin of
7 10 percent; this means a particular endpoint; or this
8 means concurrent randomized controls.
9 As that as clearly stated, and the FDA has
10 been working for a substantial period of time to talk
11 about ways you use flexibility within those zones, we
12 are permitted, we are encouraged, and we are required
13 to consider risk-benefit. But if you wind it back to
14 the gift of LPAD, we can now say it in a way that's
15 unambiguous. "When we've done this, this drug is not
16 to be used for the ordinary circumstance. Please do
17 not prescribe it from Walgreens."
18 Ed commented on the different kinds of trial
19 designs that are possible, and let me just say that
20 superiority is an important tool to have available.
21 It's always nice to do it if it's an appropriate
22 setting. But in any infection, superiority is not a

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1 good answer. Antibiotics do something unusual relative
2 to essentially all the other diseases that we treat.
3 They cure you. If I treat your myocardial infarction,
4 you walk away still having heart disease. If I treat
5 your pneumonia, you walk away without pneumonia, and
6 you live another 60 years.
7 If it's easy to run a superiority
8 trial -- given the endpoint as curative, if it's easy
9 to run that trial, something terrible has happened in
10 public health. Resistance must be so common that a
11 good choice did not exist because I was able to
12 not -- there was a group who did not get an effective
13 therapy. Except for the mildest of infections, a
14 superiority result in this area, antibiotics and
15 antifungals, means that someone got hurt or may have
16 died who didn't have to have that outcome.
17 So we want superiority trials to be
18 impossible. We can write them down on paper, but we
19 want them to effectively be impossible. And if
20 superiority is briefly possible due to a gap, the first
21 drug that fills that gap eliminates the possibility of
22 using that pathway again.

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1 Noninferiority designs have to be our main
2 tool. They work, and they enable drugs to be developed
3 now, and we as a community have to be repeatedly very
4 clear about this in our documents. Yes, we're going to
5 lay out the idea of superiority. No, we don't expect
6 you to do it other than an extremist. Everybody has to
7 be saying that. The regulators, the professional
8 societies, we all have to explain to each other why
9 we're not doing more, because it's not just a
10 regulatory problem. We're all part of this problem.
11 It's easy to be critical and ask for more. Everybody
12 does it.
13 Agencies are just the first group to ask these
14 questions, but the physicians will say, "I want the
15 guidelines to change." The payers will say, "Where's
16 my superiority data?" See above. Patients will say,
17 "Noninferiority sounds so dodgy. My doctor didn't
18 understand it anyway, so I don't like that."
19 This is a communication and education problem.
20 There's confusion and debate on the scientific
21 principles, and we must clarify this in public because
22 we have to bring everybody along with us. It's not

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1 enough to solve the problem in one corner. We have to
2 explain to the entire community why this is the
3 solution that works, not something else. You can't
4 keep wishing for a magic pony to come and carry this
5 problem away. It doesn't exist. We have to work with
6 the existing tools. By the way, in passing,
7 nontraditional agents face the same issues. We have a
8 paper in press on that in Nature Communications.
9 Here are my suggestions. We're preparing here
10 for the future. When the real crisis emerges, it will
11 be too late. For the agency, convene some working
12 groups. FNIH has been a good mechanism to develop
13 credible pathways for rare infections.
14 Engage with the tradeoffs to create and
15 publicize feasible pathways. We must use LPAD to
16 expand what is now approvable. The agencies and the
17 professional societies have to spread the word.
18 Noninferiority is not a synonym for worthless, and an
19 infection superiority comes at a huge societal cost.
20 Professional societies, get with it with the
21 guidelines. It is not acceptable to update them once
22 every 10 years. They need to be updated every year

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1 electronically online. As an example of this, colistin
2 as a systemic agent needs to cease being used in the
3 United States this afternoon. It doesn't work.
4 Industry, this is an important message, and
5 it's not about LPAD specifically, but it's saying that
6 you, we in industry, have to be focused on novel agents
7 that really move the needle. There is a need for some
8 other stuff to happen. This LPAD is only one part of
9 the ecosystem fix, but the need for pull incentives is
10 not a discussion for today. This is about FDA and its
11 regulatory powers.
12 In any future pull mechanism -- and we are
13 going to see them happen, and one is coming in the UK,
14 it's very exciting, and we think one might happen in
15 the U.S. -- not every antibiotic is going to qualify
16 for one of these interesting incentives. It has to be
17 something that really moves the needle. Also, as Ed
18 pointed out, LPAD is not a salvage tool for a drug that
19 almost does nothing. It's for specific settings.
20 So in close, at heart, I am a doc who moved
21 into industry in 2003 because of the problem of AMR. I
22 once closed an ICU and shut down the upstream ORs

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1 because of an outbreak of a then untreatable infection.
2 These are big problems. There was a thing yesterday on
3 the radio about some nursing home in the area that had
4 a bunch of people get sick with a respiratory illness,
5 probably some virus.
6 Infections are scary, and since then, I have
7 had the opportunity to walk all the sides of the
8 challenge of antibiotic R&D. I've done everything
9 from large too small. I have dealt with corporate
10 decision-making, the pressure of time, supply chain,
11 shutting down, lyophilizers. You have to live all
12 sides of this to understand the peace.
13 Tradeoff-free solutions do not exist. If they
14 did, we would be using them. Since they don't, as a
15 community, we have to find pragmatic solutions to
16 real-world problems, and we need to do that this
17 afternoon. Thank you.
18 Questions
19 DR. COX: Great. Thanks, John.
20 Any questions for Dr. Rex from the panel?
21 DR. NAMBIAR: It's more than a question; it's
22 just a comment. I think on slide 9, you referred to

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1 the focus must be novel agents that clearly move the
2 needle. I would like to hear your thoughts on the
3 novelty from a standpoint of seeing a new mechanism of
4 action versus a novelty that should actually translate
5 into a meaningful benefit for patients.
6 DR. REX: Yes. Novelty here clearly has to be
7 something that's ultimately perceptible in the clinic,
8 and it could be that it's a novel mechanism of action.
9 It wouldn't necessarily have to be, I suppose. This
10 has come up a lot in the discussions of the pipeline
11 reviews.
12 If you look at the paper from 2018, the third
13 [indiscernible] WHO pipeline review, where we went to a
14 lot of trouble to categorize new agents by the quality
15 of the innovation in them. The need for people
16 developing another same-as has a barely perceptible
17 increment over other things. That's something perhaps
18 we used to do, but that's just not going to work
19 anymore. If we're going to put new incentives in
20 place, they're not going to apply to compounds that
21 don't offer something where we can really see a sharp
22 differentiation.

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1 I'll also say something that is obvious, which
2 when you think about it, the bigger the impact of the
3 new thing, and the more it moves you from where you
4 were to a new level of efficacy, the easier it is in a
5 small program to demonstrate some of that value; even
6 if what you're doing is a noninferiority comparison.
7 The math all just becomes that much easier and that
8 much stronger if your compound has a strong effect.
9 DR. NAMBIAR: Thank you.
10 DR. COX: So maybe I'll ask one. It sounds
11 like, John, you're thinking that noninferiority is
12 still going to be an important staple of drug
13 development. So that overall patient population may
14 include patients who don't necessarily have the degree
15 of unmet need that we're targeting or hoping to be able
16 to address to some extent.
17 This sounds very much in line with some of the
18 tenets of LPAD, and I just thought it might be good
19 just to talk about this for another minute or two. So
20 you're studying perhaps a patient population that's
21 sick, some of whom have the targeted unmet need, but
22 not necessarily everybody because you need to have a

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1 patient population who can be treated with a
2 comparator. But at the end of the day, the
3 risk-benefit is being evaluated for that patient
4 population for whom there is unmet need in order to be
5 able to have the more streamlined development program.
6 Any comments on that? Is that the way you're
7 looking at it, too? It feels like that's the
8 underlying tenet or principle as one of the key
9 components to the LPAD sort of concept, if you will.
10 DR. REX: It is. And I think, to say it back,
11 you're noting that the data that lead to approval might
12 include people who, after approval, wouldn't be in the
13 limited population, and that's true. I think there you
14 get into the whole ethics of clinical trials.
15 The Nature Communications paper that's coming
16 out now has a long section. We worked with three
17 ethicists to talk in great length about why it is
18 appropriate to do that sort of thing. All of us are
19 potentially tomorrow's patients. There are lots of
20 reasons for people to be involved in this. There are
21 ways to do these things that are entirely appropriate
22 from an ethical perspective. I think that if we don't

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1 engage, then you're committing the other sin of waiting
2 until it's really easy to study the bad organism, and
3 then things are even worse, and then it becomes
4 complete chaos.
5 There's clearly a societal tradeoff to be
6 made. We as a society have agreed that clinical
7 development is an appropriate thing to do. We have
8 mechanisms for enrolling people, for protecting their
9 safety, for being sure that they understand what
10 they're getting into, and we've clearly demonstrated we
11 can do these kinds of studies in a way that makes good
12 sense.
13 I recognize that tension, and yet it's part of
14 what we have to put out in public because there are
15 people who will not see all the pieces of it. This is
16 part of the conversation here, is to bring all the
17 stakeholders together, and get everybody to, if you
18 will, argue a little bit together and educate across
19 stakeholder communities about why this is the solution,
20 that there isn't some other magic way out. There is
21 not some tradeoff-free solution that makes this all go
22 away.

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1 DR. COX: Maybe one other area to comment on
2 is that if in fact the patient population in the trial
3 is not exclusively those patients with unmet need, then
4 that gets to the question of what's the scientific
5 relevance of that information to the group of patients
6 with unmet need and in whom the drug would be indicated
7 and used, and bridging that gap scientifically.
8 I don't know if you wanted to comment on that
9 at all.
10 DR. REX: I think that group obviously
11 contributes to the safety database for understanding
12 and contributes to the efficacy demonstration as well.
13 We have this funny problem with antibiotics that we
14 define the idea of multidrug resistance, and we say
15 we'd like to know how it works when the pathogen is
16 resistant to these other things. But it's also helpful
17 to know how it works when it's susceptible to this
18 thing.
19 If you've got a pathogen that's susceptible to
20 this thing, you've actually contributed to an
21 understanding that it will work when the pathogen is
22 susceptible to your test agent, and you can compare

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1 that to patients who could have been treated another
2 way, which is the population that isn't LPAD, and the
3 patients who could not have been treated another way.
4 So it really does build your entire data set,
5 but the more you can focus on the people who have the
6 specific requirement, you also prove, by identifying
7 them, that you can identify them. That's the other
8 thing you get out of attempting to do that.
9 DR. COX: Thank you, Dr. Rex.
10 DR. REX: Thank you.
11 DR. COX: Now, we'll move to our next speaker.
12 I want to welcome Dr. Thomas Walsh, professor of
13 medicine and pediatrics, microbiology and immunology at
14 Cornell University, to our podium.
15 Thank you, Tom, for joining us today, and we
16 look forward to your comments.
17 Presentation - Thomas Walsh
18 DR. WALSH: You're most welcome, and thank you
19 so much for joining us all here today. Our mission
20 within our program is very much akin to that of many
21 others, and that is to save lives and advance knowledge
22 in this critical field.

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1 For the past four decades, my staff and I have
2 cared for -- and we're looking at these recommendations
3 for a perspective of caring -- pediatric and adult
4 patients with invasive mycosis on a daily basis,
5 conducting as well the laboratory and clinical research
6 in invasive mycosis, which has led to our understanding
7 or approval contributing to that of 12 licensed
8 systemic antifungal agents; as well as having studied
9 multiple other investigational agents; and personally
10 serving as PI or associate investigator on more than a
11 hundred clinical protocols.
12 From that perspective, I am privileged to
13 serve as a Henry Schueler Foundation Scholar in
14 Mucormycosis; working with Save Our Sick Kids
15 Foundation; a perspective of long-standing work with
16 the mycosis study group; representing as well the
17 Medical Mycology Society of the Americas in multiple
18 forums; as well as now working with the European
19 Confederation of Medical Mycology; and most recently
20 serving as the founding director for what we call New
21 York City Cares, which is a New York City collaborative
22 consortium for Candida auris research.

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1 Fundamentally, why are invasive fungal
2 infections challenging to treat and what are the unmet
3 needs? We've witnessed major advances in antifungal
4 therapy during the past three decades, yet there is a
5 high mortality even when treated with these current
6 agents. We need to ask why; why do we see this? The
7 causes are related, in part, to delayed diagnosis;
8 secondly, to an ever-evolving challenge of
9 immunologically impaired hosts; limited therapeutic
10 options; and increasingly antimicrobial resistance,
11 some of which are intrinsic and some of which are
12 acquired.
13 Within the unmet needs of antimicrobial
14 resistance -- and I'll introduce a term here of RFIs.
15 We know IFIs, invasive fungal infections, but I think
16 we need to also think through resistant refractory
17 fungal infections. Candida auris, you understand quite
18 well. Aspergillus, trizaole-resistant pathogens,
19 although not so much a threat in North America at this
20 point, it is emerging as a very deadly threat in
21 several countries and now two continents in severely
22 immunocompromised patients.

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1 Mucormycosis still carries as much as an
2 80 percent mortality. Fusarium, which we'll come to,
3 is also a deadly lethal pathogen. Scedosporium,
4 lomentospora, virtually nothing available, and other
5 continued emerging hyaline and dematiaceous moulds.
6 With that, we appreciate there's an urgent
7 need for new antifungal agents similar to that of
8 antibacterial agents with novel mechanisms that will
9 especially hit and circumvent the mechanisms of
10 activity of many of the resistant organisms; improve
11 safety profiles; minimal drug-drug interactions; and
12 predictable pharmacokinetics without the need for
13 therapeutic drug monitoring, which is especially
14 important in our critically ill or complex
15 immunocompromised patients receiving multiple
16 medications and suffering as well from end-organ
17 dysfunction.
18 Then there's also the element of patient
19 convenience, providing we can see a way to discharge of
20 going from parenteral to oral formulations. And
21 speaking of oral formulations, it's noteworthy that the
22 emergence of resistance or persistence of resistance is

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

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

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

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

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

7 Mucormycosis carries, relentlessly, a lethality
8 of 40 to 80 percent in various studies. In our current
9 protocol-defined therapy, where we're obviously
10 selecting a more enriched population that might have a
11 better prognosis, still demonstrates as much as
12 60 percent mortality. This organism inflicts painful,
13 devastating, debilitating morbidity for the survivors;
14 yet the estimated number of cases are only 1 to 3
15 million.

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

22 If we look at *Fusarium*, usually this does not

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1 rise, but as we look at the breakthrough invasive
2 fungal infections and what is plaguing our patients in
3 the wake of successful treatment of *Candida* and
4 *Aspergillus*, this organism carries lethality varying
5 from 40 to 90 percent, depending upon the host.
6 Strains may be completely resistant to triazole and
7 amphotericin B.

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

16 *Scedosporium*, *Pseudallescheria*, *Lomentospora*,
17 these are resistant to amphotericin B and echinocandins, and
18 *Lomentospora prolificans* is completely resistant to
19 all three major classes. Prior to second-line approval
20 for voriconazole, vis-a-vis second *Scedosporium*, again, might
21 offer a potential new pathway, again, targeting these
22 pathogens under the LPAD concept. These are distinct

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 Questions

15 DR. COX: Thanks, Tom.

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

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1 shouldering on an additional study to the randomized
2 trial, with the additional study being focused on the
3 rare fungal pathogens that might be occurring in a low
4 frequency rate, which would make it much more difficult
5 to accrue the usual numbers of patients.
6 DR. WALSH: Exactly. I think doing that,
7 where one can target the specific pathogen, going to
8 specific centers where one can say we know there's a
9 burden of fusarium here, and we know there's a burden
10 of Candida auris here, you only have to look at the map
11 and target that versus -- although it's an excellent
12 concept of the noninferiority trial nesting in some of
13 the interest populations, it would be too random in
14 that regard to attract them.
15 So having those parallel studies, and
16 especially focusing on centers with both the population
17 and the expertise, with proper controls and so forth
18 and all the caveats of safety and efficacy, we could
19 understand the efficacy there, bolstered by the
20 preclinical data, and then one has a traditional
21 pathway where one can demonstrate, to the point that
22 we've discussed here, does the drug work in the wider

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1 range of pathogens, such as candidemia or
2 aspergillosis.
3 DR. COX: I'm hearing in your comments one
4 other thing that probably also deserves specifically
5 pulling out. You mentioned the idea of if you're
6 interested in studying a particular rare fungal
7 infection, that you might go to the centers where this
8 occurs. So there are certain areas in certain places
9 that we might be able to pre-identify, either based
10 upon epidemiology of the particular pathogen and/or the
11 patient population that might be susceptible, and where
12 they might seek their care.
13 DR. WALSH: Absolutely. We've undertaken
14 this. In New York, we've actually recruited in, as
15 serving a greater public need, patients that have had,
16 for example, allergic bronchopulmonary aspergillosis,
17 where the expertise may be minimal. We've had a
18 special area of expanding interest in expertise with
19 that, and patients have come in, and we've been able to
20 serve their needs.
21 Candida auris, it's in the same way.
22 Certainly in the greater metropolitan area, there's a

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1 burden, but even within that, there are certain
2 institutions that have garnered the expertise in
3 managing these patients.
4 That's part of New York City Cares, where
5 basically we're harnessing the expertise, as well as
6 bringing in the potential for not only new antifungal
7 agents, but also environmental control, understanding
8 statistical data, a granular database, of what are the
9 outcomes, and how do you manage these infections above
10 and beyond the great forensic work that CDC and New
11 York State Department of Health have done.
12 DR. COX: Thanks. Yes. So it sounds like
13 that could be an area where setting up or performing a
14 clinical trial could be ideal and have a greater
15 likelihood or chance of enrolling patients and being
16 able to study a drug.
17 DR. WALSH: Absolutely. And time is not on
18 our side. These are rapidly expanding. Just from
19 Candida auris, it's devastating to see the impact that
20 it's having on lives because we have, really, extremely
21 limited options.
22 DR. COX: Any other questions from the panel?

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1 (No response.)
2 DR. COX: If not, thank you very much, Dr.
3 Walsh.
4 DR. WALSH: Thank you.
5 DR. COX: We very much appreciate you joining
6 us and giving us comments today.
7 Next, I'd like to invite Dr. Mounts to the
8 podium. She's general counsel for CorMedix, and we
9 welcome your comments, Dr. Mounts.
10 Presentation - Phoebe Mounts
11 DR. MOUNTS: Thank you everyone, and good
12 morning. I'd especially like to thank Sarah Walinsky
13 and her colleagues at FDA for organizing the LPAD
14 meeting.
15 CorMedix is very supportive of LPAD, partly
16 because its lead product in the U.S. is the broad
17 spectrum, antimicrobial, taurolidine, that is designed
18 to prevent catheter related bloodstream infections.
19 The first indication for use being developed in the
20 U.S. is for use in central venous catheters in
21 hemodialysis patients.
22 CorMedix is a small company, and like many

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1 other small companies, there are limited resources, so
2 any programs from FDA that can help us get these
3 products to market faster and more efficiently is
4 greatly appreciated.
5 CorMedix believes that preventing catheter
6 related bloodstream infections in hemodialysis patients
7 is an unmet medical need for a limited population. On
8 this slide 3, we present some background information on
9 the limited number of hemodialysis patients, which has
10 been estimated at 420,000 in the U.S., who
11 unfortunately experience life-threatening infections
12 that develop from repeated vascular access through the
13 catheter.
14 Importantly, the Centers for Disease Control
15 and Prevention have documented many drug-resistant
16 pathogens in this limited population,
17 methicillin-resistant Staph aureus;
18 cephalosporin-resistant E. coli; vancomycin-resistant
19 enterococcus; and carbapenems-resistant enterobacter.
20 This is clearly a limited population in need of new
21 antimicrobial drugs.
22 Our specific request to FDA with respect to

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1 the LPAD guidance are summarized on this slide 4. I
2 will cover each of these requests in the following
3 slides. We think LPAD is a very important program,
4 both for industry but also for the public health, and
5 the guidance will be helpful if it elaborates on the
6 agency's current thinking on how to apply and implement
7 the intention of the legislation.
8 We appreciate the inclusion of products to
9 prevent life-threatening infections and think this is
10 valuable to the public health. The request we feel
11 most strongly about is making an affirmative
12 determination for eligibility for LPAD earlier in
13 product development.
14 We think that an exclusionary criterion about
15 using the LPAD pathway not being appropriate if
16 criteria for non-LPAD approval are met is not really
17 helpful. We request more information be put in the
18 guidance on the process and timing for review of
19 promotional material if a product is approved under
20 LPAD. And I suspect this final request will be
21 frequently repeated today and is clearly a topic of
22 discussion, which is to clarify the agency's current

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1 thinking on the streamlined clinical development
2 offered under LPAD.
3 We are grateful to FDA for issuing the LPAD
4 guidance, which was required under the 21st Century
5 Cures Act, and we think it will be most helpful with
6 some added specificity on how FDA intends to interpret
7 limited population; is there a number limit?
8 The language in the guidance suggests that a
9 healthcare provider needs to be able to identify
10 appropriate patients in the clinical setting. It seems
11 that as true for most product approvals and can be
12 covered in labeling and the indications for use. For
13 example, hemodialysis patients with a central venous
14 catheter seems to clearly define the limited
15 population.
16 The guidance seems to suggest that a physician
17 education program may be required. Certainly,
18 physician education should be a focus for antimicrobial
19 drug use, and if this is a reasonable development, it
20 would be helpful for sponsors to be made aware of this
21 so that materials can be developed earlier in the
22 product life cycle.

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1 Thank you for including prevention in the
2 definition of a drug to treat a serious or
3 life-threatening infection. I have public health roots
4 and training as a microbiologist, and that tells me
5 that we really have to prevent infections. Exposing
6 pathogens to antimicrobials applies a selective force
7 to develop drug resistance, which is really the central
8 issue here.
9 My strongest plea is to make the determination
10 for at least eligibility for LPAD earlier in drug
11 development. The time of approval is too late. How
12 can sponsors take advantage of a streamlined clinical
13 development program if the decision is not made earlier
14 than after phase 3? Sponsors and FDA need
15 predictability to allocate resources, and again, this
16 is especially important for small, innovative companies
17 with limited resources like CorMedix. More
18 importantly, the eligibility decision needs to be made
19 earlier to expedite the development of new
20 antimicrobial drugs, which is really the goal of the
21 LPAD program.
22 We respectfully request that FDA does not

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1 inappropriately limit the LPAD pathway to sponsors.
2 Congress created the pathway, and if a sponsor decides
3 to pursue the pathway and qualifies, it should be made
4 available.
5 The guidance states that copies of all
6 promotional materials related to the product must be
7 submitted at least 30 calendar days before
8 dissemination. We would appreciate more specificity on
9 the timeline for review and approval. The language
10 presumes feedback before 30 days, but that should be
11 made explicit.
12 On slide number 10, the heart of LPAD must be
13 the streamlined clinical development, and we will
14 request more specificity on the FDA's current thinking
15 on the available options. Can we use real-world
16 evidence? Are postmarketing registries or other data
17 collection options available to sponsors? The real
18 issue is integrating a phase 3 program with an LPAD
19 decision delayed until product approval. We are not
20 looking for a commitment on approval; just guidance on
21 realistic options during phase 3.
22 On slide 11 and the next few slides, we have

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1 some reactions to comments from FDA officials that give
2 us some concern, so we would like to understand the
3 thinking behind these comments. On their surface, the
4 comments suggest a lack of agency enthusiasm for LPAD,
5 which is concerning.
6 For example, risk evaluation should be no
7 different than any other approval when LPAD requires
8 substantial evidence of safety and effectiveness. Of
9 course, the statute says from clinical trial[s] with an
10 S on the end, and we think the streamlined clinical
11 development in LPAD provides the option for reducing
12 that to a single robust pivotal trial.
13 The agency has at its disposal existing
14 post-approval authority to monitor and identify risks
15 for any new drug approval, including REMS, adverse
16 event reporting, and the authority to impose
17 postmarketing studies. So it's not clear why this
18 should not be adequate for approval pursuant to LPAD.
19 On slide 12, agency officials have expressed
20 concerns about off-label use. Again, this is an issue
21 that is not unique to the LPAD Pathway and FDA has as
22 its disposal mechanisms to address off-label use. I

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1 agree that indiscriminate use of antimicrobials is a
2 major issue in this area, but that needs to be
3 addressed by educating physicians and not restricting
4 use of LPAD to sponsors.
5 We are also concerned that comments from
6 agency officials may suggest that new antimicrobial
7 drugs cannot be demonstrated to be safe and effective
8 in small trials. The main goal of LPAD, as we see it,
9 is to get antimicrobial drugs on the market as fast as
10 possible to address an unmet medical need, and we think
11 with assistance from FDA, the process can be made more
12 efficient under the LPAD Pathway.
13 Slide 14 summarizes the requests we are making
14 of FDA. We will certainly file these comments to the
15 docket, but we appreciate the opportunity to discuss
16 them today with you. If I had to prioritize the
17 requests, it would certainly be to make a determination
18 of eligibility for LPAD earlier in product development
19 for predictability for sponsors to maximize resources
20 for both sponsors, as well as FDA.
21 So in conclusion, CorMedix believes that LPAD
22 should be designed to facilitate antimicrobial drug

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1 development and should be available to help in the
2 battle to address antimicrobial resistance. This slide
3 just has some citations for information on the slides,
4 and the last slide is to thank FDA, and to thank you,
5 the audience, for your interest in LPAD.
6 Questions
7 DR. COX: Thank you, Dr. Mounts. I appreciate
8 your comments.
9 I'm looking to see if there are any questions
10 from the panel.
11 MS. WALINSKY: Yes. I have one quick
12 question. You spoke a little bit about prevention, and
13 we've been working on that section in the draft
14 guidance. I would just like to hear a little bit from
15 you about how -- we're trying to craft a limited
16 population. And if the condition is rare, the problem
17 is if you're preventing that condition, it might be
18 indicated for a larger population.
19 How would you narrow that to a limited
20 population? Could you speak to that?
21 DR. MOUNTS: Yes. I think that's a
22 particularly challenging problem for our colleagues in

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

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

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

18 DR. COX: Great. Thank you, Dr Mounts.
19 Any other questions for Dr. Mounts?
20 (No response.)
21 DR. COX: Thank you, Dr. Mounts. We
22 appreciate your comments.

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

4 Welcome, Colin.

5 Presentation - Colin McGoodwin

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

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

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

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1 therapeutics and lead antimicrobial stewardship
2 programs.

3 IDSA first sounded the alarm about the crisis
4 of antimicrobial resistance and the need to invest in
5 new antibiotic research and development in 2004. Since
6 then, IDSA has led efforts to advance policies to
7 stimulate new antibiotic R&D and promote appropriate
8 antibiotic use, including legislation to enact LPAD.

9 Today, IDSA underscores the importance of this pathway,
10 as the state of the antibiotic pipeline has grown even
11 more dire. We are also pleased to offer some
12 recommendations to strengthen the draft LPAD guidance
13 to expand opportunities for antibiotic R&D.

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

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

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

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

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

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

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1 market some of the most urgently needed new antibiotics
2 and promote their appropriate use.
3 IDSA supports the policies and processes
4 outlined in the draft guidance. We are pleased to
5 offer some recommendations that we believe will
6 strengthen the ability of the Limited Population
7 Pathway to bring new antibiotics to market with
8 urgently needed indications. To maximize the potential
9 of this new pathway, the use of novel trial designs
10 will be critically important.
11 Further, while noninferiority trials are often
12 most appropriate for studies of new antibiotics, some
13 of the small studies conducted under this new pathway
14 may not be amenable to noninferiority design. In
15 instances for which superiority designs would be
16 appropriate under the new pathway, the FDA should
17 consider using a p-value of less than 0.1 or another
18 less stringent value for type 1 error control if the
19 risk-benefit ratio is favorable.
20 In some instances, it may be appropriate to
21 include data from patients in other countries given
22 that certain multidrug-resistant pathogens may be more

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1 prevalent in other countries than in the United States.
2 It is important to remember that in addition
3 to new antibiotic approvals, the new pathway also
4 offers important opportunities to promote and monitor
5 appropriate antibiotic use via the statutory
6 requirements that drugs approved under this pathway be
7 clearly labeled as limited population and that their
8 use is monitored. By approving a new antibiotic for a
9 traditional indication and not a limited population
10 indication, the FDA may essentially forfeit these
11 valuable stewardship opportunities.
12 IDSA understands that approval for limited
13 population indications may not always be feasible or
14 appropriate for a sponsor seeking this route. In such
15 instances, the FDA should utilize other tools at its
16 disposal to incent antibiotic R&D and to provide
17 critically needed new treatment options.
18 Flexibility in the package insert language for
19 drugs and studies meeting the LPAD criteria but not
20 necessarily meeting FDA indications for approval in
21 that disease syndrome may provide a meaningful
22 incentive to drug sponsors and useful information for

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1 clinicians.
2 Package insert language is essential because
3 it informs clinical decision-making and governs sponsor
4 communications regarding its products. Even if a
5 sponsor cannot achieve a limited population indication
6 for a new antibiotic, IDSA recommends the sponsor still
7 be able to share its study data from use of the new
8 drug in patients with resistant infections.
9 Given our extremely limited antibiotic arsenal
10 and increasing rates of antibiotic resistant
11 infections, clinicians are frequently forced to rely
12 upon treatment options based on extremely limited
13 clinical or even in vitro data. In this environment,
14 additional data that could inform how a new antibiotic
15 may perform in a patient with a difficult to treat
16 infection would be very useful.
17 Finally, IDSA would like to emphasize that
18 LPAD plays a vital role in the broader national and
19 global fight against antimicrobial resistance, but much
20 more work is needed to foster the antibiotic pipeline
21 necessary to meet current and future threats and to
22 stem the tide of antimicrobial resistance.

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1 The FDA has an important role as a champion
2 within our government for broader solutions. IDSA
3 calls for antibiotic reimbursement reform and novel
4 pull incentives, such as a market entry reward, for
5 targeted urgently needed new antibiotics that address
6 our greatest unmet needs to ensure fair and reasonable
7 returns on investment for antibiotic R&D. We also
8 support higher investments in AMR research and clinical
9 trials networks.
10 Equally important, IDSA continues to advocate
11 for a federal requirement for all healthcare facilities
12 to adopt antibiotic stewardship programs that align
13 with CDC recommendations. We also support increased
14 funding for our public health system to address AMR.
15 Lastly, we urge a federal commitment to sustain the
16 expert workforce needed to effectively combat AMR on
17 all fronts, patient care, research, stewardship,
18 infection prevention and control, and public health.
19 Once again, IDSA thanks FDA for its continued
20 efforts to strengthen the antibiotic pipeline and
21 promote the appropriate use of these precious drugs.
22 Thank you.

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1 Questions

2 DR. COX: Great. Thanks for your comments,

3 Mr. McGoodwin.

4 Any questions for Mr. McGoodwin?

5 (No response.)

6 DR. COX: So maybe I'll just ask one. We

7 appreciate your comments with regards to LPAD, but the

8 problem that seems that we're facing here is fairly

9 considerable, and you talked about a variety of

10 different strategies to try and address this.

11 Certainly, we at FDA will continue to do all that we

12 can to support antimicrobial drug development.

13 Any additional thoughts that you have with

14 regards to other levers that could be pulled here that

15 might help out with regards to drugs that are targeting

16 particularly small patient populations? I'll also

17 throw out the idea of clinical trial networks, if that

18 was something you wanted to comment on, too.

19 MR. McGOODWIN: For more specific comments,

20 I'd want to make sure that I reached out to my members

21 first to make sure that I didn't say anything that

22 didn't align with what they were thinking when we put

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1 this together. But I think we've worked on a ton of

2 different incentives as an organization and different

3 ways to just move. Any type of anything that will

4 strengthen the antibiotic R&D pipeline, we are all for.

5 So anything in that regard, we greatly appreciate.

6 Thank you.

7 DR. COX: Thanks very much, Mr. McGoodwin. We

8 appreciate your comments.

9 Now, we'll new move to our next speaker,

10 Mr. Jack Mitchell, who's director of health policy at

11 the National Center for Health Research. Welcome, and

12 the podium is yours.

13 Presentation - Jack Mitchell

14 MR. MITCHELL: Good morning. Like Colin, I

15 have no visual aids, so I apologize in advance for

16 that. I'm Jack Mitchell. I'm director of health

17 policy, as Dr. Cox has noted, of the National Center

18 for Health Research. We are a nonprofit think tank

19 that conducts and analyzes research with implications

20 for public health and patient safety. NCHR accepts no

21 money from pharmaceutical and medical device

22 industries, so I have no conflicts of interest to

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1 report.

2 Unlike our other members of our distinguished

3 panel, I am not a medical or technical expert. My

4 comments reflect the medical and policy expertise of

5 NCHR. I'm probably not in a position to answer a lot

6 of technical questions, but I'd like to give a few

7 comments that we believe reflect the patient

8 perspective from the many patient groups that we

9 routinely interact with.

10 As your other experts have pointed out,

11 resistance to some antimicrobials has been growing and

12 is recognized as a serious and escalating treatment

13 threat for decades. The CDC has estimated that 23,000

14 people die annually from drug-resistant infections.

15 Other authoritative estimates have put the number much

16 higher.

17 As noted by Dr. Cox earlier in his

18 introductory remarks, partially because of this looming

19 health crisis, Congress created a limited population

20 pathway program for FDA as part of the much publicized

21 21st Century Cures Act, and the agency is required by

22 law to implement it. I think as Dr. Mounts has noted,

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1 however, there may be some confusion or some

2 clarification needed about congressional intent and

3 FDA's intentions in that regard.

4 FDA, I should say, should be commended for its

5 work in attempting to resolve a long-standing and

6 thorny medical treatment problem. The FDA and the

7 Centers for Medicare and Medicaid are seeking to come

8 to an interagency agreement on the difficult economics

9 of antibiotic and antifungal new product research,

10 which has lagged because of the limited population of

11 patients affected and the enormous expense of getting

12 new drugs approved. Nevertheless, this proposed

13 guidance raises some critical questions, which we

14 believe need to be addressed and which were reflected

15 in the written comments that we've previously submitted

16 to the docket.

17 A key issue is just having more drug with

18 options on the market does not necessarily always help

19 patients. One analysis of antibiotics approved between

20 1980 and 2009 found that 42 percent, or 26 drugs out of

21 61, were taken off the market due to poor sales, or

22 safety, or efficacy problems.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 Questions

21 DR. COX: Thank you, Mr. Mitchell.

22 Any questions from the panel for Mr. Mitchell?

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1 (No response.)

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

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

13 Then you're bringing up the important --

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

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

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

7 MR. MITCHELL: We believe, as I said, that
8 there needs to be some further clarification of
9 congressional intent. There was some controversy
10 involving the language in this regard, as I recall, in
11 the original stages of the 21st Century Cures Act.

12 And from Dr. Mounts' comments, it appears that some of
13 those discrepancies or misunderstandings may not have
14 entirely been resolved.

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

19 (Crosstalk.)

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

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

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

13 I think we have a question. Dr. Adebawale?

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

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1 I guess that was the intent of that comment,
2 because you have many types of labeling. I guess the
3 main concern was in terms of communicating the science
4 to the patient. --
5 MR. MITCHELL: Yes.
6 DR. ADEBOWALE: Okay. Thank you. Thank you
7 very much.
8 MR. MITCHELL: Yes, that was my intent. Thank
9 you.
10 DR. ADEBOWALE: Okay.
11 MR. MITCHELL: Thank you very much.
12 DR. COX: Thank you very much, Mr. Mitchell.
13 We appreciate you joining us here today and giving us
14 your comments.
15 Now our next speaker is Elizabeth Lovinger, a
16 government relations and policy officer at the
17 Treatment Action Group.
18 Elizabeth, thank you for joining us today, and
19 we welcome your comments.
20 Presentation - Elizabeth Lovinger
21 MS. LOVINGER: Thank you. Like the previous
22 speaker I'm presenting on behalf of the technical

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1 experts at my organization, so I'll do my best to
2 answer your questions should you have them.
3 Thank you to the U.S. Food and Drug
4 Administration for this opportunity to offer comment on
5 behalf of Treatment Action Group or TAG. TAG is an
6 independent activist and community-based research and
7 policy think tank, fighting for, among other
8 improvements, better treatments and a cure for HIV and
9 related comorbidities, tuberculosis, and hepatitis C
10 virus.
11 From our founding over 25 years ago, we have
12 understood that both ambitious research agendas and a
13 flexible but rigorous regulatory authority are
14 necessary for achieving these advances. TAG was
15 instrumental in advocating for the development of
16 accelerated approval and parallel track pathways, which
17 paved the way for earlier but conditional drug approval
18 in response to urgent unmet medical needs, as well as
19 preapproval access under the current expanded access
20 framework. These regulatory flexibilities were vital
21 to progress against the HIV epidemic. We are proud
22 that they have endured and been improved upon to allow

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1 similar progress in other disease areas.
2 Since then, other initiatives to stimulate
3 investment in neglected diseases, including orphan
4 drug, priority review, fast track, and breakthrough
5 therapy designations have been introduced. These
6 initiatives have had utility in facilitating product
7 development in at least the disease areas on which TAG
8 works. But we cannot ignore that pivotal to progress
9 on HIV, hepatitis C, and more recently tuberculosis has
10 been investment in rigorous research. We understand
11 the challenges of securing such investments, especially
12 for diseases of little commercial interest or with
13 limited or hard to enroll patient populations.
14 In our current work on TB, this is a problem
15 we face routinely, and let's not forget that HIV was
16 once a disease that no one paid attention to,
17 especially not pharmaceutical companies or their
18 shareholders. With existing incentives and regulatory
19 flexibilities, we are concerned that already the trade
20 of rigor for speed may compromise the FDA's ability to
21 ensure drug safety and efficacy and undermine equitable
22 access.

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1 For example, the Orphan Drug Act's exemption
2 for pediatric research means children, the most
3 orphaned of all when it comes to drug development,
4 don't benefit from advances that are made. We are
5 deeply concerned that further lowering the evidentiary
6 bar for regulatory approval will do a disservice rather
7 than a favor to patients.
8 At the core of FDA's mission is the
9 responsibility for protecting the public health by
10 ensuring the safety, efficacy, and security of drugs.
11 As professor Susan Ellenberg remarked at a recent FDA
12 hearing regarding a new anti-infective drug candidate,
13 people in these desperate situations are every bit as
14 entitled, if not more entitled, to have drugs where
15 there's a definitive evidence that they are going to
16 work.
17 We support the remarks submitted by the
18 National Center for Health Research and the questioning
19 by survivor Jonathan Furman on safety issues that could
20 come under the Limited Population Pathway for
21 Antibacterial and Antifungal Drugs. If the FDA does
22 decide to go ahead with this pathway despite these

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

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

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

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

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

15 Questions

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

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

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

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

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

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

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

3 DR. COX: Any other questions? Sumathi?

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

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

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

19 DR. NAMBIAR: Thank you.

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

22 MS. LOVINGER: Yes.

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1 DR. COX: -- and getting quality evidence
2 helps to understand how the product works.
3 MS. LOVINGER: Yes. I think to clarify from
4 the standpoint of drug-resistant tuberculosis, there
5 are treatments currently that have an efficacy rate of
6 50 to 60 percent. I think we were particularly
7 concerned when we saw language about widening
8 noninferiority margins.
9 If for instance there is a wider
10 noninferiority margin of let's say 12 percent, then you
11 could have a new standard of care that has an efficacy
12 rate, from our current standard, say 38 percent. Then
13 if that drug then becomes a new standard of care, there
14 is a risk that you're allowing another drug to enter
15 the market that has an efficacy rate of 26 percent. So
16 I think from the standpoint, particularly of
17 tuberculosis, that's a serious concern that we have.
18 DR. COX: Great. Any other questions?
19 (No response.)
20 DR. COX: Great. We thank you for your
21 comments, and thanks for joining us here today.
22 MS. LOVINGER: Thank you.

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1 DR. COX: Our next speaker is David Angulo,
2 who's the chief medical officer at Scynexis, who I
3 believe presenting on behalf of BIO.
4 Did I get that correct?
5 MR. ANGULO: That is correct.
6 DR. COX: Great. Thank you, David.
7 MR. ANGULO: Thank you.
8 DR. COX: We appreciate you joining us here
9 today.
10 Presentation - David Angulo
11 DR. ANGULO: Thank you. Thank you for the
12 invitation, and thank you for allowing us to present
13 here, and thank you for really organizing this meeting.
14 I'm David Angulo. I'm the chief medical
15 officer of Scynexis. As a disclosure, we are
16 developing an antifungal agent, so you're going to see
17 my talk really focusing on how LPAD could be applied to
18 antifungal agents and why we believe it's a very
19 important tool that we need to -- it's extremely
20 important to refine as much as we can so that we all
21 can take advantage of that, the public and all the
22 physicians that really need these drugs.

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1 Why do we believe that LPAD applies fully to
2 antifungal products? And thank you for the previous
3 speakers that really have paved the way for this talk
4 to be relatively easy for me. But certainly, there are
5 serious and life-threatening fungal infections that
6 have very, very high mortality. I don't think that
7 there is a doubt that we check that box. Many fungal
8 infections are serious and life threatening. Examples
9 have been provided, but here are some of them.
10 Candida, these infections may have mortalities
11 reported up to 60 percent; azole-resistant and invasive
12 aspergillosis with mortalities up to 50 percent.
13 Serious fungal diseases, failing or intolerant to
14 existing therapies, they have mortalities close to
15 30 percent. Rare fungal infections like scedosporium
16 and fusarium infections, mortalities are higher than
17 50 percent.
18 So it's clear that there is, even with current
19 therapies, a very substantial unmet medical need, and
20 this is with current available therapies.
21 These infections occur in a limited
22 population. They are not very common. They are rare.

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1 Those patients are easily identified by healthcare
2 providers because typically they are diagnosed via a
3 culture, a biological marker of this particular
4 disease, sometimes histopathology, but you can clearly
5 identify what is the population that you are treating
6 here.
7 There are substantial unmet medical needs in
8 the antifungal space. The reality is that we have only
9 three main classes of antifungals that really are
10 commonly used to treat invasive fungal diseases:
11 echinocandins, azoles, and polyenes. Only one of them
12 is oral. Treatment for invasive fungal diseases
13 typically takes several weeks to months. So you have
14 only one oral therapy and you have patients who are
15 refractory or resistant to that particular oral
16 therapy, you have very few options.
17 One of them has significant concerns regarding
18 drug-drug interactions and other classes may not be
19 appropriate for patients with substantial risk for
20 nephrotoxicity. If we take this into consideration,
21 really, the antifungal space has a substantial need for
22 additional options because the physicians right now

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

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

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

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1 randomized-controlled trial.
2 If you think about a subset of that
3 population, those that are, I'm going to say,
4 candidiasis [indiscernible] cases, or azole-resistant
5 Candida glabrata cases that are only 10 percent or
6 7 percent of that population, it will be truly
7 impossible to really run a well-controlled, randomized
8 clinical trial.
9 So here we are claiming that what the LPAD is
10 right now identifying as streamlined approaches needs
11 to be much more open, and needs to be much more
12 creative, and needs to be willing to accept other ways
13 of redeveloping a product and really demonstrating the
14 evidence of effectiveness.
15 An example here could be a single-arm study in
16 which certainly we explain why a controlled study may
17 not be suitable. The population will be limited, and
18 the sample size of this particular single-arm study
19 will be small. Historical control data or concurrent
20 control data very meticulously collected should be part
21 of the package. However, we have an area in which
22 we're very fortunate that in vitro and in vivo PK/PD

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1 assessments in studies are typically highly predictable
2 of efficacy in humans. We need to take advantage of
3 these of these particular situations.
4 In vitro/in vivo PK/PD studies supporting the
5 activity of the drug against the target pathogen could
6 be part of the package supporting this and supporting
7 clinical studies in related pathogens or related
8 indications, even if not for that specific pathogen.
9 Obviously, the drug should show some clinical
10 evidence of safety in a sufficiently large population
11 that can come from the single-arm study, plus other
12 complementary studies that have been run, and for the
13 limited population, labeling provides adequate controls
14 for use to justify the benefit-risk, in our opinion, in
15 this situation.
16 Here are other two examples that I'm not
17 entirely sure are clearly defined as a potential option
18 for LPAD, and I think that we should think about them.
19 For instance, novel therapeutic strategies because LPAD
20 is a little bit more tailored to novel drugs, so also
21 novel therapeutic strategies, we should think about
22 them.

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1 In this particular case for fungal diseases
2 that have very poor outcomes, combination therapy for
3 fungal infections in which a single agent is
4 ineffective or the infections have suboptimal outcomes
5 with very high mortality, we can speak here about
6 invasive aspergillosis, particularly with
7 azole-resistant invasive aspergillosis. With current
8 available therapy options, they still have mortalities
9 of 40 to 50 percent, so combination therapy could be an
10 approach that could use the LPAD Pathway for antifungal
11 development.
12 Also, we need to think about novel therapeutic
13 strategies for invasive fungal diseases that have other
14 significant unmet needs that will not be suitable for a
15 traditional development path. Here is just an example.
16 If you have an osteo-articular infection due to an
17 azole-resistant candida, let's remember the azoles are
18 the only oral available therapies. These patients are
19 going to receive from 6 months to 1 year of antifungal
20 therapy.
21 If you have them resistant to the only oral
22 available therapies that are there, they only have the

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1 opportunity to keep receiving IV therapy for 6 to
2 9 months or up to one year. So we need to use LPAD to
3 try to help us and provide alternatives in those cases
4 in which the available therapies are not adequate to
5 really meet the needs of the patients and the
6 physicians.
7 I think that's it for me. Thank you.
8 Questions
9 DR. COX: Great. Thank you, Dr. Angulo.
10 I'll look to the panel for any questions.
11 (No response.)
12 DR. COX: I might just ask, you outlined some
13 really difficult conditions to try and study, thinking
14 about patients who might have infrequently occurring
15 fungal infection, some of which might be involving bone
16 and such. There are still some really significant
17 scientific issues to try and work through to gather the
18 evidence to try and understand where a therapeutic
19 might work in understanding its safety and
20 effectiveness.
21 You mentioned historically controlled trials,
22 which can in the correct circumstances provide valid

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1 scientific information, but also in other circumstances
2 can be quite challenging to rely upon. So I just
3 reflect those comments back to you. I don't know if
4 you wanted to comment any further.
5 Historically-controlled trials can be
6 challenging, where the outcome is variable and the
7 treatment effect is not so large. You might look at
8 two control groups from different studies conducted
9 similarly, and there might be a variation in the
10 control group outcome that may actually exceed the size
11 of the treatment effect.
12 So there are some real challenges here. I
13 just bring them up because I think it's important to
14 continue to keep those in mind. We always look forward
15 to trying to solve these challenging situations.
16 DR. ANGULO: Absolutely. I am totally in
17 agreement that historically-controlled trials, probably
18 by itself as a single point of evidence or single point
19 of comparison, may not be the solution, but this is
20 kind of a package of weight of evidence, what we are
21 here trying to play with.
22 Concurrent control patients that have not

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1 participated in the clinical trial with very detailed
2 information collected about them is probably the best
3 alternative, along with historically-controlled trials.
4 It is probably the best alternative that we have to be
5 able to compare the outcomes of these patients that
6 will never be suitable to do a randomized-controlled
7 trial.
8 So randomized-controlled trials in these very
9 small populations, we're not talking about that. We're
10 talking about also PK/PD parameters that are all
11 pointing in the same direction; in vitro information
12 that is pointing in the same direction; open-label
13 trials that are really pointed in the right direction.
14 So we're not talking about a single point of
15 evidence; we're talking about collective pieces of
16 information that really will provide enough information
17 to substantiate the effectiveness of the drug, at least
18 for the risk-benefit ratio that these limited
19 populations require.
20 DR. COX: Certainly, there are conditions
21 where we have enough information about the natural
22 history of disease, treated and untreated, to be able

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1 to use historically-controlled trials, and the outcomes
2 are reliably not good. And if the effect size of the
3 treatment is large enough, you can still make a
4 scientifically valid appraisal.
5 I'll mention one more thing that came to mind
6 as I heard you describing historically-controlled
7 trials and some of the challenges of doing
8 randomized-controlled trials. One of the other ideas
9 that come up sometimes is disproportionate
10 randomization. If it is possible to do a
11 randomized-controlled trial, maybe you randomized 3 to
12 1 and gather some information from some randomized
13 controls. Some have even talked about trying to
14 utilize that information along with historical
15 information so that you have some insight into what's
16 going on in the control group.
17 Any thoughts on that? It's just an idea
18 that's been batted around.
19 DR. ANGULO: Absolutely. That is another
20 option in which randomized-controlled trials, even when
21 you have very small controls, it's certainly difficult
22 to really plan -- those could be an alternative to also

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1 take into consideration. I'm totally in agreement with
2 that, with the caveat that we need to understand that
3 really doing those studies that are properly powered to
4 really demonstrate a statistical inferiority or
5 superiority is extraordinarily challenging in many of
6 these conditions.
7 We may have controls there, but with a clear
8 understanding that those are unlikely to be properly
9 powered to really put all the statistical rigor when
10 you make the analysis against the controls.
11 DR. COX: Thank you, Dr. Angulo.
12 DR. ANGULO: Thank you.
13 DR. COX: Any other questions?
14 (No response.)
15 DR. COX: We thank you for your comments and
16 for joining us here today.
17 Our next speaker is Dr. Lisa Wittmer, who is
18 the chief development officer at VenatoRx
19 Pharmaceuticals, and she's also presenting on behalf of
20 the Biotechnology Innovation Organization.
21 We thank you for joining us here today, Lisa,
22 and the podium is yours.

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1 Presentation - Lisa Wittmer
2 DR. WITTMER: Good morning. Thank you very
3 much for this opportunity, and thank you so much to
4 FDA, the organizers of the meeting, other speakers, as
5 well as the interest in this meeting. I wanted to
6 present the industry perspective on the guidance and
7 some of the precedents, and that's where I'll focus
8 most of my presentation.
9 I think what really struck the industry
10 community about the guidance and FDA's direction thus
11 far is that the guidances are really meant to be
12 layered together. There was already an existing
13 guidance on unmet medical needs for antibacterials,
14 which laid out, to some extent, the opportunity for
15 streamlined development. Then the LPAD guidance was
16 issued in addition, and I think the novel aspect of
17 that guidance was really the definition and requirement
18 for use of the LPAD Pathway in a limited population.
19 FDA has defined and exemplified what that
20 limited population could be. It could be a population
21 that is a subset of a broader population, or it could
22 be an existing small population. But either way, the

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1 population would need to be clearly identified or
2 identifiable in the clinical setting.
3 This concept makes sense, and what I'll
4 explore topically in the presentation is whether that
5 backs us into a corner of narrow spectrum therapeutics
6 and more targeted drugs, and leaves out some of the
7 innovative broad spectrum novel agents that still have
8 potential to address unmet medical need.
9 We understand readily some concepts of
10 streamlined development. This has already been talked
11 about by Dr. Cox's introductory comments on the
12 framework for using a single adequate and
13 well-controlled trial, and we do have a couple of
14 precedents here in the anti-infective space, so that is
15 helpful.
16 We also see readily in the public domain a
17 number of companies designing trials and advocating
18 for, in special circumstances, wider than established
19 noninferiority margins. These are used sparingly in
20 cases where the unmet medical need is so significant
21 that there is a critical imperative to get a product to
22 the market with the available patients for study in a

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1 clinical trial. Of course, this does come already with
2 a restricted-use label.
3 In addition, there's a concept of a nested
4 inferiority, noninferiority design that has been
5 already laid out in the unmet needs guidance and
6 reiterated in the LPAD guidance. Generally, we think
7 of a streamlined development program as being shorter,
8 smaller, and requiring fewer trials. And it's
9 certainly not that we want to cut corners and reduce
10 the amount of evidence, but we all recognize that there
11 are some populations in which the benefit-risk ratio is
12 perhaps a little bit more lenient, such that the same
13 level of evidence in a large number of patients would
14 not be required in order to justify the use of a new
15 product.
16 One thing that we contemplate is how this new
17 pathway, the LPAD Pathway, is different or similar to
18 existing expedited development pathways. For example,
19 a pathway already allowed under Subpart H regulations,
20 of course that pathway requires use of a surrogate
21 endpoint that's predictive of clinical efficacy, and
22 many of us may look at the anti-infectives space,

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1 further to the last speaker's comments, and recognize
2 that to some extent, we may already have that structure
3 available to us because of the strength and
4 predictiveness of microbiological data from in vitro
5 and in vivo studies.
6 So the question is, how is the LPAD approach
7 and streamlined development program really different
8 from the existing expedited pathways? That is
9 something we will very much like for FDA to clarify in
10 the LPAD guidance.
11 The LPAD guidance lays out a couple of
12 examples for products that would be eligible for this
13 pathway, and the examples include an agent with narrow
14 spectrum activity. In that case, the limited
15 population is necessarily defined. The second example,
16 and I'll focus on the word "only" here, is an
17 antibacterial or antifungal drug based on available
18 therapy that would only have a role in the therapy
19 armamentarium for a select population with no other
20 options.
21 The requirement that the drug, the novel drug,
22 the investigational drug, have a role only in that

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1 limited population is perhaps a challenge when we look
2 at the full spectrum of new agents in development. So
3 one of the questions to think about is whether this
4 LPAD guidance is really meant to be predominantly
5 useful for a narrow spectrum and/or targeted
6 antibacterials, and is that the intent of the
7 legislation, and in fact FDA in this guidance.
8 I wanted to just quickly walk through two
9 examples, and I'll call them a positive and a negative
10 example, to get us thinking a little bit more about the
11 application of the LPAD guidance. Arikayce was
12 mentioned at the outset and is certainly something that
13 we have all gravitated to in order to instruct us
14 specifically how the LPAD guidance is implemented.
15 Arikayce has a limited population indication.
16 This is the drug that was studied in MAC lung disease.
17 It was approved based upon a Subpart H type pathway.
18 The surrogate endpoint was sputum culture conversion
19 versus any type of clinical endpoint, but it certainly
20 seemed appropriate in this case. A single phase 3
21 trial using this microbiological endpoint was the basis
22 of approval. Of course, there was some supportive

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1 evidence from a phase 2 study as well.
2 The benefit-risk assessment here took into
3 consideration a higher incidence of respiratory AEs in
4 the novel drug treated group versus the control, and
5 still, the benefit-risk was positive because of the
6 critical need for new agents for patients with no other
7 treatment options.
8 This is an interesting case example, but a
9 little confusing to industry because, based upon Situro
10 and its approval, which is similar to this one, and in
11 that case LPAD was not yet implemented, we wonder
12 whether or not this drug could have used the Subpart H
13 pathway only and not LPAD in order to achieve approval.
14 Now certainly, we recognize that LPAD is
15 useful because it allows some of the changes to
16 labeling and the additional requirements for
17 promotional material review prior to use in order to
18 ensure, perhaps in a greater way, and have been for
19 Subpart H drugs, that the drug will be used only as
20 intended in the specific population where the unmet
21 need is greatest and that particular benefit-risk
22 profile applies. This in and of itself without other

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1 examples is quite difficult, then, to use as a roadmap
2 to implement LPAD.
3 If we look at the Zemdri example -- this is an
4 anti-infective antibiotic, plazomicin -- that was
5 approved for complicated urinary tract infections,
6 because it was approved based upon a single adequate
7 and well-controlled trial, it in fact had a
8 restricted-use label. You can see that in the labeling
9 language it's for patients with limited or no
10 alternative treatment options.
11 In addition to complicated urinary tract
12 infection, the company embarked upon a study to look at
13 infections caused by resistant pathogens. When they
14 submitted the application to the FDA, they requested
15 approval for bloodstream infections due to CRE, or
16 carbapenem-resistant enterobacteriaceae.
17 It is very difficult to study these types of
18 infections. In fact, over 2100 patients were screened
19 and 60 to 70 could be enrolled in the trial; very
20 difficult patient populations to study. And I think
21 many of the other speakers made the point that when
22 studying infections due to resistant or rare pathogens,

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1 the populations are quite small and difficult to access
2 geographically.
3 There is no approval for bloodstream
4 infections, and in fact there were potentially many
5 critiques that could be made of the data package that
6 was submitted. However, in the context of how
7 difficult it is to study these populations, it is
8 challenging to see if this is a negative case example,
9 how companies can target collecting direct evidence in
10 infections that are rare in order to achieve approval.
11 Some of the discussion we've had earlier today
12 is really based on studying inaccessible infection, and
13 then shouldering perhaps a small study in resistant
14 infections. That is one concept. Of course, if a
15 product can get to the market with an indication in a
16 more common infection and the requirements for approval
17 of a rare infection indication are unclear, then it's
18 possible industry would be disincentivized from
19 pursuing those indications. Interestingly, in this
20 example, the benefit-risk in the UTI population didn't
21 lend sufficient support, from a safety perspective, to
22 support the bloodstream infection indication.

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1 While we recognize FDA certainly cannot
2 discuss confidential information relating to this
3 product's review, I raise this as an example just to
4 ask a couple of questions. Does the concept of a
5 limited population truly enable studying of resistant
6 rare infections? Can FDA clarify the context, for
7 example, for CRE infections, of the bar for sufficient
8 evidence of efficacy?
9 Just to summarize, I would like to give a few
10 industry perspectives. One is the lack of clear
11 precedence, which is certainly not anything that we can
12 directly address. It's just because LPAD is new, and
13 it is quite difficult to identify these limited
14 populations. Is lack of precedent just the observation
15 that this may slow industry in adopting the LPAD
16 Pathway? In addition, it could be very helpful if LPAD
17 could be used for any relevant subpopulation with
18 significant unmet medical need.
19 There is clarity needed whether LPAD could be
20 granted concurrently with non-LPAD indications. This
21 gets back to the idea that the guidance specifies the
22 goal for the LPAD Pathway is really targeting a very

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

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

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

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

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

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

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

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

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1 there's a lot going on with genotypical information,
2 and that is being linked to predict susceptibility and
3 large databases are being created. These will be able
4 to be linked as well to patient databases if we do the
5 efforts to do so, which would link genotypical
6 information of pathogens directly to clinical outcomes.
7 That is going to be extremely helpful information.
8 The electronic patient records are capturing
9 so much information that at ACMED [ph], there was
10 already a presentation where a person who was able to
11 predict the presence of a resistant pathogen without
12 even testing the pathogen, so fascinating stuff is
13 going to be available and possible thanks to artificial
14 intelligence or machine learning.
15 Clinical trial networks are happening that
16 will probably help us facilitate informed consent, but
17 it will also generate a lot of information. Thanks to
18 international collaborations, we will be able to access
19 also pathogens that are regional and be able to capture
20 that information before it becomes a problem in our
21 home country. It will even allow us to test,
22 empirically, stewardship interventions because you

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1 could randomize certain sites to do certain stewardship
2 interventions and see what the real outcome is of that,
3 something that we haven't been able to do yet.
4 Then last but not least, the blurring of the
5 real-world data and randomized control paradigms just
6 because of the sheer volume of evidence. And if we
7 have good harmonized data quality checks in the
8 clinical trial networks, these two types of evidence
9 may approach each other.
10 So talking about this innovation now, and
11 bringing that, and what does it mean for substantial
12 evidence, we've heard a couple of times about
13 demonstrating noninferiority in a somewhat similar
14 population and then have anecdotal clinical evidence in
15 an open-label trial specifically addressing the
16 question about the MDR pathogen; definitely a very good
17 approach.
18 We have also heard that PK/PD is a very
19 important part of information, and it can help bridge
20 evidence generated in one body site to another body
21 site in many, many cases. Of course if we have novel
22 mechanisms of actions, it's going to be more difficult,

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1 but that is certainly an extremely important piece of
2 evidence.
3 If we have difficulty in recruiting patients
4 because they are so rare and these patients have no
5 other treatment options, very often there are
6 compassionate use programs. Is there something that we
7 can learn from those compassionate use programs, and
8 how can that be included in the substantial evidence?
9 Then of course, the control arms that we've
10 discussed before, flexibility and endpoints as being
11 applied in cancer trials, going back to microbiological
12 eradication as a surrogate marker may be helpful in
13 certain cases where we just do not have sufficient
14 patient numbers and too much confounding factors
15 because of the complexity of the infection.
16 Adaptive clinical trial design, there is clear
17 guidance from the agency, and even recently updated,
18 and I would really like to encourage the agency to make
19 best use of all of these options, not to limit
20 ourselves too strictly to the traditional clinical
21 trial design as we've been doing it, but see what is
22 possible to strengthen the power of our small studies.

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1 This slide here, slide 7, is a very important
2 one. It is about how does these drugs are tested, and
3 Zemdri was one example, tested in a complicated UTI
4 setting, so therefore it gets the label of the drug is
5 indicated in patients with clinical UTI infection. But
6 that's probably not how the drug is going to be used,
7 not necessarily. Particularly if you have drugs
8 addressing AMR, where they're going to be used is most
9 likely in situations with ventilator-associated
10 pneumonia or other infections in an intensive care unit
11 or septicemia.
12 So is it helpful to indicate a drug for cUTI
13 if you know it's going to be used or be needed in
14 another indication, and under the LPAD umbrella, could
15 the agency not come to a risk-benefit judgment in these
16 not studied indications, based on the available
17 evidence with the appropriate clarifications of course
18 in the labeling, what has been studied, and what is now
19 a possible use of that drug?
20 Specifically for the labeling, I think the
21 caveats of limited population are very important and
22 very helpful, but what I would like to see is

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1 something, like here in blue, that a drug for AMR is
2 indicated for the treatment of infections; not a
3 specific type of infection, not a body site, but for
4 the treatment of infections caused by
5 multidrug-resistant *Pseudomonas aeruginosa*, or
6 acinetobacter, or whatever problem pathogen that we
7 have. I think that would be extremely helpful.
8 Then the statement that it's based on just
9 limited data is perfectly adequate and is going to be
10 very helpful to limit overuse of the drug. And
11 actually, these types of drugs are going to be
12 controlled very much anyway through stewardship
13 initiatives at the site.
14 The last slide is about the postmarketing
15 removal of the LPAD restriction. We heard concerns
16 previously that there might be overuse of drugs, and I
17 think we are all in favor of trying to gather all the
18 information that is possible about treatment of a
19 specific indication in a specific setting.
20 So whilst the drug is approved under a limited
21 population initiative or pathway, I think it is going
22 to be useful to collect further information and make

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1 sure that we really establish efficacy and safety of
2 that product in that setting.
3 The question is how do we do that, and is it
4 sufficient to collect safety information? Is it
5 sufficient to collect real-world evidence, or does it
6 really need to be like a supplementary NDA at this
7 moment, a prospective well-controlled clinical trial to
8 come with that evidence? That is a question that would
9 be helpful to be clarified in the guidance.
10 Another point here is about the Limited
11 Population Pathway. Can you get another claim for
12 another pathogen on the same label, or as the previous
13 speaker asked, can you have a normal claim and then a
14 separate claim that says, well, for this indication
15 there's only limited evidence, and how would you do
16 that? The real-world evidence or the
17 randomized-controlled trial for the initial indication,
18 that is also an important question.
19 So the point here on this slide is, really,
20 could the agency provide a little bit more practical
21 guidance on the various options on how to address,
22 postmarketing, the LPAD restrictions? That's it.

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1 Questions
2 DR. COX: Thank you, Dr. Pypstra.
3 Any questions? I can start out with one. I'm
4 wondering, you mentioned the issue of tissue agnostics
5 and body sites, and I guess one of the challenges that
6 we've seen is when we look at the many antibacterial
7 drugs, where we've seen trials over the last 10 years
8 or so, we've not infrequently run into circumstances
9 where a drug works in one type of infection, but then
10 at another body site, much to our surprise and not
11 apparent until the clinical trial teaches this, there's
12 a deficit in another site.
13 When folks look, sometimes they do some very
14 elegant work and can understand this, I'm estimating
15 about half the times, and sometimes the other half the
16 time, we, after looking, can't quite even figure out
17 why, or at least our hypotheses are just speculative as
18 to why a drug worked at one site and not another.
19 That does raise a real challenging issue for
20 the issue of a drug and looking across body sites. I
21 know it's a tough question. I can't answer it. I'm
22 just curious if you have any thoughts on it.

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1 DR. PYPSTRA: Well, I think part of the answer
2 is that we should study the drug across indications.
3 Not each of the indications will be adequately powered,
4 I accept that, but at least it will generate some
5 information, and having some information is better than
6 having no information.
7 The situation that we're facing currently is
8 that drugs are studied primarily in UTI infections, and
9 they're going to be used in other infections for which
10 we have no information whatsoever. So I would rather
11 have a study where it's used in mixed infections,
12 adequately stratified, or using factorial design so
13 that you can compare within the groups and across the
14 different indications, and generating some evidence.
15 I think the big problems will be identified by
16 that. There may still be some differences between
17 pneumonia and intra-abdominal infections, and they will
18 probably be teased out later onwards through real-world
19 evidence data.
20 DR. COX: I'm just thinking about your
21 comments, and of brings us back I think to that theme
22 that we've heard through a couple of the presentations.

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1 And that is, are there ways that could help facilitate
2 the collection of evidence in these very difficult to
3 study infections, whether it be clinical trial
4 networks, centers of excellence and such, so that we
5 might be able to gather more data that is really
6 difficult to gather to help to address some of these
7 questions.
8 Just a comment, really -- well, two comments
9 maybe. One is that it is true that folks do study
10 indications that are feasible where they can actually
11 gather some data about the efficacy of the drug, which
12 is helpful. It doesn't address all the questions that
13 are out there, all the ways that a drug might be
14 utilized, and certainly we all would want to have that
15 information.
16 So it does bring us back to this question of
17 are there ways that we can help to gather such
18 information in these more difficult to study
19 infections?
20 I'll comment, too. I noticed on your slide,
21 you said a randomized-controlled trial, and then some
22 anecdotes. Certainly, we do try and do better than

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1 anecdotes. We are trying to get to adequate and
2 well-controlled trials. Sometimes in these difficult
3 to study conditions, you can construct an adequate and
4 well-controlled trial. Sometimes it's
5 historically-controlled trial. Sometimes it's a
6 smaller randomized-controlled trial.
7 But we do try and work with companies
8 throughout the period that they're developing their
9 drug to try and explore what might be possible that
10 might get us to an adequate and well-controlled trial
11 to really help provide the information that will help
12 us to understand how a drug works in treating a
13 particular type of infection, and recognizing that in
14 certain circumstances, the sample sizes might be
15 smaller, the degree of uncertainty might be larger, but
16 still trying to get to that threshold of level of
17 evidence, if you will.
18 Any other questions for Dr. Pypstra? Sarah?
19 MS. WALINKSY: You mentioned accelerated
20 approval in two of your slides. I didn't hear you dive
21 deeper in that, and I just wanted to hear a little bit
22 more from you. You mentioned postmarketing removal of

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1 LPAD restrictions, and again, you mentioned it earlier
2 in the endpoint flexibility as for cancer trials. I
3 just wanted to hear where you're seeing how accelerated
4 approval -- I know with Arikayce, we approved based on
5 both.
6 DR. PYPSTRA: The principle of accelerated
7 approval that I'm in favor of is that you can make the
8 drug available relatively quickly, based on limited
9 data, and that you have some kind of post-approval
10 commitment to complement the information afterwards,
11 whilst the drug is already available to patients.
12 We heard from the patient organizations that
13 they want every patient to have access to safe and
14 effective drugs, and we should all endeavor to achieve
15 that. The problem is that in the beginning, we have a
16 drug of which we do not know that information, and what
17 is then better; not to have the drug at all, or to have
18 the drug available under certain restrictions and with
19 adequate labeling? And I think it's the latter.
20 MS. WALINSKY: Thank you. That's helpful.
21 Open Public Comments
22 DR. COX: Thank you, Dr. Pypstra, and we thank

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1 you for your comments and for joining us here today.
2 At this point, we've gotten through our
3 scheduled speakers, and now we can move to the open
4 public comments. We have Carrie-Lynn Furr, who is
5 signed up to be our first speaker.
6 DR. YOUNG: I didn't sign up. I don't know
7 where to sign. I'll follow anywhere. Some of you
8 signed up first.
9 DR. COX: We'll let our speaker who signed up
10 go first, and then we'll ask you for comments.
11 DR. YOUNG: Thank you.
12 DR. FURR: I'm Carrie-Lynn Langlais Furr, CEO
13 of Bacteriophage and Drug Development Consultants.
14 Thank you for the work that FDA has put into
15 implementation of the LPAD Pathway. Like others, I
16 agree that approval under this pathway is very
17 important to increase the arsenal of antibacterial and
18 antifungal products. Thank you also for the
19 opportunity to speak for a moment. I will be brief.
20 My comment applies broadly but is driven by
21 the development of Bacteriophage based investigational
22 products. Bacteriophage therapeutics are in a novel

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

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

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

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

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

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

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

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

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

9 MS. WALINSKY: Thank you.

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

19 So you don't want to surprise your CMC people.
20 We've seen a few surprised CMC people. So as a public
21 service announcement --
22 (Laughter.)

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

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

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

14 DR. COX: Great. Thanks, Julie.

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

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

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1 other several times, U.S. Senate, Congress. House of
2 Representatives and Senate are different.
3 I'm really concerned about our society and
4 also concerned about the patient and population safety.
5 I have seen very often our government agencies spend a
6 lot of time and effort doing a lot of things for
7 development. That is good, but on the other hand, our
8 society is getting sidetracked and is very dangerous to
9 our consumers and patients.
10 Even a healthy person can be kidnapped to the
11 hospital for some kind of medication, and there is no
12 way our system is working for those people who are
13 involuntarily admitted to hospital, especially. Some
14 doctors put medication, or injection, or whatever, on
15 the patients, or ask the patient's family to administer
16 something over the counter or whatever. The patient
17 and family do not agree, especially if it's a big jug
18 [indiscernible] or liquid administered by the physician
19 only. But the staff says you must do it, something of
20 this sort.
21 Involuntary admission to the hospital, the
22 physician would say you have some kind of disease, so

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1 you have to take this medicine or we'll inject
2 forcefully. It even goes through the core procedure or
3 administrative procedure. The problem, especially, is
4 [indiscernible] will not give the administrative
5 record -- medical record, or will not give the label or
6 the prescription, and will not give maybe the wrapper
7 or something, and a special injection forcefully. They
8 have several people bind together and grab the patient
9 and still injecting something, and in the hospital,
10 sometimes the injection makes you unconscious.
11 For all these things, they don't do release
12 the instructive wrapper [indiscernible], and the cost
13 is outrageous, obviously, and they charge it to
14 Medicaid, or Medicare, or whatever. That doesn't make
15 sense because they just profit off of people.
16 There's nowhere to complain and have the
17 agency address these type of issues. I just hope FDA
18 is concerned about our health and about medication. I
19 think it's very important if you can have extra effort
20 in this area. I have been trying this for decades, and
21 it seems to go nowhere. I see a lot of patients,
22 especially the elderly, a happy couple, elderly, or a

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1 happy family, and they have an outstanding family life,
2 and if you destroy their family life, in society, it is
3 meaningless.
4 DR. COX: Thank you. I understand your
5 comments and your concerns, and we appreciate them.
6 With regards to clinical trials, all clinical trials
7 need to be ethical. There needs to be informed
8 consent, and the patients enrolled need to be
9 monitored.
10 DR. YOUNG: I have also a question about data,
11 because all the data I see, it doesn't meet
12 accountability as the first step. The government
13 agency, whatever, there is some kind of conspiracy
14 together. And every time you want to predict
15 something, they have a government attorney and police
16 officer, and there's some kind of conspiracy together.
17 Even in the court, they have social workers as a false
18 witness.
19 DR. COX: We appreciate your comments. Why
20 don't you and I talk a little bit more after the
21 meeting closes? Okay?
22 DR. YOUNG: I had something to present to the

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1 FDA before, but I got an adverse action against me.
2 I'm here again. I'm free of my life. I'm here,
3 really, as a dead man crusading.
4 So I would like for maybe you give me a
5 website, and I present you something, records, and see
6 if you can work on it.
7 DR. COX: I'm happy to do so. We'll do so
8 after the meeting.
9 DR. YOUNG: Thank you.
10 DR. COX: Thank you for your comments.
11 Katie, did you want to address a question from the Web
12 or how did you want to handle that?
13 Katie, did you want to address a question from
14 the Web, or how did you want to handle that?
15 We had one question come in from the Web that
16 I'm aware of, and I think Katie's going to address it
17 for us.
18 MS. SCHUMANN: Yes, that's fine.
19 From a Mr. Patrick Sweeney from the Web, we
20 received one question via the webcast. He asked, "If
21 otherwise satisfying all requirements, we'll a
22 currently available antibiotic delivered in a new

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

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

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

15 Closing Remarks - Edward Cox

16 DR. COX: Great. Thanks, Katie.

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

22 This is a really challenging and important

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

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

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

11 (Applause.)

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

14 Okay.

15

16

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18

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

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

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

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