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FOOD AND DRUG ADMINISTRATION

FDA-IDSA-NIH-Pew Public Workshop
Enhancing the Clinical Trial Enterprise for
Antibacterial Drug Development in the United States

DATE: Day 1: November 18, 2019

TIME: 8:30 a.m.

LOCATION: FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Great Room

Silver Spring, MD 20993

REPORTED BY: Michael Farkas, Notary Public

JOB No.: 3472551

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6 DAVID MELNICK

7 RIENK PYPSTRA

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10 CYNTHIA SEARS

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12 REBECCA REINDEL

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1 MARK ALBRECHT

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3 NICK KARTSONIS

4 RYAN CIRZ

5 SUE CAMMARATA

6 MANOS PERROS

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

2 JOHN FARLEY: So good morning,
3 everybody. I'm John Farley. I'm the Acting Director
4 of what is now called the Office of Infectious
5 Diseases at the Center for Drugs here at FDA. We want
6 to welcome you to this workshop.

7 Next slide, please.

8 So I thought we might go ahead and
9 start the morning by focusing on why we're all here.
10 This is -- should look familiar to those of you who
11 have taken a look at the recent CDC AMR threats
12 report. We've had some progress from stewardship
13 efforts, but the serious public health challenge
14 continues with 2.8 million antibiotic resistant
15 infections each year and 35,000 deaths.

16 How about this? Okay. I will lean
17 forward.

18 So I want to begin the day by just
19 thanking Ed Cox for his leadership here at the agency.
20 As most of you are aware, he left government service
21 after nearly two decades, and really a steady hand and
22 focus on science and the data on his part played a key

23

1 role in the progress over the last decade, making safe
2 and effective new antibacterial drugs available for
3 patients in the setting of AMR.

4 I also want to take a moment to thank
5 everybody who is sitting in this room for your
6 steadfast commitment, your innovation, your positive
7 dialogue, and your collaboration in the midst of what
8 has been a decade of scientific and economic
9 challenges.

10 So we at the agency really appreciate
11 your commitment. Cindy -- I was telling Cindy Sears
12 earlier, I come from the world of perinatal HIV where
13 I felt like we built a strong collaborative
14 partnership over time and there were major
15 accomplishments. And I feel like the dynamic is the
16 same here, and it's really an honor for those of us in
17 the agency to be part of that.

18 I thought we'd begin today by just
19 doing some brief introductions, and your disclosures
20 are already listed in the program, so you don't have
21 to provide any voluntary disclosures as you introduce
22 yourself. But maybe we'll start with Aaron and move
23

1 around the table from there.

2 AARON DANE: I'm Aaron Dane. I'm a
3 statistical consultant who's been working in the area
4 of infectious diseases for about 20 years.

5 ROGER LEWIS: Good morning. I'm Roger
6 Lewis. I'm the Chair of Emergency Medicine at Harbor-
7 UCLA Medical Center and the Senior Medical Scientist
8 at Berry Consultants where I focus on adaptive and
9 innovative clinical trial design.

10 DAVID MELNICK: I'm David Melnick, the
11 Chief Medical Officer at Spero Therapeutics, a small
12 biotech based in Cambridge, Massachusetts. We have
13 three active programs in the antibacterial space.

14 RIENK PYPSTRA: Hi, I'm Rienk Pypstra.
15 I'm head of development for the hospital business unit
16 in Pfizer; hospital business unit includes all the
17 antibiotics. I have also some years of experience
18 with developing antibiotics.

19 CHIBUZOR UCHEA: Good morning,
20 everybody. My name is Chibuzor Uchea. I'm a science
21 officer in the Drug Resistant Infections Program at
22 the Wellcome Trust. We are working on a range of
23

1 different interventions in the AMR space to lead the
2 program about combatting antimicrobial resistance in a
3 range of different areas. And I'll be speaking later
4 on in tomorrow's session on the use of clinical trial
5 networks.

6 VANCE FOWLER: Good morning. I'm Vance
7 Fowler. I'm the Contact Principal Investigator for
8 the Antibacterial Resistance Leadership Group and the
9 Chair of the Infectious Disease Society Antimicrobial
10 Resistance Committee.

11 CYNTHIA SEARS: Good morning. I'm
12 Cindy Sears. I'm past President of IDSA and Professor
13 of Medicine at Johns Hopkins, and I'm an infectious
14 diseases physician.

15 SARA COSGROVE: Good morning. My name
16 is Sara Cosgrove. I'm a Professor of Medicine at
17 Johns Hopkins also and also in the Division of
18 Infectious Diseases, and I am the Medical Director of
19 our Department of Antimicrobial Stewardship.

20 REBECCA REINDEL: I'm Rebecca Reindel.
21 I'm a pediatric infectious disease physician by
22 training. I'm a Medical Officer in the Office of
23

1 Vaccines in CBER.

2 LINDSEY BADEN: Lindsey Baden. I'm a
3 Physician Investigator at Brigham & Women's Dana
4 Farber, and an Editor with the "New England Journal of
5 Medicine" focusing on infectious diseases.

6 WES KIM: Good morning, Wes Kim with
7 Pew Charitable Trusts. I'm the Senior Officer of our
8 innovation workstream our Antibiotic Resistance
9 Project.

10 JOHN REX: I'm John Rex. I'm an
11 internist trained in infectious diseases. I am
12 currently the Chief Medical Officer of a company, a
13 private company that has an antifungal in phase two,
14 so not specifically a topic for this for today. And
15 also, I work for Wellcome Trust as their advisor for
16 their investment strategy and drug resistant
17 infections.

18 HELEN BOUCHER: Good morning. I'm
19 Helen Boucher from Tufts Medical Center in Boston,
20 where I practice infectious diseases and I'm the
21 Treasurer of IDSA.

22 SUMANTHI NAMBIAR: Good morning. I'm
23

1 Sumanthi Nambiar, Director Division of Anti-
2 Infectives.

3 ERIN DUFFY: Good morning. My name is
4 Erin Duffy. I'm the Chief of R&D of CARB-X. We're
5 going to talk about CARB-X later today. But briefly,
6 we're a global partnership that funds and accelerates
7 innovation and antibiotic drug discovery.

8 AMANDA JEZEK: Hi, I'm Amanda Jezek
9 with IDSA. I'm our Senior Vice President for Public
10 Policy and Government Relations.

11 KEVIN OUTTERSON: Kevin Outterson. I
12 might be the only lawyer around the table. I'm a law
13 professor at Boston University, and I'm the Principal
14 Investigator of CARB-X.

15 JANE KNISELY: Good morning, Jane
16 Knisely. I am with the National Institutes of Health,
17 National Institute of Allergy & Infectious Diseases.

18 DENNIS DIXON: Good morning, everybody.
19 I'm Dennis Kixon, also from National Institute of
20 Allergy & Infectious Diseases at NIH. I'm Chief of
21 the Bacteriology and Mycology Branch. We manage all
22 of the escape pathogens. And I've had a chance to

23

1 observe these challenging areas for nearly three
2 decades at NIH as we've developed various mechanisms
3 to shore up our defenses and had prior experience in
4 academia, political lab, and briefly in industry.

5 MARK ALBRECHT: Good morning, everyone.
6 My name is Mark Albrecht. I am the Chief of the
7 Antibacterials Branch at BARDA.

8 AMY LEITMAN: Good morning. My name is
9 Amy Leitman. I'm the Director of Policy and Research
10 at a patient advocacy group called NTM Info and
11 Research. We advocate on behalf of patients with
12 pulmonary nontuberculous micro bacterial disease,
13 bronchiectasis and other gram-negative pathogens.

14 NICK KARTSONIS: Good morning. My name
15 is Nick Kartsonis. I'm an infectious disease
16 physician, and I currently provide oversight for
17 infectious disease and vaccines at Merck Research Labs
18 at Merck & Co., Inc.

19 RYAN CIRZ: And good morning. My name
20 is Ryan Cirz. I'm currently an independent
21 consultant. But for the 16 years prior to the summer,
22 I was a founder and the head of research at a company
23

1 called Achaogen.

2 SUE CAMMARATA: Good morning. I'm Sue
3 Cammarata. I'm the Chief Medical Officer at Melinta.
4 I've been involved in antibiotic and anti-infective
5 clinical trials for twenty-some years since I first
6 came into pharma.

7 MANOS PERROS: And good morning,
8 everyone. Manos Perros, CEO of Entasis Therapeutics,
9 clinical stage antibacterial company. I'm a Ph.D.
10 scientist by training, worked in discovery most of my
11 career. And I also believe we're on the cusp of
12 something really big, probably as big as what we've
13 seen in oncology in the last two decades, and I really
14 thank the agency for organizing the day when we can
15 hopefully usher that through.

16 JOHN FARLEY: So thanks very much. I
17 want to also thank Pew, as well as IDSA for their co-
18 sponsorship of this workshop, as well as our sister
19 agencies within the Department of Health and Human
20 Services, who are supporting this workshop and are
21 focused on AMR. You've met our colleagues from NIAD,
22 as well as BARDA, and we do have colleagues here from

23

1 the Assistant Secretary for Program Evaluation at HHS
2 who are very much focused on the economic challenges
3 that all of us face in this field.

4 Next slide, please.

5 So I think we've got a great agenda for
6 this workshop. I'm very excited about it. I'm really
7 looking forward to the discussion. We're going to
8 start out talking about the current state and
9 resources for antibacterial drug trials. We've got an
10 industry roundtable focused on needs and challenges
11 that I'm looking forward to hearing those
12 perspectives.

13 Then we'll begin to focus on realistic
14 options for enhancing the enterprise. Tomorrow
15 morning, we'll talk a lot about new approaches and
16 strategies that might better support the enterprise.

17 Next slide, please.

18 So I think there's a number of
19 discussion topics that, at least from the government
20 perspective, we really want to make sure that we get
21 some good and open discussion about. The first is
22 serious infections that are in need of feasible
23

1 approaches to obtaining clinical trial data. We're
2 particularly thinking about pathways to develop
3 products for infections caused by primarily gram-
4 positive organisms. There, we certainly have a clear
5 pathway for acute bacterial skin and skin structure
6 infections, but there really are other needs such as
7 staphylococcal bacteremia, diabetic foot infections,
8 prosthetic joint infections. Let's talk through some
9 feasible pathways for development in that area.

10 I think we'll hear a lot of discussion
11 and ideas about labeling. But from our perspective in
12 the gram-negative arena, what we'd really like to also
13 include is a discussion on looking at the paradigm for
14 how we develop products for gram-negative pathogens.
15 We've got some ideas to throw on the table. Let's
16 take a feasibility check, let's talk about what the
17 feasibility challenges are, and maybe talk about some
18 strategies to overcoming those in terms of the design
19 that we would like to see going forward.

20 We're going to talk about feasible
21 approaches to updating treatment guidelines. Cindy's
22 very excited to share her perspective, and we'll look
23

1 forward to that discussion. We really want to hear
2 from you what a clinical trial network might look like
3 that would maximize impact in this area. And then
4 we're going to talk about innovations and statistical
5 approaches, design and end points that we might
6 prioritize going forward.

7 So I think I have the privilege of
8 chairing this session with Aaron, and I think we're
9 going to maybe alternate introductions and it's my
10 pleasure to introduce Sumathi Nambiar. We're both
11 pediatricians, we both trained at Children's National
12 Medical Center, but she's younger than me, so we
13 didn't know each other. But it's been my privilege.
14 She joined the agency in 2002 and kind of broke me in,
15 and she has served as the Director of what is now the
16 Division of Anti-Infectives since 2013. So Sumathi,
17 thank you.

18 SUMATHI NAMBIAR: Thanks, John. Can
19 you hear me okay? All right. So good morning
20 everybody and welcome to this day-and-a-half-long
21 workshop. Thank you for being here in person and also
22 for some of you that have joined us by web. We'd also
23

1 want to thank our co-sponsors -- IDSA, NIAID, and Pew
2 -- for helping to organize this workshop.

3 All right, so there are four main
4 topics I'd like to touch upon. And we'll start with
5 the history; how did we get here? So if you look back
6 in this from the 1960s to 1980s in antibacterial
7 trials, patients with a variety of infections -- those
8 at different body sites -- were enrolled in the same
9 trial. And there's really no plan for formal
10 inference testing in these trials.

11 The indications that were granted were
12 based on substantive body sites of infections from
13 within these trials. Indications tended to be less
14 specific; they were more broad. Early on, they were
15 as broad as respiratory tract infections, and then
16 they were refined to separate out the upper from the
17 lower respiratory tract. And within the allowed
18 indication, you had a broad spectrum of conditions,
19 and those are commonly pneumonia to bronchitis.

20 Similarly, skin infections, they want
21 separated out whether they were complicated or
22 uncomplicated; and then subsequently, they were
23

1 refined further and complicated skin infections are
2 now referred to as acute bacterial skin and skin
3 structure infections.

4 So in the '90s to the 2000, the move
5 was more towards conducting site specific trials. And
6 the reason for moving to site specific trials was
7 because there was a better understanding of the
8 natural history of the disease, and the fact that it
9 differed depending on the site of infection. There
10 was a recognition that end points and treatment
11 duration would differ, depending on the body site of
12 infection.

13 There was also an understanding that
14 drug efficacy may differ at different sites of
15 infection, and the fact that the dosing regimens could
16 also differ depending on the site of infection.

17 The two documents that many of you are
18 familiar with, the 1992 IDSA Guideline and the 1992
19 FDA Points to Consider document, recognition of the
20 aforementioned differences in these documents really
21 represented an advance in clinical trial design.

22 Around 2005 to 2006, there was
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1 significant (indiscernible) in the field and many of
2 you really were part of the discussions at that time.
3 One of the main questions that was raised was about
4 the non-inferiority trials and whether or not they
5 were scientifically justified. There was a lot of
6 effort, not only on part of the agency, but with the
7 stakeholders -- again, many of you were part of those
8 discussions, and we were able to come to
9 scientifically sound NI trial designs.

10 We were able to formulate evidence
11 based anti-margin justification for some of the common
12 indications that were being pursued. At the time,
13 trials were typically conducted for these common
14 indications, and we had two trial per indication, and
15 that's what the data package used to look like.

16 Around 2012, the focus -- you know,
17 while we continued the work on non-inferiority trials,
18 there was a greater focus on unmet need, particularly
19 to treat gram-negative infections, streamline drug
20 development programs. There was a lot of discussion
21 around that as well, and drug development programs
22 followed the approaches that were laid out in our
23

1 draft guidance.

2 And under this paradigm, usually it's a
3 single trial per indication, and the safety databases
4 for the new drug applications tended to be much
5 smaller; they were in a few hundred.

6 In the years ahead, we think there'll
7 be continued focus on unmet need programs, including
8 difficult to study indications and not just focusing
9 on infections due to particular resistant phenotype,
10 and also, the challenges associated with the
11 development of non-traditional therapies.

12 So if you look back at the approvals in
13 the last decade or so, the types of data packages have
14 varied. For standard indications, say intrabdominal,
15 UTI, pneumonia or skin, we might have had two trials
16 per indication or at least one trial per indication.
17 So the data package for a drug with gram-negative
18 active -- activate against gram-negative organisms
19 could be a trial in CIAI and a trial in cUTI.

20 For limited use indication approvals,
21 it is generally a single trial with supportive
22 evidence, which could include data from a phase two
23

1 study, invitro studies, and animal models of infection
2 relevant to the indication that was being sought.

3 More recently, we've had two products
4 approved under the LPAD pathway. For both, we had
5 very small data packages. It was a single trial that
6 was the basis for approval. The patient population
7 for which the products were approved is a very well
8 defined and limited population of patients. But given
9 the unmet need, the seriousness of the condition,
10 there was some flexibility in the benefit risk in
11 situations.

12 So then why are we all here today? I
13 mean, it's apparent that we've made progress, but
14 there's obviously a lot more work to be done. And it
15 does seem like we are right now at a critical juncture
16 in antibacterial drug development, and we as a
17 community need to think hard and formulate what our
18 plans are for the years ahead.

19 We want criticism from different
20 quarters regarding the clinical utility of some of the
21 recently approved products and the trials that were
22 conducted to support their approval. I think there's
23

1 also recognition that there continues to be an unmet
2 need, particularly for difficult to study indications,
3 and I've just given you a couple of examples.

4 I think it's very important that we
5 work together. All of us have our own role to play,
6 and we really need to work together because no one
7 individual or one group here has all the solutions to
8 the problem. We need to map out the needs and also
9 potential solutions.

10 And we do recognize that labeling is an
11 important component of the discussion. We understand
12 it's certainly going to come up in many sessions
13 today. But I think it's very important that we
14 address the scientific and feasibility issues. Once
15 we address the scientific issues, labeling just
16 follows automatically.

17 So what do some of the criticisms about
18 the recent registration of trials and, you know, I've
19 listed a few. I'm sure there might be others, and we
20 look forward to hearing them during the course of this
21 day and a half.

22 The clinical conditions studied -- an
23

1 example is, you know, it was just a urinary tract
2 infection indication that was studied. I think it's
3 important to note that such trials are feasible and do
4 demonstrate the efficacy of the product at the body
5 site of infection. It also provides reasonable safety
6 information in a population with fewer confounding
7 factors. I think one has to understand that this is a
8 new molecule that is being evaluated, and this
9 provides a good chance to assess how the product
10 behaves both from an efficacy and a safety standpoint.

11 And then starting with an indication
12 like UTI or intrabdominal allows for a step up to a
13 more difficult to study condition. I think it's also
14 important to keep in mind that one has to balance the
15 realities of drug development with the desire to study
16 difficult indications or difficult populations.
17 Certainly, trials in HAP/VAP are needed.

18 Now, all drugs are not suited for a
19 pneumonia indication, given its spectrum of activity.
20 These trials are often difficult to enroll. Often,
21 there are a lot -- many more confounding factors
22 making it harder to tease out the treatment effect of
23

1 the test drug. And from a drug developer's
2 perspective, it's often considered risky for a first
3 indication.

4 The other major criticism is there's
5 lack of data on patients with infections due to
6 resistant organisms, whatever the phenotype of
7 interest be. I think we've learned over the last few
8 years, conducting randomized control trial in patients
9 with infections due to a particular resistant organism
10 can be challenging. We've seen a few trials conducted
11 recently in patients with infections due to carbapenem
12 resistant enterobacteria, see gram-negative
13 infections. And these have been difficult not only to
14 conduct, but also very difficult to interpret, as
15 these trials were descriptive and had no pre-specified
16 hypothesis testing.

17 And as new therapies become available,
18 you know, the resistant phenotype of interest will
19 change and it will evolve. So one -- what might be
20 potential study designs, if you're interested in such
21 a study, is a demonstration of superiority over best
22 available therapy, and we've seen the challenges with
23

1 being able to demonstrate superiority of currently
2 available treatment options.

3 The other consideration -- and this
4 will come up during the course of the discussion --
5 is, now that some treatments are available which have
6 activity against a CRE, could one consider enriching
7 the trial population in an NI trial, as long as an
8 appropriate comparator is chosen.

9 The other criticism is that the trials
10 conducted are generally NI trials, and so the new
11 product is only non-inferior to existing therapies.
12 We certainly welcome superiority trials; they're a lot
13 easier for us to interpret. But I think the practical
14 difficulties in conducting and demonstrating
15 superiority is very obviously. Its opposition that
16 well conducted NI trials are interpretable and provide
17 useful information on the efficacy of a product.

18 And I think it's also important to keep
19 in mind that having some redundancy is helpful to
20 address patient needs and also to address potential
21 drug shortages.

22 The other criticism we've heard is that
23

1 very few patients are enrolled in the United States.
2 And so, I think it is imperative and we need to
3 understand what are the reasons for this limited
4 enrollment in the United States. We need to do better
5 with the infrastructure here.

6 I think what's reassuring is that
7 Steve, who will present after me one of our all Rice
8 fellows, has reviewed the data from recently conducted
9 trials, and at least they show that most disease and
10 patient characteristics between US and ex-US sites are
11 comparable. So that's reassuring, but I think we
12 still need to identify what the issues are and how we
13 might do better in getting data from patients in the
14 United States.

15 The other -- one other criticism is
16 that in these trials, patients with comorbidities or
17 those with more severe disease are often not enrolled.
18 It certainly would help if pharmacokinetics of the
19 drugs in patients with, say, hepatic arena impairment
20 or other comorbidities are evaluated early in drug
21 development so one can include them in these clinical
22 trials.

23

1 And on our part, we certainly -- we're
2 willing to exercise maximum flexibility and
3 inclusion/exclusion criteria, but we have to ensure
4 patient safety.

5 So I just wanted to spend a couple of
6 minutes talking about -- you know, I know we're all
7 trying to find solutions to the problem. But in that
8 effort, it's very important that we don't lose our
9 focus on scientific principles, because that is really
10 key here.

11 So even though the trials that have
12 been conducted have a lot of shortcomings and there
13 are a lot of criticisms about it, I think it's very
14 important to keep in mind that well-designed
15 comparative trials do teach us important and
16 unexpected lessons. I mean, I've listed a few here
17 that we've seen over the years with daptomycin and
18 binding of daptomycin to surfactant, and this
19 interaction was rarely identified after a trial was
20 conducted in patients with cap that did not meet its
21 non-inferiority margin.

22 We've seen higher mortality and lower
23

1 cure rates in trials of ventilate associated
2 pneumonia. I've given you two examples, tigecycline
3 and doripenem. Based upon the findings in these
4 trials, I think there's a better understanding that
5 pharmacokinetics can be altered in sick patients,
6 patients with HAP/VAP; acutely ill patients can have
7 augmented renal clearance and their dose requirements
8 might be different.

9 We also have a better understanding of
10 differences in drug penetration between animals and
11 humans. So I think it's important that the body --
12 that we recognize that body site of infection matters.
13 And the efficacy of drugs can be seen in one body
14 site; it may not translate to efficacy in another body
15 site. So I don't think -- I think we should keep that
16 in mind and not ignore that finding. And some of you
17 are familiar, you've got a list. And it's very
18 unfortunate, but the list does keep growing.

19 Let's spend a couple of minutes talking
20 about labeling. I mean, there are two key
21 considerations when it comes to labeling. There are
22 labeling regulations. There is a framework within
23

1 which we have to work, and that really helps in
2 ensuring consistency, not just across anti-infective
3 products, but across products that the agency reviews.

4 And it's also important to keep in mind
5 that including information in labeling, if it's based
6 on sound scientific evidence, it's helpful to all
7 stakeholders, whether you're a provider, a payer, or a
8 patient.

9 So these are the regulations, and I
10 won't walk through them. So if you look at some
11 recent approvals, what information have we included in
12 labeling. The indications section will include the
13 organisms for which we had adequate clinical data.
14 There will be information regarding limited
15 population, if that's applicable. The microbiology
16 section provides information on invitro activity and
17 relevant animal models of infection; there is a first
18 and second list of organisms. And the clinical study
19 section describes the adequate and well-controlled
20 trials that supported the indication.

21 So really to summarize, I think over
22 the last decade, we -- not just we, the agency, but we
23

1 as a community -- have made significant progress with
2 development of antibacterial drugs. New safe and
3 effective therapies are available to patients. There
4 certainly is more to be done, but it's also very
5 important that we learn from our experiences and
6 continue to refine our approaches to address patient
7 needs.

8 Some considerations to encourage as we
9 move forward, and, hopefully, a lot of these will come
10 up during the course of the workshop. We need to
11 identify the types of infections or the patients in
12 whom there is an unmet need, and how exactly do we do
13 this is important to discuss. We should consider in
14 all the study designs or end points, as long as they
15 are scientifically sound.

16 We need to work to improve the clinical
17 trial infrastructure in the United States, discuss the
18 potential role of clinical trial networks, and need to
19 identify barriers and also what we can do to
20 stimulate/investigate the interest in participating
21 and enrolling in clinical trials for anti-infective
22 drugs.

23

1 So with that, thank you very much, and
2 look forward to the discussion in the next day and a
3 half.

4 JOHN FARLEY: Thanks, Sumathi. Our
5 next speaker is Steve Bart, who's one of our fellows
6 here at FDA in the Office of Infectious Diseases.
7 Steve obtained his Ph.D. from the University of
8 Pennsylvania. His research was focused on Ebola, but
9 he's decided that antibacterial drug development is
10 much more interesting, as well as gaining
11 epidemiologic expertise to support that. His next
12 stop is the Epidemiology Intelligent Service at CDD,
13 and we congratulate him on that acceptance.

14 STEPHEN BART: Thanks, John. Can
15 everybody hear me? So like John said, I'm going to be
16 talking today about some of the work I've been doing
17 over the past year and a half or so about
18 antibacterial clinical trials and shifts in enrollment
19 and what impacts that might have on general
20 reliability.

21 So I want to first start off by talking
22 about drugs in general. And over the past few
23

1 decades, clinical trials have become increasingly
2 globalized. I'm showing this in two different ways
3 here: on the left, we're looking at the percentage of
4 investigators on INDs submitted to the FDA; and,
5 specifically, the percentage based in the United
6 States. So in 1990, the vast majority, 96 percent, of
7 investigators were based in the United States. Well,
8 by 2007, that percentage dropped to 54 percent.
9 Similarly, in 2008, over half, 57 percent, of subjects
10 in drug trials were enrolled from outside the United
11 States were interested specifically going forward in
12 antibacterial drugs.

13 And this is something that we've seen
14 no specific data on, but over the past few decades,
15 there's been a definite trend where new drug
16 applications have included increasingly more non-US
17 data. So these are excerpts from several recently
18 approved antibacterial drugs labels. And you can see
19 in all three of these cases an increase in enrollment
20 from other areas, and a decrease where there are a few
21 or no patients enrolled from the United States in
22 these registrational trials.

23

1 The drivers for these enrollment
2 changes are not particularly definitive, but these are
3 some speculated drivers that have been brought up:
4 cost, differences in clinical practice that might
5 affect recruitment, and the desire to tap emerging
6 markets worldwide. The second one, differences in
7 clinical practice is something that I think is really
8 important for antibacterial drugs, especially prior
9 antibacterial drug therapy which may present a
10 challenge to recruitment in some regions. And the
11 length of hospitalization for IV drug administration,
12 potentially dampening excitement by some -- for some
13 sites to host these trials.

14 For my talk today, I'm going to focus
15 on two major questions: how is antibacterial drug
16 trial enrollment changing, and can we quantify that,
17 and what impact does this changing enrollment have on
18 trial generalizability.

19 So in order to do this, I looked at new
20 drug applications or NDAs for antibacterial drugs that
21 have been submitted to the agency since 2001. From
22 these NDAs, I abstracted subject level data for
23

1 geography, demographics, clinical characteristics, and
2 microbiology for four different indications; so ABSI,
3 skin infections, CIAI, intrabdominal infections,
4 pneumonia, and cUTI, complicated urinary tract
5 infection.

6 I assigned subjects to one of seven
7 different regions, and they're colored coded here. So
8 each country that's filled in with a color had at
9 least one subject in the trial. And we could use
10 these classifications to determine different --
11 differences or similarities among these regions.

12 So let's take a look at some of the
13 data we've looked at -- we've collected. So I found
14 42 phase three trials from 20 different NDAs, so
15 there's 20 different products. There are 29,282
16 subjects in this dataset altogether, and there are 57
17 countries identified. So what I'm showing here is a
18 timeline of these trials. So each one of the circles
19 is a different trial, and they are organized on this
20 timeline by start date. So the first subject, first
21 visit; they're color coded by indication.

22 And you can see two distinct waves of
23

1 drug development activity from 2001 to 2009 or so, and
2 then after 2010 with kind of a dead period in the
3 middle here.

4 On the bottom, just to give a little
5 bit of context, each one of these diamonds represents,
6 and they're labeled, represent the publishing of a
7 different draft guidance by the agency in a field
8 important for drug development.

9 So in order to get a sense of how
10 enrollment might be changing, I compared trials
11 initiated from 2001 to 2009 with those 2010 to 2017.
12 So those data are shown here, so I'll walk you through
13 this here. So on the left side is 2001 to 2009, so
14 the early trials; the right side are the later trials.

15 Across the bottom are the different
16 indications we looked at with the number of trials for
17 each one of these time periods. The proportions of
18 subjects are on the Y axis, and they're color coded
19 based on region, based on the legend on the bottom.
20 So the bigger the bar, the more color from a specific
21 region and the more patients were enrolled from that
22 region.

23

1 So focusing on the left side first.
2 You see a lot of diversity and where subjects were
3 being enrolled from in the earlier trials. West
4 Europe, South America, North American and Eastern
5 Europe were all represented in all of the different
6 indications.

7 But by the second half of the study
8 period, after 2010, we saw a major focus in trial
9 enrollment for CUTI, CIA, CIAI, and CAP to Eastern
10 Europe. However, for ABSI, for skin infections, we
11 actually saw the opposite where North American
12 enrollment actually increased.

13 These are the same data just shown a
14 different way; so these are divided by indication,
15 instead of by time period. And you can really see the
16 concentration in Eastern Europe for the first three
17 indications here and in North America for skin
18 infections.

19 So we found that for new antibacterial
20 drug trials, there was a shift in enrollment towards
21 either Eastern Europe for most of the indications or
22 for North America for ABSI and skin infections.

23

1 We wanted to know what kind of impacts
2 it had on generalizability, so we looked at
3 demographics, clinical characteristics, and
4 microbiology to approach that from three different
5 lenses. Today, I'm going to focus on the clinical
6 characteristics, especially those that may have some
7 impact on recruitment and the microbiology.

8 So for these considerations, we used
9 subject level NDA data again. But the data were
10 pulled across the entire study period, so we're not
11 looking at the division by date as we did in the
12 previous slides. First thing I looked at was prior
13 antibacterial drug therapy. So for some indications -
14 - so ABSI, CAP, and cUTI -- FDA guidance recommends
15 limiting the percentage of subjects that had received
16 an potentially effective antibacterial drug
17 immediately before study enrollment because of the
18 potential difficulties that could be introduced with
19 interpreting non-inferiority trials.

20 For cIAI, the FDA doesn't have that
21 same recommendation. So we looked at cIAI patients
22 who received an antibacterial drug within the first 72
23

1 hours before randomization to try to identify
2 differences regionally in the percentage of subjects
3 that are receiving treatment.

4 You can see, compared to North America,
5 Eastern European subjects are much less likely to
6 receive prior antibacterial drug therapy. So you can
7 kind of imagine that if you're screening patients, if
8 you have a subject population that has much less prior
9 antibacterial therapy, you may be able to screen fewer
10 patients in order to -- in order to recruit an
11 adequate number.

12 So that, like I said, is looking more
13 at the cIAI/cUTI side. But we found that ABSI
14 subjects were actually becoming more and more North
15 American over time as we looked at this, so we were
16 trying to figure out why. We looked at different
17 medical history aspects and found that North America
18 subjects were much more likely to be IV drug users
19 than their counterparts from other regions.

20 So I'm showing this here on the graph
21 on the left. So across the X axis are the different
22 regions that we looked at. The Y axis is the
23

1 percentage of subjects that reported current or recent
2 IV drug use. Each dot represents a trial.

3 So you can see that in Eastern Europe
4 to the right, there are very, very few subjects that
5 reported IV drug use. However, in North America, an
6 average of about 40 percent of subjects in ABSI trials
7 were IV drug users. This is much higher than the
8 estimated prevalence of IV drug use in the general
9 population shown in the red line of about 1 percent in
10 North America.

11 We looked at where these subjects were
12 being enrolled from and specifically by zip code. So
13 the bigger the circle and the deeper the color, the
14 more subjects were being enrolled from that area. So
15 you can see that most of these IV drug users were
16 being enrolled from California and Nevada.

17 So we want to move on and now talk
18 about microbiology. I'm just going to talk a little
19 bit about that to give in a sense of the
20 generalizability considerations that we did for this
21 analysis. So we analyzed regional differences for
22 cIAI/cUTI. We focused on gram-negative aerobes for
23

1 those indications and looked at all organisms for
2 ABSI. We weren't able to look at CAP because the
3 culture rate for CAP is much lower than these other
4 indications.

5 And we used FDA recognized breakpoints
6 for specific classes of antibiotics to identify
7 resistant isolates and compare those among regions as
8 well.

9 So I'm only going to show data from
10 cIAI today, just for the sake of time. So these data
11 are shown here. So we looked at gram-negative aerobes
12 isolated from cIAI patients in all of the trials that
13 we had. Across the X axis are the most common
14 organisms that were identified. The Y axis is the
15 percentage of isolates that that species is made up.
16 And each one of the different colored bars, using the
17 same schemes as before, represents a different region.

18 So E.coli was the most common species,
19 perhaps not surprisingly. And it's set on its own
20 axis on the left from 40 to 70, compared to zero to
21 30, just to point out for these less common organisms
22 on the right.

23

1 So we did identify some differences.
2 So South American isolates were more likely to be
3 E.coli than their North America counterparts.
4 Klebsiella pneumoniae was much more common in Asian
5 isolates, compared to those from North America.

6 However, reassuringly, it seems that
7 overall microbiology is very similar among the
8 regions. It wasn't like in one region, there were no
9 isolates of a species that was much more common in
10 North America, for instance.

11 So as I said, I'm only showing data for
12 cIAI. However, we did this same analysis for cUTI and
13 ABSI and found similar results.

14 We also looked at resistance
15 phenotypes, so these data are looking specifically at
16 Enterobacteriaceae and the cUTI and cIAI trials. And
17 we used FDA recognized breakpoints to assess the
18 susceptibility of these different isolates.

19 We focused on three different classes
20 of antibiotics: third generation cephalosporins, which
21 are sometimes used as a marker for ESBL production in
22 this family; carbapenems, which, of course, are going
23

1 to give an idea of carbapenemase production; and
2 fluoroquinolones. So these data are shown here on the
3 bottom: so the indications are across the X axis; the
4 Y axis is the percentage of isolates that are
5 resistant, so not susceptible, not intermediate, but
6 resistant according to the breakpoints.

7 And you can see some regions are much
8 more -- there's a much higher prevalence of resistance
9 compared with North America, which we made all of our
10 comparisons to. And these data, I think, would be
11 helpful in the future for people perhaps trying to
12 enrich for organisms resistant to these different
13 antibiotics.

14 So in terms of the conclusions. We
15 found that enrollment trends differ by indication, so
16 cUTI, cIAI and CAP trials increasingly enrolled from
17 Eastern European sites, while ABSI trials became more
18 dominated by North America enrollment.

19 For the sake of time, I didn't talk
20 about demographics today. But characteristics such as
21 age/sex didn't differ significantly for most
22 comparisons. Perhaps unsurprisingly, there was one
23

1 difference we found; that North America subjects had a
2 higher average BMI than subjects from other regions.
3 And this is important for consideration when reviewing
4 drug exposure data that's collected elsewhere.

5 We did find that certain clinical
6 characteristics, especially those that we think might
7 affect enrollment, vary by region. I didn't show
8 these data, but we didn't identify any large
9 differences in disease severity regionally, which is
10 an important factor to consider.

11 Eastern European subjects exhibited the
12 least prior antibacterial drug therapy for cIAI, and
13 this could either be a result of differences in the
14 prescribing practices or standards of care, or it
15 could be that Eastern European sites are more
16 efficient at enrolling before the initiation of
17 antibacterial drugs.

18 North American ABSI subjects were
19 disproportionately IV drug users, and this is
20 important to consider based on differences --
21 potential differences in infection types. So ABSI
22 subjects who inject drugs are more likely to have
23

1 wound infections, for instance, and microbiology.

2 I didn't show these data, but IV drug
3 users were more likely to have infections caused by
4 oral flora isolates, potentially because of the
5 practice of licking needles before injection.

6 We found that microbiology was probably
7 similar among regions, but we did identify regional
8 enrichment for some species and resistance phenotypes.

9 So overall, the conclusions of this
10 study are that demographic, clinical and microbiology
11 similarities between regions, less than
12 generalizability concerns for antibacterial drug
13 trials. However, U.S. participation is still
14 important in these trials, given known and unknown
15 regional differences. Some acknowledgements. Thanks.

16 ERIN DUFY: It's my pleasure to
17 introduce Helen Boucher, who is our next speaker.
18 Helen, as she said, is the Chief of Geographic
19 Medicine and Infectious Disease, the Director of the
20 ID Fellowship Program at Tufts, and a professor of
21 medicine at Tufts. I think I met Helen first in 2005
22 when we were just starting (indiscernible). She was

23

1 on our clinical advisory board and she's been a mentor
2 of mine ever since, for which I'm very grateful.

3 HELEN BOUCHER: Thank you so much,
4 Erin. That's very kind. It's very nice to be here.
5 And as is my usual disclosures are shown here, I'm
6 wearing the hat of the clinician today. And I'm going
7 to start us off just coming right back to why we're
8 all here at the beginning of World Antibiotic
9 Awareness Week, and I'm really grateful to our
10 colleagues at the FDA, the NIH and Pew for making this
11 happen. A lot of us have been talking about it for a
12 long time, so we're really grateful.

13 But we'll start right away with a
14 couple of cases. So this is a very typical case that
15 many of us see routinely in 2019. This is a 47-year-
16 old lady, schoolteacher, totally healthy, who
17 initially presented to her primary doctor with pain on
18 urination and some lower abdominal pain, and she was
19 started on standard oral therapy with ciprofloxacin.
20 But, unfortunately, she got worse and came back two
21 days later, now sick with chills, nausea and back
22 pain. She had a high fever and her exam was notable

23

1 for some tenderness in the right flank.

2 Her urine appeared infected, and they
3 got some blood work that showed an elevated white
4 blood cell count with a left shift. And they advanced
5 her therapy appropriately, according to the
6 guidelines, and she looked, despite this, you know,
7 well enough to go home. She was an otherwise healthy
8 lady, so she got one dose of intravenous ceftriaxone
9 and then was started on oral (indiscernible).

10 So it got a little worse. So two days
11 later now, four days into the illness, she's really
12 sick -- high fever, low blood pressure -- comes to the
13 emergency room and needs to be hospitalized for
14 support with hydration because she couldn't eat
15 because she was vomiting. She had a fever and low
16 blood pressure, as shown here. She had an elevated
17 heart rate. She looked sick. She was in pain over
18 her right kidney.

19 And despite the antibiotics that I
20 mentioned, her urine is growing greater than 100,000
21 colonies of klebsiella pneumoniae that was
22 subsequently identified as being ESBL producing, and

23

1 was resistant indeed to the ciprofloxacin, ceftriaxone
2 and (indiscernible), with which she had been treated.
3 So she was admitted and treated with a carbapenem,
4 which is the drug of choice for ESBLs. She got
5 better. So that's one kind of a patient, sort of
6 outpatient who gets sick.

7 Another patient is a lady I took care
8 of recently, a 60-year-old lady with leukemia who had
9 had chemotherapy induction and was in remission. She
10 was in the hospital recovering when she developed a
11 fever and a cough. Her chest x-ray showed pneumonia.
12 She had pancytopenia. Her cells hadn't recovered yet.
13 The hematologist, though, thought she was going to
14 recover. You know, they were very encouraged with her
15 prognosis.

16 So she was put on standard empirical
17 therapy with meropenem and vancomycin at our hospital.
18 And then we got this result; this is about when we
19 were called. The result came back, elizabethkingia
20 meningoseptica, and the lab reports that ID
21 consultation recommended this is a multi-drug
22 resistant organism and this is what we got. And you

23

1 can see all the Rs and you can see a couple of other
2 things. So you see plasmolysis NIS, (indiscernible),
3 with numbers in NIS and that means no interpretative
4 standard.

5 So those drugs are so new and this bug
6 is so weird that the lab can't even tell us. So what
7 do we do? We look it up, we call people, and we
8 realize that that's not good either, those probably
9 mean resistant.

10 So I had to go talk to this patient who
11 was sitting in her room relatively comfortable
12 actually. She's on minimal oxygen at this time, and
13 she said, how could this be; surely, you're going to
14 find something to treat this. So, of course, we tried
15 our best. We added ceftazidime, avibactam and
16 (indiscernible) in hopes that that combination of
17 avibactam (indiscernible) would do something for this
18 organism.

19 We rushed it off to Dr. Bonomo's lab in
20 Cleveland so they could do some fancy testing, and we
21 called the FDA. And ultimately, a company who gave us
22 compassionate use of (indiscernible), under
23

1 investigational new drug status, and everything was
2 done as fast as possible. It was incredible, you
3 know. Great thanks to everybody. But the drug got to
4 us four days later; that's about as good as it gets.
5 And we changed her background therapy based on the
6 results of Dr. Bonomo. We added minocycline. It was
7 quite a combination.

8 And sadly, despite all those efforts,
9 she deteriorated. She ended up in the ICU on
10 ventilatory support and succumbed 10 days later.

11 So, you know, these cases and many
12 others tell us that the crisis of AMR is here, and we
13 all know that in this room. We all know that this can
14 affect you and me. It threatens our modern medical
15 care and we have to do something about it now.

16 I think I'm here to talk about the fact
17 that we physicians often make decisions with limited
18 or even no data. The data we have is often much less
19 than what we would want. We have data on infections
20 at standard body sites, as Dr. Nambiar told us, which
21 are a great foundation for us to build from, but we
22 have to extrapolate to the patients who we see.

23

1 Patients don't always present with a UTI, skin
2 infection, or pneumonia. And every day, we work with
3 data from a variety of sources and a variety of
4 observations.

5 So one message that I hope I'll leave
6 you with in these few minutes is that, you know, we do
7 this every day. We extrapolate a lot from PK data,
8 from invitro and surveillance studies, right, what's
9 going on. And that crazy bug I just told you about,
10 we had never seen in our hospital, and we haven't
11 again -- thank heavens. But, you know, surveillance
12 can sometimes help us. We take data from different
13 indications and we take case reports.

14 You know, I'm here to tell you that
15 I've treated patients based on one case in literature.
16 And then our pediatric colleagues -- I'm really glad
17 that we have a pediatrician here -- they rarely have
18 any clinical data, right. They have PK data and adult
19 data from which they have to extrapolate into
20 children, like mine and yours, and little tiny babies,
21 right, which aren't the same. So this is kind of
22 where we are, and I hope we won't let, in these two

23

1 days, perfection be the enemy of the good or the good
2 enough, at least for us.

3 So back to what we need antibiotics
4 for, for all the things I mentioned in those cases,
5 but really everything we do, right? Every surgery --
6 cesarean section, joint replacement, the most common
7 surgery in America -- and the intensive care that our
8 hospitals are becoming, right -- our hospitals are
9 becoming one big intensive care unit so that all of
10 our patients require support with antibiotics.

11 So Dr. Farley started us off with the
12 CDC threat report, and I wanted to come back to that
13 for a minute because I think there's an observation
14 that's really important. This is a 2013 threat report
15 that we all know and love with our escape pathogens
16 and the other pathogens that we've been working so
17 hard on the past five years.

18 The 2019 threat report came out last
19 week and lo and behold, there was a new friend on the
20 block; candida auris is an urgent threat. It was
21 nowhere on the 2013 report, right? So the message is
22 that all this work that we're doing and all these

23

1 trials that we're designing have to help us be ready
2 for the threats we know about and the ones we don't
3 know about.

4 So we need to think about going after
5 drugs and indications in big buckets so that we have
6 the robust and renewable pipeline that will meet these
7 challenges. And thank heavens there are a few people
8 working in this space that might work for candida
9 auris.

10 So what about oral antibiotics? So the
11 presentation we just saw -- and if you look at the
12 Pew, which we're going to look at a little bit later,
13 the Pew report -- most of what's been happening in the
14 last 10 years is in the IV space. But we really need
15 oral antibiotics, right, because every time we have to
16 put a long IV catheter into somebody for two weeks, we
17 put that patient at risk of yet more infection.

18 And so, I didn't want to miss the
19 opportunity again to highlight the importance of
20 thinking about pathways for oral, as well as
21 parenteral antibiotics to get our patients back to
22 work, school, and being productive.

23

1 So then this -- I wanted to make a
2 quick comment about the U.S. patients. And I know we
3 heard the great presentation on this before, which is
4 encouraging, but I just picked one study that was kind
5 of -- that I was called on about recently, the study
6 of nosocomial pneumonia for ceftazidime avibactam.
7 And a group was considering, you know, putting this on
8 their formulary and I was asked the question of, how
9 can I put this on the formulary when we don't have any
10 U.S. patients.

11 And, in fact, when you drill into the
12 paper, and you do have to kind of drill into the
13 paper, which I would submit not everybody does, you
14 will see that this trial, this big trial, right, of
15 over 350 people per arm had zero U.S. patients; it had
16 a third from China, almost a third from Eastern
17 Europe. It was a great trial and it led to the
18 approval, but I think it does leave us where we're
19 making recommendations in the United States perhaps
20 without all the information we would like.

21 So what do we need? So we need a
22 diverse renewable pipeline of both IV and oral
23

1 antibiotics. We'd like to have some efficacy and
2 safety data from patients like ours, and that includes
3 big ones, as was said earlier. We'd like good
4 surveillance data to inform our empirical therapy.
5 Susceptibility testing to guide our therapy; it's
6 really hard when you get results like what I showed
7 you where there's no criteria.

8 Data from various sites of infection in
9 various types of patients; it's already been alluded
10 to that we have patients with certainly skin and urine
11 infections, but also bloodstream infections, bone
12 infections, young and old, obese, pregnant, people
13 whose organs don't work; that was alluded to earlier.
14 And PK data really does help with antibiotics, and I
15 think that can't be stressed enough.

16 We also need the data fast, and this is
17 a message I really wanted to spend a minute on. You
18 know, we hope to see data as close to real time as is
19 feasible, right, because we have patients now who need
20 this help.

21 So FDA labeling I think gets a bad rap
22 from a lot of clinicians, but it actually is used by
23

1 physicians. It's used by our pharmacy committees,
2 it's used by payers increasingly, and I would submit
3 that what's in the label does matter to docs. And we
4 get an idea saying others have been advocating that
5 CRE data and other multi-drug resistant pathogen data
6 really should be in the labels, even when it's
7 imperfect, especially in the setting of LPAD, because
8 it's useful to us when we have to make these
9 decisions. The limitations can be clearly stated, and
10 I think we'll see some very creative ideas on this in
11 the next two days.

12 Publications. I'm so glad my friend,
13 Dr. Baden is here. And the question there is, can
14 pivotal trials be published faster, especially when
15 the data becomes public as part of the FDA process.
16 It's great to see these publications in top tier
17 journals, but the sooner the better for those of us on
18 the front lines.

19 And then we're going to have some
20 conversation, and Dr. Sears is going to talk to us
21 about guidelines. We know that it takes a while for
22 guidelines to be published and sometimes up to 10
23

1 years. So the question is, can we expedite that
2 process? Should we consider alternative processes
3 while imperfect, something like the guidance that was
4 done for Hepatitis C perhaps, to help clinicians get
5 data lacking the perfection of a true guideline more
6 rapidly, so thinking about the risks and benefits of
7 that.

8 So finally, I'm circling back to where
9 I started. We physicians do work with incomplete data
10 every day. We can't care for our patients without a
11 steady stream of new drugs. And I don't think we can
12 insist on or wait for perfect data. We need every
13 piece of information we can get about new drugs,
14 susceptibility testing, along with good stewardship
15 and linked to good data so we understand how the new
16 antibiotics are being used to optimally use and
17 preserve the new drugs that we have.

18 So with that, I'll thank the colleagues
19 who helped me and all of you. Thanks very much.

20 ERIN DUFY: I'd like to introduce Sara
21 Cosgrove, who is a professor of medicine in the
22 Division of ID at Johns Hopkins. She's also the
23

1 Director of the Department of Antimicrobial
2 Stewardship and an associate hospital epidemiologist
3 at Johns Hopkins.

4 SARA COSGROVE: Thank you so much, and
5 good morning to everyone. Thank you for inviting me
6 to speak today. The official title of this talk is
7 the role of antibiotic stewardship programs and the
8 utilization of new antibiotics, but I feel like the
9 subtitle should be, we should all just get along,
10 because I recognize that on occasion, stewardship is
11 viewed as not a helper, but a hindrance, in terms of
12 new antibiotics. And I really hope to show that I
13 don't think that way. How do you advance? Here are
14 my disclosures. I keep advancing in the wrong
15 direction. Can you advance for me? Okay. You can go
16 to the next slide.

17 So I kind of wanted to talk about two
18 issues today, and one is to discuss real-world
19 challenges with positioning the use of new antibiotics
20 in hospitalized patients, and that will be my focus
21 today -- hospitalized patients; and then discuss the
22 role of stewardship programs and implementing the use
23

1 of new antibiotics to improve patient care and
2 minimize emergence of resistance.

3 So I'll start with a little bit of
4 data. I think this paper, which is published in OFID,
5 was one looking at essentially why is it taking so
6 long for newer agents to replace polymyxins, which are
7 clearly not very good drugs. And this is one of the
8 images from this paper with the number of CRE
9 infections, or carbapenem-resistant Enterobacteriaceae
10 on the Y axis. Polymyxins show up three times;
11 they're light blue, dark blue and gray. And this is
12 because the authors estimated proportions of the
13 numbers of CRE infections treated with polymyxins
14 before ceftaz-avi was available; and those are their
15 three different estimates -- 45 percent, 32.5 percent
16 and 20 percent.

17 They also note that in the data they
18 were using from IQVA that the data on route was not
19 provided. There is a fair amount of colistin that is
20 used in the inhaled form in the United States. And
21 so, they estimated for the purpose of this study that
22 65 percent of the use was IV.

23

1 And so, if you look at the red, which
2 is ceftaz-avi and (indiscernible) and plazomicin, they
3 note that using that mid-range estimate of colistin
4 that it was around December of 2018 that we started to
5 see more use of newer agents compared to colistin.

6 So that's a little late. And, you
7 know, I think we would all agree that we really should
8 have been using newer agents, instead of colistin and
9 polymyxin before that. Can you go to the next slide?

10 These are some data that came from
11 Anthony Harrison and Katie Goodman, looking at data
12 from the premier database. And these -- we just kind
13 of ran last week; this is a dataset that we have, and
14 I was curious what it looked like in premier. Premier
15 is 576 U.S. hospitals; about a fifth of them are
16 teaching, you know, more academic and the rest are
17 more community oriented. And in this, the Y axis is
18 days of therapy for 1,000 patient days, the blue are
19 the polymyxins, and the green is ceftaz-avi,
20 (indiscernible), And we have (indiscernible) in
21 there, but there wasn't any (indiscernible) being used
22 in this time period, which is 2016 to '17.

23

1 So in this dataset, we see the cross
2 more in the Spring of 2017. So, you know, where we
3 get our data from, you know, may indicate that there's
4 different uptake in different settings across the U.S.
5 And this data does include inhaled colistin, but only
6 3 percent of the use was inhaled colistin. It doesn't
7 change the graph at all if you take those out. Next
8 slide, please.

9 As part of the study in the first of
10 the graph that I showed you, there was a concomitant
11 survey done of pharmacists on guidelines for anti-CRE
12 infections that they had in their individual
13 institutions. The survey was 110 pharmacists in 41
14 states, and it was done in December of 2018. And what
15 I thought was interesting in this is that when
16 surveyed -- and it was 2018 when we saw that
17 crossover, but still a fair amount of polymyxin use.
18 But when surveyed, ceftazidime-avibactam and
19 (indiscernible) bactium were actually positioned in
20 these hospital survey to be first line therapy in the
21 majority.

22 So if you look at that pneumonia
23

1 column, for example, of 54 plus 32 percent, that's
2 pretty high. So most of the hospitals surveyed here
3 were saying, yes, these are first line agents and we
4 should be using them. They also asked about polymyxin
5 and aminoglycosides, and the one area where
6 aminoglycosides were still first line was in urinary
7 tract infections.

8 I added below this, ceftolozane
9 tazobactam and (indiscernible), which they did not ask
10 about in the survey because they were focused on CRE,
11 but just to remind us that those are two other drugs.

12 And then we've talked already in the
13 session about what things do get approved for. But in
14 the FDA approval column, as everyone knows, there's a
15 lot of complicated UTI approvals, which is a bit of a
16 stewardship issue sometimes. Next slide, please.

17 So why is uptick slow? We've talked
18 about this already today. The primary studies for FDA
19 approval are non-inferiority studies in patients
20 without resistant organisms, and pneumonia indications
21 and dosing information is late or doesn't exist. And,
22 you know, a lot of the patients who are dying of CRE

23

1 infections and resistant pseudomonas infections in the
2 hospital have pneumonia, and so that is a challenge.

3 I would say that this is not particular
4 a challenge for stewardship programs because we seek
5 to have access to these drugs as soon as possible. We
6 have people coming to us saying what can I do, what
7 can I do, as Helen demonstrated in her cases. And so,
8 we work around this, but it is potentially an issue.

9 We've also discussed low numbers of
10 patients with CRE and MDR pseudomonas in studies for
11 fast-tracked FDA approval. And I will say that we
12 don't actually want in the United States to have a
13 robust number of patients to enroll in studies with
14 CRE and multi-drug resistant pseudomonas. So, again,
15 you know, I don't want that. I think it's good that
16 we have trouble enrolling patients, to some degree.
17 But when you do show these data to people who are, you
18 know, data driven, they say, whoa, those numbers are
19 pretty small.

20 So you can see in this little graph
21 here, you know, the numbers for the new agent with
22 Mero/Vabor and (indiscernible) were 32 and 21, and
23

1 best available therapy were 15 and 10. So those are
2 pretty small numbers. You can see I put in
3 parenthesis the success rate with both of those. They
4 still do look better than colistin.

5 Post approval studies, which I think we
6 ultimately rely on, and I think it was really the
7 publication of studies that showed that these newer
8 agents were better than polymyxins, the post-marketing
9 studies that really started pushing the use more, but
10 they take a little bit of time. You know, even if you
11 adopt these drugs as soon as you have access to them,
12 it takes a little time to gather up enough patients to
13 publish that data.

14 Obviously, these agents are expensive,
15 and I can't leave that off. So there's always a
16 little bit more, you know, cajoling, negotiating that
17 might have to be done in some institutions to make
18 sure they get on formulary. And then initially, there
19 were difficulties with susceptibility testing. This
20 is largely resolved, which I think is a huge win. But
21 many will remember the time when you really couldn't
22 get ceftolozane/tazo testing done easily at all; and

23

1 that, of course, limits our ability to use those
2 drugs. But, again, I think it's a win that this has
3 been improved. Next slide, please.

4 So what are some of the stewardship
5 considerations with regard to new agents? I think
6 that stewardship programs recognize that these are the
7 agents of choice for resistant gram-negative rods. I
8 think ASPs are often the primary driver of formulary
9 additions of these new agents. We are watching the
10 studies, we are trained in infectious diseases, we
11 push to get these things added to formulary.

12 And then clinically, we often
13 coordinate issues with micro-testing, selection of the
14 optimal agents, selection of combinations of agents
15 that may or may not work, and also advise on duration;
16 that's kind of all in the role of stewardship. And I
17 think we're also critical in recommending optimal
18 dosing strategies. And so, you know, when an agent
19 comes out at a lower dose approved for complicated
20 UTI, I think we all in the hospital have to keep in
21 mind if we're going to use it for pneumonia, probably
22 need to use higher doses. And so, that's what we pay

23

1 a lot of attention to, what actual dosing do we want
2 to use in our patients in the hospital.

3 I think we also desire to ensure that
4 agents are used in a way to preserve their utility
5 though, and we have a lot of concerns about emergence
6 of resistance. We don't want to see resistance to
7 these agents across the population. We don't want to
8 see emergence of resistance to these agents within a
9 patient that we observe under our own eyes.

10 And we want to avoid treatment of
11 colonization, because treatment of colonization leads
12 to resistance; it's the best way to get resistance.
13 And I worry a little bit about some of the studies
14 that poll just data on CRE infection reports that a
15 lot of that may actually be colonization, and we need
16 to be very mindful of that.

17 And I think ASPs at this time, just
18 because we view these agents as so precious, are
19 unlikely to support routine empiric use. And I know
20 that that is a problem in terms of getting hospitals
21 to put these drugs not so much on formulary, but
22 getting them to be used and support the market. But I

23

1 fear as a steward that if we use these routinely for
2 empiric use, we will see faster emergence of
3 resistance. So next slide, please.

4 Just a little bit on this resistance
5 topic because I do think it's a major concern for us
6 clinically. I just have some examples of large-scale
7 data that show there is some baseline resistance to
8 all of our new agents; not bad, but it is something
9 that we still have to keep in mind we do need to test.
10 We can't, you know, assuming a hundred percent
11 susceptibility with all these agents.

12 And then some data from our own
13 institution, which is just pseudomonas
14 ceftolozane/tazo susceptibilities in 2017 to 2019, and
15 there was a huge difference depending on the
16 population we looked at in terms of baseline
17 resistance. So amongst CF patients, cystic fibrosis
18 patients, our susceptibilities at baseline were 38.5
19 percent, which is, of course, exactly the population
20 we want to use this drug in. And then in non-cystic
21 fibrosis patients, much better at 75 percent. Next
22 slide, please.

23

1 There's also some data on emergency of
2 resistance during therapy for both ceftazidime-
3 avibactam and ceftolozane/tazo. For ceftaz-avi, this
4 was a series from Pittsburgh of 37 CRE infections of
5 mixed etiology. In the study, clinical success was
6 seen in 59 percent of cases, but there was macrobiotic
7 failure in 27 percent of cases. And there was
8 resistance seen in 3 of 10 failures that developed at
9 a median of 15 days, so resistance is a reality for
10 us.

11 Data from my own hospital using
12 ceftolozane/tazobactam looks pretty similar in a way.
13 We had 35 resistant MDR pseudomonas aeruginosa
14 infections, saw clinical success in 46 percent of
15 patients, micro failure in 26 percent of patients, and
16 resistance. You know, so when I say resistance
17 emerging, I mean, we had a susceptible isolate and
18 then we went on to have a resistant isolate in that
19 same patient in 6 of 10 of our failures developing at
20 a median of six days. Next slide, please.

21 So why does this matter? Most of the
22 patients that we're treating with MDR gram-negative
23

1 infections have significant medical complications.
2 Many of them have major issues with source control,
3 particularly when the infection is intrabdominal. And
4 many of them have future medical needs, a need for a
5 lung transplant, a need for a stem cell transplant, a
6 need to undergo chemotherapy and become neutropenic.

7 So often, we're in the position of
8 having to say when should we pull the trigger on the
9 use of these new drugs so that we get the person over
10 the hump, so that we -- we can't just start it if we
11 have concerns that resistance is going to develop. We
12 have to time that in a way that we get them through
13 the procedure that they need to get through. Next
14 slide, please.

15 One other challenge I wanted to mention
16 was paying for new agents after patients are
17 discharged from the hospital. So insurance often does
18 not cover outpatient antibiotics; sometimes, it
19 doesn't cover any outpatient antibiotics regardless.
20 But when they're used off-label, that can be a big
21 issue that you have to fight with insurance companies
22 about; and sometimes, they still say no, even though
23

1 it's clinically obvious to you.

2 And then nursing homes, where sometimes
3 we have to send our patients, don't have these agents
4 on their formulary, and they often balk about
5 obtaining them due to the cost. And then changes to
6 the inpatient perspective payment system and the long-
7 term care hospital perspective payment system for
8 FY2020 don't actually address these problems. So this
9 is a constant battle in patients that are in the
10 hospital that stewardship teams and ID clinicians are
11 dealing with. Next slide, please.

12 I just wanted to mention briefly
13 stewardship's role in agents that are not directed at
14 MDR gram-negatives. As we know, these are approved on
15 the basis of non-inferiority studies for infections
16 that we don't have a big problem with, you know, that
17 we have a lot of cheap existing drugs to treat, and
18 they cost 10 to 25 times more than standard therapy.
19 So I struggle with this as a steward because, on the
20 one hand, it's hard for me to advise the hospital to
21 bring these un-formulary and use them for CAP or skin
22 infections.

23

1 But I also recognize that these agents
2 may have a lot of promise for future treatment of
3 infections that we don't even know about yet. And
4 just as an example, a metacycline may have a
5 significant role in treatment of (indiscernible) or
6 perhaps (indiscernible). And so, we don't want, as
7 stewards, to have these drugs go away. We want to
8 have the ability to see future studies that show that
9 they work for these rarer issues, but it's still
10 financially a hard sell to a hospital to bring agents
11 that cost this much onto formulary. Next slide,
12 please.

13 So what can be done? I think we're
14 going to spend the next several hours talking about
15 this. I do think that there's still a proportion of
16 ID clinicians, of critical care clinicians and so
17 forth that may still be using polymyxins, and we need
18 that to stop. And so, what do we do about that? And
19 I think the idea of guidelines or probably guidance,
20 because we don't have tons of clinical data, are a
21 good idea to really push forward the idea that these
22 are the agents that we should be using and getting
23

1 those messages out to our colleagues.

2 I think we need to continue to push for
3 post-approval data on utility for multi-drug resistant
4 gram-negatives from all sites and think about new
5 study design, such as adaptive clinical trials, to
6 really get at which agent should be used for what and
7 how. I think we need to develop approaches to predict
8 which patients may benefit from empiric treatment with
9 these agents because we want to avoid overuse. We
10 need to think about predictive models that might help
11 with this, the role of surveillance cultures, and then
12 the role of rapids, because if you can get rapid
13 diagnostics and say use it quickly, then that helps.

14 I think that the change in colistin and
15 polymyxin B breakpoints will change; basically,
16 nothing is susceptible anymore to colistin and
17 polymyxin B. CLSI did this on purpose, and I think it
18 is a real win that they did this because clinicians
19 will see intermediate or resistant now every time they
20 send the test for colistin susceptibilities.

21 And then I think we need to continue to
22 ensure and keep going the good work we've done with

23

1 ensuring that we can get susceptibility testing for
2 the new agents. Thanks.

3 JOHN FARLEY: Thanks very much, Sara.
4 So it's my pleasure to introduce Amy Leitman, who's
5 the Director of Policy and Research and NTM Info and
6 Research. It's a nonprofit patient advocacy group
7 with patients with non-tuberculous micro bacterial
8 lung disease and related comorbid diseases. I've had
9 the pleasure of working with this organization for
10 about the past decade in the NTM space. And in my
11 view, we need more organizations like this in the AMR
12 space. So thanks very much for joining us, Amy.

13 AMY LEITMAN: Thank you. Thank you for
14 having me here today. I'm going to touch on various
15 aspects of the patient perspective in clinical trials.
16 Some of them I'll go into more detail and some of them
17 I know we will hear about later from CTTI, so I'm
18 going to leave those parts alone for the other
19 experts. These are my disclosures.

20 So I'm going to start with what do
21 patients need and want in therapies. So we've heard
22 some already about the antibiotic challenges, the
23

1 challenges in developing antibiotics. And one of the
2 things that I've noticed is patient-reported outcomes
3 are not really integrated into the development of
4 antibiotics, and I think that this is something that
5 we should be looking at more carefully.

6 There are other areas of drug
7 development where the pipeline is much more robust.
8 They've started to integrate PROs much more, and
9 they've had better results because of it.

10 So what do patients need and want? To
11 start, they need better options, especially, you know,
12 we're facing this rising tide of multi-drug resistant
13 organisms. They need more options. They need other
14 therapies: sometimes, they are allergic to a
15 particular therapy; sometimes, they have a pathogen
16 that's resistant to one and not another; and
17 sometimes, they have a susceptible pathogen and the
18 therapy simply fails. So having more options is going
19 to be better for patients.

20 They also want new and creative
21 options. Antibiotics just, they're not going to be
22 enough, I don't think. We're facing -- we're up
23

1 against evolution. To put it bluntly: these bugs are
2 just better at evolving than we are. They're smart,
3 and they're designed to evolve to resist. There are
4 other areas that should be explored; some of them are
5 already being explored and developed in combination or
6 adjunct therapies.

7 So I've seen some of the early research
8 that has been done on sort of these compassionate use
9 cases for bacteriophages. It suggest that
10 bacteriophages working in tandem with antibiotics can
11 be effective. It's a very difficult area of
12 development, but I think it's something that we should
13 be looking at. We probably should have been looking
14 at it sooner, and I think it could be a huge step
15 forward for the use of antibiotic therapy as a
16 combination.

17 Targeting the bugs themselves, and
18 specifically those mechanisms that confer drug
19 resistance, is another possible avenue, as is
20 developing antibiotics that essentially trick the
21 pathogens' defense mechanisms and avoid resistance.
22 And I know there are a couple of companies that are

23

1 sort of in the early stages of looking at these
2 things. But overpowering a mechanism of resistance is
3 a therapy that might be useful in terms of allowing an
4 antibiotic that was previously resistant to go in and
5 work effectively.

6 And tolerating treatments is also an
7 issue, and this is a big challenge in clinical trials,
8 because it's not enough just to get them into the
9 clinical trial; they have to be able to take that
10 therapy through the clinical trial and get through it.
11 So I think this is an area that we don't address well
12 enough. I think there are other disease states that
13 do a better job of addressing it, and I think there
14 are valuable lessons to be learned there.

15 One of the biggest frustrations I've
16 heard from patients is about clinical trials
17 themselves. The criteria are often exclusionary to
18 the point of hampering the enrollment. The design
19 doesn't take into account the impact that the therapy
20 might have on the patient and whether that should be
21 measured.

22 And the end points don't often enough
23

1 include patient reported outcomes from tools that
2 assess this patient over an appropriate period of
3 time. And that's another question that we need to ask
4 and it's really going to depend on what is the
5 infection, where is the infection, and how is it being
6 treated. So determining an appropriate length of time
7 to assess that is important.

8 So what else helps them? Better and
9 faster diagnostic tools can help make a difference in
10 clinical trial enrollment, and identifying a pathogen
11 sooner can help determine that they are eligible to
12 enroll in a particular clinical trial.

13 Likewise, being able to identify
14 susceptibility of the pathogen can make a difference,
15 particularly if you need to explain to the patient or
16 their loved one that they have an infection that is
17 drug resistant and will be extremely difficult or
18 nearly impossible to treat.

19 Only focusing on the pathogen in the
20 tube, we're missing critical information. We need to
21 also learn more about the infection in the patient and
22 how that patient's body reacts to it, in order to
23

1 properly determine and understand how we figure out
2 what the susceptibility is to the drug.

3 So I touched on the first two,
4 bacteriophages and other adjunct therapies. But I
5 want to talk a little more about what else is going to
6 help patients, particularly when we're talking about
7 clinical trials. One of the objectives I mentioned is
8 to get that patient to stay on the therapy because
9 that's how you see if it works. So this is often call
10 retention, but patients actually usually refer to it
11 as enduring or endurance.

12 So the cancer community has actually
13 become quite adept at this. A lot of cancer treatment
14 centers offer a variety of supportive therapies to
15 help mitigate or manage some of the more severe side
16 effects, including gastric effects, and resulting
17 dehydration and malnourishment. It's actually routine
18 to pretreat a patient with an antiemetic, and the
19 American Society of Clinical Oncology has a clinical
20 practice guideline actually specifically regarding
21 this.

22 And I know that some of the key opinion
23

1 leaders in NTM now have actually started in their
2 presentations talking about the fact that when they
3 have to treat with a drug like triglycine, they've
4 started pretreating with ondansetron because it helps
5 the patient better tolerate the therapy, and they're
6 getting better results with that.

7 So one area we need to better
8 understand also is the relationship between our own
9 microbiome and immunity and inflammation. The gut
10 microbiome has historically not been that well
11 understood, just that it's there and it serves a
12 purpose, and disrupting it can cause gastric and other
13 issues.

14 More recently, our understanding
15 encompasses the idea that as part of a whole system,
16 this microbiome is a valuable part of the body. We
17 emphasize to our patients that they must take a
18 probiotic while they're on an antibiotic. The
19 literature that we put out, what's on our website,
20 emphasizes this as well. But it also tells them
21 something else; it tells them how to take a probiotic.

22 We tell them don't take it at the same
23

1 time as an antibiotic because you're effectively
2 neutralizing it. This sounds pretty basic and simple,
3 but you'd be surprised at how many people go, oh,
4 right, okay. You have to actually communicate to the
5 patient in a way that they're going to understand, and
6 you have to make sure they're getting all the
7 information that they need, especially when you're
8 dealing with life-threatening infections. There's a
9 lot coming down at them.

10 So we've talked about respiratory
11 infections as well, and I'll get into that in a little
12 more detail afterwards. I want to talk now about some
13 key challenges. Time is the first one when we're
14 talking about critical infections in particular. This
15 doesn't allow of time to determine enrollment; that's
16 why rapid diagnostics could be very useful.

17 Another issue is that 24-hour rule.
18 Sometimes, you have this concept where if a patient is
19 on therapy for more than 24 hours, they can't enroll
20 in a clinical trial. But I guess, you know, one of
21 the words we're used to using is refractory, when the
22 infection is refractory, and we've seen clinical
23

1 trials where they have to have refractory disease
2 before they go into the clinical trial.

3 But, you know, if you're talking about
4 different kinds of infections, what defines refractory
5 then; when do you determine that a UTI or a skin
6 infection is refractory? What defines failed therapy?
7 Because even if it's more than 24 hours of
8 antibiotics, at some point, if they're not responding
9 to therapy, then the therapy has failed and it's
10 probably time to consider something else, and you may
11 want to think about enrolling them in a clinical trial
12 at that point.

13 And I want to emphasize here the
14 wording because this is something we hear a lot and,
15 again, this is about how we talk to patients and talk
16 about patients. The patient doesn't fail therapy; the
17 therapy fails the patient.

18 Decision capability. As a health
19 crisis increases, the patient or legal representative
20 hears things more through this, what I call, a filter
21 of fear. So, again, they've got this information
22 coming at them, and they have to make these often, you
23

1 know, life critical decisions. How you word things
2 and how you say things may also matter, but
3 identifying early risk factors to infection and having
4 rapid diagnostics together, I think, would be a very
5 powerful tool to enrolling.

6 Pre-consenting for a clinical trial
7 would mean that as soon as it's apparent that a
8 patient is or may be an appropriate candidate, they
9 can be started on the consent process, so that if they
10 become more critically ill, you don't have to wait for
11 that process to start. It already takes a little
12 while to get them enrolled; you start that sooner.

13 Exclusionary criteria are another
14 issue. Two major populations of patients who need
15 antibiotics -- diabetics, cancer patients -- are often
16 excluded. They're more prone to infection. I know of
17 several patients who, when they were starting their
18 cancer treatment, were told don't go for a manicure or
19 pedicure because you might get an infection that we
20 can't treat. So that really tells you there's a whole
21 population out there of patients that could be pre-
22 consented to enroll. That's how great their risk is,

23

1 but they're routinely excluded.

2 One more point to make about barriers
3 and issues. Financial challenges are a barrier and
4 that was touched on earlier. This is also a challenge
5 in clinical trials. If you're running a clinical
6 trial, you should be prepared to bear the cost of the
7 patient testing because, oftentimes, their insurance
8 won't. They think about other things: they think
9 about, you know, how much work am I going to have to
10 miss; how much will I need to do for this trial,
11 what's the time commitment; will I be able to afford
12 this, how far do I need to travel?

13 I want to present a case study now. So
14 this illustrates how at various points intervention,
15 better treatment options, and early consent might have
16 helped this patient. This information was provided by
17 his closest friends and family, who were present
18 throughout the course of his illness, and it includes
19 their observations on measures which might have helped
20 this patient. They've given their consent to have me
21 share his story.

22 The patient in question was a 43-year-

23

1 old male with multiple comorbidities, including
2 obesity, poorly controlled diabetes, and corresponding
3 poor dietary habits. And based on their description
4 of increasingly antisocial behavior, probably
5 undiagnosed and untreated depression.

6 The patient developed pain in his left
7 foot, but did not seek immediate treatment. After 10
8 days, he was taken to the hospital where a severe MRSA
9 infection was identified. Over the course of a 10-
10 month in-hospital stay, the patient underwent
11 extensive treatment with antibiotics, had his pinky
12 toe and surrounding tissue amputated. He had multiple
13 treatments with a hyperbaric chamber and, overall, had
14 approximately 50 surgeries to debride additional
15 tissue and muscle. He was discharged after
16 approximately 10 months of treatment.

17 About six months later, the patient
18 once again developed symptoms, including discomfort in
19 his foot and leg. Motivated by his previous
20 experience, he sought treatment quickly and was
21 hospitalized for two weeks, receiving additional
22 antibiotics and more hyperbaric treatment.

23

1 Four to five months after his second
2 hospitalization, the patient became symptomatic again
3 and sought treatment, receiving additional antibiotic
4 therapy. After approximately three weeks with failing
5 treatment and showing symptoms of sepsis, the patient
6 lost consciousness. He was comatose for two weeks and
7 died of multiple organ failure at the age of 44.

8 As they related this story to me, his
9 loved ones and his friends made several observations
10 that I thought were really critical to talking about
11 critical trial design for antibiotics. First, that
12 lack of treatment option certainly contributed to his
13 death, and had there been better treatments available,
14 he might be alive today. This speaks to the growing
15 need for therapies that fight this rising tide of
16 drug-resistant bacteria.

17 Another observation they made had to do
18 with the clinical trials. At no point had anybody
19 discussed with them or his family enrolling in
20 clinical trials. But they noted that for someone with
21 comorbidities like obesity and diabetes where the
22 patient is not taking proper measures to control them,
23

1 simply being at risk might not be enough.

2 Their observation that fear was a
3 motivator for the patient to seek treatment faster the
4 second time the infection presented prompted their
5 observation that prior history of infection could be
6 used to identify at-risk patients who will be more
7 amenable to the idea of early consent for clinical
8 trials, and this is particularly true when you're
9 dealing with certain comorbidities.

10 Finally, when discussing the totality
11 of care, his loved ones observed that at no point in
12 his treatment was he given psychological counseling,
13 despite the physical trauma he had endured, that
14 included again more than 50 surgeries.

15 Interventional therapies are necessary
16 for many different patients for many reasons, and they
17 increase the chance of a positive outcome. In
18 clinical practice, these interventions are often used
19 and desired. So, again, I want to raise this
20 possibility that they should be considered in a
21 clinical trial setting. It helps reflect a more real-
22 world practice that you would want, and it helps to

23

1 possibly optimize an outcome. It helps possibly
2 increase positive outcomes for the trial and for the
3 patient.

4 So what else should we be measuring?
5 We've talked about microbiology and symptoms. Some of
6 these things are obvious, symptoms such as fever,
7 swelling, redness and discharge; these things can be
8 measured clinically. But there's another set of
9 measurements that we've discussed briefly. I want to
10 get more into that now, and that's patient reported
11 outcomes.

12 So what can patients tell us about
13 their illness? This is a host of symptoms that
14 infection patients, including those with sepsis,
15 chronic respiratory infections and acute respirator
16 infections such as pneumonia, have reported. They're
17 generally difficult to measure in a lab, but there is
18 an entire area of science dedicated to developing
19 tools that measure these things. These symptoms range
20 from pain and fatigue to respiratory symptoms and
21 mental symptoms, among others.

22 This is a table showing the use of
23

1 patient reported outcomes, more than 500 in oncology
2 clinical trials. These data were collected through
3 clinicaltrial.gov postings over a six-year period from
4 September 2006 through December 2012. A good example
5 was a trial for small cell lung cancer using a
6 particular symptom list. That looks remarkably
7 similar, doesn't it, to the previous slide displaying
8 symptoms reported by those with respiratory
9 infections.

10 So there are a number of PRO tools that
11 are validated for various diseases and, in particular,
12 for oncology. And instead of reinventing the wheel,
13 these are possibly tools that we could be looking at
14 for use in infection disease spaces.

15 How far out do we measure with a PRO?
16 So, again, that's really going to depend on the
17 infection; where it is, what it is, and what outcome
18 we're looking for. We need to answer those questions.
19 They're going to be difficult to answer, but this is
20 part of developing a good PRO.

21 Sepsis survivors have reported similar
22 experiences to other respiratory infections, and
23

1 patients with chronic respiratory infections, the
2 matter complicated even more by their prolonged course
3 of treatment. And it means that their symptoms may
4 not resolve for a long time, and it also means that
5 their side effects may be confused with symptoms.

6 So I want to talk a little bit about
7 messaging, messaging matters. I've not really heard
8 of many patients walking into the doctor's office and
9 saying, hey, doc, I have dyspnea. But they do say
10 things like, I'm short of breath or I'm having trouble
11 breathing. And to a doctor, that means dyspnea. And
12 actually, when we conducted a patient survey on
13 preferences in treatment and so forth back in April,
14 when we talked about their side effects and their
15 symptoms, we put shortness of breath and then the word
16 dyspnea in brackets, making sure we use patient-
17 focused language.

18 So messaging matters. Patients and
19 their loved ones want to gather as much information as
20 possible, so talking to them is important. Speaking
21 clearly and plainly without making them feel confused
22 or uneducated makes them feel valued and that they're
23

1 doing something valuable; it can help them feel
2 empowered and that their loved ones feel that they're
3 helping -- something helping the patient as well.

4 And just as an example. We actually
5 had a meeting last week for one of our research
6 consortium projects, and I believe the word was
7 borborygmus or borborygmi. There were 12 of us in the
8 room and 6 of us were wondering what it meant. It
9 means a loud stomach, in case you're wondering.

10 So I just want to leave you wish this
11 little anecdote about messaging. This is the Panthera
12 Tigris, that's what the scientists named him, he's
13 very cute is a lovely creature. He's renowned for his
14 -- yeah, he's very fuzzy and cute, isn't he --
15 renowned for the hunting prowess, largely due to a
16 combination of the powerful legs, strong jaw, razer
17 sharp teeth and claws, and those claws are curved and
18 retractable. So this tiger is beautiful and everybody
19 loves a fuzzy creature.

20 But when the ordinary citizens of the
21 internet started renaming animals, we came up with
22 very big cat and danger kitty with murder mittens. It
23

1 sounds ridiculous. But my point is this: when you're
2 trying to teach someone who doesn't know what a tiger
3 is about the risks associated with them, this might be
4 as good a place as any to start. Thank you.

5 ERIN DUFY: Thank you very much. Okay,
6 now I'd like to introduce Wes Kim. He's a Senior
7 Officer of Innovation at Pew Trusts. His work is
8 focused are research and, in particular, policies that
9 help to drive antibiotic research and development.

10 WES KIM: Great. Thank you, Erin, and
11 appreciate the opportunity from FDA for me to present
12 our work in the antibiotics analysis.

13 So I think most, if not all, in this
14 room know that Pew tracks a global pipeline for both
15 small molecules and non-traditional. Today's
16 presentation will be strictly focused on the small
17 molecules, and we started tracking in 2014 and have
18 continued to do so up to today.

19 And about a year ago, we said wouldn't
20 it be cool if we took a five-year historic analysis
21 and see if we could identify any trends or something
22 that would inform future R&D, advocacy, investments.

23

1 So today's presentation will dive into what we found
2 in the past five years, and then our most recent
3 updates.

4 So overall, there were 67 total small
5 molecule antibiotics in the clinical development.
6 Additional notes for the scope: this doesn't include
7 TB drugs and doesn't include antifungals. Within this
8 five-year timeframe, we saw 20 new entrants with an
9 output of 10 approvals. Also, there were 15
10 discontinued products or candidates, and 10 that
11 stalled, which are essentially those that started --
12 where we tracked, started tracking clinical
13 development in 2014 and there weren't substantial
14 updates to that program.

15 So this is a snapshot of what we found
16 in 2014 to 2018 analysis, so let's take a deeper dive
17 into what individual types of the candidates. So as I
18 mentioned, 67 to start with. Now, if you come a gram-
19 negative to a gram-positive, we see about a 40 and 60
20 percent split across the 67. About 17 were targeting
21 against CRE, another 11 were targeting against C.diff.

22 And so, it will be interesting over the
23

1 next 5-10 years how this balance between gram-negative
2 and gram-positive pans out. Certainly, there's a lot
3 of -- there's a big spotlight on gram-negative
4 pathogens, but also as we've seen in the prior CDC
5 report and current CDC report, that C.diff is still an
6 urgent pathogen.

7 Now, I want to talk about the novelty
8 of drugs, so let's take a look between the gram-
9 positive and gram-negative and how they break out
10 between a candidate that has a novel component versus
11 those that are candidates that are building off prior
12 generations or prior scaffolds.

13 On the gram-negative side, you see
14 about 4 out of 26; if my math is correct, that's about
15 15 percent on the gram -- sorry, that was g gram-
16 negative. On the gram-positive side, 13 out of 41; I
17 think that's about 30 percent. It's hard to say if
18 that's a coincidence or a correlation. We don't have
19 enough data to make that kind of distinction, but I
20 just wanted to share what we've been seeing.

21 And then in terms of those that
22 ultimately came out on the end for either approvals or
23

1 for those that were in development or stalled, you
2 see, as a mentioned in the previous slide, there's 10
3 total approvals, 6 of those are targeting gram-
4 negative and 4 are gram-positive. So for those who
5 are all in on the gram-negative team, then that's not
6 too bad.

7 But let's take a look now at the
8 approvals specifically. So as I mentioned, 10 within
9 the 2014-2018 timeframe, and then the bottom three, I
10 updated with the recent approvals this year, including
11 the one, (indiscernible) that was approved last week.

12 If you look at the column that has
13 novel components, you see three that has a checkbox:
14 two of those are the beta lactamase/BLI combinations,
15 the BLI components being the novel component; and then
16 (indiscernible) was a (indiscernible) that was
17 discovered in 1950s and is novel in the sense that
18 it's for systemic use.

19 I will note that what we saw in the
20 remainder of the pipeline that there's a six other
21 candidates that are beta-lactamase/BLI combinations.
22 Whether we'll see more of those in the pipeline, it
23

1 will be interesting to look at. We don't track pre-
2 clinical candidates. I know WHO in their forthcoming
3 update will provide a summary on the pre-clinical
4 landscape and looking forward to that.

5 If we look at the column with activity,
6 again, it's gram-negative escape pathogens, I think
7 there's a pretty good distribution of and the
8 checkmarks, so, you know, we should celebrate these
9 wins.

10 In terms of those that are indicated
11 for WHO critical pathogen, how many of you guys think
12 -- or how many checkmarks do you think we'll see in
13 this column? Actually, none, and I think that's part
14 of the discussion that we'll continue to have today.
15 And, you know, this is something that we track, of
16 course, in our pipeline, and we would hope to see some
17 ways to -- obviously, some of these drugs are being
18 treated -- or being used empirically for CRE
19 infections and other critical pathogens, but they are
20 not indicated per se.

21 So those updates were from 2014 to
22 2018, the cutoff being December of last year. And

23

1 since then, we've updated our clinical pipeline. So
2 as of June 30th, you see a total of 42 in the clinical
3 development. So if you count, the numbers don't add
4 up, that you see 37 total in pill bottles, but those
5 are the ones that are in phase two -- phase one, two
6 and three.

7 There are four NDAs at that time under
8 view, and one complete response. Since there, there
9 are three approvals and, unfortunately, one company is
10 seeking a development partner after their phase three
11 trials.

12 We did not see any new entrants. And
13 year over year, total number of candidates have been
14 steady. So over the past five-six years, it's ranged
15 from upper 30s to low- to mid-40s, so we haven't seen
16 a spike or a complete downturn in terms of the total
17 number of candidates. So we've -- this seems like
18 over the past five-six years, about 40ish is kind of
19 the steady state.

20 I do want to focus on the phase three
21 clinical development candidates. There are 13: three
22 are based on novel candidates, so that's excluding;

23

1 but, unfortunately, one has since been now
2 discontinued. So that highlights the kind of
3 challenge of phase three or clinical development.

4 For those who are well steeped in the
5 probability of success in phased clinical development,
6 generally speaking, phase one is pretty high, then you
7 see a dip in phase two. But once you show that proof
8 of concept and have successful pivotal trials, you're
9 probability of success for phase three does tend to
10 come up a little bit. However, that's no guarantee,
11 as we saw from one of the drugs that had been
12 discontinued since. Six within the 13 are expected to
13 have activity against CDC threat -- or urgent threat,
14 according to the most recent publication.

15 So we talked about activity against
16 gram-negative escape pathogens. 17 of the 42 have
17 activity, so that's a decent percentage, but we still
18 need more. And I had mentioned, you know, if we think
19 about the call for action for more novel candidates
20 treating these escape pathogens, particularly gram-
21 negative escape pathogens, one of them had activity,
22 one that was novel and activity. But, unfortunately,

23

1 as I mentioned, this has been terminated since. So we
2 don't, at this point, have a novel candidate that's
3 targeting gram-negative escape pathogens.

4 So to wrap up, I'll just tee up some
5 questions that, you know, keeps me up at night: How do
6 we reinvigorate the antibiotics pipeline; how do we
7 populate the pipeline with more differentiated
8 antibiotics? And by differentiation, I'm not -- it'd
9 be great more novel scaffolds making these actions.

10 But to what Dr. Boucher talked about
11 earlier, you know, a product can be differentiated
12 based on the route of administration. So the more we
13 have clinical tools for our ID docs, the better.

14 And then other than financial push and
15 pull incentives, this has been a hot topic for the
16 past few years. What other levers are available to
17 facilitate and reinvigorate in the clinical pipeline?

18 And with that, just quick
19 acknowledgements. My colleague Cara Lepore, she does
20 the grunt work and the heavy lifting in our clinical
21 pipeline, and then our expert reviewers who we pick
22 their brains and help us characterize accurately each

23

1 of the individual candidates. So thank you.

2 JOHN FARLEY: I want to thank all of
3 our speakers from this morning. We wanted to quickly
4 get some data updates and different perspectives on
5 the table. We do have time coming for clarifying
6 questions and discussion with the audience. We're
7 going to take a 15-minute break at this point. And
8 why don't we make a point of all being back here at
9 10:35, so 10:35. Thanks.

10 (Break)

11 JOHN FARLEY: Thanks, everybody, and
12 for our next workshop, John Rex and I have decided on
13 a different coffee plan, so, we apologize for the long
14 line. John will be buying coffee for everyone. No,
15 I'm just kidding.

16 So we're now going to turn to a review
17 of the current federal efforts to support
18 antibacterial drug development and our first speaker
19 is Dennis Dixon, well known to many of us, who's the
20 chief of the bacteriology and mycology branch at NIAID
21 and the National Institutes of Health. Thanks,
22 Dennis.

23 DENNIS DIXON: Thank you. Thank you,

1 Leslie. So I think most people know that the NIH is
2 their research agency within the federal government
3 and we do research that's basic in nature,
4 translational, and clinical.

5 And if you want to look at our strategy
6 for antibacterial resistance, you can use the search
7 engine of your choice and put in NIAID AR PDF and you
8 should see this pretty document which goes through a
9 lot of our activities from years -- several years ago
10 and the resources available and the philosophies on
11 what new strategies we need to do.

12 This will be updated shortly. It's
13 been revised, updated, even had input from the
14 community, and will be appearing in a similar spot on
15 the web when it is released. So basic research.
16 Well, what's that got to do with product development?

17 It certainly provides seeds for new
18 targets, for new drugs, vaccines, and diagnostics and
19 that's what all of the research is ultimately aimed
20 at, as you can see from the graphic, but that is truly
21 what we're focused on in NIAID is looking for better
22 means of diagnosis, prevention, and treatment of
23 disease.

1 And I'll cite just one R01 that's
2 pretty remarkable and within the group that I oversee,
3 and it was by Andrew Myers for total synthesis of
4 tetracyclines which led to the spinoff company,
5 Tetraphase, which led to one licensed drug and several
6 other candidates in the pipeline.

7 That went through a number of other
8 grant awards in NIH and then moved on to BARDA and on
9 to licensure. So right out of an R01 grant. We have
10 a lot of translational opportunities that I'm going to
11 spend some time on and some clinical opportunities
12 that I will also talk about.

13 So a lot of stuff on this slide. I'm
14 going to turn it into a story momentarily, but a
15 couple of points to make first are that this doesn't
16 require a grant application. These are free services
17 for product development for someone who has a bona
18 fide product development plan and wants to move toward
19 a product.

20 So these are things you can request for
21 free to assist with product development and just to
22 look in the lower left, you can see that the kinds of
23 things available are MIC tests, animal models, too,

1 synthesis and CMC, ADME assays, pharmacokinetic
2 safety/toxicity. These are administered through
3 individual service contracts.

4 They're in place to conduct these
5 services and they are at the ready for bona fide
6 customers to come and use. Just in my branch alone, I
7 see several of the people who are involved with this
8 who have written these task orders under the contracts
9 or who oversee them or meet weekly as we hosted last
10 year, 58 different calls and meetings, to talk about
11 these services.

12 And the story I would tell about these
13 services is back when I had the privilege of living in
14 Basel, Switzerland and working at Hoffmann-La Roche
15 for an extended two-year sabbatical, a beautiful
16 campus spanning two sides of Grenzacherstrasse and
17 overlooking the Rhine, my lab where I worked had a
18 beautiful view of the cathedral. It was 60 feet from
19 the Rhine.

20 The point is, this campus housed labs
21 for screening for running MICs, an animal suite where
22 you could go and put these same experiments through
23 animals, larger animals up through non-human primates.

1 The animal tissues you could get back and sent to
2 histopathology and have the fungal stains or anything
3 else you want run on them, the histopathology and so
4 for, and have them interpreted.

5 If that compound wasn't quite right,
6 you could meet with the chemistry labs over on the
7 other side of the street and talk with them for
8 optimization. And so structure activity relationship
9 could be defined, new discussions with chemists on how
10 to go at this a different way.

11 Pilot lots could be manufactured for
12 screening in all of these assays, and ultimately there
13 was a section on the campus where large-scale material
14 was made for distribution. We've sort of disassembled
15 all those different parts, all those different labs,
16 and all those different services and provided them
17 under contract for people to ask us to use.

18 We also provide clinical services.
19 These are, of course, early phase development -- Phase
20 1, some Phase 2 -- and we have done some post
21 marketing studies that you would probably call a Phase
22 4. Our typical point of handoff is after Phase 1,
23 maybe Phase 2, and help for the proof of principle to

1 have been made by that time so that this could be
2 picked up in more -- more totally by a company.

3 And so we have a similar process where
4 presently, these services are awarded under contract
5 and they're in two types, Phase 1 clinical trial units
6 or vaccine and treatment evaluation units. Both can
7 test antibiotics and just to show the map here, the
8 point here is that these are either existing academic
9 centers with experts or existing companies that
10 provide CRO type services to conduct a Phase 1 and get
11 the first inhuman data.

12 And these are provided free of charge.
13 Sure, it might take a little longer than if you were
14 in the company and raised the money and did it
15 yourself, but free is pretty good and if you're really
16 stuck and can't get forward without this assistance,
17 this helps to de-risk the enterprise by providing
18 those services and giving the data back to the
19 intellectual property owner.

20 Not only do we assist with the
21 development of new antibiotics, but while we're
22 waiting for them, we also work to optimize existing
23 drugs and to use them in new ways, and so I wanted to

1 include that a little bit because there are some
2 lessons learned here that I think will be relevant to
3 the discussions we'll be moving into for the rest of
4 today and tomorrow.

5 And so in 2007, we started a series of
6 what we called strategy trials. These are not
7 efficacy trials. These are not A versus B to prove a
8 drug. It's to see if a particular practice has a
9 comparative effectiveness in the community and so back
10 in the beginning when the CA MRSA epidemic was
11 sweeping the country and people were (indiscernible)
12 worried about seeing patients in an emergency room
13 setting and sending them back out before you had
14 susceptibility testing data.

15 Is it okay to give them last -- the
16 last line agents, the off-patent drugs? Or do you
17 need to give them something like IV vancomycin or
18 linezolid? And so we answered those questions by
19 conducting, in one instance, the drugs such as
20 trimethoprim sulfa, clindamycin, and even a
21 cephalosporin in things like abscesses or cellulitis
22 and so forth.

23 And those are published now

1 (indiscernible) England Journal but it's basically,
2 which drugs to you use, how much to you give, how long
3 do you give them. Or even if you can drain an
4 abscess, do you need to give a systemic antimicrobial
5 at all, if you've got proper wound care and proper
6 drainage?

7 And it looks like, much to our
8 surprise, you probably do if you want to get better
9 faster and don't want a relapse, don't want to have as
10 much pain.

11 The only one I'm going to talk about is
12 one that's still underway. We had eight of these
13 total. I believe we're going to complete six, so
14 that's pretty good success rate for a large, basically
15 Phase 4 type studies in difficult situations and I
16 think this is the toughest of them all.

17 The title of the study is OVERCOME. I
18 think one of the challenges was coming up with this
19 acronym and I think by doing that, we'll probably come
20 to the end of the study and we'll get an answer. You
21 can look it up in ClinicalTrials.gov. The principal
22 investigator is Keith Kay. It's been a labor of love.

23 We started the award in 2009. It took

1 us three years to get it through launch and starting
2 to enroll. These are all done, by the way, under I&D.
3 They're a little bit different in that I think the FDA
4 is kinder and gentler when you're not going after a
5 label indication. You're looking at off-patent drugs
6 to see how they work best.

7 And the question here, and I think
8 still, is what's the best available therapy for MDR
9 gram negatives and the model we arrived at through
10 competitive review was colistin alone versus colistin
11 plus a carbapenem in the populations where that tough
12 population of pneumonia -- hospital pneumonia,
13 HAP/VAP, and bacteremia, and we took sort of an
14 operational approach.

15 These are the microbes that don't
16 respond to anything but colistin, so it's the MDRO,
17 XDROs in some instances, starting off carbapenem-
18 resistant Enterobacteriaceae, pseudomonas, and A.
19 baumannii. They're flipped in order now because
20 during the long conduct of this trial this has become
21 an Acinetobacter trial instead of starting out as a
22 carbapenem-resistant Enterobacteriaceae trial because
23 of the shift in the epidemiology at the centers.

1 And so it's good we provided that in
2 our target organisms at the beginning. So the reason
3 I want to talk about this is what we learned and a
4 drive for this is, if we can't figure out how to do
5 this with a model study, we'll never figure out how to
6 do it with the newer agents. And so that -- please
7 consider it from that aspect.

8 I'll also be very pleased when we get
9 an answer because there are people around the world
10 that tell us the answer, do you really need to add a
11 carbapenem? If you don't, we need to know that
12 because it's driving carbapenem resistance in many
13 places of the world. And if you do, we need to know
14 that, too because we want to use it to benefit the
15 patient. So there are large places in the world that
16 this is a really important question.

17 And so as you can see, the first -- we
18 started enrollment in 2012. Didn't really start until
19 2015. The first 12 sites in the United States that
20 had a CRE epidemic saw that epidemic and had no more
21 real population for enrollment moving forward. So
22 where do you go to find the others? That's what we
23 spend the remaining years to try and find.

1 It's not straightforward. We started
2 in (indiscernible). All of the U.S. sites except for
3 one was closed. We now have added 12 in other parts
4 of the world. In my opinion, the most lucrative in
5 terms of density of patients in a small number of
6 centers is Asia and so what is it about other parts of
7 the world that are better than America?

8 Most of these sites outside of the U.S.
9 have 2,000 beds per hospital or more. I've heard that
10 the average hospital bed size in the U.S. is 80. So
11 right there, you're going to need a lot more hospitals
12 to equal 2,000 beds to generate the risk population
13 for your infections and the gram negatives are
14 particularly concentrated in Asia, in China, for
15 example, in Thailand -- always one of our high-
16 enrolling countries -- and in Taiwan.

17 And so we've had to resize the study
18 because although it was set at 444 in the beginning,
19 colistin resistance has emerged. It's still low in
20 the United States. In Greece, it's high. We've got
21 Greek sites. And in some places in Italy, it's high
22 and we've got Italian sites.

23 And so we did not have the end points

1 and the procedures to screen for that in the beginning
2 of the study. We do now, and we screened out and now
3 have to replace the patients who have colistin
4 resistant isolates.

5 Some other things we ran into along the
6 say is, you know informed consent is going to be tough
7 in intubated patients and the -- most of the VAP
8 patients were -- and so legally authorized
9 representatives are not permissible in several
10 countries, including those in our trial to that pretty
11 much means that we are skewed toward bloodstream
12 infection or those who are not incubated to get those
13 patients involved.

14 Other thing is prior antimicrobial use.
15 We started out like we should with no more than 24
16 hours of prior antimicrobial therapy. Nothing was
17 happening, so we realized we would still keep our I&D
18 if we just said, okay, we're going to allow 48 hours
19 and we tried that for a couple of years. We're now at
20 72 hours because that's what is -- basically, what
21 you're going to find in ICUs in places like this on
22 what people get.

23 And so our answer will apply to people

1 who want to use it that way, so I think that there's a
2 certain logic to a comparative effectiveness kind of
3 an answer in this population.

4 These targets trials were pre-ARLG and
5 ARLG, the Antibacterial Resistance Leadership Group,
6 you can see Vance Fowler is here and he may talk more
7 about this later. I've stolen here from the cover of
8 the 2017 CID article that describes what the group is.
9 You can see here they've been quite productive. And
10 the reason I put this up here, first of all, is to
11 show the value of the MDRO, Multi-Drug Resistant
12 Organism network, for access to population planning.

13 In my opinion, the two biggest
14 limitations in succeeding an antibiotic, licensure and
15 survival, is access to the populations. Few enough
16 hospitals with enough patients to test and answer your
17 question in a financially feasible and timeline
18 fashion and the second, I think, is after marketing,
19 after licensure, is access to the revenue flow to keep
20 them on the market so they don't go down and void all
21 the use of the prior development.

22 And so this study will help with that
23 because it started by David (indiscernible) who was

1 looking at let's do a laboratory based starting point.
2 MDRO is identified in the laboratory. Pull the case
3 records for that patient. Do a thorough evaluation to
4 work up and follow the course of that patient to
5 determine contaminant or infecting agent.

6 What are the conditions in that
7 patient, how do they get treated, and how did they do?
8 You, essentially then, can know when
9 inclusion/exclusion criteria would work in that
10 environment and you'd also know which environment
11 would work for enrolling the trial you want to work.

12 So that was expanded to, as you can
13 see, 91 hospitals in the U.S. and then expanded and
14 first to South America and then into China, and I'm
15 particularly proud of the entry into China where we
16 have visited 10 hospitals, we have about half of them
17 in a study that is going through the enrollment data
18 to get this information.

19 The ARLG has also produced some
20 statistical value in terms of desirability of outcome
21 ranking, DOOR -- I think people may talk more about
22 that later -- but some very clever statistical
23 manipulations to help with some of the challenges in

1 interpreting the data.

2 And you're probably going to hear Kevin
3 Outterson talk next about CARB-X. The things I
4 described about our preclinical services are our role
5 in CARB-X, so I'll stop there because this red light
6 is flashing in my face.

7 JOHN FARLEY: Thanks very much, Dennis.
8 You're actually going to hear Erin Duffy talk about
9 CARB-X and Erin is now chief of research and
10 development at CARB-X and we're looking forward to her
11 presentation.

12 ERIN DUFFY: Okay, hello, everybody.
13 Again, my name is Erin Duffy. I've been at CARB-X for
14 2.5 months, so it probably would've been better to
15 hear from Kevin about CARB-X, but here we go. And as
16 we talked, John suggested I put myself in context
17 here.

18 Prior to joining CARB-X, I was the
19 chief scientist at Rib-X and then Melinta Therapeutics
20 until we closed our research site last year. We were
21 a CARB-X awardee and so this is a pretty personal
22 thing for me to see antibiotic research continue.

23 So thank you, Dennis, for introducing

1 this slide. So what is CARB-X? I doubt anyone in
2 this room doesn't know, but in the event that you
3 don't, we are a global partnership led by Boston
4 University that's accelerating science in the
5 discovery and early development space to fight drug-
6 resistant bacteria.

7 You see on that first and second row we
8 have a collection of very strong backers and funders
9 including BARDA and ASPR, the Wellcome Trust, NIAID,
10 in a form of preclinical services which we'll talk
11 about later, very valuable to our drug developers, the
12 UK government and the German government as well as the
13 Bill and Linda Gates Foundation.

14 I'll come back to this topic of
15 accelerators at the end, but we do want to introduce
16 here that CARB-X is more than a funding mechanism. We
17 feel -- again, you'll see this -- a lot of our
18 companies are very small companies in some cases, and
19 less than five people who are doing everything. And
20 in those cases, we've put a strong shell around them
21 of business and scientific support to help them really
22 transition from a neat idea to something that can be
23 clinically valuable.

1 So we have a lot of money to invest,
2 about half a billion dollars between 2016 when CARB-X
3 was first founded and 2021, and we're really focused,
4 again, in that discovery to early development space
5 and I want to stop here for a second because early
6 this morning we saw a slide where you started to see a
7 bunch of acute bacterial skin and skin structure
8 infections.

9 New drugs for those trials come to
10 market sort of in the early teens up to and including
11 this year. And there are they who say, you know, we
12 don't need any more ABSSI drugs and, you know, MRSA.
13 You know, let's focus on priority pathogens. And, you
14 know, for those of you who don't do research it's not
15 like you go back to your shelf when your CEO comes and
16 says, hey, you know what we're going to do today,
17 we're going to focus on Acinetobacter.

18 Okay, so you don't just, like, go back
19 to the shelf in the lab and pluck something off -- I
20 know you see that in movies, but it's not true -- and
21 then it goes into clinical trials. It can take for
22 even, you know, an improvement on an existing class,
23 10 years to get to the clinic let alone something

1 novel.

2 And so what we're doing today is
3 building a pipeline so that when that next -- I can't
4 even pronounce the bug that Helen introduced to us
5 today -- but when that next weird bug comes, we have a
6 variety of solutions that are there.

7 The other part of this is the cynical
8 people in the room, and I've certainly been among them
9 at times, would say, you know you're building a bridge
10 to nowhere, given what Kevin's going to talk about
11 next which are the market challenges and I know some
12 of us feel this very acutely. And the answer is no,
13 because again, we're building something not for today
14 but for the future and we believe -- and I think for
15 the good of all of us -- there has to be a solution.

16 Okay, so let me just go on. So what do
17 we fund? We do fund traditional and non-traditional
18 therapeutics. We've brought in one recently to our
19 portfolio, vaccines, microbiome approaches in
20 antibodies. And we've also added a diagnostics arm
21 that in the short term has been focused largely on
22 bacterial ID and AST, but we're going to expand that
23 and part of how we do that, I think, is listening here

1 to what might be helpful.

2 Again, the emphasis is on pathogens of
3 high priority, both in the CDC list and the WHO list.
4 So we do focus early. We're not focused on basic
5 science, so there needs to be a hit and then we will
6 fund everything up to and including a Phase 1 program.
7 Our goal is to have these programs Phase 2 ready.

8 Likewise, in diagnostics, different
9 terminology but we certainly fund, again, from early
10 feasibility demonstration up to and including system
11 ID and testing. So I'll give you a look at what the
12 portfolio today looks like and I'll do this in a
13 couple of slides.

14 So when you think about direct acting
15 therapeutics, these are the companies in our
16 portfolio. If the company is named in green, that's
17 because they've graduated our program which typically
18 means completion of a Phase 1 trial. In the case of
19 that very first box on the left, that's Idera and we
20 supported their product which is now in Phase 3.

21 And so you can see as we go across from
22 left to right, certainly we have representation in all
23 of the very well validated clinical targets with the

1 exception of RNA synthesis. We don't have a program
2 in the portfolio there. We have other targets like
3 fatty acid biosynthesis being conducted at Debiopharm.
4 And then we have some innovative programs where the
5 mechanism has yet to be determined.

6 Also in these boxes next to the company
7 names are their date when they jumped into the
8 portfolio, probably less important piece of knowledge,
9 but also staged, so again, you'll see population
10 (indiscernible) optimization, preclinical, Phase 1 if
11 you hit to leads.

12 And then in each box to the right is
13 the pathogen set that they target, so if the letter is
14 in black, that means it's something they target so we
15 tried to use the ESCAPE acronym there and so you can
16 see representation. We have a lot of CRE. We have
17 some that are aspirational for really broad coverage.
18 We have some Neisseria gonorrhoea programs and as
19 you'll see also some C. dif programs.

20 So again, a lot of diversity, we think.
21 A mix of novel -- truly novel targets or classes as
22 well as some next generation classes. And here,
23 again, I'd like to say beauty and also novelty is

1 often in the eye of the beholder.

2 As I mentioned, we do focus on
3 nontraditional approaches as well, so we have some
4 anti-virulence programs, (indiscernible) programs,
5 bacteriophage, and (indiscernible), which are, again,
6 new to us -- we will be growing -- microbiome as well
7 as some other approaches. And again, you see a
8 diversity in pathogen coverage and also stages of
9 program.

10 As I said, we're starting to embrace
11 vaccines and immunotherapies so you see we have three
12 vaccine approaches under the hood right now, one
13 antibody-based program. We had a very successful call
14 this year in this area where I believe we'll be adding
15 a lot more innovation into these boxes.

16 And then we also have a growing
17 diagnostics portfolio. We've had our first graduate
18 there, T2 Biosystems, and T2 is now partnered with
19 BARDA so that's a very exciting thing for us as well
20 as companies coming through, again, at several stages.

21 So I'm not going to belabor the point.
22 This is that same collection. I do want to say, if
23 you can count up the rows there, that we have now had

1 50 programs come through the portfolio and that's
2 really exciting and I must credit Kevin and certainly
3 John Rex who's in the room as well, Barry Eisenstein,
4 and people who aren't here, Karen (indiscernible) and
5 Rich Lawson for bringing us to this stage that we
6 really have 50 programs that are innovating for the
7 future, and the haven't just started and sort of
8 stalled.

9 We've seen a lot of progress and that's
10 what the dark blue bars mean and then goal is
11 graduation because it matches that tassel on your cap.

12 Okay, so we did have four funding
13 rounds this year, the last of which opened last week,
14 last Tuesday to be exact, and you can see we really
15 span the range of things for which we were looking.
16 We had a very healthy nontraditional round as well as
17 vaccine and biotherapeutics and a really dynamite
18 diagnostics round and I'll be very excited to see what
19 comes out of all of these.

20 We have a poll internally for how many
21 direct acting small molecule therapeutics we're going
22 to have. Kevin and I are going to duke out our
23 position because we chose the same number, but suffice

1 it to say, I think this is also going to be a very
2 large pool from which to choose.

3 So as I said, CARB-X is a lot more than
4 funding and one of the things that we're rather proud
5 of is this global accelerator network that we've built
6 and again, you can see the little dots and the names
7 around the world and these are places that both have
8 scientific expertise and business expertise, so again,
9 for those companies where the CEO is also the chief
10 bottle washer and the bathroom cleaner and maybe the
11 CSO, too, having groups that can really help them
12 understand how to build the business and drive
13 programs, gain funding, in addition to the funding
14 that we are giving, all very important.

15 I didn't say this, but of course we do
16 have a cost-share element and so helping those
17 companies to navigate that very important. But
18 through our advisory board and also through these
19 networks, there's a strong scientific focus as well
20 and I'll call out two groups in particular, ILSE which
21 is led by Keith Bostian in New Jersey and BaselArea
22 Swiss, where Malcom Page is a very large figure,
23 certainly very helpful. Lot of years of experience in

1 the area of antibacterial drug discovery and
2 development.

3 And they bring teams to bear that can
4 really support holes in any of our programs and very
5 important for us to do. I'll call out (indiscernible)
6 which is a federation in Germany which is really quite
7 terrific for not only our European colleagues but also
8 U.S. colleagues who are looking particularly for
9 guidance in the EU and FIND, of course, in the area of
10 diagnostics, very large.

11 So again, what they offer is a range of
12 services. Here again, I do want to call out the NIAID
13 preclinical services. Dennis mentioned them to you.
14 I can tell you again, not only in my own case when we
15 were CARB-X awardees, but also our company's case,
16 having access to assays that you just can't do
17 internally or, frankly, are very weighty in terms of
18 budget, having that access, having the flexibility, I
19 know both Ann and Anita are in the room here.

20 They work with the teams to really come
21 up with the studies that you need and this can be
22 activity, efficacy, safety, all to support your
23 clinical development package.

1 And I want to end -- so we built this
2 R&D group and we're actually still building it at
3 CARB-X, because we wanted that internal capability as
4 well to drive programs. And one of the things that
5 we're lucky enough to do now here, having had a few
6 years in the portfolio, is we're starting to see some
7 cross-portfolio challenges but also opportunities for
8 us.

9 And these become very important when we
10 think about how these data packages and these
11 molecules are going to move through these clinical
12 trials that we're going to spend the next day-and-a-
13 half talking about.

14 Certainly gives us an opportunity to
15 establish best practices among our network and to
16 guide our developers, and in some areas, to really
17 lead the field -- and I'm going to talk about a few of
18 these -- and again, an ability to provide information
19 within our portfolio in a way that's actually very
20 difficult to do across competitive companies.

21 And so we've identified a number of
22 areas here, so when Wes talked about the current
23 portfolio and certainly expressed some sadness about

1 the one program in Phase 3 for priority pathogens that
2 was a novel class, that fell out because of a safety
3 concern, and this is a safety concern across many
4 programs and companies and this is nephrotoxicity and
5 so we're looking at how might we get involved in
6 identifying or at least clarifying what the right
7 models are that can really help us so that when we
8 transition into the clinic we at least have a better
9 sense that this isn't going to be an Achilles heel
10 that you're not going to uncover until Phase 3.

11 Areas we do have some programs looking
12 at CF, so translation of preclinical data into the
13 clinic there, the animal models of questionable
14 utility and this might not just be true for CF. Some
15 of our portfolio companies are targeting GC and I'm
16 going to be very excited to see how Zoe
17 (indiscernible) work here with GAR-P. we're certainly
18 cheering it on.

19 My colleague, Sue Cammarata, and I
20 certainly were in the wars there and it's a difficult
21 thing. There aren't really good animal models because
22 of the nature of the condition and then the single
23 dose in the clinic. How do you translate that? And

1 so these are things we're thinking about. We have
2 some virulence programs, anti-virulence programs into
3 the clinic. Again, animal models and regulatory path,
4 very unclear.

5 We'd like, really, to work with people
6 in this room on those, and then other areas, working
7 with our product developers to really be honest about
8 the microbiological profile and look at preexisting
9 trends of resistance. This is an area where we can
10 study all of our developers' compounds in large
11 surveillance panels and really help educate them and
12 educate us on what the portfolio looks like.

13 Again, PKPD, we talk about this all the
14 time but in areas where you're looking for single
15 pathogen indications, this is an area we'd like to
16 contribute to as well as ways that we might leverage
17 our diagnostics portfolio with our therapeutics more
18 creatively. I am at the end, but this is a shameless
19 plug and an important one.

20 So if you know anybody who would be
21 really interested in joining our team -- look at how
22 happy we were. We're a happy team. We also could use
23 a little more testosterone, okay, so we've got this

1 great Richard Alm on our team and -- anyway, that's a
2 little facetious, but we are looking for people to
3 build out our team. Thank you very much.

4 JOHN FARLEY: Thanks, Erin, and our
5 last speaker for this round is Mark Albrecht from
6 BARDA, who's the chief of the antibacterials branch
7 there.

8 MARK ALBRECHT: Well, good morning,
9 everyone and thank you for having me here today. It's
10 always a pleasure to know that so many people are
11 interested in the work that you're doing, particularly
12 within the antibacterial space.

13 As was highlighted a moment ago, there
14 are definitely a lot of products that are in that
15 early stage of development. BARDA is the bridge to
16 bringing those products into the clinic and hopefully
17 transition them out into use and into a physician's
18 hands.

19 So with that, I -- introducing our
20 program here that I am managing. As you can see, this
21 highlights our mission, really revitalizing that
22 antibacterial pipeline through innovation as well as
23 focusing them on reducing the morbidity and mortality

1 cause by multi-drug resistant infections, particularly
2 those that you see during a mass casualty event.

3 Of course, BARDA was initially stood
4 with the focus on a variety of different threats:
5 Chemical, biological, radiological, nuclear threats;
6 pandemic influenza; and emerging infectious diseases.
7 This branch is focused on those bacterial threats and
8 this includes anthrax, plague, tularemia, melioidosis,
9 and glanders.

10 We also look at the fact that following
11 any one of these mass casualty events, you're likely
12 to see opportunistic infections that are going to
13 complicate that response and really be a challenge for
14 our first responders. That's why we focus in on both
15 that biodefense as well as public health and focusing
16 particularly on products that span both those spaces.

17 Now, in order to accomplish this, we
18 have to have a holistic strategy, one that focuses on
19 novel products, novel mechanisms, those that overcome
20 a lot of the drug resistance that we're hearing about,
21 that we've talked about this morning, and looking at
22 new technologies, new modalities, whether that's a
23 vaccine, a nontraditional therapeutic like a phage,

1 microbiomes.

2 And, of course, we're also partnered
3 internally with the diagnostics branch of BARDA to
4 understand and help develop new diagnostics for AMR.

5 Now, in addition to having that
6 holistic strategy, you need to have a holistic
7 pipeline and we've heard a little bit about carbaxin -
8 - I'm going to also labor that point in a moment --
9 but you can see that BARDA now is supporting product
10 development in an end-to-end capacity, starting with
11 carbaxis as our early-stage program and portfolio that
12 we're supporting and really excited to see the level
13 of innovation within that portfolio.

14 That brings us up to our bread and
15 butter. That's our advanced research and development
16 portfolio that really takes over at that post-I&D
17 Phase 1 stage and brings products all the way through
18 clinical development, hopefully to NDA approval and
19 out into the commercial market.

20 And then finally, we have project
21 BioShield. This is really our acquisition and
22 advanced, advanced development, Phase 4 clinical
23 trials and eventual product development and

1 procurement of those assets. Now, I highlight a
2 variety of our interagency and international partners
3 at the bottom, really to highlight the fact that it's
4 not just one organization doing this. It's an entire
5 city of organizations that are supporting product
6 development.

7 You cannot do this alone. It takes
8 both our interagency partners, our international
9 partners to solve this problem. So when you do a
10 little bit of a deeper dive into the -- each of those
11 individual components starting with CARB-X, as Erin
12 really well highlighted and drove home the message,
13 that this really is an amazing portfolio of innovative
14 products.

15 You can see some of the highlights
16 here. We're equally excited about the fact that
17 there's been 50 different products that have been
18 supported by CARB-X and there's been an unprecedented
19 level of innovations within this portfolio, as Erin
20 talked about. The one thing that we're really excited
21 about is the fact that six candidates within this
22 portfolio have entered the clinic.

23 This has really helped us realize one

1 of the goals for CARB-X, to see that early stage
2 clinical pipeline become repopulated with new
3 candidates. We're also equally excited about the fact
4 that we see T2 Biosystems now showing up within the
5 BARDA portfolio, another metric that we had for CARB-
6 X, is kind of that graduation of products from CARB-X
7 into our advanced development portfolio.

8 Now, this gets us to the advanced
9 development portfolio that BARDA manages. Right now,
10 we have 11 different partnerships that are highlighted
11 here on this slide and they're developing 16 different
12 candidates. Now, it's important to note that five of
13 these partnerships are occurring under BARDA's other
14 transactional authority.

15 This is a flexible authority that
16 enables us to enter into a partnership with a company
17 to support not just one product but multiple products
18 that they are working on, kind of a portfolio within a
19 portfolio, if you will. Now at this time, there are
20 seven different products within this portfolio that
21 are in Phase 3 clinical development and we're hopeful
22 to see some of these products transition through a
23 successful NDA and out into the market.

1 This brings us to, really, a lot of the
2 successes that we've seen, noting VABOMERE, Zemdri,
3 and Xerava. Each one of these approvals really
4 highlighted the fact that the BARDA model is working,
5 providing non-diluted funding that's multiyear,
6 subject matter expertise within that technical space
7 covering clinical manufacturing, nonclinical, as well
8 as ensuring that each one of these companies has
9 access to our interagency partners to really support
10 this product.

11 That model, that mission, is successful
12 in bringing products to market and it's exciting to
13 know that there's going to be future product
14 approvals.

15 Now, having said all that, I would be
16 remiss if I didn't highlight the fact that there are
17 definitely some commercial challenges that we've been
18 witnessing. I think this is something that everyone
19 here in this room is thinking about and definitely
20 trying to come up with new solutions and new ways to
21 overcome this challenge. BARDA has heard all of you.

22 We recognize this problem and are
23 internally discussing different avenues and different

1 approaches to solve this. In fact, two of those
2 strategies I'll highlight right now, one is Project
3 BioShield. As I introduced earlier, this is really
4 our acquisition fund within BARDA. This enables us to
5 procure products for our first responders.

6 This year, for the first time, we're
7 going to be using Project BioShield to support that
8 advanced development and eventual procurement of a
9 product into the strategic national stockpile, the
10 idea being that through this mechanism we'll be able
11 to either bring about a supplemental indication that
12 further advances that product within the commercial
13 market but at the same time, those procurements create
14 a level of a commercial market for that product.

15 The next effort that we're beginning to
16 look into is a clinical trial network. Clearly, as
17 has been discussed, there are several challenges
18 surrounding product approvals. Number one, it's
19 really easy to get an indication for cUTI and inter-
20 abdominal infections but is that showing the true
21 measure of value for that product? Are we actually
22 deriving clinical value for that indication, and is it
23 really enabling that product to adequately enter the

1 commercial market?

2 Clearly, this criticism argues for the
3 need to investigate these products in new ways, in new
4 structures. So this has brought us to this idea of a
5 clinical trial to try and reduce the barriers for
6 product development, both in time, risk, and enabling
7 each of the partners that would use this to have
8 adequate access to different sites that would have the
9 patients that they're looking for.

10 At this time, we're definitely reaching
11 out to our interagency partners to kind of discuss the
12 challenges that they've seen with clinical trial
13 networks in the past as well as their lessons learned
14 and what they would like to see in the establishment
15 of another network. Clearly, there are several
16 advantages with a network such as this. It has a
17 multiplier effect.

18 You can have multiple products going on
19 in one trial. This would, of course, also require a
20 centralized oversight system that would definitely
21 involve the FDA as well as all the partners supporting
22 this effort. And we believe that it would enable a
23 more efficient startup of the program.

1 Basically, with a clinical site already
2 on board, already under contract, you'd be able to
3 immediately begin to bring a product developer to
4 them. And finally, this is ultimately going to
5 improve our understanding of these antibiotics, their
6 use, and yield us with additional data to help us know
7 how to better use them and how they could be better
8 advantaged within the clinic.

9 So in closing, BARDA is going to
10 continue to invest in the development of products.
11 We're going to continue to support CARB-X, that early
12 stage pipeline, continue to be in the space of the
13 advanced development pipeline and leveraging Project
14 BioShield to begin to create more of a commercial
15 market for new products.

16 This isn't going to change. We
17 continue to see these challenges and we're listening
18 and supporting you and everyone within this space.
19 And in closing, I just want to thank Marina Kozak,
20 Tina Guina, Brian (indiscernible), Oksana Sovanova,
21 (indiscernible) Hawk, for supporting this program.
22 They are the project officers behind this program and
23 really are there to ensure its success. Thank you.

1 ERIN DUFFY: Thank you, Mark. Okay,
2 it's always questionable to introduce your boss in a
3 talk, but I'm going to do that. So now we're going to
4 hear from Kevin Outterson. As you know, Kevin is a
5 law professor at Boston University. He's also the PI
6 and executive director of CARB-X.

7 He teaches health law and corporate law
8 at Boston University and my personal goal is to be
9 able to say a sentence in legalese with the same
10 facility as he does in AMR.

11 KEVIN OUTTERSON: You know, you're
12 working in law school. We can work that out. So my
13 name's Kevin Outterson. I stand between you and
14 lunch. You've heard a lot about CARB-X already. I'm
15 not talking about CARB-X now. Here's my disclaimer.
16 I'm going to talk about other economic issues within
17 the industry.

18 So just think about systems. How do
19 you know when one is broken? How do you know that
20 something is mixed up? One way is to look at the
21 outputs. Maybe the rate of output is too slow. If
22 you have a machine designed to create one widget per
23 hour, it's giving you one per week, so the rate or the

1 number or the type or the quality is different from
2 what you're expecting or hoping for.

3 And we have some data for this on
4 antibiotics. Surely, the approvals were down prior to
5 2002 and I'm talking about the article from CID that
6 several people in the room were part of and everyone
7 here probably knows, but then we also had issues with
8 the withdrawals and the second article there -- either
9 subsequent withdrawals or products that were
10 discontinued because the companies couldn't support it
11 in the market.

12 And so there is something going on with
13 the outputs to the R&D -- antibiotic R&D system in the
14 world. When you think about another way to look for
15 whether the system is broken is that you look for
16 smoke. If the toaster is smoking, it's a problem. If
17 a patient is febrile, it's a problem. Something's
18 wrong with the system.

19 In your car, you get the check engine
20 light, right? And that check engine light doesn't
21 tell you exactly what's wrong, but you know that
22 something is wrong. You really need to go take it in
23 and have it diagnosed and find out what's going on.

1 So I'm here to tell you that the check engine light is
2 on for antibiotic R&D. Everyone here understands
3 that, but just to use that language explicitly.

4 Some of the inputs going into the
5 system, I have green check marks. I think we're doing
6 a pretty good job on the inputs. CDC report 2014 said
7 we need more gram negatives. Let me tell you, the
8 preclinical pipeline has responded. The GAIN Act gave
9 some clear direction.

10 The whole CARB process, the combating
11 antibiotic resist bacteria program throughout the U.S.
12 government gave clear signals and mobilized things
13 within HHS and other agencies, all the things that
14 were just discussed as well as everything the CDC is
15 doing and everything FDA is doing, rolls into that
16 CARB process.

17 All the basic research funding -- so,
18 Dennis, thank you. All the things that are in
19 preclinical that we see in CARB-X, a lot of it just
20 wouldn't exist if 1,000 R01s had not been funded and
21 everything else that NIH and other basic science
22 funders around the world do. It's important, and so
23 we've done some things well.

1 On the output side, I've got some red
2 marks and some green and I'm going to cover a couple
3 of these in some more detail. The clinical pipeline
4 is fragile. Wes, is that still a good word for it?
5 He's shaking his head yes, let the record show. The
6 preclinical pipeline, I want to say, is actually
7 working. And there's an article coming out, Ursula
8 and myself and Andres Carlin and Alec Ingle -- should
9 be out next week, I'm told, but I have a slide for
10 that coming up in a moment.

11 The question is, what should physicians
12 value? What do they want? I have a little bit of
13 discussion about guidelines. And then more to the
14 topic that I was given, what does the market want.
15 And let me tell you, what the market wants is inhaled
16 amikacin because that is the product that is driving
17 the most market response in the entire antibacterial
18 field today.

19 And the market caps for everybody else
20 is pretty low and they have to raise money for
21 commercialization, these companies, even after market
22 approval. If they're popping a cork for Champaign,
23 it's a very inexpensive bottle because they have to

1 save every nickel to commercialize and they're unable
2 to raise with small market caps the funds that they
3 need to do that commercialization to where is that
4 money going to come from.

5 About half of the recent approvals in
6 the U.S., new approvals of antibiotics, are being
7 threatened with insolvency today. So there's a lot of
8 things on outputs. I'm going to run through a couple
9 of those, not all of them.

10 So the preclinical pipeline. It's must
11 more encouraging than the story that Wes told on the
12 clinical pipeline. This is from that forthcoming
13 article in Nature Reviews Microbiology, supposedly out
14 next week. But look at the little green dot. This is
15 -- the WHO did a similar analysis but WHO required
16 that every preclinical company release their data into
17 the public.

18 And so a lot of the companies didn't
19 want to do that and so we used the enable data, the
20 repair data, CARB-X data. We collected it, preserving
21 the confidentiality of the companies and then
22 published the summary results here. So 46 percent of
23 that preclinical pipeline is direct acting and within

1 that, 70 percent would qualify for the novel tag that
2 Pew Charitable Trust -- we were talking about earlier.

3 There's a lot of excellent things going
4 on in there and the vast majority of it also targets
5 gram negative bacteria, so we can say that lots of
6 good things are happening in the preclinical side, but
7 Erin mentioned this. A lot of this is very small
8 companies. The smallest, I think, we've had is three
9 in CARB-X, three FTEs, and lots of nontraditional
10 products with an article that John and I wrote
11 together.

12 There's a lot of questions about the
13 regulatory path for some of those types of
14 nontraditionals, shortages of funds. The BARDA money
15 for Phase 2 and 3 right now is the lifesaver in this
16 space. So more encouraging, but still some
17 challenges.

18 On guidelines, what do physicians want
19 to know and when do they want to know it? I had to go
20 back to a different impeachment era. We have --
21 guidelines may actually help physicians who are busy
22 people and having to see patients every, I don't know,
23 10 or 15 minutes or less. I'm looking at the

1 clinicians, how much time you actually get with the
2 patients.

3 They cut through the noise and you see
4 this data from C. dif here and when the new guidelines
5 came out, the sales move up. And then down below for
6 oral vanco, you see that when the data is published,
7 there isn't an increase, but when the guidelines
8 finally came out several years later, there's a
9 significant increase.

10 So we know this. Physicians do rely on
11 expert guidance. They do rely on this sort of
12 material. Let's get that out more quickly. Everyone,
13 I think, here agrees with that.

14 On the economics for the companies, 17
15 public (indiscernible) companies, small companies
16 today in the space -- it was 18 but (indiscernible) is
17 bankrupt. The most valuable of them, I show here,
18 their main product is inhaled amikacin. Melinta filed
19 a 10K with the Securities and Exchange Commission last
20 week that openly discusses the potential -- the grave
21 potential of bankruptcy. Go read it and see the
22 language specifically.

23 And several of these other companies

1 listed here would have stock prices below \$4. In that
2 sort of setting, they have difficulty -- that's the
3 nicest word I can put on it -- raising the necessary
4 funds to do commercialization. And so the market
5 side, the market signals that they're sending, are
6 very fraught in the system today.

7 So what could be going wrong? There's
8 a couple things. It could be a bad signal. We could
9 be -- have encouraged companies to bring the wrong
10 sort of product to the market. If we were running a
11 Soviet-era socialist economy with a five-year plan,
12 that could be a problem. But if you have functioning
13 markets, they send the right signals back -- that's
14 the market system working -- that is the problem, I
15 think, not so much that we're sending a bad signal.

16 The signal could be distorted. The
17 companies misinterpreted it or (indiscernible)
18 circumstances change. You feel bad for the companies
19 that thought that some specific bug was going to be a
20 bigger problem and five or 10 years into the program
21 it turns out that it's not as big of a problem.
22 That's not really the company's fault; the ground
23 shifted under their feet.

1 You might have some questions about the
2 (indiscernible) drug. We have plazomicin. And be
3 those as they may, but if everybody in the industry is
4 in the same boat, then it's really a system problem,
5 not really a fault of any one particular team. And
6 then finally, the market distortion which is where I
7 think the largest issue probably is.

8 The market is not valuing the products
9 that we actually need appropriately, partially because
10 these products are designed not necessarily for just
11 today but today plus tomorrow. So some lines of
12 action, some ways that we can respond. We could
13 improve the inadequate signals to physicians and I'm
14 only going to talk about labels out of that list.

15 We've already had discussions about
16 these others. There's some frictional things, you
17 know, just delays in formulary option, delays in
18 getting the diagnostic integration and the break
19 points updated with good news lately on that. And
20 then just the fact that the market is responding
21 inappropriately and we cover two of those items in
22 bold in the next couple of minutes.

23 So on the labels. So we have a couple

1 of labels that I'm just going to look through and the
2 question I want you, in your mind, is what can we do
3 to account for additional clinical information -- I'm
4 not talking about microbiology, but clinical
5 information -- in an LPAD environment in a way that
6 could help move forward some of our goals and
7 objectives here?

8 So here's plazomicin. They start off
9 with a black box which is just based on the safety
10 data, obviously. And here, this is not the label
11 because the label is a package of all sorts of written
12 materials, but this is the thing at the top of the
13 label and this is really, when people colloquially
14 call the label, they think about this.

15 And this is what they got, and
16 obviously, it's urinary tract infections and they
17 limit that with that really LPAD sort of sentence in
18 the second sentence. And then at the bottom,
19 something akin to a stewardship sort of moment and
20 this is the main message that goes out to physicians
21 and to hospital committees. Lots of data to back it
22 up as well, but this is the summary that the FDA puts
23 out.

1 Here we have for (indiscernible) you
2 see something similar and I just want to not go
3 through the whole thing again, but they do have the
4 stewardship provision in there as well but notice the
5 updates. So they went in with supplemental new drug
6 applications. They got additional label extensions.

7 This is a drug that's actually making
8 money. They can afford to do that, but that's
9 obviously where we want everyone to go, is to come
10 back with more data later. And the most recent drug
11 on this list, approved only -- I think they've been in
12 the market now seven or eight weeks in terms of
13 actually available in the market, and here again,
14 different community acquired bacterial pneumonia, but
15 also with the stewardship sort of message.

16 And so my question is, is there a way
17 that we could get some additional clinical information
18 up in that part of this FDA materials, but in a way
19 that is true to the science but also helps advance --
20 the way that we know the physicians are actually going
21 to be using these drugs, because we don't really want
22 them to be using the drugs, necessarily, for the
23 conditions that are described on the previous couple

1 of slides.

2 And so this is just a thought
3 experiment. It's just my idea to throw out into the
4 room, but instead of a black box warning, a gray box
5 statement that's based on clinical information. It's
6 not sufficient for approval, but it's still clinical
7 information to guide what you -- the sort of patients
8 you actually think are going to use the product.

9 And maybe there's some way to do
10 something there. I know that FDA surely has lots of
11 questions and comments on this. I want to note that
12 let's sunset it; give the companies some time to get
13 this supplemental new drug, the label extensions
14 worked on so it's not there forever because we don't
15 want to disincentivize them to actually do that work,
16 but sunset it. All right.

17 DRGs, diagnostic related groups. A
18 clever idea from the Reagan Administration to try to
19 reduce hospital costs, inflation in Medicare. It
20 bundles all the things together that happens in a
21 hospital. You get a single price. So antibiotics, if
22 they're \$1 or \$1,000, the difference is that the
23 hospital will have to eat the \$1,000 and I believe

1 Sara said that antibiotics are expensive.

2 I still think these new agents compared
3 to the oncology world or the orphan drug world, for
4 somebody that cares for somebody who would otherwise
5 die from -- I think they're still very cheap. But
6 that these DRGs did, they did their intended job well.
7 The drove down costs to Medicare.

8 They drove down the average length of
9 stay, LOS, but then the clever hospitals discharged
10 people quicker and so the Medicare had to respond with
11 additional rules to fill in the gaps in the things
12 that people were doing to respond to these economic
13 incentives. It's a cautionary tale. Any time we lay
14 out an economic incentive, somebody will follow it in
15 a way that's unanticipated -- DRGs is an example --
16 and we might need to modify it as a result of that.

17 There's been some efforts, something
18 called a new technology add-on payment, NTAP. Give
19 two or three years. There's reasons why it doesn't
20 work for antibiotics, because if they're not actually
21 used in those first two or three years, it never gets
22 baked into the DRG recalculation. And the companies
23 themselves are asking for a carveout, either through

1 legislation from Congress or through the IPPS 2021
2 rule.

3 Go look at the most recent blog post
4 from the administrator of Medicare, if you want to
5 know more about that. But just to put it in
6 perspective, this is daptomycin, allegedly the most
7 successful antibiotic in the last, whatever, couple
8 decades, and this is its launch curve to loss of
9 exclusivity, and then we have Keytruda, okay?

10 So in most of these sales, these sales
11 were largely in Part B because a clever thing that's
12 not as well understood is that (indiscernible) did a
13 lot of its sales in OPAT which got it outside of the
14 Part A bundle, enabled them to sell, but even with
15 that being marked out, they weren't exactly tearing up
16 the world in terms of shifting volumes or prices.

17 The prices actually got something close
18 to 2.75 percent increases from the beginning to the
19 end, so they did have price increases. But you can
20 see the overall effect on revenues is rather modest.

21 The last thing I want to say is that
22 the social value of antibiotics is huge, and that was
23 true in the ERG report done for ASPE, the Department

1 of HHS, or a part of HHS in 2014. The social value is
2 greatly in excess of what we're paying for them now.
3 Some of the work done for the UK (indiscernible) model
4 at the University of York, has some out with this,
5 what we call study.

6 These different ways to think about
7 other values for antibiotics, namely the spectrum
8 value. Everyone says do narrow spectrum, but you're
9 going to get fewer sales. You need a premium if
10 really what you're going to do is a narrow spectrum.
11 And transmission, you prevent other cases. But how
12 does the company make money on prevention of other
13 cases?

14 Good luck with modern medicine without
15 antibiotics. But who will pay for this enablement
16 value? There's nobody that's going to step up and
17 volunteer to do that. The industry, actually, is
18 thinking about this in a broader level. Diversity.
19 Choices are good. Clinicians would like to have two
20 or three choices, not just one.

21 And the insurance value, the fire
22 protections in this room, it will save our lives if
23 this room burst into flames. They didn't make the

1 company or the workers who installed that or built
2 that equipment wait until the fire started before they
3 got paid. The optimal number of fires in this room is
4 zero and yet, they got paid.

5 But for our companies, we put them on
6 the shelf. We're very careful with the drugs and as a
7 result, the companies are moving towards bankruptcy,
8 so a lot of the things that I could talk about are
9 well outside of the FDA's purview and these are my
10 concluding remarks, summarizing what I've said before.

11 But let's advance the conversation, the
12 pieces the FDA can help on. I'm grateful for your
13 help and thank you (indiscernible) and John for
14 inviting all of us me to be here today.

15 JOHN FARLEY: Thank, Kevin. I think we
16 have a little bit of time before lunch for clarifying
17 questions or topics that you want to get on the table
18 that aren't on the table yet, so I'll invite the --
19 start out with the panel, invite you to put your tent
20 card up on the side so that Erin and I can see you and
21 take a few minutes for questions and discussion.

22 WOMAN 1: (indiscernible).

23 JOHN FARLEY: Thanks, John.

1 JOHN REX: (indiscernible) too slowly
2 writing my notes. Dennis, the OVERCOME trial, how
3 much -- what's the whole study cost of that project?
4 (indiscernible) that I have -- I'm currently holding
5 an email from somebody that says, well, we could do a
6 400- or 500-patient study for \$2 million.

7 DENNIS DIXON: It's under \$15 million.

8 JOHN REX: It's under 15. And the --
9 under --

10 DENNIS DIXON: Between 10 and 15 and
11 it's closer to 10.

12 JOHN REX: And does that include paying
13 for the people who do the data collection, the study
14 coordinators, the --

15 DENNIS DIXON: Yes.

16 JOHN REX: -- site audits?

17 DENNIS DIXON: Yes. It is the most
18 efficient of all of the targeted clinical trials that
19 we have done. They generally run two to three times
20 that.

21 JOHN REX: All right. And in that
22 study, are the data being collected, are the data
23 being audited? I mean, is this a pivotal trial

1 quality dataset?

2 DENNIS DIXON: It's not a pivotal
3 trial. It's not --

4 JOHN REX: A distinction, the quality
5 of it.

6 DENNIS DIXON: PPD does the monitoring
7 and they make regular return visits with data quality.
8 And they all did, so there were -- we also, I should
9 say, we partnered with the combat network overseas and
10 that helped us to identify sites to survey and from
11 that site survey, we filtered down to only a portion
12 of them actually had the numbers they could deliver.

13 And even with this, by the way, our
14 screening rate is 1,000 screened for one enrolled.
15 And only patients who get enrolled, does reimbursement
16 go to the enrolling site. So that's one reason this
17 is cheaper.

18 JOHN REX: So you don't pay for
19 screening?

20 DENNIS DIXON: And there's also money
21 to a local staff person to pay them and the
22 coordinator there, so there's infrastructure support
23 costs for that and so there's the combat site visited

1 the places, we site visited the places, then we did
2 startup visits and then we do monitoring visits to
3 them. So it's pretty close to what you would do in a
4 registrational trial, but not -- a lot cheaper than
5 what you do for an actual registrational trial.

6 JOHN REX: That's it.

7 DENNIS DIXON: If we'd spent more, we
8 might be done, so -- and we do expect to be done
9 within a year or by summer of next year.

10 JOHN REX: And the rule of thumb
11 estimate for a 400-patient trial would be that it's
12 \$40 million. I mean, that's -- so you're saying
13 you're about a third of the cost of a study of that
14 size, because you're leveraging other resources.

15 SUE CAMMARATA: Actually, I had a
16 question for Kevin. This is regarding your question
17 around a gray box and I assume we'll get into this
18 discussion later. You put that forth as a potential
19 for the FDA, but my question is, since guidelines and
20 guidances from professional societies are so well
21 followed, especially in the ID world, why not a group
22 of ID physicians, pharmacists, and not the FDA as far
23 as the black box? Their remit is different. It's

1 really efficacy and safety versus use, to me, is a bit
2 beyond that and that would need a wider input from a
3 different group of folks, so that's my question is why
4 could a gray box have to be in the label versus part
5 of a guidance in more real time than what we're
6 getting right now?

7 KEVIN OUTTERSON: So it's a thought
8 experiment to see if people think it's helpful.

9 If we had our perfect, you know, really
10 quick guidance system, then maybe we don't need those
11 but I've heard from a lot of people that more
12 information on the summary section of the label would
13 actually help in market penetration and help with all
14 the hundreds and thousands of decisions that people
15 have to make with stewardship and getting on formulary
16 at hospitals.

17 So I'm not trying to make any work for
18 anybody. It's only if companies and the FDA think
19 it's a worthy and helpful thing.

20 HELEN BOUCHER: So I'll just pick up on
21 that. I think that having information in the label is
22 important. First and foremost, it's information from
23 studies that were done to a registration trial

1 standard and a lot of studies that we publish are not.

2 And that's not to say they're not
3 important and they wouldn't be included in the
4 guidance documents, but if people go to the trouble
5 and I think one thing that wasn't said out loud, but
6 I'll say it out loud, is we have at least three
7 companies, if not four, who've gone to the trouble to
8 do these CRE trials and screen many, many, many
9 patients, spend a lot of dollars to get small numbers
10 of evaluable patients but they're there, and those
11 data are not in the labels.

12 And to me -- that's the problem to me
13 as a physician is that they should be because I think
14 that the payers and the pharmacy committees and
15 everybody else will recognize that those data were
16 obtained in the process of doing registration-level
17 trials, if it's there. And that's just one -- my
18 personal view, but I think it's important.

19 SUE CAMMARATA: Can I just make a
20 response to that? I think one of the challenges is
21 that for a lot of these trials, since they are
22 descriptive, they're hard enough to get -- there are
23 challenges to getting those published because they're

1 not randomized, regular trials. So to ask the --
2 again, I'm fully supportive, but then to ask the FDA
3 to put stuff on the label that you actually are having
4 trouble getting published because it's a descriptive
5 trial, that's something we'll have to get to later on
6 in the discussion is, it's a challenge which I can
7 understand why the FDA has that issue.

8 JOHN FARLEY: Sure, I think Cindy was
9 first. Do you want to --

10 CYNTHIA SEARS: Ann was --

11 JOHN FARLEY: Ann was -- okay.

12 CYNTHIA SEARS: I think I would say
13 both of these approaches are likely complimentary,
14 providing different information. The gray box would
15 not be likely to provide sufficient context; whereas,
16 a rapid guidance or whatever you want to -- words you
17 want to attach to that, could provide more guidance.
18 There is a way to rapidly publish results.

19 They are not peer reviewed, but the
20 medRxiv system, whatever you want to call it, is
21 specifically set up for the health sciences. Now,
22 that may preclude review by some journals. I tried to
23 look on the website this morning. I couldn't figure

1 it out, but the number of journals that will accept
2 papers that are posted there has expanded greatly
3 since that started. So there is a way. I don't know
4 if the New England Journal allows that, but we can get
5 that answer.

6 JOHN FARLEY: Since it's specific to
7 publication, why don't we go out of turn and have
8 Lindsey respond and then Pam and then John.

9 LINDSEY BADEN: No, I mean, I think
10 that this group is very provocative which is the
11 intent. I think that the, how to get quality
12 information to the community is what we all want to
13 have happen and have it happen quickly. And I think
14 Kevin was trying to provoke that in how to think about
15 different ways of doing is.

16 And the challenge is, what are quality
17 data and what is the value of vetting of data and a
18 positioning of data and completeness of data and then
19 the temporal cost of that versus the need for it to be
20 correct?

21 If we think that is a valuable
22 parameter to sort of weigh, but not correct at the
23 point where it's an eternity and so I think our

1 balances and ways to get information, I think part of
2 what Helen was raising is the issue of also payers and
3 other collateral groups are incredibly important and
4 the data are not acknowledged somehow, then it may not
5 be accessible even if we as a community think that
6 it's appropriate.

7 So there are many metronomes we have to
8 balance as we try to get information to the community
9 rapidly and correctly, and bioRxiv is a complicated
10 matter that is worth discussing at another forum.

11 PAMELA TENAERTS: So, hi everyone. So
12 the issue I wanted to bring up is something that I'm
13 sort of surprised doesn't come up more when I come to
14 infectious disease meetings, and we do a lot of
15 clinical trials work everywhere, so I'm not an ID
16 person at all, but sort of, Rob Califf told a couple
17 of us over and over that I would not want to have a
18 disease that does not have a patient advocacy group.

19 Well, you're kind of in that group.
20 You kind of don't really have an easy patient advocacy
21 group and they can advocate for things and I've heard
22 a lot of woe is us, woe is us a little bit in this
23 community which I understand. It's frustrating and

1 I'm sure -- just sent my daughter a text.

2 Go get your flu vaccine. I'll pay for
3 everyone for a drink of all your friends who goes with
4 you, so they have herd immunity. But what I would
5 like to say is maybe -- I mean, even in the outputs
6 today, you talked about what do physicians want, but
7 what do patients want? You know, sort of that
8 question, I feel is missing here sometimes and I think
9 -- I don't know if there are ways to harness them to -
10 - there really isn't a disease that is just infectious
11 disease that you could -- sort of like cancer, right?

12 They advocate for their -- and you
13 don't have that, but to maybe organize a better effort
14 around that. I don't know. That could behoove -- I
15 mean, that could help you guys because you have --
16 you're missing voices, both for advocating for all the
17 things you want economically and all those things but
18 also in looking at your diseases and what matters to
19 patients.

20 HELEN BOUCHER: So I'll just take a
21 stab from the IDSA perspective. It's a very valid
22 concern and one that we share. I think there are some
23 reasons why we don't have the patient group that

1 breast cancer does, for example. Some of our patients
2 can't speak because they're not here.

3 And the whole issue of drug-resistant
4 infections is still somewhat complicated in that no
5 hospital wants to be known as a center of excellence
6 for antibiotic resistance. And any time there's a
7 question of a patient speaking to the press, we have
8 to clear it and then there's a whole process because
9 that infection can't be obtained at a -- you know, it
10 has to come from somewhere else.

11 So those are issues that are
12 complicated. I would say that there has been some
13 progress and IDSA has the faces of antibiotic
14 resistance campaign which is a group of 14 patients
15 and their stories and there is a big effort underway
16 to grow it. But the fact that antibiotic resistance
17 undermines a variety of types of medical care is
18 really catching on and I think that's the good news.

19 There's going to be a big summit about
20 geriatric infections and the problem of AMR and we're
21 sort of working on that in terms of sort of
22 collaborating with other groups to get the message
23 across because if it's -- as the problem is impacting

1 our ability to do surgery and take care of these
2 groups, it's becoming more real, but it's a huge issue
3 so thanks for raising it.

4 JOHN FARLEY: Amy, did you have any
5 comments that you wanted to interject at this point?

6 AMY LEITMAN: Yeah, sure. Yeah, you
7 don't need one patient advocacy group. You need all
8 of them. It's going to affect everybody, so they all
9 need to be made aware. I mean, when I was preparing
10 for this workshop, I come from a disease of basically
11 one space and related comorbidities. So I started
12 talking to all kinds of different patients.

13 I talked to, you know, somebody who's
14 had skin and soft tissue infections. I talked to
15 somebody who had pseudomonas UTIs repeatedly
16 throughout pregnancies. I talk to somebody -- I
17 talked to the friends and family of someone who was
18 diabetic and died of a multi-drug resistant
19 infections, so that was diabetes. I've talked to
20 several cancer patient advocates. I've talked to a
21 sepsis patient advocate. I talked to a neurology
22 patient advocate.

23 So I cross as much of the spectrum as

1 possible because -- and there's no question it's
2 something that most of the general public aren't aware
3 of. It's something that I, frankly, bang on social
4 media all the time about. My friends are just
5 starting to get it, and it's been over a year since we
6 lost a friend to an MDR infection, and it's like the
7 lightbulb is starting to go off.

8 But in order to get the message out,
9 the message has to be very plain and very clear and it
10 has to go out to where the people are, and frankly, as
11 much as we hate to joke about Dr. Google and Dr.
12 Facebook, that's where they are. They're online. And
13 when you want to find patients and build networks of
14 patient advocates and networks for clinical trials,
15 you go find them where they are, and they're online.

16 They're finding support online. If
17 they've survived a critical infection, they've been
18 through something incredibly traumatic and they're
19 finding support from each other online. We had an
20 incredibly robust patient network. We have two online
21 forums for our patient. We have our own Facebook
22 page.

23 Each one of our support groups, and we

1 have more than 30 of them, has their own private
2 Facebook group in addition to more than 30 of them
3 actually meet in person regularly. It didn't happen
4 overnight. When we started, there were maybe five or
5 six patient groups in the United States, one in
6 Canada. Now we have one that's across Australia. We
7 have one forming in England. We have one in the
8 Netherlands.

9 I mean -- and you have to put the
10 information out there in a patient-focused, patient-
11 friendly manner, and that includes information about
12 the antibiotics because we've been talking about
13 labeling and labeling scares people when they don't
14 understand what they're reading. They don't
15 understand the datasets the way the medical community
16 does.

17 So part of what we do is we bridge that
18 divide with language so on our website we have a
19 patient pamphlet. It's what our patients call their
20 (indiscernible) bible. It's a 36-page patient
21 pamphlet. It's in 11 languages now. There's a
22 medication chart and it lists the most important side
23 effects in plain language and it talks about the

1 screening that should be done and at what intervals to
2 make sure that they're monitoring for side effects.

3 And that's talking to patients, but
4 this is a network that has to be built and I know that
5 we are short on time with this, for this kind of
6 problem, but the messaging has to get out there and
7 every patient advocacy group across every disease
8 state and every patient state should be involved in
9 this. We should be going out to every single one of
10 them and saying, we're out of time, you guys.

11 This is going to hit you and it's going
12 to hit you now and then it's going to hit your kids
13 even harder and then your grandkids and if they need
14 an appendectomy, good luck. And that's really how I
15 put it to people. There's going to be a very high
16 mortality rate for something like a simple
17 appendectomy. It doesn't occur to them that that's a
18 high-risk surgery but it will be.

19 JOHN FARLEY: Great. I think we're
20 going to do comments from John and David and then
21 we're going to break for lunch.

22 JOHN REX: All right. Well, and just
23 to finish that line. A few years ago when IDSA was

1 trying to pick up cases to tell the story, there were
2 a lot of (indiscernible), but you look at the really
3 great stories and unfortunate stories like in the
4 CDC's new report, the language that Wellcome Trust has
5 developed about how to talk about this in cultures
6 around the world -- it's everybody's problem -- and
7 maybe, Amanda, it's time for IDSA -- it might work
8 differently this time.

9 You tried hard before and I know how
10 hard it was to find those patients. So my question is
11 really for Dr. Nambiar. You put on one of your slides
12 something that, I think it's a language issue and I
13 want to be sure that we are all saying it the right
14 way. You said there were three types of data
15 packages. You said there was a standard approval, two
16 good sized trials.

17 There was a limited use approval where
18 the wording was one good sized trial. And then an
19 LPAD approval where you used the word small. Now, I'm
20 not asking you to define small, but I think I have
21 heard some blurring of the words limited use and LPAD
22 and I think that's going to come up and I wonder if
23 you might take a minute or two and just be -- explain

1 it to us in a way that we can all use the words
2 correctly.

3 SUMATHI NAMBIAR: Sure, let me try. So
4 as our thinking has evolved and as drug development
5 has proceeded over the, say the last decade or so,
6 early on we just had the standard development
7 programs. We had two trials per indication. And we
8 did not have the LPAD authority, right? LPAD didn't
9 exist.

10 But we already were providing guidance
11 on how smaller development programs can be conducted
12 and that they would suffice for approval if safety and
13 efficacy was demonstrated, as long as the product had
14 the potential to address an unmet need. So we had
15 that information in hand.

16 Then we were advising companies that
17 they could potentially do smaller programs and smaller
18 programs could be a single trial with supportive
19 evidence which had come from either a Phase 2 study or
20 -- and/or in vitro studies, studies in animal models
21 of infection.

22 So if you look at some of the products
23 that were approved since 2015, and I think

1 (indiscernible) might have been the first one approved
2 under the paradigm, it is a very different approach
3 and there was language included in the labeling which
4 said that only limited efficacies and safety data
5 available -- I don't have the exact verbiage, but
6 something like that.

7 And then subsequent programs came along
8 which also had a single trial as the basis of approval
9 and they got the limited use language. It's very
10 important to understand that each of these drugs,
11 there was a potential drug to address an unmet need so
12 it just wasn't a mechanism for people to get away by
13 doing one trial for a standard indication.

14 And then we have LPAD, within the last
15 couple of years, so the difference between the two is
16 for it to be an LPAD drug, the population for which
17 the product is being approved should be very well
18 defined and a limited patient population and it would
19 still be a single -- could be a single trial but I
20 think the key is defining the population.

21 So it has to be very well defined,
22 limited patient population in whom, because of the
23 small database, there are a lot more uncertainties.

1 We have a little more flexibility in the benefit/risk
2 considerations. So that's where it gets a little
3 complicated, so there is limited use but there's also
4 limited use with LPAD and I think what really is key
5 is defining the patient population because it is
6 really a limited population antibacterial, antifungal
7 drug pathway.

8 So it's really in defining the
9 population, but the underlying requirement that you
10 have to have at least one adequate and well controlled
11 trial does not change. So just want to make sure that
12 that's clear and I think early on, in the early days
13 of LPAD, there was a lot of confusion that one doesn't
14 need to meet the statutory standard's effectiveness,
15 and that's not true.

16 You still have to have an adequate and
17 well controlled trial along with other supportive
18 information. What's different is that the population
19 is very well defined and it should mean something to
20 clinicians. We have seen attempts at defining patient
21 populations that is really not relevant to clinical
22 use, so one has to be able to define that so it means
23 something to physicians who are treating these

1 patients. They can identify those patients in whom
2 there is no greater uncertainty but the risk/benefit
3 calculus might be a little different. Did that
4 explain? Thank you.

5 DAVID MELNICK: Yeah, I wanted to come
6 back for a minute to the subject of stewardship. I
7 don't think there's anyone in this room who does not
8 believe in careful and targeted use of new
9 antibiotics. We work awfully hard to make these drugs
10 and the concern is to maintain their utility for the
11 longest possible time.

12 But too often, from the perspective of
13 a drug developer, stewardship programs really come
14 across as cost containment and I was wondering, Sara,
15 if you might address whether you think there's a role
16 in stewardship programs for careful instruction within
17 the hospital setting and potentially outside of the
18 hospital about the appropriate uptake of new
19 antibiotics?

20 I mean, for example, you look at the
21 data for (indiscernible), I worked on that program,
22 and the slow replacement of the polymyxins by the beta
23 lactam and beta lactamase combination. It's

1 incredibly frustrating.

2 SARA COSGROVE: I think first,
3 stewardship programs probably did originally come
4 about -- and I'm talking 20 years ago -- as a cost
5 containment mechanism, largely conceived by pharmacies
6 and lots of discussions of picking the cheapest thing
7 to put on formulary and that kind of thing. But I
8 would really say that that really shouldn't be the
9 conception of what stewardship is now.

10 And I do think that has evolved. I do
11 not think that most institutions consider their
12 stewardship program as having the primary goal of cost
13 containment, but rather that that's a possible good
14 side effect of a stewardship program now, and so I do
15 think that we should try to reframe that notion that
16 stewardship is really all about cost containment.

17 I, personally, don't think that the new
18 drugs that are for gram negative resistant -- gram
19 negative organisms that are highly resistant are
20 expensive, but if you look at them compared to their
21 antibiotic friends they are expensive, relatively, and
22 I think we should think about, from a societal stand
23 point, redefining that because if they can save lives,

1 if they can get you to a lung transplant, if they can
2 do good things, then we shouldn't keep saying that
3 they're expensive, but we still have to say they're
4 expensive right now because they are more money than
5 pip tazo and I think we should think about how to
6 reframe what is the worth of these drugs.

7 And as I said in my discussion, I
8 struggle with the drugs that are pretty -- not to pick
9 on anything, but omadacycline is expensive for what it
10 is approved for, given the other drugs that you can
11 use for those indications, but it has a lot of
12 potential, as do all these drugs. (indiscernible) may
13 have potential for abscesses.

14 There's all kinds of exciting things
15 that often take us five, six, seven or more years to
16 figure out. And we also need to determine how do we
17 make sure that we're not losing drugs that may have
18 excellent value and importance but we just don't know
19 what it is yet.

20 But I do think that to say that we have
21 to rely on the existing market approach where the
22 hospital puts it on formulary and their use is
23 encouraged is not necessarily optimal. I don't know

1 if I answered your question, but, just some more
2 comments.

3 JOHN FARLEY: Great, thank. So great
4 presentations. Great discussion. We're running a
5 teeny bit behind, but we will catch up. So we're
6 going to take a lunch break until 1 p.m., so 1 p.m. be
7 right back here for an industry round table that will
8 definitely keep you awake.

9 (Break)

10 KEVIN OUTTERSON: Great, thanks. So,
11 great presentations, great discussion. We're running
12 a teeny bit behind but we will catch up. So, we're
13 going to take a lunch break until 1 p.m. So, 1 p.m.,
14 be right back here for an industry roundtable that
15 will definitely keep you awake.

16 (Break)

17 MODERATOR: But I'm turning the chairs
18 over to Kevin Outterson and Amanda Jezek. So, take it
19 away.

20 KEVIN OUTTERSON: So, thanks for coming
21 back. Amanda and I are pleased to have this panel of
22 industry to be able to speak. The thought, if you
23 turn and look at the program at the top of Page 3 is

1 that each of these folks are going to speak for about
2 five minutes in the order shown. They're going to
3 stay in their seats so that we don't have a lot of
4 time shifting up and down.

5 And after that group is done, then
6 Amanda and I will -- we may have a couple of questions
7 of our own and then we'll moderate some questions from
8 the panel and maybe -- I don't know, John, if the room
9 as well after that.

10 So, that's the plan. We're going to
11 start with Ryan. And let's hear from what the
12 companies, especially the smaller companies, have to
13 say about what they need today.

14 RYAN CIRZ: Great. Thank you, Kevin.
15 So, as a reminder, I'm Ryan Cirz, formerly from
16 Achaogen. Just as a disclosure, I am a paid
17 consultant for Cipla, who markets plazomicin under the
18 trade name Zemdri in the U.S. But, obviously, all the
19 opinions I formed were really my own at my time at
20 Achaogen for, basically, 16 years watching a molecule
21 go from first synthesis through approval last year.

22 Also another disclosure: I'm a little
23 bit of an outsider, and I was honest with the panel

1 about that, that I'm not what I would call a trialist,
2 the person that understands the nooks and crannies of
3 every inclusion and exclusion and how that can affect
4 the outcomes.

5 I am a scientist and enjoy applying
6 first principles to a lot of the problems we're
7 solving, so, hopefully, can add some value there. And
8 obviously I was in the rooms on the core team as we
9 were thinking about things like superiority mortality
10 trial, so watching the teams struggle with those
11 issues.

12 You know, as an advocate for the field
13 and continue to be, despite my non-employment in the
14 field currently, you know, I have to say just as an
15 observer, there's been a clear focus from my
16 perspective on the patients for the last 15 years in
17 that no matter what I say, I think there's been a lot
18 of movement as one team to actually make progress.

19 I mean, there's always frustration and
20 there's always restrictions on what we can do, but
21 overall, if I look back 15 years ago, I think we've
22 certainly advanced quite a bit. And maybe we're not
23 quite at perfection but I'm pretty proud of some of

1 the work that was done in combination with the
2 companies, our partners in the government, like CARB-X
3 and BARDA especially, and obviously with the
4 regulators.

5 So, my early years were sort of formed
6 around the -- the biocreep thesis, which I think is a
7 strong thesis and a concerning one, but it was also
8 the era, as a scientist, where I first heard the
9 phrase "placebo-controlled HAP/VAP study" uttered, and
10 I think we've evolved a long way from that sort of
11 line of thinking.

12 Achaogen was one of the first small
13 entities to enter forth with a drug that we thought
14 was for a severe unmet need. Our foundation was
15 really centered on gram negatives. Plazomicin just
16 happened to be the first of the four programs we put
17 through INDs in our history that went into the clinic,
18 and we were really challenged by the idea of being
19 able to attract the funds to run a 6,000-patient, you
20 know, total Phase III program that eventually led to
21 the Care Study, which was our mortality superiority
22 study, meant to be registrational and run
23 predominantly in places like Greece and Turkey, where

1 the rates of KPC *Kebsiella* were almost 40 percent at
2 the time. This was several years before any new
3 agents were approved, so Colistin was essentially
4 standard of care.

5 There's a whole workshop dedicated to
6 the challenges enrolling that study that I don't want
7 to dwell on too much because it's pretty well-
8 documented. As a scientist and sort of an advocate
9 for the space and wanting to see your creations be
10 studied in a rigorous way, I think obviously the
11 frustrating challenges were things like the Apache
12 Range issues where you had patients that were either
13 too sick or too healthy to be entered. That was a big
14 challenge.

15 Ultimately, it was a superiority study
16 for severe infection, including pneumonias, but
17 obviously having -- not only having cultures but
18 having non-polymicrobial cultures to get a confirmed
19 CRE was a big challenge.

20 But the most frustrating to me as sort
21 of a long-term scientist in the space was the
22 emergence of Colistin resistance during the study and
23 that forcing -- not forcing but enabling the opening

1 of an open label cohort, which to me as a scientist is
2 the ultimate test -- is basically, again, that we're
3 year before AVYCAZ's approval. You've got Colistin-
4 resistant CRE in an open-label cohort. And one of the
5 bigger challenges, which I fully accept, again, not
6 being a trialist, but it was frustrating to watch that
7 data be largely ignored at later stages when it was
8 being evaluated by advisory committees, etc., because
9 of the lack of a control.

10 And I think that's really influenced me
11 as a scientist and a developer to think about the fact
12 that that's just not going to happen. The only way we
13 do superiority is if we have inferior therapies on
14 market, and there's effectively that last chance of
15 showing an open label, this is what happens, didn't
16 really support any sort of data or approval -- it's a
17 time to move on. That said, the Tier B, what we call
18 the Limited Use Indication appears to be open. And it
19 looks very clear to me as someone that would have to
20 take quite a bit of risk and spend 5-7 years of my
21 time to get something back in the clinic as a viable
22 path. But there are clear consequences in the
23 marketplace that I think we just have to think

1 through, and, again, just sort of serving some of my
2 peers.

3 Obviously, the study itself I think was
4 required to sort of open the discussion about doing
5 limited population development. So, there's nothing
6 you can do to change that history. But if we were
7 where we are today then, we would've been to market
8 three to four years earlier and had saved between 30
9 and \$50 million.

10 If we ever got these drugs to where
11 they need to be, which is peak revenues around \$300
12 million to make the enterprise work, that's over a
13 billion dollars in money that I lost for my investors
14 in that delay. So, then you have to look at the up
15 side. And, of course, the publication -- I'm sure the
16 team is incredibly proud of in the New England Journey
17 -- Lindsay stepped out. But ultimately one of the
18 challenges is that data from a severe population such
19 as therapeutic drug monitoring, which didn't occur in
20 our standard NI study, appeared in the label for a
21 CUTI drug. Probably because it's really important to
22 inform when you're treating severe populations, but
23 this hybrid sort of issue of a standard trial with

1 this descriptive data managing its way into that label
2 with that context I think set some challenges for the
3 team after the launch.

4 And then, finally, there was a comment
5 earlier about dosing that's really interesting and it
6 may be unique -- and it was Sarah's comment -- to the
7 way we developed. Because we designed the drug to be
8 able to treat things like HAP/VAP, the dose was
9 actually set with that in mind. Now, when we did the
10 supportive study secondarily, the UTI study, to
11 provide the safety data for that same dose, you don't
12 change the dose.

13 And so when you actually show up to
14 market, you can imagine the dose that's appropriate
15 for HAP/VAP in reality approved for UTI. And so I
16 think as we think through of people doing this
17 prospectively, which we did not, that's something to
18 just think about with the new unmet pathway.

19 KEVIN OUTTERSON: I didn't warn you
20 that I had my timer going, which, you actually
21 finished with 27 seconds left, so I appreciate that.
22 And I guess Manos will take your 27 seconds.

23 MANOS PERROS: Yep. And also those

1 from Sue and the others. So, Manos Perros, Entasis.
2 Once again, thank you for the opportunity to
3 participate. Let me start my timer and then we can
4 compare.

5 So, I will start by disagreeing with
6 Kevin. I agree with most of the things, probably
7 everything else that Kevin says, but actually I don't
8 believe that the system is broken. I think what we're
9 witnessing is a change, a very rapid and radical
10 change in the way in which antibiotics are being used.
11 And that's because we've been successful as a
12 community in inventing, and developing, and
13 commercializing good, safe, effective drugs.

14 And I'm thinking of drugs like Cubicin,
15 I'm thinking of all the carbapenems. And if you think
16 back 20-30 years ago, when these were not available,
17 it was a very different picture.

18 So, the place that we are today when
19 we're thinking of what is clinically relevant for a
20 clinical trial or for a label, what is clinically
21 relevant was on some of the slides that were shown
22 earlier today. The WHO, the CDC do not call UTI or
23 HAP/VAP, the medical need. The medical need is in

1 drug-resistant pathogens. And yet our labels speak to
2 polycyte indications.

3 Now, these are important -- the points
4 that Dr. Nambiar made -- you can't extrapolate from
5 the test tube to a human being. But also you can't
6 extrapolate from one bug to another or from a drug
7 sensitive to a drug resistant. And without having the
8 solutions -- I introduced myself earlier, I'm a
9 chemist -- we need to find the solutions that would
10 make our labels more relevant to the way in which
11 antibiotics are used today, which is for a far more
12 targeted patient population than we're used to.

13 I think Dr. Cosgrove showed earlier,
14 data from her own institution, 30-40 prescriptions.
15 These are not the thousands that drugs written with
16 antibodies would treat. These are much smaller
17 numbers. And there comes the challenge: How do you
18 actually trial the kind of patient that needs our
19 treatments today? The kind of patient who failed
20 Daptomycin, who failed carbapenems?

21 And I believe that the solution has got
22 to be scientist. We need to dig into the science and
23 we need to think as scientists, which is what we are

1 today, and put the clinical data in the context of the
2 microbiology, put the microbiology in the context of
3 the mechanistic biochemical data that we have, and put
4 the whole thing together when we're considering how a
5 drug is going to be labeled, how a drug is going to be
6 licensed and offered to physicians to use.

7 I think the agency does an amazing job
8 pooling the data together from each section. And for
9 those physicians who bothered to actually read the
10 entire label before they decide to use an antibiotic,
11 they will find all the information that they might
12 wish to have and make the connections. But I believe
13 we need to do a better job at helping them make that
14 connection.

15 Where there is an outcome where
16 physicians spend almost an hour trying to cut data
17 from 45 patients through four different ways to make
18 sense, and there is no connection back to the
19 preclinical science to try and put in the context -- I
20 think we're missing an opportunity. When looking at
21 microbiology and we don't make the connection backed
22 by chemistry to interpret data that might not be
23 clear, we're missing an opportunity.

1 So, I'm calling for a rethink of how we
2 use the totality of the scientific evidence, clinical
3 and nonclinical, within the boundaries of what the
4 agency has to deliver to get labels that are more
5 relevant for the way in which the drugs are going to
6 be used. We heard numerous times today that this is
7 important. This is important because it will drive
8 use, this is important because it will drive formulary
9 inclusion, this is important because it will drive
10 pricing differentiation. Nobody compares modern
11 oncology treatments today with the price of
12 chemotherapy of 30 years ago. No one. And there is a
13 good reason for that -- it's because the labels are
14 actually very different labels.

15 But we compare today's modern
16 antibiotics in price to the antibiotics that have been
17 on the market for 30 years, for which their
18 (indiscernible) costs have been amortized and which
19 cost pennies to produce.

20 So, it's important that I think we have
21 that conversation. I think as an agency obviously
22 your role is to regulate, but by regulating you're
23 also driving the way in which we, as developers, do

1 our work. And I think it's important that you help us
2 do our work in a way that's going to be more relevant
3 to what patients need today. I'm giving you another
4 25 seconds back.

5 KEVIN OUTTERSON: No, I think we're
6 good, thank you. Not all the companies that are going
7 to speak today are small companies. And I think Nick
8 is next.

9 NICK KARTSONIS: Yes. So, I'm from
10 Merck, as you heard earlier. And today I was going to
11 talk about the challenges in doing difficult to treat
12 studies such as HAP/VAP. HAP/VAP, as many of you
13 know, is a very common condition and it's probably one
14 of the conditions that we probably want to have these
15 drugs available for to treat patients who need the
16 most. And, in fact, I mean, I think we can all agree
17 that since the 10 x '20 Initiative has come forth,
18 we've now had 14 new drugs come to the market, which
19 is fantastic. But there are few companies that have
20 actually been involved formally in actually doing
21 studies in HAP/VAP.

22 Streamline Development has afforded a
23 quicker path to do studies in UTI and IAI. Of the 14

1 drugs approved, I think there are five that have done
2 HAP/VAP studies. And I guess fortunately or
3 unfortunately, depending on what your perspective is,
4 I've been involved with three of those five studies,
5 so I figured I'd share with you a little bit today
6 about what we've learned regarding sort of the lessons
7 learned and the challenges that are associated with
8 those, to help sort of form a broader debate on the
9 particular topic at hand.

10 On the surface, HAP/VAP's a great
11 indication, right? I mean, there's a lot of cases
12 that you see. Over 150,000 per year in the United
13 States. My marketing colleagues salivate over this
14 indication. This is the indication they really want
15 because it shows severe infections. But if you
16 actually look at the review of data from 2006 to 2010,
17 before these companies started doing it, the average
18 recruitment time for these studies was on the order of
19 about 3 to 3-1/2 years.

20 So, there are many challenges as to why
21 companies kind of shy away from this area, putting
22 aside all the issues around diagnosis of pneumonia.
23 Obviously, the fact that -- we've actually done a

1 pretty good job, within infection bundles and
2 infection control, to reduce the number of cases of
3 HAP/VAP, and as a result of that there's been less
4 cases of HAP/VAP that are easier to identify in
5 particular trials.

6 And as you had heard -- I think it was
7 Helen who said it better yesterday -- the market
8 research we get when we seek out investigators is "No,
9 thanks. I don't want to be the center where I enroll
10 the most patients in a HAP/VAP study." And so that's
11 really something that you have to keep in mind in
12 terms of that as well.

13 The FDA guidance has been great for
14 HAP/VAP but there are still challenges with that. We
15 talked about the 24 hours of antibiotics, the need for
16 a Gram stain, if you're going to do both HAP and VAP,
17 they need to have 50 percent of your patients in VAP.
18 These are all necessary evils but they do come at a
19 cost in terms of recruitment and what have you.
20 Consent for ventilated patients is not easy. We've
21 tried early consent but that didn't work very well in
22 terms of that. The different regulatory differences
23 between the U.S. and Europe -- you all know about

1 that. But the biggest issue probably is cost.

2 So, of our three studies, two of them
3 were outsourced and the cost of those outsourcings
4 were \$130 million each. So, just the outsourcing of
5 it. If you add in the internal resources, it goes
6 over 150 million. The one study we did do in-house
7 cost \$40 million. So, it's a lot easier to do it in
8 house but if you're a smaller company, that would be
9 very difficult to help make that work.

10 So, we did three studies with
11 Tedizolid, Ceftolozane/Tazobactam, as well as more
12 recently with Imipenem/Relebactam. I'm going to share
13 with you some statistics, so hang onto your seats
14 here. Each of these were sample sizes of 536-726
15 patients. Each study had at least 200 sites involved
16 with it. And the total recruitment for each of these
17 studies, the mean was 47 months, so four years. And
18 that was 42-53 months to get those studies done from
19 first site ready to last patient, last visit.

20 U.S. recruitment was 4-8 percent in
21 these three studies, despite having over 30 percent of
22 the sites allocated in the U.S. The actual patient
23 site per month was .05 patients per site per month,

1 which over the course of the studies, only 2-3
2 patients per study.

3 Screening randomization at best was
4 10:1. And the monthly recruitment was on the order of
5 about 10 patients per month -- of site per month. And
6 you have to deal with all the issues like drug supply
7 challenges that you often face with the comparators.
8 Each study had an average of two of those study issues
9 on top of that.

10 But we learned a lot, so I want to also
11 not just kind of be doom and gloom. I figured I'd
12 share with you some of the lessons we learned from
13 that. First is we did try using a clinical trial
14 network in Europe. It was really challenging to get
15 them on board contractually, but when we did, even
16 then recruitment didn't really come up. It was one of
17 our rescue mechanisms and it didn't really help us
18 that much in terms of that.

19 The long IRB times also makes it hard
20 to get started. And you're often having issues with
21 different IRBs telling you different things, and
22 trying to manage that across a large study is never
23 easy.

1 We did almost all of our recruitment in
2 Eastern Europe and there's a lot of reasons for that.
3 You heard about the less prior antibiotic use. But
4 another reason is those patients there, their standard
5 of care is not a carbapenem. So, everybody's getting
6 something that's good and above what their normal
7 standard of care is so it's easier to recruit in those
8 particular places.

9 It's also cheaper to do the studies
10 there. Our closure site rate was on the order of 30
11 percent. So, you know, if you're going to do these
12 kind of studies, prepare for rescue sites because I
13 think they will go a long way in terms of that. We
14 strongly implemented 24-hour around the clock at each
15 of our sites and we actually paid for people to be
16 available. Because the patient usually comes in on a
17 Saturday night, and waiting until Monday -- too late
18 in terms of making that work.

19 We also had a fully committed
20 recruitment team at headquarters, which, basically,
21 their job was to do things like refreshers, and
22 regional meetings, and repeat site visits,
23 newsletters, gratitude messages, inspirational

1 tagline. We had it all, to try to get people...
2 Every time somebody would enroll a site, we'd get down
3 on our knees and thank them for doing that because it
4 was always a major accomplishment to meet that in
5 terms of that. So, it was a big issue in terms of
6 that.

7 I'll just close by saying that there
8 were two other things that I would plan on. One is
9 that know your investigators. Make sure you're
10 finding the right investigators in your institution
11 because they're not always the infectious disease
12 doctor. In fact, I would tell you they're never the
13 infectious disease doctor, or rarely the infectious
14 disease doctor.

15 And the final thing is expect site
16 fatigue and data overload. Sites get tired so they
17 will go on holidays, a little bit of breaks. They
18 need it just to kind of get on top of that. So, in
19 the end, we completed these three studies -- and
20 there's my timer, but I'll just leave one more message
21 if that's okay and then we'll go with regard to that -
22 - which is that it does differ whether or not you do a
23 VAP-only study versus HAP-plus-VAP.

1 VAP-only -- our mortality rate was 27
2 percent, actually. HAP and VAP, our mortality rate
3 was 20 percent. But it was because it was 10 percent
4 for HAP and 27 percent for VAP. So, in the end, we
5 were able to make it out in terms of that but that
6 needs to be balanced in that regard.

7 And one of our studies, of course, as
8 many of you know, we presented ID Week. We met on the
9 FDA endpoint but we didn't meet on the EU endpoint so
10 we are not moving forward with that approval going
11 forward. So, I'll just close on that point.

12 DAVID MELNICK: Nick, you're
13 (indiscernible) from a big company to a small company
14 and -- does the 27 seconds still move on? So, we are
15 a small company and I think the key points that I
16 wanted to raise is whether or not we can do a better
17 job in terms of both time and cost efficiency by
18 making use of networks and potentially platform
19 trials.

20 So, our Phase III compound is an oral
21 carbapenem that's currently moving through its pivotal
22 trial. And we have a Phase II program, a DNA gyrase
23 inhibitor that's being developed specifically for

1 patients with pulmonary manikin faction. Being one of
2 those small companies where everyone wears a lot of
3 hats, efficiency is just key. You know, we don't have
4 the luxury of an endless timeframe and endless
5 resourcing.

6 In terms of trial networks, these two
7 trials pose a very, very different challenge. The
8 Phase III compound -- again, in CUTI, we've customized
9 the trial but basically it follows a well-described
10 path. There are numerous investigators, the CROs have
11 experience, we know the trial sites, and there's a
12 clear path to follow.

13 The second candidate is going down an
14 untrodden path and we've had the challenge of
15 developing a regulatory pathway, and we thank our
16 colleagues around the table here and in the NTM
17 community who've helped us develop that pathway. But,
18 again, patients are uncommon, they're difficult to
19 identify, care is highly concentrated in the hands of
20 a few investigators, so it's a very different
21 situation in terms of potentially utilizing a trial
22 network. But that would seem to be the sort of
23 disease entity which would be very well-suited to the

1 development of a platform trial.

2 In terms of platform trials, you know,
3 we've seen wide utilization of platform trials for
4 targeted therapy in the oncology space, and even
5 though antibiotics are perhaps the prototype for
6 targeted therapy, we've not really made much use of
7 that approach in our trials. You know, we can
8 potentially utilize an adaptive design both to explore
9 the potency of individual candidates and potentially
10 move toward combination therapy downstream. And, you
11 know, I think that's going to be increasingly
12 important as we move toward the use of combination
13 therapy for suppression of treatment-emergent
14 resistance. So, I think there's a great opportunity
15 here.

16 In preparation for this meeting, I
17 pulled together my Spero colleagues and sort of asked
18 them their opinion about this idea of utilization
19 networks. And I was surprised that there was a fair
20 amount of pushback. The first priority that was
21 raised, and maybe it's off target for this meeting but
22 we've certainly discussed it so far, is that fixing
23 the efficiency of trial design and delivery isn't

1 going to make much difference until we fix the
2 marketplace, that we need a new commercial model. And
3 until we do that, we're going to have trouble.

4 There are certainly some good
5 precedents for these trial networks in the AI space --
6 the ACTG, the TB Trials Consortium. And in addition,
7 as an example, in terms of antimicrobial surveillance
8 activities now, multiple sponsors have gotten together
9 to use a common system where they share data from a
10 single vendor. So, certainly we can learn to play
11 together in the same sandbox.

12 But, you know, despite -- you know, as
13 others have pointed out, despite the fact that we're
14 really focused on the activity of these novel
15 compounds versus resistant pathogens, we're still
16 stuck in the world of doing indication-based trials
17 and there, a master protocol could potentially be of
18 great use. You know, we go through this exercise with
19 every trial of reinventing the wheel. We go through
20 the same exact steps, We go to CRUs -- CROs that do
21 feasibility studies. You know, based on their last
22 trial, they charged us an arm and a leg. My number
23 for comparison is that about 40 percent of our total

1 trial cost turns out to be CRO cost. So, finding ways
2 to share that across sponsors would be very useful.
3 You know, there's the obvious benefit of decreased
4 cost and time.

5 In terms of drawbacks, the obvious one
6 of confidentiality and IP, the risk of antitrust
7 inclusion issues being raised if we join forces to
8 work through a platform trial. The obvious
9 intercompany competition for sites -- what do we do if
10 there are two patients in the queue who are doing
11 similar trials?

12 Probably the biggest concern was the
13 concern about increased bureaucracy -- that
14 interposing another level of administrative oversight
15 between the sponsor and the site would be difficult.
16 I think that the quote I like best from our pre-
17 meeting discussion was, quote, "The idea of a central
18 CRO makes me absolutely crazy." So...

19 So, I think the last point -- no
20 offense to anyone sitting at the table -- the existing
21 networks in our space, ARLG, excuse me, Combat Care,
22 you know, the IMI networks have been cumbersome to
23 use. They've been slow. There is a lot of

1 administrative bureaucracy involved. And as we move
2 forward toward looking at new networks, we need to
3 find ways to make that more user-friendly.

4 RIENK PYPSTRA: You can leave it on.
5 So, I'm Rienk Pypstra. I have indeed some also 25
6 years of experience in developing drugs since working
7 on new formulations for Augmentin in the mid-'90s.
8 And, yes, things have improved significantly since, so
9 that is the good news.

10 But let me first address one of your
11 points. I don't have unlimited resources either, and
12 I am competing with my colleagues in other therapeutic
13 areas such as cardiovascular and oncology, who can do
14 more with more money than I can. So, it is important
15 for us as well to get this environment right.

16 But, as I said, the environment has
17 been improving but it has been improving at different
18 paces in different places in the world, and that is a
19 topic that I would like to highlight here -- that
20 doing a clinical development program is an expensive
21 endeavor and you want to make sure that whatever you
22 do suits as many regulatory authorities in the world
23 as possible.

1 Now, again, there has been good
2 progress, and the FDA and EMA in particular have come
3 together. Their guidelines are not identical but they
4 don't contradict each other. Still, there are some
5 problems in the sense that the endpoints are not the
6 same. And so you're supposed to take two endpoints
7 and you won't get a statistical penalty for testing
8 two primary endpoints because each one will look just
9 at one, but you get into difficulties that the same
10 study, as Nick just alluded to, the same study is
11 acceptable for one area and not for the other area.

12 It was still one dataset. And that is
13 only for Europe and the U.S., but we also have
14 difficulties in convincing other authorities, and the
15 big ones are China and India, Japan. Those are the
16 big authorities to negotiate with. But we are also
17 submitting in hundreds of countries all over the world
18 and that is a typical big pharma problem. Small
19 pharma companies just don't have the resources to do
20 it. But for every agency, you have to submit a file
21 that has different formats and you get different
22 questions, and some questions are more relevant than
23 others.

1 But coming back to the design of such a
2 global program, ideally, you make one program that
3 works everywhere but then you need to implement it.
4 So, imagine that you found a way forward, you have a
5 study design, it is accepted by EMA, it is accepted by
6 FDA, it will probably be okay for the other ones. You
7 start to implement it, and then you see that it takes
8 you about one year to activate the sites in China.
9 And you have all the practicalities that the pathogens
10 that you're connecting in China and India or any blood
11 samples, you cannot get them out of the country. No
12 central lab possibilities. Again, practical issues
13 that make it pretty difficult to implement good
14 quality data.

15 Now, we saw this morning in the
16 presentation as well, and I was fascinated by that
17 presentation -- there was some stuff that I really
18 didn't know, but it does resonate -- the pathogens are
19 not the same everywhere, the resistance patterns are
20 not the same everywhere. And what was not mentioned,
21 the patients are not necessarily treated in the same
22 way. Sometimes they get different antibiotics because
23 different antibiotics are approved. But besides

1 antibiotics, there's also a standard of care. What do
2 they get besides the antibiotics? So, that brings a
3 lot of background noise in those trials that you're
4 trying to do because you have to do them globally in
5 order to be able to have a single program that works.

6 So, given all these difficulties, the
7 question is -- and one more point I wanted to make
8 about difficulties. This is just for the standard
9 antibiotics as we know them today. IF we go to the
10 next generation of products with novel mechanisms of
11 action where we don't even know whether an MIC is
12 predictive of what happens in the patient, you can
13 imagine that the expectations from the regulators will
14 be even more widely different and it will be even more
15 difficult to test -- to demonstrate something
16 homogeneous and meaningful scientifically.

17 So, what would we want to have? Well,
18 first of all, the science comes first. We have to
19 make sure that whatever we demonstrate in a global
20 trial can be interpreted. And so as we heard this
21 morning, that it is important that when you do your
22 clinical trial you have to limit yourself to one body
23 site, I would argue that you would also try to

1 homogenize the type of medical setting where you're
2 in. And certain settings, it probably will not matter
3 too much whether you do the study in Southeast Asia,
4 in Africa, or in Western Europe, or in Northern
5 America; but in other settings, the standard of care
6 is going to make a big, big difference. And so I
7 think we should try to make sure that, from a
8 scientific perspective, we have a homogeneous
9 population. We have homogeneous pathogen description,
10 homogeneous type of infections that is also by body
11 site. But from those datasets we have also to
12 interpret them cleverly and smartly.

13 It is not because there was no U.S.
14 patient involved in a certain study that the study
15 would not be applicable to the U.S. situations. So,
16 we have to dare to extrapolate from the data. And
17 sometimes we'll have to generate additional datasets -
18 - PKPD datasets, additional surveillance data, in
19 order to be able to make that translation from the
20 clinical data that have been generated, that have
21 demonstrated something, to extrapolated, to the
22 relevant populations. That is about interpreting the
23 findings and then coming to that, how do you interpret

1 that? How do you put that in a label?

2 Is it important to have in the label
3 just what you did, what has been studied? Yes. But
4 it's also important to say what can be deducted from
5 that. The agency has been working for months on those
6 data. They have come to a good interpretation, and in
7 case of doubt, they have a scientific advisory panel
8 meeting to give additional guidance.

9 The physician who is facing the latest
10 new bug has got a couple of hours or a day to try to
11 find out what might work in that situation. So, it's
12 not comparable. The agency is in the best position to
13 do a meaningful interpretation of that data and to
14 translate that ideally in a label and, of course,
15 within the constraints of the current code of federal
16 regulations.

17 But the gray boxes that Kevin mentioned
18 I think are a great idea. You could give your
19 indication based on the data that has been generated
20 and then interpret within the constraints and within
21 the risks that you have identified how this drug could
22 also be used such that these other uses that seem
23 perfectly appropriate to people who are well-versed in

1 the art would not become dismissed as just "Oh, well,
2 that's off-label, we cannot reimburse that."

3 So, the dichotomy between being
4 indicated and off-label, that is a problem, and if
5 some of the off-label is perfectly appropriate -- and
6 if it is appropriate, it has to be considered somewhat
7 like an on-label indication. Thank you.

8 KEVIN OUTTERSON: Thank you. And last
9 for the opening statements is with Sue.

10 SUE CAMMARATA: I'm Sue Cammarata. I'm
11 the Chief Medical Officer at Melinta. And I came
12 onboard at the company about six years ago when it was
13 going -- transitioning from Riesbeck's to Melinta and
14 how I met Erin Duffy. That was when Riesbeck's was
15 recapitalized. So, for the last six years I've been
16 there.

17 We went from 30 people at that time,
18 around that -- and now about a couple hundred people
19 with four products. So, Melinta has attempted to roll
20 off products. There's been a lot of discussion about
21 that -- to be able to consolidate, so that's what
22 we've attempted to do.

23 I've been involved in anti-infected

1 trials for 20-plus years. I started out -- my very
2 first study was a HAP/VAP trial for Zyvox way back in
3 the day when it was in Phase III. And I have been
4 affected by this rollercoaster that has been
5 antibiotic clinical development. So, for the folks
6 that have been here during that time, you've seen it
7 wax and wane and it almost died once before. So, most
8 of my comments have been -- are going to echo what
9 other people have said to some extent.

10 Drug developers, all of us, have some
11 understanding of what clinicians need. We're
12 clinicians and we hear from clinicians, so I think we
13 understand what you guys want. But, as been
14 mentioned, we have to design clinical trials that meet
15 the regulatory needs globally. So, we have to meet
16 the requirements to show efficacy and safety. We also
17 have to think about standards of care that may be
18 different in different regions. So, those are all
19 considerations that we have to take in that makes it
20 very challenging for the companies.

21 In the days of big pharma -- so, when I
22 did Zyvox, that was Pharmacia, which wasn't quite big
23 pharma but got sucked up by Pfizer -- in the days of

1 big pharma, you had a lot more money and you could
2 remember that there could be many trials that you
3 could do for registration as well as post-approval.

4 With the exit of most of big pharma,
5 it's now all the small pharma biotechs. And I think
6 almost every single product that's been approved
7 recently came from some small company. So, they're
8 doing all of the antibiotic discovery and development.

9 But that takes people, and time, and
10 resources, and when I say people, time, and resources,
11 that all equates to money every single... So, I've
12 tried to cut down saying money in my talk but really
13 time, and resources, and people equals money. And
14 they're not often internal to a biotech. So, if you
15 have a small company, as been mentioned, you have
16 companies that have 30 people, five people -- they may
17 not have an in-house toxicologist, they don't have an
18 in-house pharmacologist, they don't have a formula
19 person.

20 So, when I was at Pharmacia, I could
21 turn and say, hey, let's have a project team where a
22 bunch of people come. When you're in a small biotech,
23 no, you have to go find those consultants, you have to

1 find the CRO, you have to find the contractors that
2 are going to work for you. So, you don't have the
3 personnel in place to easily do all these studies.

4 So, we've contracted those. You may
5 only -- you'll see one study done at a time. You do a
6 HAP/VAP trial that may cost you \$100 million if you're
7 a small company, depending on the number of patients
8 you enroll; you can do a UTI CAP trial that will cost
9 you \$50 million, hopefully, not too much more than
10 that but it all depends on the size of the trial.

11 And this is the cost of doing trials
12 where there is agreement in how to do the trials. So,
13 we're not even talking about doing osteo, we're not
14 talking about prosthetic joint -- just to do UTI and
15 HAP/VAP trials -- their guidance on those approach.

16 (sic)

17 So, do I want to do another UTI trial?
18 Do I think we need another UTI drug? I don't think we
19 need the indication, but for a small company with no
20 money who can only do one trial at a time, you're
21 going to put a bet on something that you know you can
22 do that there's a clear guidance it can get approved,
23 and that you can probably successfully complete it.

1 And maybe in the past get investors to invest.

2 So, we're also going to talk to some
3 extent about, you know, all the issues of things we --
4 how we can go forward. But I would point out we're
5 not in the big pharma era. We're not going to be 15
6 trials for 10 indications. It doesn't happen like
7 that anymore. As you may remember, it has happened
8 like that before. So, we have to be creative within
9 the confines of regulations and statistics, but we're
10 always up against the specter of time and money.

11 We have the tools. I think Dan's going
12 to talk about stats and how we do various things. A
13 lot of this has been discussed in many venues before,
14 so we have some of the tools. And if you've been in
15 the rare disease space, there are tools. The rules
16 are no different for rare diseases as there are for
17 antibiotics. So, they're not getting a special
18 dispensation particularly.

19 So, in the words of the Rolling Stones,
20 you cannot always get what you want. We have to be
21 honest. It is unlikely that one or two registration
22 trials will answer all the question that every
23 clinician has about an antibiotic. It's just not

1 possible within the construct of a non-inferiority
2 trial, which is what we typically are dealing with.
3 It's very rare to be able to do a superiority trial.

4 I think everybody here that antibiotic
5 development is currently imploding. We're not going
6 to solve that today. But the economic reality that is
7 killing antibiotic development is behind many of the
8 challenges that you -- that we're going to be
9 discussing today. Pharmas having difficulty funding
10 clinical trials. And I also have heard that academic
11 investigators are seeing money drying up. They're not
12 getting money for grants, they're not getting money
13 for investigational trials that they used to be able
14 to explore, some of the questions that were out there.

15 So, I'm looking forward to discussion
16 options regarding antibiotic clinical trials. But I'd
17 also like to understand the options to gather and
18 disseminate information that clinicians and patients
19 need that are not specifically funded by pharma and
20 are not reliant on registration trials. I think you
21 just have to understand the paradigm is changing and
22 we have to come to grips with that. Thank you.

23 AMANDA JEZEK: Thank you to all of our

1 speakers for this session. I will start us off with
2 an initial question. So, a couple of you spoke
3 specifically about labels and what content you'd want
4 to see in labels, so I wanted to give the other
5 speakers an opportunity to comment on what information
6 you'd want to see in the labeling.

7 And because this is not a terribly new
8 idea, I'll throw in a follow-up question: Why do you
9 think we're not yet seeing the kinds of changes that
10 experts want to see in labeling, and how can we
11 overcome those challenges? And because that's kind of
12 a bigger picture question, I think after we hear from
13 our speakers, we can see if there are others on the
14 full panel who have comments on that one.

15 Oh, and Kevin just reminded me, if you
16 would like to comment on this one or you have
17 additional questions, please turn your attend card
18 over and we'll keep track of those who want to speak.

19 NICK KARTSONIS: So, I think you heard
20 about -- we've had a little bit of a discussion about
21 labeling this morning, and I think if I was to tell
22 you what Merck would have on the label -- obviously,
23 they'd like to be able to reference their resistant

1 infection studies that have been completed. And I
2 think we'd all like to do that.

3 But, you know, I'm also not naïve to
4 the fact that the agency is bound by guidance and
5 labels are really there to inform efficacy and safety.
6 And, frankly, none of these studies I think that have
7 been done for resistant infections have actually been
8 anything but descriptive in nature. So, you know, at
9 the end of the day, there is a little bit of a leap of
10 faith in terms of accepting what the data are in
11 particular with regard to those labels.

12 But on the flip side of it is if you
13 actually look at the five studies that have been done
14 that I think have been completed, four of the five
15 numerically show an advantage for the new drug versus
16 the older drug. Now, the only one where the
17 information is in the label is where the one was
18 inferior to the product, okay? Which, of course,
19 became more of a safety signal as opposed to an
20 efficacy finding.

21 So, you know, it is -- you're a little
22 bit damned if you do, damned if you don't, right?
23 Because if you do -- if you put it in there -- if you

1 do the study and it works to your advantage, you can't
2 talk about it, but if it's negative it may end up in
3 the particular label.

4 So, I mean, I get it. You can't put
5 this information on the label because it doesn't fall
6 within the guidance with regard to that. But if
7 that's the case, then I think fundamentally we should
8 ask ourselves is there another mechanism by which we
9 can do that? And so I offer up the idea of -- you
10 know, the FDA has a guidance on consistent with
11 labeling, you know, that you can actually promote
12 based on information based on what's called CFL. And,
13 fundamentally, I do believe that these studies kind of
14 fall within those particular confines in the sense
15 that they are within -- provided those studies that
16 have been done are within the same indications, they
17 are, in essence, studies where you show that they're
18 susceptible for certain organisms that were tied to
19 the ones that you have within your particular label.

20 So, that's another something outside
21 the box we could think about -- is there a way we can
22 marry up that information? Because at the end of the
23 day, what the pharmaceutical companies want besides

1 the guidelines and the labeling, they really want
2 their reps to be able to go out and talk about their
3 studies, right? Irrespective of what we think, there
4 still is a component of the importance of the
5 commercialization of these products and people do have
6 to pound the pavement to some extent to be able to
7 share that particular information.

8 So, I offer that up as a particular
9 thing to think about, and I'll stop there.

10 RYAN CIRZ: I guess I'm more interested
11 in introducing some concepts that maybe will get
12 commented on further. Just putting my first
13 principles hat on again -- you know, when I hear we
14 want to see a drug studied in severe infection or
15 resistant infection, I separate those two pretty
16 dramatically in my mind. You know, the severity issue
17 of the pharmacology -- the physiology of a patient
18 undergoing severe disease makes total sense to me.
19 Most of the drugs we work on are water soluble,
20 they'll go where water goes. And as water equilibrium
21 is all messed up in severely ill patients, it makes
22 sense we need to understand that. And a lot of the
23 example failures were largely attributable to not

1 understanding that.

2 The harder one for me is sort of that
3 we need to see resistant pathogens. And despite the
4 fact that my entire research team no longer works in
5 this space, they were still willing to answer a text
6 message at 6 a.m. in California for me and do a
7 protein alignment.

8 So, here's the thing I struggle with as
9 a scientist. I can show you data against a CTXN
10 pathogen pretty readily. Much more common, right? An
11 ESBL. There are four amino acid changes in that
12 enzyme near the active site relative to a KPC enzyme.
13 And so to spend a decade to show you directly that a
14 drug that isn't even a beta lactam will be impacted by
15 these four amino acids that make an ESBL a CRE just
16 seems like it's a huge waste of our time and
17 resources.

18 So, when I separate, the severe disease
19 makes total sense, and the mechanism goes back to
20 like, what makes sense? Like, if I'm a drug that's
21 affected by that, let's study it. But if I'm not, why
22 do we start with the assumption that some magic change
23 is going to happen and the drug suddenly won't work

1 anymore when it's really just enzymology? So, those
2 are sort of the two buckets I'm separating and
3 struggling with.

4 RIENK PYPSTRA: Yes, going back to that
5 question about labeling, part of the reason why these
6 resistant pathogen studies have not been included is
7 because they also -- not only are they not well-
8 controlled but also they don't restrict themselves to
9 the very narrow indication that has been given. The
10 indication was just for UTI and these pathogens have
11 been collected in HAP/VAP, have been collected in
12 bloodstream infections or all kinds of infections.

13 And so, therefore, my plea would be to
14 -- as that is a legal requirement that whatever
15 information you put is linked to the indication, my
16 plea would be to be a little bit more lenient on the
17 indication and not restrict the indication
18 specifically to just the body site. I know that is
19 what was investigated but that does not necessarily
20 need to be what is indicated.

21 AMANDA JEZEK: Sumathi?

22 SUMATHI NAMBIAR: Thanks. I just to
23 make sure I understood your comment. So, the three or

1 four trials that we've discussed which were really
2 focused on patients with CRA infections were all
3 descriptive studies. They were not necessarily tied
4 to the indication.

5 So I think there's a disconnect there
6 because we did allow the trial. If you look at the
7 Achaogen trial, it included more than one body site.
8 It was designed for superiority. Had that study been
9 completed and there was a finding of superiority, that
10 would have been a successful trial. So, it didn't
11 have to be tried to UTI. So, I just want to make sure
12 that that's clear to the group.

13 And even in our unmet need guidance we
14 do allow superiority trials where you can pool across
15 body sites. We just make it clear that there are some
16 uncertainties there because we've seen drugs behave
17 differently at different body sites. And if you
18 really have a deficit in one body site, it may not be
19 very apparent when you do one of these mixed body site
20 studies.

21 So, I just want to make sure that there
22 is no requirement that this resistant pathogen study,
23 if it is done, should only be in the indication for

1 which the product is otherwise being studied.

2 RIENK PYPSTRA: But it is related to
3 getting the information in the label.

4 SUMATHI NAMBIAR: Right. So, that's a
5 totally different discussion.

6 RIENK PYPSTRA: Yes.

7 SUMATHI NAMBIAR: You get it in the
8 label -- what we are looking for is a trial that we
9 can interpret. And as Nick had mentioned, all the
10 trials that have been done recently were descriptive
11 studies. The plazomicin trial, the CARE study was
12 meant to be a study that could have been analyzed. It
13 was designed as a superiority trial. For many reasons
14 that Ryan pointed out, the trial was terminated early.
15 And at the time, there was no plan for any kind of
16 hypothesis testing. So, at the end of the day, it was
17 a descriptive study. So, those are two different
18 issues. So, I think we'd be happy to include... I
19 mean, I know I cannot answer all the questions about
20 labeling but the underlying issue was can we interpret
21 the trial or not? Could there be other mechanisms and
22 ways to put it in labeling is a different question.
23 But I think the basic scientific issue was the fact

1 that these trials could not be interpreted because
2 there was no hypothesis testing plan.

3 AARON DANE: Yeah, I think part of it
4 might be, for those resistant pathogen studies, how
5 can we get more out of a small set? Because we can't
6 do bigger studies much of the time so we've got to
7 work out how to interpret that.

8 But the other thing I wonder from
9 something Ryan said was that -- our design means that
10 as soon as we get resistance, those patients just
11 don't form any part of the evaluation because you
12 can't randomize anymore. So, I'm wondering whether
13 there's something else we should also think about --
14 is when we have that situation, whether we can start
15 to use external controls, for example.

16 So, I know there can be problems with
17 external controls, but in that sort of setting where
18 there should be quite a big difference, it feels like
19 that can be more informative and that could inform the
20 label at that point then -- for those patients of most
21 interest.

22 SUMATHI NAMBIAR: If I can just...
23 Yeah. So, in terms of historic controls, I think you

1 know better than I all the shortcomings with historic
2 controls and there are some settings where they're
3 appropriate and some where they aren't. I think the
4 antibacterial space where there's so much variability
5 and treatment effect -- and even these so-called pan
6 resistant organisms, you really don't have the kind of
7 treatment effect you would see with some of the other
8 indications. It's not 100 percent yes or no response.

9 So, I mean, that's been a struggle.
10 There have been some instances where we were allowed
11 to use a historic control where we had a lot more
12 certainty with treatment effect, you know --

13 AARON DANE: Yeah. I guess for me, it
14 wouldn't be a blanket use of that approach, but just
15 maybe being open to that idea that they could be used
16 in some of these settings where you are -- the
17 patients can receive nothing else so they can't be
18 randomized. So, we must be able to put that result in
19 context in some way if this is the only therapy that
20 they can take.

21 AMANDA JEZEK: Manos and then Lindsey,
22 and if anyone else wants to speak, please turn over
23 your attend cards so we can identify you.

1 MANOS PERROS: My comment was going to
2 be on your second question, so if there's more
3 discussion to be had on what should be included in the
4 label I think that should go first.

5 LINDSEY BADEN: I also had a label
6 comment but -- so I guess my -- I think the label --
7 I'm not convinced that the label is the most flexible,
8 rapidly changing, informative document, given its
9 structure and its regulatory environment. And sort of
10 Nick's comment -- are there other ways to get credible
11 information into the community and it not be, you
12 know, pinned to the label?

13 And I guess to the industry colleagues,
14 is that unattractive because the label is the be all
15 end all, or can the label have what meets the
16 statutory requirements and then other venues help
17 expand the dataset which is much more dynamic and
18 changing and, therefore, has to have an environment
19 that can allow for new information of different
20 quality?

21 AMANDA JEZEK: John?

22 JOHN REX: That wasn't where I was
23 going to go but that's a great question. Because it's

1 a variation on this notion of what defines a normative
2 dataset that we all accept? And the reason that the
3 label is viewed as such a strong thing is that a
4 completely independent arbiter has said, this is what
5 we believe.

6 There's a group that has no conflicts
7 of interest, has no reason to say anything that they
8 don't believe is correct, and they say this is it.
9 Because I was formulating this notion of, you know,
10 maybe there is some sort of another level of data that
11 we begin to accept, but who's going to judge it? And
12 I think, again, that's the thing that -- it's what we
13 pay the FDA to do, is to judge the data that has come
14 in front of them.

15 And so I was actually sort of
16 (indiscernible) thinking, well, it's adequate and
17 well-controlled when it's enough for Helen to know how
18 to use it.

19 KEVIN OUTTERSON?: We would have no
20 problem letting Helen be the arbiter.

21 MAN: You found your arbiter.

22 JOHN REX: Well, I mean, because, in
23 effect, that's the other end of this -- is ID docs,

1 you know, I've never had -- I've treated meningitis
2 many times. How many times have I used a drug for
3 which there was an indication for meningitis? None.
4 Ever. Right? So, in that sense I'm also a
5 pediatrician who are never using drugs that are
6 indicated for anything other than something unrelated
7 entirely to what they're doing.

8 So, I think that is a really good
9 question because I like -- we were discussing over
10 lunch the notion that data change fairly rapidly and
11 the thing -- sort of the downside of the label is it
12 takes a while to get it organized and then to make a
13 change takes more time, right?

14 Is there a way to approach this
15 question of a version of the information that people
16 are willing to talk about? And I have not heard
17 before this CFL idea, consistent with FDA-required
18 labeling. That's CFL, right? I missed that entirely
19 somewhere along the way.

20 But the danger with that is that, you
21 know, I'm invested in my compound and I'm going to
22 push my story as hard as I possibly can and I'll do
23 everything I can to pretend that it's consistent with

1 FDA-required labeling because that's what you do,
2 right? You know? And if I'm selling a new iPhone,
3 that's okay, I can make pretty graphics about how
4 wonderful the new camera is. But if I'm selling a new
5 drug, it's different.

6 So, you know, but this'd be a great
7 long debate about how do you set this intermediate
8 level of rules in a way that is fair and trustworthy?
9 Dr. Nambiar would like to respond to that.

10 AMANDA JEZEK: Please go ahead and then
11 we can go to Dennis.

12 SUMATHI NAMBIAR: It's more a question
13 -- I think on many different occasions we've heard
14 nobody reads the label, but sometimes some people do
15 read the label so obviously there's a disconnect.
16 I've heard both sides of the story. One is we don't
17 read the label. Some others say, we need everything
18 on the label because that's what we read.

19 I'm just trying to understand is there
20 any utility to the reviews that we post? Because what
21 was studied and what we've reviewed, even though it
22 doesn't get people an indication, it's usually
23 captured in our reviews and it's posted publicly

1 within a few days -- few weeks of our approval of an
2 NMA. Has that -- does anyone look at it other than
3 other companies, when you're looking to see what my
4 competitor did? I hear that all the time.

5 Other than that, is it of any utility
6 to clinicians, people who write guidelines? I mean,
7 I'm just curious.

8 JOHN REX: I didn't. Before I went
9 into industry, I did not know those things existed. I
10 never knew to look. I know do look at them. You
11 know, I even go back and read FDA ad-com transcripts
12 because there's stuff in there -- well, I mean,
13 there's stuff in there that --

14 MAN: We've got to get you out more.

15 JOHN REX: Yeah, I know, you've got to
16 get me out more, right. That there is stuff in there
17 that you come to appreciate -- you can get the nuance
18 out of it. But when I was Dr. Busy back at the
19 university, you know, I really kind of wanted to go
20 find one paper online and then get onto the next ten
21 consults, because it was already 4 o'clock.

22 SUMATHI NAMBIAR: I mean, it might be
23 too much to expect every clinician to read our

1 Advisory Committee documents and our 2 or 300-page
2 review. Even if you read the summary, it's good, but
3 maybe there is a role for the IDSA or Guideline
4 Writing Committee to look at that. Because there is a
5 lot of valuable information there, and a lot of time
6 has gone into it, and like Rienk mentioned, we spend
7 eight, or nine, or ten months reviewing the data so we
8 do capture this information. And I just wanted to
9 hear from others whether utility or lack thereof
10 (indiscernible).

11 AMANDA JEZEK: Sure, if it's on the
12 same thread, go ahead. And I know we've got a couple
13 folks who've been waiting patiently.

14 HELEN BOUCHER: Sorry. So, I think one
15 thing that bears mentioning is that clinicians think
16 differently. And so reading -- understanding how to
17 read an FDA review, you have to really understand how
18 to read it. We're looking -- the clinicians need it
19 in plain English. The reason there's no SERI
20 indication is because there was no statistical test.
21 That's -- it needs to be that plain. And I would
22 venture to guess if you read the review, it's not
23 quite that direct.

1 And even people who watch the FDA
2 Advisory Committee miss that, even though it was
3 discussed in a public forum on TV. So, I don't know
4 how to say it but I just think that part of it is
5 because we want to hear what we want to hear, right?
6 We want -- they looked pretty good, right? More
7 people lived who didn't get colistin. That's the
8 message we want to hear, but also it needs to be
9 presented in a way that's understandable to the non-
10 regulatory sophisticated audience.

11 AMANDA JEZEK: Sure. And then, Dennis,
12 I promise we'll get to you.

13 LINDSEY BADEN: Sure, no, because,
14 Sumathi, I mean, your presupposition is that the
15 moment it goes to the agency for approval, that's the
16 sum total of the data. And what I think is more
17 complex is over the next three years, all sorts of
18 data come out. A case report, a retrospective series,
19 uncontrolled data, renal insufficiency, liver
20 insufficiency. How do those data make it into the
21 label that are even more complex quality but may be
22 very influential clinically, which are not at that a
23 magic moment of formal FDA review, but speak to

1 practice? And that I think is part of the complexity.

2 In my view, it's a very dynamic process
3 and I think of agents very differently after two years
4 of clinical use than at the moment they were approved.

5 And how does that get incorporated into the label?

6 How does it get incorporated into communication in
7 normative data, as Dr. Rex says. You know, how do we
8 have those data available to guide practice?

9 Is it the guideline and is that too
10 clumsy or not? You know, what are the mechanisms to
11 update both unexpected safety or important information
12 about how to use it?

13 AMANDA JEZEK: Okay, we need to let
14 some other folks weigh in. So, I think the order we
15 have is Dennis, David, Manos, and Amy.

16 DENNIS DIXON: Thank you. So, first, a
17 comment about the topic here and then my question
18 after that. So, when we did our target at clinical
19 trials we did them under IND but we did not do them
20 with the request or suggestion of a label change. And
21 so some criticized us for that. "Well, what did you
22 even do them for if you didn't do them for a label
23 change?" It's because we felt that providing the data,

1 the evidence to guide appropriate therapy was all we
2 needed to do. And because these are off-patent drugs,
3 then they're cheap.

4 And so I think that's different than
5 not getting in the label for a drug an indication that
6 may be 10 or 100 times more expensive than the other
7 drug. So, how can you justify for reimbursement
8 purposes, and how can you even justify for marketing
9 purposes if you don't have that validated claim in the
10 FDA label? The literature alone I don't think would
11 do it. So, that's just my comment.

12 The question is -- we've seen several
13 drugs that made their registrational approval for what
14 you, John, would call UDR, Usual Drug Resistance.
15 That is not the MDR pathogen. It's for the pathogens
16 normally presenting in UTIs most often. And a hint of
17 maybe some activity for the resistant pathogens but
18 nowhere near enough of them to make reasonable
19 statistical inferences.

20 So, is there a trial design that's
21 scientifically logical and acceptable to the
22 regulatory agency whereby that trial's historical data
23 could be used as the control for continuing enrollment

1 post licensure to generate more useful data to
2 increase the numbers to where you can make statistical
3 inferences?

4 And that does two things: It gives you
5 a chance to generate new data in a new trial, but
6 there is some revenue flow taking place with just the
7 given label change while you're waiting to see if you
8 can add something to the label.

9 JOHN REX: So, the challenge with that
10 sort of continuously occurring dataset is that we'd be
11 criticized because what you know today influences how
12 you -- the patients you enroll tomorrow. And so I
13 would be very concerned about that impact on the
14 dataset.

15 And the other thing is that these
16 datasets don't -- we talk about -- we stop the study
17 and we analyze the data. It -- between last patient
18 in to last subject, last visit is, you know, some
19 period of time. And then it's another three or four
20 months before you've got an audited dataset, and then
21 another month or so before you've got the various
22 processing data. You can't -- it doesn't -- it's not
23 on Monday that we go to Tuesday and we have a

1 decision, then on Wednesday we can change our minds
2 and we'll change our minds again on Friday.

3 Sort of the chunkiness of time really
4 messes with what you can do with these datasets. And
5 I think unless you've lived through collecting one of
6 these datasets and getting it cleaned up -- I'm
7 looking at David Melnick and thinking about the time I
8 saw him with huge boxes of paper from a skin study,
9 for goodness gracious. You know, weeks, and weeks,
10 and weeks just to get that audited and cleaned up.
11 It's not like an experiment you do at the bench where
12 you did one today, I can do a different one tomorrow,
13 because yesterday is completely done. And I think
14 that's very hard to appreciate in this space, that
15 time thing.

16 DAVID MELNICK: You know, I wanted to
17 come back to the point that Lindsey made. You know,
18 anyone who's tried to do a trial on the resistant
19 pathogen space has had the same experience -- that
20 it's basically impossible to enroll these patients
21 into a prospective, particularly indication-based or
22 even cross-indication trial in a feasible period of
23 time. And yet, thinking about ceftazidime and

1 Rubactum, the literature clearly evolved after that
2 staggered approval process.

3 And, you know, we had studies like the
4 CRACKLE Study. CRACKLE-1 and CRACKLE-2, which clearly
5 demonstrated that there was an advantage of the drug,
6 at least to my way of thinking, clearly demonstrated
7 an advantage of the drug over the polymyxins. And
8 yet, there's not a mechanism -- you know, the data
9 gets published, it gets discussed at meetings, but
10 there's no way that that works its way into the label
11 at this point to allow us to take this to a formulary
12 committee and justify, you know, a price point for a
13 compound. And finding some way to communicate that
14 information would be incredibly useful.

15 MANOS PERROS: Following on the same
16 theme, I would like to highlight two points. One is
17 the level of complexity or simplicity that we need to
18 have when we communicate our information, and the
19 second is timing. I think Helen and Rienk make the
20 point in different ways, but the point being
21 physicians don't have the time to sit down and put
22 together data from across the board from preclinical
23 all the way to clinical trial results and draw their

1 own conclusions. The agency has the luxury of time to
2 review the data and what needs to be presented in a
3 way that is relatively easily digestible and
4 adoptable.

5 That goes for physicians, that also
6 goes for pharmacists. And imagine how much time
7 payers would have when they have to go through the
8 data and understand whether the product is actually
9 worth the premium relative to inexpensive generics.
10 So, the labels -- the customer is not only the
11 physician. For that to make a difference to industry
12 it needs to be across the board. So, that puts one
13 hurdle.

14 The second one is timing. I love the
15 idea of some way to present the data that will be more
16 rapidly evolving and more adaptive. But the labels as
17 they stand today as a means to launch a new product
18 clearly don't work. To Dennis' point, there isn't any
19 revenue really in the way in which we launch
20 antibiotics today. Companies with lots of money start
21 losing money and the small company can't afford to
22 lose money for three or four quarters before going
23 bankrupt. And we're seeing that time and time again,

1 and we need to stop seeing that. So, whatever we put
2 together I think needs to be simple and it needs to be
3 available at the time of launch. You don't easily
4 launch a product twice.

5 So, the last point I'd like to make is,
6 I think, to your question, Amanda, how come we haven't
7 yet adapted? I think the yet is a little bit unfair.
8 Because antibiotics can be used in a certain way
9 forever, and have been used in a certain -- that
10 empiric prospective way very successfully forever.
11 And moving afield from where it has been forever and
12 very successfully so to the place where we are today,
13 which is actually a relatively recent place -- and
14 John Rex, and I had multiple conversations about that
15 less than a decade ago, where we now have to focus on
16 exclusively drug-resistant patients where the medical
17 need is. I think it's great that we're having this
18 conversation and I don't think it's too late, but we
19 need to have it.

20 AMANDA JEZEK: Amy, followed by John
21 Rex, and John Farley.

22 AMY LEITMAN: Thanks. So, well, first
23 of all, I just want to say I agree with Dr. Rex about

1 reading the transcripts. They're not exactly
2 barnburners but they've got a lot of good information
3 in there a lot of times.

4 So, I wanted to speak also to Dr.
5 Boucher's point about the language that's used in the
6 labels. It is very dense. And one of the things I do
7 hear actually a lot from doctors is that they don't
8 have time to sit down -- because of the constraints of
9 your jobs, you don't have time to sit down and read
10 through the label and, you know, pick through the
11 language, and how do we use the drug and how do we
12 dose the drug, etc.?

13 I think presenting all of that
14 information in an easier to digest format would be
15 probably really helpful for the doctors. And just
16 speaking to the point of, you know, figuring out the
17 use of the drugs, you know, I know that a lot of times
18 these drugs are approved and they're not tested on NDR
19 pathogens, they're tested on more susceptible
20 pathogens. And it's really hard to figure out how to
21 capture data on using it on an NDR pathogen. It's
22 something that I've sort of wondered about for a long
23 time. And we wondered about it in our disease space

1 because we've used a particular drug as a salvage
2 therapy for, I think, a couple of decades now and
3 we're finally getting around to a clinical trial to
4 evaluate its efficacy.

5 I would love to see people put their
6 heads together and figure out ways to capture the data
7 in the real world, because what I hear from doctors a
8 lot of times are, you know, if I'm trying these drugs
9 and, you know, these drugs that are approved for this
10 pathogen aren't working and then I realize this is a
11 multidrug resistant pathogen, I'm going to look at a
12 drug that's approved for a susceptible version of this
13 pathogen, I'm going to throw it at them anyway and see
14 if it works. Kind of like throwing the spaghetti at
15 the wall and see what sticks.

16 Sometimes when your patient is really
17 sick and your back's to the wall, that's what you're
18 going to do. It would be nice to figure out more
19 creative ways to capture those data in the real world
20 setting and just bring that back in and analyze it,
21 and see if there's a way to either get another
22 indication or at least use that to design some kind of
23 clinical trial that can demonstrate that, yes, this is

1 another indication we can get for this product.

2 AMANDA JEZEK: John Rex?

3 JOHN REX: So, I actually wanted Ryan
4 to share something that he didn't talk about, which is
5 the cost of an antibiotic once it comes to approval
6 and some of you may have been at the meeting in Boston
7 six weeks ago where we had an extraordinary
8 presentation on this. Those of you who weren't really
9 need to hear the comment about "What is it like if a
10 drug comes to you and someone hands you the plazomicin
11 package?" They sign over the lease for the building,
12 they sign over the manufacturing plant, they sign over
13 the patent and they say, "Here, plazomicin is yours."
14 How much money do you need at that point and why do
15 you need that much money? And the place I want you to
16 go with this is what could be done to reduce that
17 number?

18 RYAN CIRZ: Thanks, John, for the
19 opportunity to plug that workshop. Well, the first
20 thing I'd say is you don't want to assume a lease in
21 San Francisco, so cancel that right away. I mean, I
22 think that workshop was a little bit of a genesis with
23 the struggle I've seen trying to get people past the

1 endgame. Like, we can make the trials free and it's
2 not going to fix it. We can do all these things for
3 free. I mean, quite honestly, we're getting quite a
4 bit of support anyway -- to blend with investor money,
5 it's still not fixing it.

6 So, I think the idea there is we tried
7 to break it down to things that were sort of
8 undeniable. And they're the things that you have to
9 do to own a license to a product. I think there's
10 still a lot of doctors and other people that think you
11 can just have it and just let it sit there. It's
12 actually not legal to do that.

13 And so upon approval there's a minimum
14 set of requirements: Additional clinical trials,
15 pediatric studies, surveillance studies, your AST
16 development and then, of course, the supply chain
17 investments. And I think one of the challenges with
18 the rollup thesis, and I think it's a good one in the
19 long game, but if all of the things you're rolling
20 together are cash flow negative, it amplifies the
21 problem.

22 And at the end of it, of course, you
23 have one team managing four or five products, seven

1 products, eight products. But to see that day will
2 require seven or eight years, and so the early stages
3 of that just amplify the problem. And the estimates
4 from my colleagues who did all the speaking, that
5 worked on drugs all the way back to cefepime all the
6 way through to plazomicin and I think almost all of
7 the new agents at some point was in their experience
8 integrating three or four of those experiences as you
9 spend about \$400 million before you get to cash flow
10 positive.

11 And the only way for us to raise that
12 is the public markets because we don't have revenues.
13 And so I think the market cap slide Kevin showed
14 really shows you -- imagine you want to renovate your
15 house and spend \$5 million but it appraises for
16 100,000. You just can't do it. And so we're in this
17 trap right now that's causing an acceleration of the
18 collapse as we realize that the companies can't
19 finance to sustainability -- forget about profit.
20 Just being able to pay your bill for what you have to
21 do.

22 I don't know how to make it better. My
23 first point I said jokingly last week to someone

1 that's in tech ops at BARDA -- I said, oh, we'll just
2 reduce quality. That's the easiest way, right? And
3 then one of the greatest challenges -- and I have
4 colleague that works in the rare disease space now,
5 that they're trying to explain -- he's in CMC -- that
6 the CMC package for a drug does not change whether
7 you've got 10 million patients or one. And that's a
8 fixed cost, and we're really trying to understand how
9 to drive that down. But that will become an
10 undeniable denominator.

11 And then the requirements, everyone
12 agrees we should be studying pediatrics, etc. But we
13 left out any kind of optionality like let's do a Phase
14 IV study and see -- nothing optional, what you have to
15 do, and that was the ultimate thesis was that it's a
16 pretty substantial multi-\$100 million loss. And you
17 can even look at drugs that I just heard earlier said
18 were successful and take all of the revenue they've
19 made since approval and they've probably spent it all
20 already on these requirements and have not yet made a
21 single dollar for their investors if you actually put
22 those things together.

23 AMANDA JEZEK: John Farley?

1 JOHN FARLEY: Sure. So, just a couple
2 of points of information, which are sort of related
3 and there are follow-ons to a couple of things that
4 have come on. So, Amy, one of the things I wanted to
5 mention, and you brought it up this morning, is that
6 the FDA's website was, unfortunately, not put together
7 by Amazon so it's not particularly usable even to
8 those of us who work there.

9 But after each drug approval, there's
10 something called a Snapshot written, which is by our
11 staff that focus on communication to people who may
12 not be as sophisticated. And there's even a section
13 for physicians that's a little simpler than the
14 density there. So, I think those are useful in terms
15 of discussing trial results and presenting trial
16 results. I even use them with colleagues in Baltimore
17 who are in primary care, and want sort of the simple
18 version. So, that's something to think about.

19 I think one of the things that I just
20 wanted to follow up on is in terms of a lot of the
21 labeling, like what you're interpreting as policy and
22 guidance in the agency, is actually based on
23 regulations. So, regulations are written basically to

1 describe through notice and -- there's a notice and
2 comment rulemaking process, which you would have had
3 the opportunity to participate in. How is the agency
4 going to implement the law?

5 So, when Sumathi and I are proposing
6 things where we're basically saying to our upper
7 management that the agency should violate its own
8 regulations and do this, that's kind of a heavy lift
9 for us. Just so you know. And those meetings usually
10 don't go well. So, it's something to think about.
11 So, there are some confines to what we can do.

12 In terms of the updating of labeling
13 with new information, my observation is that that
14 works much better in the HIV and the Hep-C space where
15 there's a lot more industry resources in play.
16 Because the agency -- excuse me, the company actually
17 owns the drug label. So, if they want to update it,
18 they actually have to submit a supplement.

19 Now, since in the last few years there
20 isn't a charge for those supplements, but as folks in
21 the industry will assure you, there's a lot of work
22 involved. I think one of the things in the Hep-C
23 space that I've also observed is that the guidelines

1 are living that are online, and how they're used by
2 the field seems to be a little bit different. So,
3 it's just something to think about. Because there
4 will be limitations, A, as to what we can put in
5 labeling for regulatory reasons but also in terms of
6 what's practical and what other information that may
7 be very useful to clinicians can end up in the
8 labeling. It's just a big effort and some may not be
9 what we would call label-worthy information. But they
10 can end up in these living guideline documents. And
11 how those get used, at least in the Hep-C space, they
12 really impact practice.

13 The other thing that happens, and
14 Sumathi's going to kill me because she doesn't have
15 enough medical officers as it is -- but in the Hep-C
16 space we do have folks who sit on the guideline
17 committees and will actually sort of provide some
18 context for the contents of a review as the guidelines
19 are updated in very real time.

20 AMY LEITMAN: So, you're in good
21 company. Clinicaltrials.gov is just as hard to use
22 and patients are supposed to go there to find clinical
23 trials.

1 But with respect to making -- yes, your
2 snapshots are very useful. Sometimes it depends on
3 the audience. You know, if you think about how the
4 label -- to me, a label looks like one of those --
5 remember those old-fashioned triptychs that you would
6 go to AAA and get? That's what those labels -- those
7 monographs remind me of. It's difficult, I think, for
8 -- especially, like I said, physicians have a limited
9 amount of time with their patient. They need to pick
10 through this information, so they really want to be
11 able to just draw out what do they need to know right
12 away? They can go back and look at the other stuff
13 later. So, yeah, the snapshots are useful.

14 And then in terms of communicating with
15 patients, which is a different level of communication,
16 we always look at what the information is, how is it
17 being provided, and then what patient population are
18 you talking to. With our patient population it's a
19 little bit different. They experience something that
20 they call brain fog or drug fog. They're on so many
21 medications they don't -- they have cognitive
22 dysfunction.

23 And actually, as I've talked to more

1 and more patient advocates about various infectious
2 states, if it's an acute infection in particular they
3 experience that a lot. And that actually lingers
4 after their infection is gone as well. So, those are
5 the kinds of things where, if they look at that
6 monograph, they're either going to cry or throw it in
7 the garbage.

8 So, yeah, you want to make it as easy
9 as possible in very short bites. So, those are the
10 kinds of things where really breaking it down into
11 those easy soundbites is going to be helpful.

12 AMANDA JEZEK: And, Vance, did you want
13 to make a comment? I thought I saw your attend card
14 up.

15 VANCE FOWLER: Yeah, okay, I will. So,
16 I want to get back on this thing about the control --
17 the use of controls and contemporaneous controls.
18 Because, you know, I think it seems like -- as
19 evidenced by the fact that we're all assembled here,
20 we've got a problem. And guess what? We're not going
21 to get -- we're looking for perfect data. We're not
22 going to get perfect data.

23 And everyone's like, well, we need this

1 STAT, we need this data to be able to -- for the
2 clinicians. See, here's the thing. Helen's going to
3 have to go back tomorrow and she's going to make
4 decisions based on what's available at that time. I'm
5 going to go back and I'm going to make decisions based
6 on what is available. And if I don't know, I'll call
7 somebody. And if they don't know, then, you know, you
8 still have to make a decision.

9 So, I think these events that are being
10 captured with patients that were desperately difficult
11 to find in these drug-resistant trials, they're just
12 sitting out there. I mean, okay, we don't have a P
13 value, it's not adequately powered, but it's
14 informative. Because guess what? I've made decisions
15 in the last week on -- single case reports, one
16 patient. That's not perfect. Okay, I get that but
17 you have to make a decision.

18 This data is out there. We're sort of
19 obliged, in my biased opinion -- we're kind of a
20 little bit ethically obliged to make this data
21 available so that it's part of the decision-making
22 process. And if there's a means by which those data
23 can be clarified, the meaning of those data can be

1 clarified using some control group, that's helpful.
2 That advances the overall mission. Whether that is a
3 historical control -- you know, we talked about that
4 and it was no, we can't do historical controls.

5 Then it was like, okay, what about
6 contemporaneous controls? What about if we had some
7 means by which to simultaneously enroll subjects in an
8 ongoing network -- let's call it, you know, the kind
9 that John Rex described in that 2016 paper, where
10 there's a warm base ongoing and you enroll basis with
11 the same CRF. Use those individuals who have
12 fundamentally the identical CRF and, thus, that's
13 fundamentally the same data that's captured on these
14 subjects of interest, and use those as a comparator.

15 You know, get an independent third
16 party to oversee the selection of your controls. You
17 know, use a 10:1 propensity match, use something that
18 most reasonable -- you know, that a reasonable third
19 party could look at and say, yeah, okay, that's a
20 reasonable start. Then it makes these data available
21 and helps people who have to make decisions, you know,
22 tomorrow, whether we like it or not. I'll stop there.
23 Thank you.

1 KEVIN OUTTERSON: So, we have about 15
2 minutes before I think it'd be time for the public
3 comment, and I wanted to give a little bit of framing
4 just for this last -- I see several people out there
5 with their tents up. They may go right back up. So,
6 thinking about the information -- we can try to
7 increase the quality of the information. And a lot of
8 our discussion was get better information.

9 The second one is reducing the cost or
10 the time, right? And we haven't talked much about the
11 clinical trial networks. A little bit. So, increase
12 the quality and decrease the cost or the time
13 required.

14 The third, which has really been the
15 bulk of our discussion, is how do we tell the story
16 better? And, particularly, I'm thinking about John
17 Rex's comment. The FDA is an impartial arbiter of
18 truth and method, or maybe just method, and so people
19 trust what the FDA has made it through their grid in a
20 way that's different than they trust even the peer-
21 reviewed literature.

22 And so, Lindsey, you know, the New
23 England Journal article, the excellent article by the

1 Achaogen people, you know, in the world's greatest
2 medical journal, yielded sales of \$800,000-and-some-
3 odd worth of plazomicin in the nine months before
4 bankruptcy. If instead there had been some way to
5 take the snapshot or some other material and to put
6 that clinically relevant information in some format
7 that physicians would actually take notice of, I don't
8 think anyone here wants John or somebody or any of our
9 good friends at the FDA to ever violate a rule or
10 regulation. But perhaps with LPAD, perhaps with real
11 world evidence there's a way to come up with something
12 that works for everyone.

13 So, with that as kind of framing, 10-15
14 minutes left, have your best shots.

15 AMANDA JEZEK: I can start with...
16 Sure. John Farley, please.

17 JOHN FARLEY: It is sort of related to
18 your question and kind of a follow-up. Because one of
19 the things I sort of forgot to mention, and also a
20 follow-up to Vance's point because we had actually
21 talked about this about ten months ago. I think there
22 are a variety of ways that one -- a trial can be
23 adequate and well-controlled, which is defined at 21-

1 CFR-314.162 for your general information. And Sumathi
2 and I actually spend a lot of time being reminded of
3 that in meetings.

4 So, I think my observation -- and I've
5 really kind of been observing over the last few years
6 before sitting here -- is sort of wondering why some
7 folks have chosen not to pre-specify a hypothesis.
8 Because what you need to know is that that's one of
9 the definitions, and that's usually the thing we're
10 called upon the most.

11 The one thing that our leadership does
12 not like is post-hoc analysis. They -- that drives
13 them nuts, and should, I mean, scientifically. It
14 causes all sorts of questions. So -- and there are a
15 variety of ways to do that but sort of toward your
16 idea, there can be more sophisticated hypothesis
17 testing planning. We have Erin here, and Dan, and a
18 number of folks who may have some ideas in that
19 regard. There are ways to combine information from a
20 contemporaneous control with external data, and we're
21 open to discussing that. The devil's in the details.
22 We're not going to work it out today but that is a
23 possibility. The Achilles heel has been not pre-

1 specifying.

2 AMANDA JEZEK: John Rex, then Ryan, and
3 then Sue.

4 JOHN REX: So, let me just say
5 something I think I'm hearing emerge as a concept,
6 which is if you look -- I just pulled up the HCV
7 Guidelines description, how it is that this rapidly
8 updated thing comes to be. And they say, you know,
9 it's a panel of folks who are looking at the best
10 available data and they update it regularly. I mean,
11 that's the short summary of a long page. Fair enough?

12 And if you think about what we've just
13 been debating -- you look at like, the snapshot -- I
14 pulled up the Zemdri snapshot. Unfortunately, it is
15 limited to UTI. And that's probably the way it's
16 supposed to be written. I'm sure that was the rule.
17 But is there a place here to do what you've pointed
18 out, which is to take the more details -- summary
19 basis of approval, and have a -- have Helen, and
20 Cindy, and Sarah as nominated as my committee chairs
21 here, to look at that for drugs being approved, and
22 then write down the other stuff that an ID doc ought
23 to know and make use of. And maybe that's not in the

1 label but if the community came together and said,
2 guys, that's what you have to use. You could then
3 say, well, the idea -- this is what you use. You take
4 that to the payers and say, this is what you use, the
5 label and this thing over here, that's the kind of
6 shift that this group could potentially foment.

7 RYAN CIRZ: Yeah, just going back to
8 sort of trying to optimize for lack -- or minimal
9 waste in terms of our time and resources, since
10 there's a limited -- and touching on kind of what
11 Dennis had brought up before is, you know, a lot of
12 the recent studies we go out -- you know, multi-drug
13 resistance. We just didn't get the CRE, right, or
14 that one step before. We're greasing the 90s, right?
15 We're seeing 20 percent ESPL. We're not quite 20
16 percent CRE until it jumps to E. coli.

17 But I struggle scientifically -- you
18 know, from a severe infection versus UCTI, completely
19 understand -- different pharmacology, different
20 physiology. Resistance, though, when people say, we
21 need to see it directly shown to us, that when you
22 change from a CTXM gene to a KPC gene that some
23 magical thing doesn't happen in your drug and it

1 completely doesn't work anymore doesn't make any
2 sense. And it seems like a huge waste of time and
3 money.

4 I mean, my limited maybe three years I
5 spent in the biodefense space partnering with BARDA,
6 how do you show something works on gentamicin-
7 resistant plague? You can't. You can show it works
8 on sensitive plague but you can't create a strain of
9 gentamicin-resistant plague to show it. That's
10 illegal, right? It's a violation of international
11 law. But we show everything else in our power to show
12 the things that make gentamicin not work anymore don't
13 affect the new drug. It's super simple and it's very
14 logical and it makes sense. And we're able to do that
15 without a loss in time and efficiency.

16 So, when I hear like, if we had 20
17 percent CRE in a UTI trial, some magical new
18 revolution would be revealed when your drug isn't
19 affected by the enzymatic mutations that make a CTX a
20 KPC, as a scientist, that's sort of where I'm like,
21 there's a place we can make some inroads.

22 AMANDA JEZEK: Sue, then Cindy, then
23 Aaron.

1 SUE CAMMARATA: I had a couple of
2 comments. One is -- this is around the idea of -- as
3 the FDA has pointed out, a lot of the tools that we
4 have are there. When I was in the rare disease world,
5 the rules are not any different. I keep hearing ID
6 people saying, oh, if we were a rare disease, we'd be
7 able to get approved. That is not true. The rules
8 are the same for all the different therapeutic areas
9 and all the different indications.

10 Now, how they're implemented and how a
11 trial is designed, that's where you have to talk to
12 the FDA. Whether you look at the statistics, pre-
13 specify, and complete the study, I think if you can do
14 that, that's the challenge -- can you do that? So, I
15 think you have to go in to all of the trials with
16 realistic expectations.

17 I've been doing this and I still am
18 approached by people saying, you have to do X and
19 enroll these kind of patients. And I will say,
20 probably impossible but I don't want to be the
21 development person that's always saying no, so I'll
22 say, I'll try. The realistic point you have to
23 understand is that it is just hard to enroll some of

1 these trials.

2 The other comment I would have is back
3 to this idea bout labeling in general. I'd have to
4 ask, is there any other physician group that asks the
5 FDA how to use a drug to put it in labeling? I would
6 say that that's pretty unusual, because usually the
7 physician groups probably get together. So, I would
8 ask, can the physician group, such as IDSA, in some
9 way implement and help the ID community to understand
10 how to put this information together to give guidance
11 on these new antibiotics?

12 I just think it's a bit much to be
13 asking to be putting this into the label and asking
14 the FDA how to use a drug that... Because they don't
15 have their own personal experience, they have the data
16 that is out there. It's in the -- it's out there in
17 the public domain. And it's in the reports if you had
18 guidances, and a way to do that, I think that would be
19 very helpful. But I think it is a challenge to say,
20 put it in the label.

21 AMANDA JEZEK: Cindy?

22 CYNTHIA SEARS: So, I want to thank
23 John and Sue for their comments, and I hope we return

1 to this topic in the next discussion round. I turned
2 my thing up because I wanted to respond directly to
3 what John brought up, which, if I understood it
4 correctly, was sort of suggesting transitioning
5 something like the HCV guidance to AMR or, you know,
6 using AMR as a topic.

7 The one thing I'll point out is the HCV
8 guidance started at a time when trials were appearing
9 very rapidly in the HCV field. And so that was
10 rapidly developed to discuss those rapidly emerging
11 trials. And I know that because I was on the IBSA
12 Executive Committee and we were the review group for
13 the HCV guidance. So, we would get asked do they want
14 to modify it maybe even twice a month, and we would
15 review it within 24-48 hours and get it back to them.
16 It was short and sweet at that point.

17 As time has gone on, there have been
18 many more HCV trials and the document was just updated
19 for the first time in a year this past August. And,
20 again, the IDSA Executive Committee took that task on.
21 But now the document is 150 pages and is like a bunch
22 of bricks that have been put up and probably needs a
23 sound edit. I had to restrain myself at points from

1 trying to fix some of the inefficiencies that were
2 there in the language.

3 So, they're very different situations.
4 You don't have large trials that were powered, so the
5 type of data that you're asking to be assembled for
6 the clinician rapidly is quite different. Now, I
7 think that that's an important point and, again, I
8 hope we return to this later in the afternoon. So,
9 I'll discuss what's going on at IDSA shortly and I'd
10 love to hear your reactions.

11 AMANDA JEZEK: Erin and Lindsey?

12 ERIN DUFFY: So, two different things.
13 Ryan, I wanted to clarify this point that you've made
14 now twice about ESBL and CRE. Because I think the
15 intention there -- if you have ten ESBL strains, five
16 of them might just be ESBL, in which case, for
17 instance, an aminoglycoside would work but the other
18 five are going to have friends that have come along
19 that might alter permeability or upregulate efflux.

20 And so might it not be more about
21 what's the breadth of ESBL coverage when ESBL is ESBL
22 plus friends? And, in that case, demonstrating that
23 is of value?

1 RYAN CIRZ: Yeah, I mean, the
2 fundamental principle is it's all driven by the
3 microbiology unless otherwise proven. I'm just sort
4 of making the point that we act as if when you elevate
5 from an ESBL to a CRE, some magical thing happens.
6 Equally probable, an ESBL can have some horrible
7 super, you know, RMT-type pan resistant mechanism or
8 CRE could, and that will change every other year. But
9 the fixation on needing to directly prove it in a
10 trial versus relying on the surveillance and the
11 micro, that's kind of where I think there's just a
12 little bit of a loss of efficiency -- as if it's a new
13 disease, the resistance itself. That's where it feel
14 like a lot when it's discussed.

15 ERIN DUFFY: Yeah, maybe it's just an
16 unfortunate way that we're naming some of these
17 things. The same with MRSA. Why would a quinolone
18 not have activity against methicillin-resistant staph
19 aureus, right? So, it's a similar story, I think.

20 But then I wanted to address a
21 completely different thing, and this is the support
22 for the concern over post-hoc analysis. So, Sue will
23 laugh I think hard at this but when Sue first came to

1 Melinta, we had just completed a Phase IIB trial with
2 delafloxacin and ABSSSI, and we showed superiority
3 over vancomycin. It wasn't intended. It was a Phase
4 II trial. And because I'm a theoretician by training,
5 I was asked to analyze the data and there was a single
6 reason for that superiority and that was the
7 performance in obese patients. Not because vancomycin
8 necessarily worked any differently but because, for
9 whatever reason, delafloxacin looked really, really
10 good.

11 And so we went into Phase III thinking,
12 hey, you know this is -- because this is a big
13 population, no pun intended, but it is. And so, you
14 know, in one Phase III trial we didn't pre-specify,
15 and in the other we did, and wouldn't you know it? In
16 the one trial where we pre-specified is the one trial
17 where we didn't see it.

18 And so, again, this value of small
19 numbers I think is helpful but often when you do
20 larger studies, I learned painfully it doesn't always
21 work out.

22 LINDSEY BADEN: So, just to amplify
23 Ryan's point, which I think is a conceptual one we

1 have to come to terms with. If what we want are
2 effective antimicrobials for very resistant organisms,
3 particularly the ones that don't exist yet or only
4 exist in rare parts of the world as they are in the
5 process of spreading, then how do we develop the
6 dataset or datasets to give us reassurance that we've
7 developed a countermeasure that's effective?

8 And, obviously, the preclinical models
9 need to be done fully, but how do we think about the
10 clinical models when by the time it's prevalent it's
11 too late, and before it's prevalent it's really hard
12 to study? And how do we find that balance with the
13 clinical dataset?

14 AMANDA JEZEK: I think we just have
15 three minutes left. I've got John Rex, Aaron, and
16 Sue. I don't think I see anyone else. Okay, great.

17 JOHN REX: There's only one public
18 speaker, right? Yeah, okay. Okay. So, I want to
19 respond to a couple of things -- to Cindy's comment.
20 What I was thinking of simplistically was not an
21 omnibus rewrite but a one-by-one drug update of the
22 stuff -- the other stuff that's not in the label that
23 you might like to know about that drug. So, PK and

1 other body sites, the data from a less -- an imperfect
2 trial. It's that secondary information that you might
3 dig around and find somewhere, but at least here you
4 found it and you know that some of your peers have
5 proofed it and that this document then becomes
6 something that actually, by definition, almost meets
7 the rules for -- consistent with FDA-required labeling
8 kind of. I mean, it's the stuff that, if I'm the
9 sponsor, I can happily promote it because I can say it
10 actually has been kind of cleaned up and tested.

11 So, that to me is sort of the advantage
12 of doing this. It creates an arbiter that's other
13 than me, the sponsor, to summarize the data that when
14 I D-doc I wanted to know, and that's what I was
15 pointing out.

16 This thing about the MICs, we have
17 spent a lot of time debating this language about MICs
18 and I don't want to give a whole talk on it. But at
19 the end of the day, the antibody can only influence
20 the portion of your disease that's due to the
21 bacteria, and anything else I can't touch. All the
22 information that is relevant to the drug is in the MIC
23 and the PK. And that has been proven over, and over,

1 and over again by our colleagues, that if the MIC --
2 "It's the MIC, dummy," as Paul Ambrose would say if he
3 were here in the room. So, the susceptibility to
4 other drugs is interesting but it's actually not
5 relevant to the activity of Ryan's new thing. Zemdri
6 works on Zemdri's susceptible pathogens when the drug
7 gets to the body site. And I think that's sort of the
8 core idea that we need to get at on this.

9 And my third comment is about orphan
10 drugs. And I think we ought to at least briefly visit
11 the question that sometimes come up: Why aren't
12 antibiotics orphan drugs, and would it help if they
13 were? Would that change things in a way that was
14 useful?

15 And I'm pretty sure I know the answer
16 to that but it's a question that I do hear from time
17 to time, and I think it would be -- just so that we
18 have sort of collectively toured all the ideas, why
19 isn't suddenly declaring CRE an orphan -- which,
20 numerically, CRE is an orphan -- why does or -- why
21 does that or does that not make a dent in this
22 problem? It's worth saying the answer to that
23 question.

1 AMANDA JEZEK: Aaron and then Helen.

2 AARON DANE: Yeah, I just wanted to
3 come back...

4 SUE CAMMARATA: Sumathi, do you want to
5 respond to the orphan drug question?

6 SUMATHI NAMBIAR: Yeah, I think the
7 short answer to that is even for orphan products and,
8 as Sue has mentioned, the rules are the same. So, you
9 still need to have adequate and well-controlled
10 trials. Now, how you design the trial, what you
11 control on might be different but in terms of trial --
12 the requirements for demonstrating substantial
13 evidence of efficacy doesn't change.

14 AARON DANE: I wanted to come back to
15 the idea of pre-specification. Obviously, as a
16 statistician, I completely agree that we should pre-
17 specify what we're going to do for all the reasons
18 given. I guess what we need to do, though, is be
19 clear on what success looks like.

20 Because for an orphan -- orphan drug --
21 for a rare pathogen, we know that there's going to be
22 absolutely no power to actually show a statistically
23 significant effect, which means that no one's going to

1 run the study. So, we need to think about what the
2 criteria might be for -- what would be good enough for
3 an approval in that specific setting. Or it might be
4 how we use the other data.

5 As you say, if there are other
6 randomized trials, could we use augmented control
7 designs where you use some of the control arm data
8 from other randomized studies or other external data?
9 You know, maybe just a more open view to looking at
10 all of those things more generally and not using them
11 when they're of poor quality or they're not reliable.
12 But at least being able to look at them more because
13 we need to do something like that because we know
14 we're not going to get it from a randomized trial.

15 So, I guess we might pick up some of
16 those things tomorrow as well. But it just feels like
17 that's the bit we need to do is, pre-specify yes, but
18 then what is it they're pre-specifying?

19 HELEN BOUCHER: So, I just wanted to
20 come back to the prior discussion about, you know, if
21 we found a way to communicate this other information
22 not on the label and take it back to Dr. Kartsonis and
23 the other colleagues from industry.

1 So, if we agree that that happened, so
2 there wouldn't be a labeled indication, so probably it
3 couldn't be promoted in the traditional sense but it
4 might be able to be discussed on a, you know, peer-to-
5 peer with the MCL type thing. And PNT committees and
6 stuff. So, how do you all view that, if that were to
7 occur?

8 SUE CAMMARATA: I was just going to
9 make a comment that every company does a global value
10 dossier, which is not just label information. So, I
11 think it's really how to make that more useful. But
12 it is the intent of that that includes all this
13 information. Off-label information. So, that exists,
14 I'm not sure it has made a difference but it does
15 exist.

16 I did have a comment about the -- one
17 comment about -- this is more about conducting
18 clinical trials and this whole idea of rare disease.
19 The one clear challenge for anti-infectives, most of
20 them -- and this is not, for example, for the NTM but
21 for the acute infections. When you're in the rare
22 disease world, you have more chronic diseases. There
23 may be 30 patients that you need to enroll but they

1 can be found. They can be found ahead of time, and
2 you can fly them across international or continental
3 borders to do trials. You can't do that with the
4 anti-infectives.

5 So, that is the one challenge for sure
6 for anti-infectives, that you just can't do that. So,
7 that's why to me, some of the appeal of a clinical
8 trial network where you do have sites that are up and
9 running that can be initiated to enroll those patients
10 in real time would be... I understand the appeal of
11 it. Again, I'm not sure how doable it is but it would
12 be very appealing in that respect because we can't fly
13 a HAP/VAP patient across international borders to
14 enroll in a trial.

15 RYAN CIRZ: All right. I don't have
16 enough experience watching launched products to know
17 if it would make a difference. I know everyone that
18 works in the field tells me it will make a difference.
19 Like, oh, if it was in the label -- if only.

20 I guess the one behavior -- well, if we
21 started doing it and it doesn't change anything, we'll
22 know the answer. I guess the one thing that I'm
23 interested to watch is if we fix reimbursement -- so

1 plazomicin had something like a 96-98 percent
2 formulary acceptance with whatever data it had. 90
3 percent of the use was in the outpatient setting from
4 launch where the economics work. So, it'll be an
5 interesting question: Which is more important, and
6 actually will the data make the difference or is there
7 some other market pressure that's actually creating
8 this incentive to not use these drugs?

9 KEVIN OUTTERSON: So, I think we're
10 drawing to a close now. I thought that we would have
11 more discussion about the clinical trials network
12 today, and the few discussions we had were actually
13 concerns about making sure it didn't become a
14 bureaucratic machine that made things harder.

15 Tomorrow morning there'll be two
16 sessions, I believe, that we'll take that topic and
17 maybe additional discussion can happen then. John,
18 are you going to take this next piece? Okay, thank
19 you.

20 JOHN FARLEY: Thanks, Kevin. So, we'll
21 turn our attention now to formal public comments.
22 Folks were asked to follow the procedure outlined in
23 the Federal Register Notice for this meeting, which

1 required contacting us in advance. Dr. Luthy has done
2 so and we'll invite her to the podium at this point
3 and ask her to confine her comments to about 5-7
4 minutes, if that would be okay.

5 CONNIE LUTHY: Yes. And I have some
6 slides.

7 JOHN FARLEY: And we have slide up. I
8 always wanted to say that.

9 ERIN DUFFY: Well done.

10 CONNIE LUTHY: So, I'll start talking
11 while I wait for the slides to come up. So, I'm
12 Connie Luthy, I'll introduce myself in like, the third
13 or fourth slide. And I want to thank John Farley and
14 Sumathi Nambiar, and our other FDA hosts for creating
15 this brainstorming workshop on how to make the whole
16 clinical trial process more efficient, and useful, and
17 productive. It's all toward what Kevin Outterson
18 brought up, which is increased productivity. So, this
19 left arrow advances the slide? No. Oh, no arrow.
20 Okay, okay.

21 So, the workshop goals are to better
22 understand the state of antibacterial drug development
23 and consider studies to enhance antibacterial drug

1 development. And the way of doing that was to
2 assemble a diverse array of subject matter experts in
3 infectious disease.

4 Like Ryan Cirz brought up, I too am an
5 outsider to this group. I'm a subject matter expert
6 in medical product development, having developed a
7 diverse array of global manufactured medical products,
8 and here are some examples of that.

9 So, I worked a lot with sterile
10 unpreserved drug products. They have to be pyrogen
11 free, biological products, and Class III medical
12 devices. So, to me, the overarching goal is to
13 consider strategies to enhance the development of
14 antimicrobial drugs that change lives. So, that means
15 being more productive through the whole process.

16 So, one of my appeals today is would it
17 be possible to assemble a group to brainstorm on the
18 materials that go into these? So, there are two ways
19 that I see to better enhance (indiscernible) drug
20 development. One is to increase the quality of
21 product candidates entering the clinical trials. So,
22 that's what I'm suggesting we might figure out a way
23 to facilitate. And, two, to fund candidates in

1 development for global distribution. This is a global
2 problem. That's quite clear. And that's the way to
3 do things efficiently, is to address the product in
4 ways that can help everyone.

5 So, one of the questions -- since
6 leaving Alcon, one of the things I have done is
7 studied innovation and new product development and
8 what makes successful products. You know, nearly nine
9 in ten products fail, generally because they're not
10 solving a customer need. So, it's a very complicated
11 decision that mostly folks in large companies are
12 exposed to in figuring out where to invest the money.

13 As Rienk pointed out, no one's got
14 unlimited budgets, not even the big companies. So, in
15 order to make funding decisions that result in
16 successful products you need to know where you are in
17 the industry. So, one of the things I'm hoping for
18 this group -- and there are some funders represented
19 here -- is that the programs of CARB-X and others
20 won't suffer the low productivity that the NIH and NSF
21 SBIR programs do.

22 There's a huge difference in the
23 program -- the SBIR programs operated by DOD and DOE,

1 and BARDA is apparently the only group represented
2 here that now has this acquisition end. And that
3 difference is the decisions are being made by the
4 folks who are going to use it. So, it's a whole
5 different -- it's a whole different way of assessing
6 things.

7 So, I'm encouraging the large companies
8 that are represented here to have their employees get
9 more involved in serving on SBIR review committees,
10 serving on CARB-X's review committees, and encouraging
11 those of you who -- those of you -- I assume almost
12 everyone in this room is a scientist or engineer --
13 who are working in the government entities and the
14 private foundations funding some of this work to
15 seriously try to recruit folks with experience
16 developing products. So, you know, are these
17 decisions being made by scientists or by
18 businesspeople?

19 I had the fun experience two weeks ago,
20 the day before my homecoming at Rice University, to
21 judge a graduate student presentation competition.
22 And as we were preparing -- being prepared for the
23 presentations, one of the students organizing it asked

1 me how I decided to become a businessperson. And I
2 was like, really surprised. I mean, I'm a scientist.
3 Every day I'm reading papers, designing experiments,
4 etc. I mean, even after doing an MBA program, which
5 was 19 years after my Ph.D., it didn't change me into
6 a CPA. I'm still a scientist. I'm still doing
7 product development.

8 I expect that those of you in the room
9 who are product developers feel the same way. That
10 you're still doing scientists maybe more like an
11 engineer, because you're working towards product
12 specifications but it's still doing science.

13 So, one of the things that I was never
14 -- I never thought about that much until I was in the
15 MBA program, is the difference between science and
16 technology. And science is really a method that those
17 of us trained in that method used for obtaining laws -
18 - knowledge about the laws of nature. Whereas the
19 technology as the result of a design process begins
20 and ends with a solution is the product of human
21 thought. The scientific method is used in testing the
22 designs. So, the purpose of science is to gain
23 knowledge, and the purpose of technology is to change

1 the material environment.

2 So, during your career, have you
3 developed a product, a technology, or discovered the
4 laws of nature? I think all of us have been involved
5 in discovering the laws of nature and I would even
6 include Ph.D. economists who -- that's a science and
7 they're discovering different laws of a different
8 kind, but still laws of nature. And basically go by
9 what are you selling. Your activities. If you're
10 doing scientific research, you're selling information.
11 Technology development, you're selling a component or
12 a tool. Product development, a finished product.

13 Now, this one also is a little
14 different perspective from perhaps most of you. So,
15 in a medical product development team you've got lots
16 of different functions represented. As Sue pointed
17 out, with a small company you also have to outsource
18 some of those functions to consultants.

19 But as we go through the process, as
20 things flow kind of from left to right, there are the
21 makers, and the testers, and the documenters, and
22 communicators, and, yes, trialists. Those of us on
23 the maker side think of you as testers. So, I am

1 trying to help figure out ways that we can make better
2 materials to be tested and how that process might be
3 made more efficiently.

4 So, my request for those representing
5 big pharma and big biotech is get your folks out into
6 the community more, more involved helping startups,
7 more involved serving on these volunteer -- basically,
8 volunteer committees reviewing the grants to small
9 business and the grants from the private foundations.

10 Some advice to small companies is new
11 product development is not taught in school. And the
12 place it's most efficiently and effectively taught is
13 inside profitable companies in the same industry. So,
14 if you're not able to attract employees with
15 appropriate experience, outsource.

16 So, for new product development -- and
17 this is not just medical product development; all of
18 new product development -- it's really a combination
19 of the product strategy, registration strategy, and
20 the management team that will lead to the efficient
21 use of money, and the well-defined products are
22 funded, developed, approved, and change lives. Thank
23 you.

1 JOHN FARLEY: Thanks very much. All
2 right. So I think we are ready for a break. And so
3 we'll take a break at this point and reconvene at 3:15
4 for Session 2A. Thanks.

5 SUMATHI NAMBIAR: All right. So,
6 welcome, everybody, back to the next session. It's
7 Session 2A on Antibacterial Clinical Trial Innovation:
8 What Are the Realistic Options for Enhancing the
9 Antibacterial Clinical Trial Enterprise. The first
10 speaker in the session is Dr. Baden, who is associate
11 professor at Harvard Medical School, and who you've
12 already heard is the Deputy Editor at the New England
13 Journal of Medicine. And we've had the distinct
14 pleasure of working very closely with Dr. Baden in his
15 role as the chairperson of the Antimicrobial Drugs
16 Advisory Committee, where he has done a phenomenal job
17 discussing some very challenging topics.

18 LINDSEY BADEN: Thank you. We shall
19 see if I can master the technology.

20 So, I'm going to tell you nothing new.
21 What has been discussed this morning I will amplify, I
22 will frame a little bit differently through my lens.
23 But the group that has been assembled has tremendous

1 depth in this set of issues that we are struggling
2 with. And hopefully through discussion, we can find a
3 better path forward for us as a community.

4 So, what is it depends on who wants to
5 know about it. And since I'm brought here as a
6 journal editor, alliteration has resonated in my head.
7 So the six Ps, which have no real meaning other than I
8 kind of liked it. The practitioner, the producer-
9 developer, the purveyor, the investor, the permission
10 grantor, the patient, and then asked to talk as the
11 publisher, although I also am a practitioner,
12 investigator, patient, and care provider.

13 But the question that all groups care
14 about is new findings; what does it mean to me? What
15 does it mean to me? And what has been discussed
16 earlier is how do I know about it and how do I know
17 about it in a credible, informative, balanced way?

18 So it depends on your frame of
19 reference when new data emerge and it depends where
20 you sit, what you're looking for, what your metronome
21 is, what you want to do with the data. And all of
22 these different perspectives are true, but they're
23 different and they may approach data with a different

1 goal. And one can look at an image, and you can look
2 at it in all sorts of ways. I need to get from here
3 back to Boston, I want to build one of these, I'm an
4 engineer. All of these are true representations of
5 the data, but, boy, are they different
6 representations, and they're different for the
7 different communities of relevance. Ultimately what
8 everybody is after is truth. What is truth and what
9 does truth mean for how these data are to be used?
10 And so there are major challenges in identifying what
11 truth is.

12 Human biology is complex. Clinical
13 trials are really, really, really hard to do. They
14 really are. And I think all of us has struggled with
15 them from the different vantagepoints where we sit.
16 And we must do the trials that answer the question so
17 we answer the question, but we will never answer all
18 the questions. In fact, we have to highly-constrain
19 the question to get an answer that is valid, but then
20 limited generalizability, which we then lament. But
21 at least we can answer the question.

22 This is colored, as discussed earlier
23 by Dr. Boucher and others, our patients are sick. The

1 need is urgent. We don't have time. I need to make a
2 decision tonight when I get back and round. How do we
3 manage that? How do we manage bias? And the bias is
4 not a straightforward bias. I've spent ten years of
5 my life working on this. You know, the financial is
6 the easiest to manage. But to all other sort of bias,
7 including hope to cure my illness. And this has to be
8 managed so we continue to approach truth. And then my
9 favorite is the P of 0.05 is the altar we worship at.
10 I don't know what it means, I don't believe it's
11 truth. With all of my hats that I wear, I do not
12 believe it's truth, yet it is our altar. And we need
13 an altar to minimize the play of chance. Because that
14 is such a tricky parameter to manage.

15 So mission of journals, I don't need to
16 say, we want to find the best work, we want to report
17 it dispassionately, as Dr. Rex advocates. We want to
18 help advance science, we want to improve patient care.
19 In fact, we all want to improve patient care. I think
20 we are unified in our mission and our interest in this
21 room no matter where we sit. But then how do we do
22 that and how do we do that efficiently and how do we
23 do that in an ecosystem that is self-sustaining? And

1 so at a journal we bring rigorous peer review. At our
2 journal we have multiple, multiple layers of review,
3 including multiple content experts, statistical,
4 editorial board. Multiple, collateral experts will
5 comment to make sure we can identify the best work and
6 what it means. If it is favorably viewed at our shop
7 -- and I can't speak for all journals, but I think
8 most journals sort of feel the same way, of how do we
9 get it right and how do we get it into the hands of
10 the people who need to know. But at our shop, post-
11 acceptance also not a trivial issue is how do you
12 communicate it. And this was alluded to before with
13 the gray box.

14 And what I put -- and this is from the
15 SHINGRIX study showing how to -- a new vaccine against
16 shingles. And what's beautiful about this is this
17 figure has both zero-to-one access, it's twenty-fold
18 amplified to see the real difference. You have the
19 number of people at risk, the number of events. In a
20 short box there is a lot of information if you want to
21 understand the finding and the strength of the
22 finding. But this gets to the issue of how do you
23 communicate the data so people can understand it

1 efficiently from their vantagepoint.

2 And there are intrinsic tensions when
3 we publish, from author sponsors, people who are
4 promoting a viewpoint. How do we as arbiters weigh,
5 balance, and then share? And so this is a simple
6 slide, which is we all want something to be right, and
7 that is our guiding principle. The question is how do
8 you know it's right with all of the other pieces that
9 need to go with it? So there are issues and
10 implications of what we publish.

11 And this is just highlighting a little
12 bit, which is was the study designed well, did they
13 analyze it as they designed it. But then which
14 outcome do we care about? Do we care about the day
15 five, the day 10, the day 14, the one year, the
16 microbiologic, the symptomatic, the integration, the
17 efficacy, the side effects? Is it the IT, the MIT,
18 the micro TT, the PP? Is it inferiority design, a
19 superiority design? Does that influence which of
20 these parameters we favor? Does it matter if it's the
21 resistant bug or not? Yet why don't we just take
22 every data available and slap it on the label?

23 I just think that that gets to the

1 complexity of the data. And I find whenever we talk
2 about let's just report the data, I sit here and
3 struggle with what are the data. Because I would like
4 it to be transparent, but I don't find it so
5 straightforward to know what the data are that
6 everyone needs to know in the context that gives it
7 meaning to how they want to use it.

8 So, some clarity about publishers and
9 publications. We're not a regulatory agency. We don't
10 make regulatory decisions. We may look at the same
11 data or not even the same data. They have statutory
12 authority over all the data; we don't. But we have
13 community input. We have a different review process.
14 We look at the protocol and the analyses, because
15 sometimes studies may be designed to have a high
16 likelihood of making the product look good whether or
17 not that really represents what the product can do.
18 That doesn't mean it doesn't work, but how do you then
19 present that in a way which is a little fairer as to
20 what is found?

21 Publications allow community awareness,
22 debate discussion, as we are doing here, independent
23 expert review to bring in more perspectives on what

1 the data may mean. We help with the data
2 interpretation presentation. And the graphic that I
3 showed you from the SHINGRIX study was just an example
4 of how you can communicate a whole lot of data I
5 believe efficiently. But that's just one way of
6 presenting the data. And I didn't even tell you if it
7 was the ITT, MITT, PP, you know, which analyses we
8 even presented there. And should all of them have
9 been presented and then have you work your way through
10 the data? And we don't make corporate decisions as to
11 what go forward or not, as the plazomicin discussion
12 pointed out, although hopefully we helped with it
13 getting on to formularies because we helped show what
14 the activity of the agent was.

15 So I like real examples of things that
16 happened. Theoretical is great, but practical, real -
17 - these are what happened and these are examples of
18 three compounds that came before the agency in the
19 last 18 months. So whatever about them is antiquated,
20 these are the data of things that we as a community
21 evaluated in the last 18 months. For whatever reason,
22 these are current in my view.

23 So I'm not going to go over the

1 specifics of the data. I want to just point out
2 certain things about the data. One is this is a CUTI,
3 not something we need plazomicin for. However, it is
4 a scenario where you can demonstrate efficacy and
5 safety. They studied about 300 active 300 comparator,
6 and they showed efficacy. You know, terrific, we know
7 it works.

8 They also were able to look at key
9 subgroups and show that in subgroups. It works in
10 bacteremia, it works in the few non-susceptibles that
11 were there. When we publish the data, we can publish
12 it with these kinds of figures, we can publish it with
13 these figures, which is impossible to read. But
14 doesn't it matter which bug, which resistance
15 determinant, which resistance determinant for the
16 active versus the comparator? And these are the
17 simple data to present, let alone all the other data
18 we're talking about everybody wants.

19 And then we do side effects, and it
20 behaves like aminoglycoside with renal dysfunction.
21 My point here is if you enroll 300 people, a one in a
22 hundred side effect you might be able to see. So they
23 might be able to see one in a hundred side effects.

1 But if you see one in a hundred side effect and it's
2 serious and not really expected, you may then call it
3 noise, which it might be. So how do we actually
4 declare safety?

5 And one of the things we do in the
6 supplement, for particularly new compounds, is list
7 the safety data more expansively, because you don't
8 know which safety data are noise and which safety data
9 when the next thousand people experience this compound
10 actually turn out to be a pattern. And it gets very
11 hard to know which data we care about, because there
12 are a lot of noise in sick patients with resistant
13 bugs.

14 Then the HABP/VABP BSI, which failed to
15 complete because of futility, but yet we all are aware
16 that there was a mortality signal. So what do you do
17 with these signals? And the agency is under different
18 obligation to interpret data that are post-hoc,
19 redesigned, shrunken, halted study than we are when we
20 can present the data for what they are; is this true,
21 is this noise? But there is a signal that looks very
22 encouraging, and it's important for the community to
23 be aware and to debate. And so there looks like there

1 is a mortality benefit in the plazomicin compared to
2 the colistin-treated group in this type of post-hoc
3 redesigned study because of practicality issues.

4 So when we publish the data, we publish
5 the research, we can publish letters with additional
6 research, we can publish commentary that helps put the
7 research into context given the complexity. And this
8 gets to the tempo. These were the data available at a
9 certain time. As a year or two go by and more data
10 can be generated, and then it supplements how we think
11 about a compound and how do we as a community of a
12 dynamic nature to be able to absorb new data that
13 emerge that may not be as well-pedigreed or created,
14 but still may be informative.

15 Cefiderocol, which is another agent for
16 resistant REM-negative organisms, three different
17 trials. CUTI study is done, published about a year
18 ago in Lancet ID, showed that in green on the right
19 there is a non-inferiority to imipenem and maybe even
20 superiority with a substantially better outcome by
21 composite response, microbiologic response, clinical
22 response. And then in the publication, they showed
23 different body sites, different organisms. The

1 farthest plots are different ways to try and slice
2 these data to understand them. But for the most part
3 a fairly consistent finding that it works against
4 these kinds of organisms.

5 But then you have the credible data.
6 And this is an early look. But now in red -- green
7 being good, red being bad -- you see a mortality
8 signal. But these are immature data. They're not
9 complete. It's not the way the study was designed.
10 They're doing a look because they see a signal. So we
11 have the plazomicin where you see efficacy. I want to
12 believe that. And now the credible where I see
13 mortality, well, that has to be noise. I don't know
14 what's true in either case. I don't. But the data
15 are the data. And we as a community should be
16 discussing them and we as publisher should be
17 publishing them to allow discussion to know what they
18 mean to help inform the next round of studies, and
19 also so the community is aware of the uncertainty.
20 And then as the data gets stronger or filled in or the
21 study is completed, then the data can be updated, and
22 maybe this finding doesn't hold when the complete data
23 are available.

1 Three days ago this was approved and
2 Dr. Farley made some comments. I think the issue of
3 limited and no-alternative treatment option is
4 something we as a community need to think more about,
5 is how do we position, just like oncology drugs, that
6 maybe it shouldn't be a yes/no light switch, but there
7 really are ways for us to caveat antibiotics of last
8 resort or antibiotics for very special pathogens that
9 live in a bucket that is both different from an agency
10 standpoint, but different from a use standpoint so
11 that they are used in a way that is commensurate with
12 where the need is and where the benefit potentially
13 is.

14 With inhaled amikacin, I think want's
15 important about these findings -- and it was
16 interesting to see how this compound is a success in
17 the marketplace, but when this went to the committee,
18 to the agency, to AMDAC, it was striking that it
19 cleared the cultures but had no measurable health
20 benefit. Oxygenation, walk test, mortality, anything
21 with a clinical benefit, we couldn't see. Or at least
22 not in the data they had. But it did clear the
23 cultures. So there is a benefit. I don't quite know

1 what that benefit means.

2 And this gets for Dr. Fowler and
3 others, what are the surrogate endpoints that we
4 design for studies that inform us? I believe clearing
5 cultures is a good thing. But that does have to be
6 linked to some kind of benefit that has even greater
7 meaning. But it is an important element. We know
8 with TB and other bacteria that clearing cultures and
9 ultimate outcome may not be correlated as well as we
10 would like it to be.

11 So as a publisher, we have to balance
12 the data needed for regulatory approval, how do we
13 optimize patient benefit, how do we protect the
14 community benefit. And then the elephant the room is
15 how do we have the incentives to really allow the
16 antibiotic development to grow in the way we need it
17 to. So we have to manage information flow. As
18 journals, trust is the most important thing. And as
19 Dr. Rex said, who is the arbiter of new information.
20 And that trust is really important. With new agents,
21 it's a different complexity than an agent we
22 understand the safety profile. And with new agents
23 and new data, the uncertainty is really high because

1 we don't know what to look for. And that becomes very
2 tricky in how we then deploy those new agents and
3 report on them. And then we need to understand what
4 do we know, when do we know it, who curates it, how do
5 we share it, and then how do we update it.

6 So in conclusion, I think the role of a
7 publisher is to facilitate, air, provoke discussion
8 from all perspectives. We need to provide factual,
9 interpretable, and relevant information. The data
10 means different things depending where you sit. By
11 publishing data, hopefully we more completely inform
12 the risk/benefit balance. We need to deal with the
13 data we have; not the data I want. We can push the
14 community to develop the data we want, but the data we
15 have have to guide us. And all of this has to be
16 wrapped up in a format that allows a virtuous cycle
17 with antimicrobial development.

18 So our goal is to find the best work,
19 publish it dispassionately, help advance science,
20 improve patient care. And I would argue that's the
21 goal of everyone in this room. Thank you.

22 (Applause)

23 HELEN BOUCHER: Thank you very much,

1 Dr. Baden.

2 Now it's my pleasure to introduce Dr.
3 Cynthia Sears, who is Professor of Medicine and
4 Oncology at Johns Hopkins, as well as Professor of
5 Molecular Microbiology and Immunology at the Bloomberg
6 School of Public Health. Dr. Sears is an ID expert
7 who is focused on GI infections and is the recent past
8 president of IDSA. Thank you.

9 CYNTHIA SEARS: Thank you, Helen. I
10 want to thank the FDA and the other co-conveners for
11 the opportunity to come and talk to you a little bit
12 in general about guidelines, as well as what's going
13 on at IDSA in guidelines. We've already heard
14 guidelines come up in many capacities today. And I
15 think this will reinforce some of the ideas that have
16 been floated. These are my disclosures.

17 So I'm going to start off with this
18 slide from the Magic Foundation, whose goal is to
19 increase value and decrease waste in the healthcare
20 system based on evidence ecosystems. And the reason
21 I'm showing you this is that what we're discussing,
22 the production, dissemination of guidance or
23 guidelines, is really only one component of a much

1 more complex ecosystem of information needed to
2 actually do excellence in guidelines. I think this is
3 all well-known to you, but just to review what the
4 purpose and promise of clinical guidelines is. The
5 purpose is to provide evidence-based, trustworthy -- a
6 word we've heard quite a bit today -- recommendations
7 to support patient care and to develop a framework for
8 determining acceptable clinical care.

9 The action is systematically
10 synthesizing typically complex data into a format that
11 can be used by physicians and other healthcare
12 providers to inform patient care decisions. And the
13 promise or hope of guidelines is that this will
14 support more uniform care for patient, yielding better
15 patient outcomes and diminishing health disparities.

16 However, they are not dictums. And so
17 physicians and healthcare providers must be able to
18 judge the quality of the evidence and assure
19 themselves that the recommendations apply to their
20 patient or populations in care.

21 Now, the next two slides just show some
22 of the ups and downs of what we know about how
23 guidelines may affect outcomes. this is a paper from

1 2009 from the U.K. where they were trying to assess
2 whether the publication of the U.K. National MRSA
3 Treatment Guidelines impacted 28-day all-cause
4 mortality. And as you can see in the table pre and
5 after the guidelines were published, there was no
6 change in 28-day survival. However, this is a very
7 weak study because it actually didn't look at some of
8 the critical features that are important to assessing
9 that result.

10 This paper and others, and as the
11 discussion has highlighted today, have questioned the
12 clinical acceptance of guidelines, the impact of
13 guidelines on care, and the voracity of guideline
14 processes. And there is no question that over the
15 last 20 years there has been many formats for
16 guidelines that have differed a lot.

17 This slide you already saw by Dr.
18 Outterson. Alan Carr and Helen Boucher shared this
19 with me. Recently presented at ASM and ESCMID just
20 this year.

21 And these data suggest that publication
22 of C. diff guidelines by IDSA modified use of
23 fidaxomicin and vancomycin. But again, this lacks a

1 lot of nuance that we would like to know about the
2 impact of guidelines. And in general I would say that
3 our data on the impact of guidelines remains pretty
4 weak or limited.

5 So the standard today for guidelines
6 really stems from the seminal report from the
7 Institute of Medicine in 2011 titled Clinical Practice
8 Guidelines We Can Trust. And the IOM set seven
9 standards for trustworthy guidelines. These are
10 establishing transparency, management of conflict of
11 interest, systematic review, establishing evidence
12 foundations, and rating strength of recommendations,
13 articulation of the recommendations, external review,
14 and updating.

15 And I would say that in stages, IDSA
16 has sought to implement these IOM standards to its
17 guideline process.

18 So IDSA guidelines within our society
19 are the highest-rated IDSA member product, critical to
20 member satisfaction. In parallel, our members, others
21 outside the society, and our guideline panel members
22 in fact have all expressed dissatisfaction with the
23 long timelines for development and update.

1 That said, the production of guidelines
2 by IDSA has been pretty stable. Over the last 20
3 years since 2016, 19 guidelines produced.

4 So what really constitutes the
5 guidelines process, attempting to meet IOM standards?
6 There is a lot of argument about this. But in a
7 recent review looking at various approaches, they
8 really all led to what's called GRADE, which stands
9 for Grading of Recommendation, Assessment,
10 Development, and Evaluation. This is a complex
11 process. Pre-development phase, development phase,
12 post-development phase. And I'm just going to run
13 through this so everyone understands the challenges in
14 the room.

15 So in the pre-development phase, you're
16 composing your panel, you're finding a methodology,
17 you're figuring out the COI, and you're setting up
18 agreements, usually with multiple societies since most
19 guidelines have collaborating groups.

20 There are three phases to the
21 development phase. The first is to define the scope
22 of the topic; frame typical questions that typically
23 should apply to a large proportion of patients, and

1 select patient-important outcomes. The second phase
2 is the systematic literature search. Requires a
3 librarian. They are hard to find. Literature screen,
4 assessing risk of bias. Then evidence synthesis and
5 grading. And lastly, the development and grading of
6 the recommendations by the panel and writing the
7 manuscript.

8 Post-development it's reviewing the
9 process, reviewing the manuscript and approval, and
10 then the guideline dissemination and implementation.
11 We've heard about all of these steps during the course
12 of the day.

13 The estimated and optimal process to do
14 this is one-and-a-half to two years. But there is no
15 question there are issues. Most of the people doing
16 guidelines are busy physicians and their time is at a
17 premium and sometimes can't be fully devoted to this
18 process. There is a paucity of methodologists and
19 librarians available to do this work and in general
20 the process has been poorly understood. But I have to
21 say since IDSA has invested in educating the panels
22 and in workshops, panels are enthusiastic about this.
23 Once they understand it, they actually find it to be a

1 good way to try to put the data together.

2 So the next three slides are just
3 giving you an idea of the scope of the work. We have
4 three types of guidelines, IDSA-led guidelines. And
5 the ones marked in red are those that involved
6 antibacterial therapy. Most of the IDSA-led
7 guidelines currently do. We have jointly-developed
8 guidelines. These are led by a different society, but
9 we have a formal role. All of these are linked to
10 antibacterial therapy. And then we have IDSA-endorsed
11 guidelines. These are led by another society. We may
12 or may not have a representative, and a subset of
13 these are linked to antibacterial therapy.

14 However, there has been a lot of
15 discussion about what are the other options for
16 conveying science-derived, actionable bedside advice
17 to clinicians. And as has already come up, there's
18 probably two marquee examples we would all discuss.
19 One is the HCV guidance, which was a collaboration or
20 is a collaboration between AASLD and IDSA and has been
21 very successful for the community. And a second
22 actually would be AIDSinfo which is a DHH-NIH HIV
23 guidelines, but they are not great.

1 Other names are applied to these types
2 of documents; clinical consensus statements, practice
3 guidance, provisional clinical opinions. And these
4 are generally thought to be most applicable when the
5 evidence base is considered to be insufficient for a
6 clinical practice guidelines. But there are
7 significant practice variations going on and there's
8 many opportunities for quality improvement.

9 Now, I will tell you if you talk to the
10 people who are experts in GRADE, they disagree with
11 this statement quite a bit. In general, these
12 recommendations are not done with a formal process
13 like GRADE. But there are in the literature potential
14 hazards when some of these processes are reviewed,
15 including accuracy, completeness, conflict of
16 interest, and transparency. All topics that Dr. Baden
17 brought up as well.

18 So the overall key challenge is
19 upholding methodologic rigor while meeting a reduced
20 development timeframe. Recently there has been a
21 discussion of rapid guidelines meant to meet certain
22 conditions. And similar documents have been put out
23 by the CDC, U.K. National Institute for Health and

1 Care Excellence, and WHO, all given different names.
2 However, a key limitation is it requires a high
3 concentration of skilled resources to be rigorous and
4 rapid. And each of these documents has been subject
5 to the types of criticisms I brought up on the
6 previous slide, including transparency and process.

7 So I'm going to tell you a little bit
8 about an activity at IDSA this last year. And you'll
9 see why in a moment. We went through a strategic
10 planning process. This involved data collection, tons
11 of conversations, and a lot of debate. We applied a
12 business model to our discussions called the Run-Grow-
13 Transform model. And I'll just say a Run initiative
14 is one in which you have a base, but you intend to
15 invest to improve it. And Transform is an effort to
16 have long-term, high-impact effect.

17 I bring that up because we've recently
18 published the 2019 IDSA Strategic Plan and CID. There
19 are four initiatives for the next five years. And two
20 are quite relevant to discussion today. One is to
21 optimize guidelines, and the other is to invest in and
22 lead efforts to decrease AMR with our partners.

23 We fully acknowledge there is a gap.

1 Trustworthy, real-time, focused guidelines guidance on
2 treatment of antimicrobial-resistant infections is a
3 gap in our repertoire. So this is a moment of
4 opportunity. A completion of the 2019 strategic plans
5 means we're gearing up to invest significant staff and
6 financial resources beginning in 2020.

7 So what's under discussion? So we
8 intend to expand IDSA's guidelines program to meet the
9 needs of the clinical ID community. There are a lot
10 of things on this slide, but I'll just point out our
11 intent is to expand the portfolio of guidance products
12 and to provide interim recommendations and rapid
13 updates to supplement standard clinical guidelines.

14 So I'm floating a proposal under
15 discussion in which your feedback would be welcome.
16 So using a title of Antimicrobial Treatment Alert and
17 Clinical Commentary from IDSA. And components that we
18 might envision in this is the rapid dissemination of
19 emerging trial and drug data on antimicrobials put
20 into context by clinical experts. Considering
21 developing comparison charts of new versus current
22 therapies for bacteria involved. And I was fortunate
23 enough to be able to modify this slide. But listening

1 to what was going on this morning, I put in there
2 inclusion of in-progress antibiotics, listening to
3 Helen's patient and trying to figure out what in the
4 world you're going to do with a patient for which you
5 don't have a drug. It would be nice if there was a
6 resource that would help you know who to call quickly.
7 And also inclusion of delineation of questions that
8 need further research.

9 So as I've tried to say a couple of
10 times today, this is a moment of opportunity. We
11 really would love your suggestions and input. Some of
12 the questions I would like to hear discussed later is
13 what should be the format and components of real-time
14 AMR treatment advice, who is the clinical audience,
15 what will be the requirements and standards for data
16 inclusion, and perhaps even more importantly, what
17 will be the criteria for changing that advice. How
18 would we best disseminate this, and what are your
19 concerns about such a process and approach?

20 So, thank you very much, and I look
21 forward to the discussion.

22 (Applause)

23 SUMATHI NAMBIAR: Thank you, Dr. Sears.

1 If we can maybe spend five minutes and see if there
2 are any clarifying questions for either Dr. Sears or
3 Dr. Baden. Then we can go into the panel. Also
4 wanted to mention that as this is a workshop, members
5 of the audience are welcome to participate as well.
6 So if you have any questions, feel free to -- there
7 isn't a microphone. Oh, there is one right there. So
8 please feel free to come to the microphone and
9 introduce yourself and ask questions.

10 Any clarifying questions for Dr. Baden
11 or Dr. Sears? No? Okay. Seeing none, we can go into
12 our moderated panel discussion. So we have three
13 questions. We'll start with the first, and then
14 depending on how much time we have, whether or not we
15 can get to the second and third question.

16 So the first one is -- yeah, thanks.
17 Thank you, Cindy. So the first question is what are
18 some serious infections -- and you've just listed a
19 couple of examples here, staph aureus bacteremia,
20 prosthetic joint infections, diabetic foot infections
21 -- for which there is a clinical need for new
22 therapies. What are some feasible approaches to
23 obtaining clinical trial data in patients with these

1 types of infection?

2 So the reason for bringing this
3 question up is, you know, as we have heard today and
4 we've heard in other prior discussions as well, that
5 there doesn't seem to be a need for new therapy for
6 say a UTI or intraabdominal infection. And those are
7 not the kinds of infections clinicians are actually
8 treating their patients for these days. So we would
9 like to hear from everybody here what might be some
10 serious infections for which there is a need for new
11 therapies and how do we go about putting together such
12 a list. And I think also very importantly is how do
13 we work to design trials. You know, we at the agency
14 don't have the experience of having design trials for
15 some of these indications. So what would be the next
16 steps to build up on the list of indications we come
17 up with? How do we design trials and what might be
18 some feasible approaches to obtaining these data?

19 So I'll see if there's anyone who wants
20 to volunteer and have any thoughts. Vance?

21 VANCE FOWLER: I'll volunteer. I note
22 you have staph aureus bacteremia on there. We can
23 talk about that one all the livelong.

1 You know, I think that practical steps
2 -- I would say that's one of the few trials in this
3 space for which there actually was a successful model,
4 and there no longer is. And what I mean by that is
5 that I think some of the restrictions that I have
6 personally seen -- and I've been involved. And as a
7 matter of fact, Dr. Cosgrove and Dr. Boucher were
8 involved with essentially all of the Phase IIIs that
9 have come through on bacteremia. And the general
10 trend has been sort of a gradual, inexorable
11 tightening of the noose to ultimately futility. And I
12 would demonstrate or provide as exhibit A the
13 (indiscernible) study in the same space that the
14 (indiscernible) study was done.

15 Some specific examples in that space
16 which I feel like would sort of resurrect that
17 approach, an incredibly clinically-needed indication,
18 would be revisiting the current approach towards PENS,
19 specifically the potentially effective non-study
20 antibiotics. And for those in the audience, that
21 means in trials complicated trials. You know,
22 patients in real life, people get a lot of
23 antibiotics. Right? And sometimes a person will get

1 an antibiotic for some period of time that's not a
2 part of the study. And then the question is what do
3 you do about it and to what level can you attribute
4 the ultimate outcome of the trial to the
5 investigational agent of choice versus the compound in
6 place.

7 And I feel like -- and granted I'm
8 biased because I was part of the adjudication
9 committee for the dapto trial. But I feel like the
10 dapto trial had it pretty close to right because there
11 was the ability for clinical interpretation of those
12 data by an objective third party. And I personally
13 have seen from my own involvement in several of these
14 subsequent trials the gradual erosion of that clinical
15 ability for interpretation. And I think to the
16 detriment of the trial and, frankly, the detriment of
17 the compound.

18 And I've probably caused enough
19 trouble, so maybe I'll stop there for right now. But
20 that's a good place to get things going.

21 HELEN BADER: And I'll just ask a
22 follow-up. So who can help think about doing these
23 trials? Are there any particular groups that we

1 should be including in this discussion?

2 WOMAN: I think the point Vance is
3 making is that there was an incredible value of having
4 infectious disease physicians review the cases of
5 PENS. Because in contrast to most other infections
6 that we treat now, where we've seen five days, seven
7 days, and so forth is fine. That's not the case still
8 for staph aureus bacteremia. And so specifically when
9 you're at the tail end of a four-week course of
10 therapy, there is a good chance that someone sent a
11 urine culture and they get three days of Bactrim. And
12 clinically three days of Bactrim has no relevance to
13 whether the 28 days of whatever the drug being studied
14 is was effective for staph aureus bacteremia. The
15 problem in staph aureus bacteremia is we can't clear
16 the blood cultures in staph aureus bacteremia. So if
17 three days of Bactrim at the end of the course of
18 therapy was going to solve all the problems, we would
19 have figured that magic bullet out already.

20 And yet those patients become failures.
21 And then you have such an enormous bias in these
22 studies towards failure, that you don't end up with
23 useful information about the drug. So I think the

1 people that can help are people who take care of
2 patients with staph aureus bacteremia, you know, to
3 make these distinctions amongst different infectious
4 disease syndromes.

5 SUMATHI NAMBIAR: Yes. So it's
6 certainly -- any other comments?

7 SARA COSGROVE: Well, the only other
8 comment I wanted to add was just understanding from a
9 pharma point of view is how you bring in other -- the
10 challenge of doing some of these trials is bringing
11 the viewpoint from other regions. So here is a
12 roomful of U.S. focused people. And the problem is
13 that I need to design a trial that can go to China,
14 Latin America, Europe. And so not only is it the
15 challenge of the agencies talking together -- which we
16 know they talk. Obviously they do talk. But it's
17 trying to get consensus there. But also the medical
18 communities, because the standard of care or the
19 opinion or the approach to disease could be very
20 different in different regions. So that would be the
21 other thing to make sure from a pharma point of view
22 that everybody remembers; they have to be global
23 trials typically.

1 JOHN REX: So is there another way to
2 frame this question? And I am wondering whether we
3 could be doing some sort of a systematic approach with
4 one or two drugs to help us know whether or not site-
5 specific PK is a useful tool. And I guess I'm trying
6 to come at it from a more generalizable approach to
7 interpreting the kind of data that we live with. And
8 I guess I've always assumed that the concentration of
9 the drug in in the CSF meant something, and whether I
10 should choose it from meningitis or not, is there a --
11 I don't have any clinical data on that. And if I even
12 had that once, that might actually improve my comfort
13 with using that sort of information. And I realize
14 I'm just posing another question without an answer,
15 yet I think that you will -- what's driving this if I
16 take every drug that comes along the way, I'm never
17 going to have data on sites A, B, C, D, and E that are
18 off the short list. And I would like to have a way to
19 generalize to sites A, B, C, and D.

20 SUMATHI NAMBIAR: So your comment is in
21 general terms, right? Not specifically with regard to
22 staph aureus bacteremia? You're just saying for a
23 drug should we be collecting PK at a variety of all

1 these sites.

2 JOHN REX: Right. And it's an ill form
3 of the question. But let's take prosthetic joint
4 infections. That's one that I'd like to know how
5 better to manage those. But it's a combination of
6 surgery and drug therapy. And is there a way to,
7 short of studying a series of drugs -- am I going to
8 compare a oxazolidinone with a beta-lactam with
9 something else for PJI? No, none of that's every
10 going to happen. But maybe there -- but is there a
11 way to get at something from a PK-PD standpoint that
12 would be helpful here? And maybe I just answered my
13 own question. I think the answer to that question is
14 no.

15 I was really just spinning off of is
16 there a way to provide information that is more
17 generalizable than one-off studies with individual
18 agents. And I don't know the answer.

19 HELEN BADER: Well, just to be a little
20 more provocative, what about getting more pragmatic?
21 What about getting to a much more pragmatic trial in
22 staph aureus bloodstream infection, right? It's
23 really common in my hospital right now. It's really

1 common because of the opioid epidemic. What about
2 something where you don't even get to the minutiae
3 that Vance was talking about with the composite
4 endpoint with the 22 parts. What about we're going to
5 give Drug A, Drug B to real people with staph aureus
6 bloodstream infection. Maybe not with left-side
7 endocarditis, but everybody else, and follow them for
8 42 days. Count the bodies, see what happens to the
9 blood cultures.

10 VANCE FOWLER: So I really see -- and I
11 guess I'm probably going to address this to some
12 degree tomorrow. I really see there's sort of two
13 silos of work here with fairness. I think there's the
14 registrational element, which is absolutely critical,
15 necessary. But I would respectfully submit
16 insufficient to fully inform clinical practice. And I
17 think parallel and also by itself insufficient is the
18 need to answer clinical questions. And I feel like
19 ultimately the trial designs of those two inextricably
20 important needs are going to be different.

21 And so as an example of which, to carry
22 on staph aureus bacteremia, you know, when you're a
23 hammer, everything's a nail, right? But we've

1 published earlier this year in CID that the average
2 screen to enroll rate for staph aureus bloodstream
3 infection, in complicated in particular, is at least
4 30 to 1. Okay? And that's from three different
5 studies, including the telavancin experience with
6 their Assure study, of which I was a small part, and
7 two others.

8 Now, compare that -- and the cost of
9 course was prohibitive. And the data was ultimately
10 truncated by the fact that they had stopped the study.
11 So compare that for example from the perspective of
12 strategy trial to what's going on now in Australia
13 where they are really taking the play of borrowing
14 from the playbook of the cardiologist and sort of
15 taking simple questions, randomizing adequately-
16 powered samples, and then letting this -- it's not
17 going to meet the level of stringency that of course
18 needs to be in place for an FDA trial. But they're
19 two different purposes I would submit.

20 So what's my point? I guess my point
21 is that I really see there is sort of two needs here.
22 There is the need to get drugs to market, and then
23 there's the need to know how to use the drugs once we

1 get them to market. And I think the trials are going
2 to have to reflect that reality. And I'll stop there.
3 Thank you.

4 SARA COSGROVE: I'm just going to
5 respond to what Vance said, because I can't remember
6 what I was going to say originally. But -- I actually
7 do remember, but...

8 So, I think that it's important to note
9 that the study that Vance is referring to, the big
10 one, was called the MERINO Trial. And it looked at
11 whether we should be treating ESBL bacteremia with
12 meropenem versus pip/tazo. And there were no U.S.
13 sites. And that is because it really was too
14 difficult for U.S. sites to become involved. And we
15 must fix that. Because not only are we not taking
16 advantage of all of our patients and their experiences
17 in the United States, we're also not getting any
18 information from the United States.

19 And so I really think that we need to
20 figure out how to make it so that these kinds of
21 approaches can be operationalized in the United
22 States, whether we're participating with the global
23 group or doing it ourselves in the United States.

1 SUMATHI NAMBIAR: Aaron, you had a
2 comment. And then we'll come to you, Pam.

3 AARON DANE: I was just going to pick
4 up on the idea of a pragmatic trial. So I guess even
5 from a regulatory perspective, a pragmatic trial and
6 an inferiority trial would be problematic because of
7 all the different elements of noise. But I guess if
8 it's a superiority study and you're aiming to show
9 that something new is better, then -- I mean, I'm just
10 checking. But wouldn't that be more acceptable
11 because come of those concerns in non-inferiority are
12 less prominent in a superiority study?

13 SUMATHI NAMBIAR: That's true. I mean,
14 if you look at the KARE study -- I don't remember all
15 the specifics -- but we didn't have all these concerns
16 because it was designed as a superiority trial. So
17 maybe 96 hours. But fair amount of prior therapy was
18 allowed. So yes, and that was the problem with the
19 KARE trial. After it was completed, one couldn't even
20 try to interpret it as an NI trial because it had all
21 these other issues which confounded an NI assessment.
22 But in a superiority trial, if you get a lot of prior
23 therapy, other concomitant therapy is going to be just

1 harder to demonstrate superiority. But if you can
2 still do so, I think that's much easier to handle.

3 AARON DANE: Yeah, that's what I'm
4 thinking. So when we talk about some of these areas,
5 it's not going to be universal. But in some of them
6 it might be that a pragmatic trial could be possible
7 if we are in a situation where something new is going
8 to likely be better.

9 PAMELA TENAERTS: And I think I'll
10 continue a little bit on the pragmatic trial, because
11 I think -- first of all, people have discussions about
12 what is a pragmatic trial. But the truth of the
13 matter is every trial could be more pragmatic than
14 what it is right now. I mean, it might not be total
15 pragmatic with a three-page CRF and everything, but --
16 and the way to get there is really changing the
17 approach that you design your protocol. And Vance has
18 heard this before, is a quality by design approach
19 where you bring everybody around the table, including
20 the physicians, the clinicians, the coordinators, the
21 patients. In a drug development program, the
22 statisticians, the operational people. Everyone
23 together and walk through a series of things that you

1 need -- how you set up your trial so that you can make
2 it as simple as possible and focus on the things that
3 matter and not focus energy on in the end things that
4 don't matter.

5 And by the way, ICH E8 has gone through
6 a draft guidance, so it's E8(R1). And they are
7 proposing exactly that approach; that for
8 registrational trials in the ICH communities, which is
9 basically everyone at this point, you should use a
10 quality by design approach. And I think that is very
11 different than whoever is sitting in their offices
12 dreaming up the trial, and then the clinicians go, oh,
13 this doesn't work. Well, then talk to the people and
14 see what will work and what will work for everyone,
15 and create those trials. And then they should be
16 streamlined, only collect the data you need, and all
17 those good things.

18 VANCE FOWLER: So, Pam, just -- part of
19 that -- your point is totally valid. Part of the
20 concern arises from -- well, my understanding, not
21 being in industry, but my impression, is that part of
22 that arises from industry's very legitimate concern to
23 be able to respond to questions that are posed in

1 public forum, which is an ad board meeting or -- you
2 know what I mean?

3 And so I would be interested in getting
4 the perspectives of some of our industry colleagues on
5 that point and what could assuage that perspective.

6 PAMELA TENAERTS: That's exactly right.
7 And we did a project a couple of years ago when
8 pragmatic trials were still called large simple
9 trials, if somebody remembers that. And so we did a
10 project then that was actually asked us to -- that the
11 FDA asked us to do, because they wanted to see -- and
12 I say sort of generalizable. But some people wanted
13 to see more large simple trials.

14 And what we found is exactly that; the
15 resistance of industry saying, but what if I didn't
16 answer a question you're not going to ask me. And the
17 same resistance was actually at the FDA when we did
18 the surveys, that, well, what if I ask a question and
19 they don't have the answer. And it goes back to --
20 and I think the publication was published in JAMA.
21 Mike Lauer was one of the -- and then (indiscernible),
22 that maybe it's not the ideal pragmatic trial, but
23 just make your trials more pragmatic, like make them

1 more real world. It doesn't have to be that you don't
2 collect any data. You can still collect what you
3 need. But yeah, your point is well taken.

4 JOHN REX: And that's something that
5 we've all been picking at; the question of smaller
6 amounts of data. Whether it's a small amount of data
7 on a large number of patients or a larger amount of
8 data on a small number of patients. And we've not yet
9 seen that actually done. I remain fascinated by the
10 fact that the EMA says in their guidance, just bring
11 us some randomized data. And we understand if it
12 can't be fully powered, just bring us some randomized
13 data. All right? And, Ryan, you brought them some
14 randomized data. You know, that is randomized. The
15 critical CS or the little study that only got 40, 50,
16 60 people in it, right? That's randomized data. And
17 the problem is the heterogeneity that's implicit in
18 anything where the N is less than a hundred. And even
19 when you get up to 200, the heterogeneity. Every
20 person is -- it doesn't take much to move it.

21 Remember, for noninferiority, the
22 central point estimates of the two usually can't be
23 more than three or four percent apart. If it's more

1 than that, then the -- even 10 or 15 percent
2 confidence, balance will be out of whack. You know?
3 But the point estimates have to be really close, and
4 you can't be off by very far. So I'm going to take
5 that idea and say the theme here is that this is the
6 community that understands that it wants the drugs.
7 It understands that it wants the data. And we as a
8 community have to say out loud we get it that this is
9 all there is. It's not going to get better. And we
10 have to quit whining about it. And there's that word
11 normative. We have to say to ourselves and to our
12 peers that put up or shut up. You know? This is it.
13 And you can't have it both ways.

14 So somebody earlier said -- the comment
15 about qualities of data. And I'm sorry, I can't quote
16 it right now. But we're blowing hot and cold out of
17 both sides of our mouth. We can't have it both ways.
18 We have to declare that this is all there is, and
19 there isn't some hidden trial. Industry's not keeping
20 some secret in the corner and not telling people that
21 they'll do it that way. Rant over. Sorry.

22 SUMATHI NAMBIAR: Vance, I have a
23 follow-up question to your earlier comment, that there

1 are registrational trials and then there may be need
2 for additional trials.

3 So say if a new gram-positive agent
4 came along. And the traditional way has been, you
5 know, do skin trials first and then think of follow-on
6 indications later. But that's exactly the criticism
7 we are hearing; we don't want another skin trial. But
8 if you didn't do that and you didn't get the product
9 available, how would you do your pragmatic trials? So
10 I just wanted to know what your thoughts what might be
11 and what other indications we could think of if skin
12 is not the way to go.

13 VANCE FOWLER: That's a fair question.
14 I guess my response to that would be largely being the
15 one who says we don't need another skin trial. And my
16 response to that largely is we don't want only another
17 skin trial. I actually understand why the skin trials
18 are done and the complicated UTI trials are done. It
19 makes sense. These are entities that are clearly
20 well-described. There's airtight guidance that's in
21 place. You know how to do the trials. They're
22 affordable, the patients are there. And it gives you
23 data on performance and it gives you data on safety.

1 So I actually understand that. The question is what
2 next. Because realistically if there were a viable
3 next step for these compounds, for tedizolid and
4 dalbavancin and all these drugs that are staking up,
5 delaflox, and just stacking up like cord wood out
6 there. They've all got ABSSSI indications. And then
7 what? Nobody's using them because they're too
8 expensive. Right? So you get stacked.

9 So let's say they did their skin study
10 and then there was some other thing, that for the
11 purposes of discussion, may not be quite to the level
12 of rigor as the skin studies. Get them through the
13 gate, but then you do some other trial whereby there's
14 some flexibility on both sides in an indicator that,
15 with respect, clinicians actually care about. Like
16 osteomyelitis. Okay?

17 If you talk about gram-positive, okay,
18 you can treat skin and that's fine. But the truth is,
19 you know, one of the leading indications folks with,
20 you know, NID you're dealing with now is osteo. And
21 we don't have the first idea, or at least I don't,
22 about how to do it. The studies that have come out
23 have been studies from Europe. There was that one

1 paper in the Lancet about the six weeks versus three
2 months for vertebral osteo. There's fundamentally no
3 real strong guidance in those spaces. And so, okay,
4 could there be some means by which you get it out
5 there, you get your baseline safety and all that kind
6 of stuff. Do the PK, do whatever is felt to be
7 rigorous and responsible and appropriate. And then
8 there's some flexibility on more of a strategy trial
9 kind of approach in clinical questions that are
10 relevant to clinicians. And I use osteo just as one
11 example. If you put it in the gram-negative space,
12 then maybe it's bloodstream infection. But that's the
13 concept that I think is probably worth thinking about
14 a little bit.

15 MAN: So, in listening to this
16 discussion, I think we're trapped a little bit into
17 thinking of different infection sites as being exactly
18 the same or completely different. And neither one of
19 those mental models serve us very well.

20 Clinically, we often share information
21 across diseases that have various degrees of
22 heterogeneity. Osteo in one bone we pretty much treat
23 like osteo in another bone. But if it's not the bone

1 and it's the cartilage or not the bone and it's the
2 muscle, then those are more different.

3 And I think there are statistical
4 methods that are used in other areas of medicine for
5 quantifying the degree of similarity and learning
6 about the degree of similarity of treatment effect
7 across infection types or disease types that are
8 similar, but not completely similar, and different,
9 but not completely different.

10 And so one of the thing I hope to do
11 tomorrow, in a shameless plug for my talk at the end
12 of the day, is to actually give some specifics about
13 the statistical modeling that can be used to directly
14 address this question of how do you leverage the data
15 you can get -- for example, in skin and soft tissue
16 infections -- to indirectly address and supplement the
17 harder-to-get information on these other diseases.
18 And I feel that throughout the day, we've had the
19 lumpers and the splitters. And the lumpers will be
20 challenged by evidence of heterogeneity of treatment
21 effect. The splitters will be challenged by never
22 having enough data in any particular group into which
23 they've split the patients. And as long as we are of

1 those two different philosophies and we don't
2 quantitatively and rigorously and in a prespecified
3 method have a plan for falling in between, we're going
4 to be hopelessly hogtied. And I think that one of the
5 things that I think is interesting as both a
6 statistician and a practicing clinician is that
7 clinically we do this all the time. The patient I'm
8 going to see tomorrow night at midnight in the ER --
9 I'm a little bitter about that -- is not going to look
10 like any other patient that I see. But I am going to
11 borrow information that I can recall at that time of
12 night to try to make a treatment decision.

13 So I think we need to bring the thought
14 process that we use clinically, combine it with
15 rigorous statistical modeling, and come up with ways
16 of learning the same way from our trials that we do in
17 clinical practice.

18 HELEN BADER: That's really great,
19 thank you. Can we do -- Lindsey Baden had a comment.
20 Lindsey, go ahead. Sorry.

21 LINDSEY BADEN: That's the problem with
22 being tucked in the corner. The conversation,
23 Sumathi, that you and Vance were having, I'm having a

1 little bit of trouble in that the cUTI study is, as
2 Vance sort of said, there's a way to do a study for
3 regulatory approval that has parameters we all
4 understand and therefore can measure efficacy and
5 safety. And then there's the complexity of all of the
6 other conditions that we treat in real life.

7 And I guess, Vance, are you proposing
8 that the only studies you can do have to be
9 registration studies, or can't there be studies which
10 are designed for registration and then studies which
11 are designed to inform practice, realizing they may
12 have different metronomes?

13 VANCE FOWLER: I thought that was
14 exactly what I said, the latter scenario. Essentially
15 there's the registrational trials, and there's
16 strategy trials. Tomorrow I have two columns. It
17 says strategy trial, registrational trial. And it
18 will be more clear. But yeah, I think that's
19 precisely what I'm saying. I'm saying that both have
20 objectives and responsibilities that they need to
21 address. But neither in and of themselves is
22 sufficient to address all that needs to be done.

23 In other words, for a new compound,

1 it's important in my view to pursue a pathway along
2 the lines of what's being done with registrational
3 trials. Because there's a great deal that's not
4 known. The safety is not known, the efficacy isn't
5 fully known. And so you really want to test the drug
6 and not the test. By which I mean put it in --
7 evaluate it in a situation whereby most of the other
8 potential area for variation is minimized. That is
9 skin study, complicated UTI study. Having done that
10 and gotten a base -- let's call it a baseline of
11 understanding in terms of the performance, the
12 relative areas of weakness or strengths of a compound,
13 that you then focus that subsequent effort in an area
14 that actually addresses more of the clinical need.
15 Because the unmet sort of clinical need that the drugs
16 have the potential to address. So that's exactly what
17 I'm saying --

18 LINDSEY BADEN: So for osteo, it would
19 be terrific to have agency guidance on here is the
20 right way to do an osteo study. Prothesis, yes/no.
21 Bug, yes/no. You know, which bone.

22 However, that doesn't stop you from
23 designing such a study and determining if drug X works

1 for osteo.

2 VANCE FOWLER: That's correct.

3 LINDSEY BADEN: Because the study can
4 be done. It's a matter of can we design it in a way
5 that the community thinks is meaningful and
6 achievable.

7 VANCE FOWLER: Yeah. Basically what I
8 mean there is that if these are the studies that the
9 community needs, then the community may need to be
10 ultimately responsible for designing, implementing
11 them, and funding them.

12 AARON DANE: And it remains off-label.

13 JOHN REX: Philosophically I'm very
14 sympathetic. So that's my warning that I'm now going
15 to disagree with you a little bit.

16 And something that I often think about
17 is FDA -- you're to assume between a trial that's good
18 enough for the FDA and a trial that's not good enough
19 for the FDA. FDA is not really any different than any
20 of the rest of us. They are docs who are asking the
21 questions that you will ask when you get the data.
22 And if the trial wasn't good enough to be interpreted
23 by Sumathi and John, when Helen gets it, she's going

1 to say I don't know what to do, either. And so are
2 you.

3 And so I want to flip it around and
4 say have we seen examples of we'll call it lower-
5 quality pragmatic trials that people actually
6 believed? And what was the characteristics of those
7 studies and how do we get at those?

8 VANCE FOWLER: ARREST Trial, Lancet.

9 JOHN REX: Which one?

10 VANCE FOWLER: 2018. It was a Guy
11 Thwaites study, randomized. Rifampicin or placebo to
12 patients with staph aureus bacteremia. You know, I
13 guess I'd say there are different needs for different
14 things. I've got a pickup truck that I drive since
15 1993. It's very effective for -- you know, down on
16 our farm, we've got our family farm. It's great down
17 there. I don't drive it to Washington DC because, you
18 know, because I've had it, well, since 1993.

19 So I'm saying these are fit-for-purpose
20 trials. You don't need a \$250 million study or a
21 study where -- whatever it was in the dapto study for
22 instance, a hundred thousand dollars per patient
23 enrolled? Do you really need that to answer every

1 single question about staph aureus? Of course not.

2 So I would say yes there are trials
3 that have different purposes, and that there are fit-
4 for-purpose studies that if we actually want to get
5 some answers to these questions, we're going to have
6 to look at how folks are doing it and the rest of the
7 world.

8 I'll give you another example. CAMERA2
9 study. Steve Tong and Josh Davis down there comparing
10 vancomycin or -- with or without an antistaphylococcal
11 penicillin to confuse the issue with facts with
12 regards to whether this combination therapy in terms
13 of staph aureus bacteremia makes a difference or not.
14 That study was done for less than \$2 million, and it
15 provided an answer that will fundamentally change
16 clinical practice. Was it done to the level that
17 absolutely has to be done in this context of answering
18 the questions that the FDA needs answered? No,
19 probably not. Was it good enough to help me know that
20 combination therapy is probably not in the best
21 interest of patients with MRSA bacteremia? Yes, it
22 was. And I'll stop there.

23 JOHN REX: But it's noninferiority, so

1 you don't know whether the test was valid or not.

2 HELEN BADER: Well, it was superiority,
3 right? But it's a little different than the focus of
4 our question, which is about new drugs. Right? So I
5 think what we're getting at is the notion of whether
6 we the community need an indication for some of these,
7 quote, more meaningful or more serious infections, or
8 are we happy to get -- and again, I'm the simplistic
9 simplistic person. But are we happy to get a skin
10 indication and some PK/PD data in bone and other
11 things to help us bridge to the right does and those
12 things? And then ARLG or some other network or
13 somebody else does the trial, and it gets published in
14 New England Journal because it's such a great study
15 and it informs practice.

16 So, Dr. Cosgrove?

17 SARA COSGROVE: Well, I kind of
18 wondered if there was appetite for further discussion
19 -- and this is directed at industry colleagues and FDA
20 -- figuring out if there is any interest -- I mean, if
21 the federal government has to fund these studies,
22 that's a separate issue than if we thought that
23 somehow you could tie these pragmatic clinical trials

1 to the label, or to something that would be beneficial
2 in terms of marketing the drug. And I'm just curious
3 what people think about that.

4 MANOS PERROS: If I can take a stab --
5 oh, sorry. Go ahead.

6 RIENK PYPSTRA: I just wanted to
7 comment on the previous question. If it is indeed
8 enough to just have the skin indication or the cUTI
9 indication and practice be guided by some other
10 information that is not reflected in the label, then
11 we may not need an indication at all in the label
12 anymore. It would just say this antibiotic is
13 approved, full stop.

14 HELEN BADER: It was a purposely-
15 provocative statement, but I think that to circle back
16 to where we started at the beginning of the day, that
17 is where a lot of us are in our day jobs, right? We
18 have these product, right? We have these products
19 that were approved, one of which is maybe not
20 available, but that have a spectrum of activity
21 against the more resistant pathogens. They're
22 approved for a less-serious illness. And I've got a
23 patient with a bloodstream infection or pneumonia.

1 So I was being provocative. Of course
2 that's not what I'm suggesting. But I wanted to
3 generate the dialogue.

4 RIENK PYPSTRA: Yeah, but to be clear,
5 we want just a bit more in the labels, not less.

6 MANOS PERROS: If I may build on that
7 why, this idea of an approvable trial followed by an
8 additional trial that could get you additional data
9 for indication. If you want to see new drugs
10 developed for osteomyelitis or for multidrug-resistant
11 pseudomonas, this is not a single trial; this is a 15-
12 year R&D investment. And if you wanted to see a drug
13 that's already approved for something else being used
14 for osteomyelitis, that may be enough. You might be
15 able to just put the data out there. The investment
16 in the study is relatively small. The cost of
17 developing and commercializing the product have been
18 amortized. Maybe someone will put it on the market.
19 But if you want a company or companies to invest in
20 R&D project who will get you a new osteomyelitis drug,
21 I suspect you need to have something on the label that
22 will get approval, and you'll be able to go out there
23 and promote the product.

1 RYAN CIRZ: Just listening here, sort
2 of --

3 JOHN REX: Or in something you can use
4 in a similar, Good Housekeeping Seal of Approval way.

5 RYAN CIRZ: It just seems like as an
6 early-stage scientist, that's predominantly where my
7 passion is; new things. It seems like there is an
8 opportunity to help a little bit, especially the
9 physicians and pharmacists, with explaining that to
10 their peers, that this is a way we get drugs approved.
11 Because it is hard to hear, like, oh, another drug for
12 UTI. That's not how we do discovery. That's not how
13 it works in the lab. We do chemistry and we test
14 against resistant pathogens and look for spectrum
15 gaps. And when we find them, we say ah, this works on
16 something that nothing else works on. And then we say
17 how do we find those pathogens in an easy way so we
18 can show the new drug works just like the old one when
19 the old drug works. But it will work when the old
20 drug doesn't work based on the micro. And just to
21 work for a decade and then have everybody sort of
22 shrug and say oh, another UTI drug. And that's not
23 actually the intent. Everyone here knows that. But

1 actually we could use your help explaining that.
2 Because they're not going to believe it from us,
3 honestly.

4 PAMELA TENAERTS: And I think the other
5 reason why you're probably not happy with just UTI
6 studies is that how are you going to get the approval
7 for all the -- when you're using it off-label, so to
8 speak. We've heard this morning about issues with
9 hospitals not really jumping at the bit to provide
10 drugs that are not approved in an indication and give
11 those as part of DRG. So I think there is other
12 things that need to fall in place, too, and other
13 reasons why you may want more studies.

14 NICK KARTSONIS: And if I could just
15 add one other thing. That's part of the reason why we
16 did all those HABP/VABP studies, was not because we
17 were masochistic, but because we really wanted those
18 additional indications to help support us. And,
19 frankly, outside the U.S., those are critical for
20 reimbursement purposes and help drive value.

21 Now, studies like the osteomyelitis.
22 If we were to pursue a path like that, we probably
23 would say we won't do that as an -- I'm speaking for

1 big pharma right now, right? But we wouldn't do that
2 for an indication, but we probably would try to
3 support those through investor-initiated programs and
4 what have you. And we've used those kind of programs
5 before to try to fill these in when we know ultimately
6 we're probably not going to pursue an indication, but
7 are valuable from a strategy standpoint, to the extent
8 we can do that, right? But those are subject to
9 receiving proposals that pass some sort of muster as
10 well.

11 SUMATHI NAMBIAR: So, Nick, as a
12 follow-up -- Nick? Sorry. As a follow-up, when you
13 said you wouldn't want to do such a study to seek an
14 indication, what is the main reason? Is it the risk
15 or is it the cost? Oh, sorry, I didn't --

16 NICK KARTSONIS: Yeah. I mean, I think
17 at the end of the day it's going to come down to a
18 business case. Right? I mean, I hate to be
19 commercial about it. But at that point the company is
20 going to say, okay, Nick, give me the financial return
21 of doing -- if the study is going to cost \$30 million,
22 I want to see an MPV that's going to say that it will
23 be positive. And you showed the (indiscernible) and

1 daptomycin slide earlier. By the way, I will never
2 show that to my senior management.

3 But at the end of the day that's
4 basically how it comes down to. I mean, because they
5 could invest that money in oncology study and try to
6 make those tough decisions in that particular way.

7 SUE CAMMARATA: And it's not only the
8 money; it's just trying to get consensus on how to do
9 those trials. I mean, you think about all the
10 clinicians in the room. Do you all approach these
11 diseases in the same way? The patients are somewhat
12 individual and the problems you might have, the bugs
13 you may have. So it's the challenge of cost, time,
14 money. And then for these difficult indications, just
15 getting a consensus around -- again, I'm going to
16 emphasize around the world, because we have to think
17 about it in that respect.

18 DAVID MELNICK: You know, we're
19 struggling to expand our value dossier to support
20 reimbursement at the same time we're trying to do the
21 \$300 million worth of post-marketing requirements and
22 commercialization costs. I mean, what we're talking
23 about comes very close to the pragmatic approach that

1 the companies take. We use a core indication to get
2 to market, and then we do, to the extent that's
3 possible, these small value expansion studies to try
4 to demonstrate the value of the antibiotic. But we're
5 in a position where we can't really discuss that in
6 the marketplace to the clinical community.

7 ROGER LEWIS: It strikes me that we're
8 stuck with a common dilemma of having to make choices
9 between options that are actually available to us.
10 There's one option, which is to -- and in the setting --
11 -- and I think the comment about us talking about new
12 drugs, not pragmatic use of older drugs is really
13 important for context.

14 One choice is to get very good data
15 that meets the traditional regulatory standard and
16 defines labeling on the easier-to-study indications
17 for which we have drugs, because they were easier to
18 study. And then to allow the clinicians to fly
19 relatively blind in terms of their use of those drugs
20 for other indications. Not absolutely blind, but
21 they're trained clinicians. They recognize how these
22 diseases work. But relatively, because there's both a
23 relative lack of well-collected data that has been

1 interpreted by the regulatory agency. The regulatory
2 agency is not in a position to write language of any
3 sort of guidance such as might be contained into a
4 label. Therefore the marketing can't reflect the
5 agency's input. And there are things like
6 investigator-initiated studies which are another form
7 of marketing. And we just have to ask, is that really
8 the right situation for us to be in?

9 I also suspect that the comments and
10 the perceptions on antibiotic stewardship reflected in
11 this room come from a highly-selected set of
12 institutions that don't reflect the level of
13 antibiotic stewardship that exists in most of those
14 80-bed hospitals in the U.S. And in those hospitals,
15 if a brand-new antibiotic comes out and its indication
16 is UTI, it seems like fair game to treat a UTI. And
17 that is a real problem in terms of the development of
18 new resistant organisms or multiply-resistant
19 organisms.

20 So I think that we really need to look
21 for opportunities that allow us to both study the
22 diseases that we can study because they're practical
23 to study, and also collect objective, randomized data

1 on those harder-to-study indications and have the
2 regulatory agency or agencies, if it's a multinational
3 situation, show a little more flexibility in how they
4 use that data that is of lesser quantity, but not
5 quality, in order to inform clinicians and therefore
6 marketing and how those agents should be appropriately
7 used, and in a way that really does support
8 stewardship.

9 What I'm really concerned about the one
10 more drug for complicated UTI is the degree with which
11 that approval with that language and only that disease
12 systematically undermines the public health imperative
13 for stewardship at the hospitals that don't have the
14 stewardship programs that are reflected in this room.

15 AARON DANE: I think I was going to
16 echo some of that, which was something Roger said
17 earlier actually. Because we moved back towards
18 saying, well, you do a skin study or an osteomyelitis
19 study. But I wonder whether that is an area where you
20 do a study with both and you have the core of the
21 skin, but then you do borrow information or do
22 something like that so you don't need to do the fully-
23 powered osteomyelitis study, but you can draw on what

1 you've got there. Obviously that would involve more
2 detail looking into the design, but it's just the idea
3 that rather than just saying, well, it's two
4 completely separate studies of a similar size, you
5 actually -- that other aspect could mean that it's a
6 lot smaller if we can draw heavily on the skin data
7 that we've got. So there's a number of areas we could
8 do something like that and maybe consider that as a
9 way of getting it both within the same study.

10 VANCE FOWLER: So, I mean, there are
11 things that we can do and we can't do. It seems like
12 one of the things that would be at our disposal if the
13 intent is, again, focusing solely on new compounds and
14 stand on that line, okay. So the trials that need to
15 be done aren't being -- look at the question of why
16 are the trials that need to be done not being done.
17 And, you know, at least from my experience with
18 working with sponsors on staph aureus bloodstream
19 infection in osteo in particular, a lot of it probably
20 has to do with what they're encountering in terms of
21 the regulatory pieces. The PENS example is one. The
22 timing of follow-up for osteo patients would be
23 another.

1 In fact, there was a beautiful idea, I
2 think Barry Eisenstein proposed it maybe ten years
3 ago. Still one of the coolest ideas I've ever heard
4 in terms of trial design about using surrogate marker
5 for osteo at the time of a two-step revision whereby
6 if you found culture or acute inflammation, which
7 would be actionable items clinically, that you could
8 use that as your endpoint.

9 So, you know, finding means whereby
10 this would be, again, get your skin, get your
11 complicated UTI. But then for that second study, you
12 find some means of flexibility whereby some of these
13 restraints are revisited in a way that still achieves
14 the goals of the FDA, but at the same time makes --
15 the study is doable. And I'll stop there.

16 HELEN BADER: All right. I think we'll
17 move on to question two in the interest of time.

18 DAVID MELNICK: Could I just add one
19 thing?

20 HELEN BADER: Sure.

21 DAVID MELNICK: You know, this is a
22 perfect segue to the idea of networks and platform
23 trials. You know, if we used a core indicator, you

1 know, sort of a market entry indication to establish
2 safety and demonstrate the performance of a drug, if
3 there were standing networks dealing with skeletal
4 infections or bloodstream infections or HABP/VABP or
5 resistant pathogens, one could then feed the new
6 agents into those master protocols. And in fact you
7 find that in a HABP/VABP study, somebody's got
8 Acinetobacter, they go in one direction. They have
9 CRE, they go in another direction. They have
10 (indiscernible), they go in another direction.

11 So to me that's one way where we could
12 amortize the cost of developing this downstream data
13 across a number of products and hopefully have some
14 central support to do it.

15 HELEN BADER: Okay. So question two.
16 As there are some approved therapies to treat CRE
17 infections and others in development, future
18 noninferiority trials could enrich such organisms.
19 For a future new agent targeting gram-negative
20 pathogens that retains activity in the presence of
21 certain resistance mechanisms, what should the design
22 of clinical trials look like to get interpretable
23 data? Please comment on the choice of comparator, the

1 patient population, and enrichment strategies,
2 something that some of us have talked about before.

3 JOHN REX: Reading this again, I'm
4 thinking here about the notion that now that -- we now
5 actually have drugs that treat CRE. It's not every
6 one of them, but at least some of the time we do. And
7 so if I now did a randomized study of new drug versus
8 Zemdri, new drug versus (indiscernible), I could
9 reasonably go to a place that has a lot of CRE and say
10 rock on. You know? Sign them up. And if we happen
11 to get 10 or 15 percent CRE, then great. That would
12 be a wonderful thing.

13 I think I had not processed this
14 question fully until I was just reading this slide
15 again just now. So is that really what you guys were
16 thinking as you wrote that question down?

17 SUMATHI NAMBIAR: So I think the
18 lookback may be four or five years ago when we didn't
19 have these products that were CRE active agents. We
20 had to do the kinds of trials that were done just
21 enriching -- just in CRE with CRE patients. But now
22 you have two or three therapies, there's more in the
23 pipeline. So hopefully they will be available as

1 well.

2 Then it really is like the MRSA
3 paradigm. Now in skin trials or bacteremia trials,
4 you can enroll in MSSA and MRSA because you have an
5 appropriate comparator. So then that really raises
6 the question, do we need one of these standalone CRE
7 studies which we've heard are difficult to do and then
8 difficult to interpret and really cannot get into
9 label? Are you then better off doing a noninferiority
10 trial for your standard indication, use the
11 appropriate comparator such that these trials can
12 actually have patients with CRE infections and they
13 will be described in labeling? That would make our
14 lives a lot easier. So I just wanted to bring that up
15 for discussion. Because things have changed, right?
16 The discussion we had five, six years ago was not --
17 is not where we are today. And so I just wanted to
18 get everybody's thoughts on that.

19 I mean, we've had some of these
20 discussions with some of you individually when you
21 have come to meet with us, at least some of the
22 practical challenges we've heard is these comparators
23 are certainly a lot more expensive, so it adds cost.

1 It's probably not available in a lot of the counties
2 that are enrolling. But I think a lot of those could
3 potentially try to overcome if the net gain is that
4 then you don't have to do the CRE study, which costs a
5 lot of money and really doesn't seem to be very
6 helpful. So that's the background for this question.

7 HELEN BADER: Okay. So it looks like
8 we have Nick, Ryan, and then Roger. So, Ryan.

9 RYAN CIRZ: I think this question was
10 sort of the genesis of the earlier comments that I
11 made. And Aaron rightfully corrected -- you know,
12 sort of trying to simplify. When we went to Phase I
13 with plazomicin, I think we looked and said, oh, it
14 would be hard to get enough VSPLs in a trial. But it
15 took us a long time, and it's actually really easy.
16 And I think we'll get there with CRE, unfortunately.
17 That's why we're still working in the space. Maybe it
18 will be 10 or 20 percent. But it's still this
19 interesting logic trap.

20 And so again, just to use an example
21 because they're different, and to use it on an equal
22 playing field, let's just say complicated UTI
23 (indiscernible) and Zemdri. Right? If both agents

1 are active, you could potentially show that they're
2 both noninferior to one another. If the CRE has a
3 (indiscernible), it won't work in (indiscernible), and
4 you won't be able to show that because you can't
5 enroll. And if you have a Class B metallo,
6 (indiscernible) won't work and plaso might. But you
7 can't show that because you can't enroll.

8 And so the idea of showing plaso as NI
9 to (indiscernible) isn't any different to me than
10 showing plaso is NI to meropenem on ESBL. It's just a
11 genetic change. So we could do it, and I think it
12 will happen by mass action, but I don't understand the
13 scientific point of worrying about doing it.

14 AARON DANE: I guess my question was on
15 that. It does sound like a good idea. But what you
16 would be able to say about CRE after a study like
17 that. So are you in a better position than now with
18 the situation of a study where you can say anything on
19 the label, would you actually be able to make some
20 statement about CRE in a noninferiority study?

21 SUMATHI NAMBIAR: So why -- I mean, we
22 could say something about CRE, right? They were part
23 of the study. It would be like how we describe

1 microbiology data currently in the label.

2 AARON DANE: Yeah. I suppose it's this
3 disconnect between do a properly compatible study and
4 can't say anything about it whereas if you do it as
5 part of a noninferiority study, you can. But I guess
6 if that's possible, it feels like it an option.

7 SUMATHI NAMBIAR: Right. As long as
8 your comparator is -- I mean, if you're going after
9 NDMs, certainly you cannot have (indiscernible) or any
10 of the currently-available as your appropriate
11 comparator. But if you've chosen an appropriate
12 comparator, could you not enrich and include patients
13 with CRE in the trial?

14 AARON DANE: I think so, yeah. I think
15 it wasn't so much the design; it was more what you're
16 going to be able to say about CRE afterwards given
17 you're only going to have the same number of patients
18 as they had at the moment. That was all.

19 SUMATHI NAMBIAR: They will be part of
20 the overall population, and that's all you can
21 describe.

22 HELEN BADER: It would be like MRSA in
23 a skin study or pseudomonas in a HABP/VABP study.

1 ROGER LEWIS: So this is actually --
2 I'm stealing the microphone from you, because this is
3 exactly what I was going to address. I think your
4 answer is actually potentially a bit concerning.

5 So when we enroll patients with a
6 variety of pathogens, and we simply list all the
7 pathogens that were included in the study, what we are
8 implying is that we think they are all exchangeable.
9 We have no reason to believe that one pathogen is more
10 or less likely to respond to either the comparator,
11 the test, or at least the delta is expected to be the
12 same. And that may be true in many cases. It's
13 probably not true if you've specifically enriched for
14 CRE. Just the way you folks talk about CRE -- I'm not
15 an ID person. The way your body changes when you talk
16 about CRE, okay? You clearly think that organism is
17 different than the other organisms. Okay? So that
18 violates the assumption that you should just think
19 about them the same.

20 So I think the prior question was
21 really good in the sense that the amount of enrichment
22 for CRE and the fact that you get some representation
23 -- and I don't know in your mind if you're thinking 20

1 percent or 30 percent. It's not -- that doesn't mean
2 you can just assume they're all the same suddenly
3 because you had enough of them. There has to be some
4 sort of quantification of whether you have enough
5 information to justify lumping them all together, or
6 you have to have enough that you can separate out and
7 make some sort of estimate of whether there is
8 evidence of heterogeneity of treatment effect with a
9 confidence bound around that estimate of the
10 heterogeneity.

11 And so the way the question is worded,
12 it sort of implies that, well, if we have some magic,
13 enough fraction of CRE, because it's like the other
14 things we throw in, isn't that good enough? It may
15 fit tradition, I'm not sure it fits inferential rigor.

16 HELEN BADER: Good point. Rienk?

17 RIENK PYPSTRA: I would like to respond
18 to that. You're absolutely right if you can only look
19 at clinical results. But we have the advantage of
20 being in infectious diseases. We have the pathogens
21 separate, we have the pathogens in animal models. We
22 have a whole body of evidence. And what I hear from
23 Ryan, and I fully agree with you, is we need to look

1 at the whole science, at the whole data package. And
2 there is no reason to believe that a CRE is going to
3 behave differently than the completely sensitive
4 E.coli if you are confronted with a drug that acts
5 through a different mechanism of action. And that is
6 the crux. And so why would you have to go through all
7 the effort in demonstrating it if you can make the
8 argument very logically?

9 RYAN LEWIS: Right. And I certainly
10 didn't want to debate the relative validity or
11 assuredness that is available from preclinical and
12 ancillary studies or laboratory evaluations of
13 clinical isolates. But if we believe we need new
14 randomized clinical data that includes CRE, we can't
15 at the same time say we don't. If you do need it, you
16 should know why you're collecting it and what
17 threshold of evidence you need from it. If you don't
18 need it because, sorry, Ryan is correct and he can
19 predict these things, that's great, too. But we
20 shouldn't be internally inconsistent in our logic.

21 HELEN BADER: Ryan?

22 RYAN CIRZ: Maybe a useful study or a
23 publication from the community would be something --

1 you know, it's not that I'm not openminded that a
2 change in a genetic sequence of an enzyme that
3 degrades a beta lactam could completely change the
4 pathology of the organism. I just wouldn't start
5 there as the first principle. But if there was a
6 study that suggested that, it would be really
7 interesting, and maybe it could be true. But why
8 start with that as the base case, which
9 overcomplicates everything for everybody. And I've
10 been struggling with sort of my history of why do we
11 think it's different. And then you all are much
12 better at figuring out co-variants, things like, well,
13 if you have CRE, maybe you've been on six rounds of
14 antibiotics because you're immunosuppressed, or all
15 these other things that scare us more that are just
16 co-associations. But one that strikes me a lot is
17 kind of the traumatic experience in the narrow necks
18 before the new agents.

19 And one of the tragedies of the KARE
20 study as sort of an arcadian historian was when we
21 showed up in Greece -- remember, this was seven years
22 ago -- people told us colistin isn't that bad and
23 these patients are just sicker. You know? The

1 colistin is fine; it's these patients that have CRE,
2 they're just sicker than everyone else. And I think
3 that impacted the potential of the treatment effect.
4 And honestly if we had known the number of patients
5 that it might have taken to show that, we probably
6 would have kept the study going, but we didn't. We
7 thought it was going to take another 300 patients I
8 think was the estimate.

9 And so part of my bias goes back to
10 that fear from maybe a poor-performing drug for a
11 period of time, putting this idea in our head that
12 this organism is somehow different. Completely open-
13 minded that it is. I just haven't seen any evidence
14 that it is.

15 HELEN BADER: Manos?

16 MANOS PERROS: I'm delighted to hear so
17 much support for taking in the totality of the
18 scientific evidence. I'd like to make a slightly
19 different point, which, apologies, might be obvious.
20 But by the time you have a pathogen or indication for
21 which there are a number of adequate treatments, the
22 medical need is lower. So though that question is
23 important, it's not as important as the question of

1 can you do that for drug-resistant pathogens.

2 HELEN BADER: Sara?

3 SARA COSGROVE: I think there are a
4 bunch -- I mean, CRE means carbapenem-resistant
5 Enterobacteriaceae. So obviously there are not all
6 the same. They have different resistance mechanisms.
7 So some are enzyme producers and some have other non-
8 enzymatic mechanisms. So I do think you actually have
9 to think a little bit about what mechanisms you're
10 interested in when you think about that question.

11 But I do think that something that
12 keeps nagging at me is that there is no patient that I
13 have treated with any of the new agents that is
14 anything like the patients that were in the clinical
15 studies. And that's really the problem for me right
16 now.

17 So can I feel confident that these
18 drugs are safe in the patients that I am using them in
19 who have -- I mean, I can't even succinctly explain
20 the problems of the patients that I have been using
21 them in. And that does worry me a little bit. So we
22 can enrich for CRE, but if it's still for complicated
23 UTI, it's still not going to have the patients I'm

1 using the drugs in in the study.

2 NICK KARTSONIS: If I could make a
3 comment to that. I bet you the resistant infection
4 studies are more like the patients that you treat,
5 right? You know, the KARE studies and the Restoria
6 studies, they are very heterogeneous and they're very
7 difficult to interpret from a statistical standpoint,
8 but they probably are more real-life in that regard.

9 RYAN CIRZ: And that's the exact
10 genesis of why earlier I was trying to separate the
11 resistance piece. It's just biochemistry. I get it.
12 The severe physiology condition is a whole different
13 ballgame. Although it is something that if you
14 separate the two suddenly and say it's not the CRE I
15 care about, it's the severity of the condition, then
16 you can start to think about different ways to get
17 evidence to give you information on performance in
18 those settings. Putting them together is what gets us
19 into the we have to run this \$50 million, ten-year
20 trial.

21 SUMATHI NAMBIAR: So should the
22 approach then really be trying to enroll patients with
23 comorbidities and these sicker patients in the trials

1 that we are currently doing? Should that be the focus
2 moving forward? And that's something we've always
3 encouraged, but I think there are practical
4 difficulties in enrolling them in these trials. So
5 that's the tension here.

6 Certainly the resistance phenotype
7 comes usually with the host, right? It's really the
8 host that matters at the end of the day. And whether
9 or not it works against a resistant phenotype XYZ
10 really is not that important. Because if it's
11 susceptible to the test drug, a point that you made
12 earlier, that's what we really need. It doesn't
13 matter what else it's resistant to or not resistant
14 to.

15 But if you're really looking for the
16 most sick patients, because those are the kind of
17 patients who are being treated, then maybe that's what
18 we need to focus on. And how can we get those kinds
19 of patients and what are the limitations in being able
20 to enroll such patients? I mean, it's not just
21 studying the pharmacokinetics and renal-hepatic
22 impairment; they're only one part of it. But what
23 else do we think we should focus on moving forward?

1 JOHN REX: Isn't that in effect what
2 we've now seen two or three drugs do? They have run a
3 -- pick an indication trial. And then they have in
4 parallel typically at the same study sites -- it could
5 almost have been one study. Okay? Here's Study X,
6 here's your study. It's got two arms. Arm A, cUTI,
7 kind of ordinary cUTI. Arm B, whatever. And you're
8 randomizing and it's a stratum. Arm A has one
9 randomization and Arm B has another randomization.
10 And two-and-a-half years later you -- actually, 18
11 months later, your cUTI study is done, 400 patients
12 there. And you've got 82 patients in Arm B, and you
13 analyze it. And that's what you've got. And I don't
14 know how to do better. I mean, honest to Pete. What
15 do we do that is consistently and predictably better
16 than that? And I can't really run it for five years.
17 I need to get to done. I need to have made a certain
18 -- you know, think about it. All the CMC stuff. How
19 much drug product do I have to have had available to
20 run this study and to be at these sites? And then
21 there's the plant I've got to -- I can only have so
22 much stuff available at the time I do the Phase III
23 study. It's not an infinite universe. And I'm going

1 to run out of money because I've just now spent \$70
2 million, and that's the last I'm going to get out of
3 anybody, ever.

4 So to me, I'm really -- you know, Roger
5 has brought in this notion of why aren't we more
6 willing to borrow data across body sites and
7 indications? And we would like better data and we
8 would like a pony, too. You know, I'd really like to
9 -- but a pair of sandals is better than walking
10 barefoot. And I think that's the theme that we're
11 getting at here, is that the pair of sandals is better
12 than walking barefoot. And yes, I'd prefer to ride,
13 but I'll walk if I have to; just give me the sandals.

14 HELEN BADER: So is there any
15 inferential question we can ask?

16 JOHN REX: No. It is -- and it's going
17 to -- we're thinking here about what -- because the
18 confidence (indiscernible) are going to be too broad.
19 Dan's head is going to explode. And as it should.
20 We're not saying that it is of the quality that we
21 would like, but it's the quality we're stuck with
22 unless we want nothing. I mean, your choice is sort
23 of between a sin of omission and a sin of commission,

1 if you will. I mean, is there another choice?

2 AARON DANE: Well, I think the reason
3 it's worth thinking about that is because this
4 question, which is specific to CRE, may work. But
5 that relies on there being three therapies available.
6 So when you get to the next pathogen that hasn't got
7 that, you're stuck again. And so it feels like we
8 need a way of knowing how we're going to do this for
9 both situations, both when there is a comparator there
10 and when there isn't. Otherwise, we're going to keep
11 going round the same cycle every few years.

12 HELEN BADER: Point. Nick? Left over?
13 Okay. Lindsey? Sorry.

14 LINDSEY BADEN: No, I just think John's
15 decoupling too many issues at once. Because I think
16 Ryan's point about decoupling the microbial resistance
17 determinant, because there is a strong logic, one
18 could imagine really pushing that logic to make sure
19 it makes sense. I'm still not convinced that the same
20 antibiotic is going to work the same in CNS and in
21 lung and in prostate without more evidence that it
22 behaves that way. But I could imagine a study that
23 looks at pneumonia and doesn't only target the

1 incredibly resistant organism. Because that's the
2 decoupling that might make these trials more
3 approachable. And then one has to believe that
4 whether or not the genetic, not the phenotypic
5 resistance determinant being present or absent is not
6 the critical element.

7 So I think that decoupling has the
8 potential to reframe some of these trials. It's a
9 bridge that is even further if we no longer need to
10 look at the different body sites for in vivo activity
11 and just assume in vitro activity.

12 JOHN REX: So I think that the
13 preclinical community has convincingly proven that if
14 you have two isolates with the same MIC to drug X but
15 different MICs for drug Y, drug X will work the same
16 way on both of them. The drug on the bug in a plastic
17 dish or in a mouse will work the same way. So you
18 have two isolates. They have identical MICs for drug
19 X and wildly different for drug Y. Drug X's effect
20 will not be impaired by the presence or absence of
21 activity for drug Y in the test tube. And just
22 provided the drug concentration is adequate -- I mean,
23 Paul Ambrose has done that over and over and over

1 again. The MIC tells you -- but the two patients who
2 are infected -- that's where you're going. The two
3 patients that have those two isolates, they might have
4 different clinical responses because the patients
5 themselves, as Ryan said, having the wildly resistant
6 organism is a marker of your comorbidities or your
7 other illnesses.

8 LINDSEY BADEN: No, not necessarily. I
9 was agreeing that it's worth really thinking about the
10 decoupling for presence or absence of genetic
11 resistant X. Decouple that and say maybe that isn't
12 the in vivo element that is critical to the study.
13 The in vivo element that's critical to study is new
14 drug works in pneumonia in critically ill patients the
15 same as standard drug for the isolate that isn't
16 necessarily the resistant genotype.

17 And because I do worry that critically
18 ill folks have different physiology and I do worry
19 that drugs and sites don't always behave the we
20 predict. But the genotypic issue the data are --
21 there's a strong rationale to be able to overcome the
22 genotypic concern, which is I think what Ryan was
23 getting at as the two parameters that make it

1 impossible. You need critically ill plus you need
2 genotypic proof in order to study it. And that
3 becomes undoable. But if you only need critically ill
4 syndrome and the right organism, then you might be
5 able to study it using the other data to bridge the
6 genotypic issue.

7 And part of the reason I think that's
8 so important is that ultimately we want
9 countermeasures for bugs that are rare, because those
10 are the ones I'm most concerned about. I'm most
11 concerned -- you know, 1990 we didn't care about VRE
12 because it didn't exist. I'm worried about the bug
13 that doesn't exist or does exist in a limited place
14 that is about to be amplified and expand globally.
15 And in order for us to have data on how to treat that,
16 by definition we can't study it in vivo because it
17 doesn't exist in large enough numbers.

18 So these other data are able to be
19 strong enough for us to say we think it should work.
20 And then it would need to be confirmed when one can.
21 But is there a regulatory path to allow that? And I
22 think that's part of what Ryan is suggesting. And,
23 you know, there's strong rationale for that.

1 HELEN BADER: Okay, thanks. So we'll
2 do David, Roger, Ryan.

3 DAVID MELNICK: It seems to me we're
4 cycling back to the current starting point, which is
5 that sponsors have struggled mightily to deliver these
6 resistant pathogen studies unsuccessfully. We've
7 tried to enrich our trials for resistant pathogens,
8 we've tried to deliver cross-indication RP studies,
9 and we've failed. Maybe the one exception was the
10 CAZ-AVI resistant pathogen study, which worked only
11 because the resistant pathogens had become very, very
12 prevalent.

13 So, you know, I think this idea that
14 somehow we can drive our current trial designs to
15 deliver data that's going to be adequate for
16 inferential testing, not going to happen. And it's
17 certainly not going to happen in this commercial
18 environment.

19 So we need -- I think we need to look
20 at alternatives, whether they're pragmatic trials or
21 making use of some other data source that comes in
22 after the fact to provide evidence to support the
23 utility of these new compounds outside of their core

1 entry indication. Otherwise, we're never going to
2 win.

3 ROGER LEWIS: So I think we're
4 challenged when we have a single threshold for what an
5 inferential criteria is. Oh, sorry. I think we're
6 challenged when we have a single threshold for
7 inferential success. And the conversations have been
8 illuminated by lots of examples of ancillary
9 information or augmenting information that should
10 appropriately change that threshold.

11 So it appears that there are situations
12 in which folks might reasonably think you don't need
13 new data because you know so much about the organism
14 and the site and the penetration, the MIC and the PK
15 that you just -- you can put all the organisms
16 together and write that on the label.

17 There are settings in which the
18 diseases are different enough that you wouldn't want
19 to simply assume they behave all the same; meningitis,
20 osteomyelitis, settings of foreign bodies. But if you
21 started to have some supporting information and the
22 information supported the idea that the treatment
23 effect was homogeneous across multiple diseases, that

1 would meet a reasonable inferential threshold. And
2 there's a different setting when the disease is so
3 different or the organism is so poorly understood or
4 new or we can't even pronounce it as a panel, that you
5 really need standalone information.

6 And I think the thing that we need to
7 struggle with is how to have informed,
8 multidisciplinary conversations about how to adjust
9 the threshold for considering the inference strong
10 enough to support recommendations to clinicians that's
11 good enough for the right situation. And again, I
12 think that if we stick into sort of an all-or-none
13 where it's either the standard threshold which we can
14 never meet, so we're going to throw up our hands and
15 give people no guidance and collect no data, that
16 seems like a really sad conclusion from a group with
17 the intent of improving public health and the
18 information that guides medical care.

19 RYAN CIRZ: And just to go I guess one
20 step deeper on kind of demystifying logically why
21 would a drug work in one site and not another, I think
22 there's plenty of reasons. But we never quite sit
23 down and list them and then say how do we start

1 knocking these out, that that's not true. We just
2 sort of say you have to show it directly. But, you
3 know, the lung lining fluid is like the number-one
4 example, right? And I can only think of one where
5 there was a really unique situation where the drug was
6 inactive in that compartment. In almost every other
7 case, it's just a matter of, especially in the gram-
8 negative drugs, they're all incredibly water soluble.
9 They have to pass through interstitial barriers, it
10 takes time, and the drug's clearing out of the kidney
11 while it's dialyzing. It's all the same principles
12 affecting every polar drug. And there are ways to
13 study this and get our head around it without a
14 complete trial and try to prove it. So two potential
15 cases. There's less drug there than there is in other
16 sites, or the drug works differently when it gets
17 there than in other sites. And I never see a real
18 logical sort of walking through that. Just sort of,
19 like, show me, because I can't believe it unless I see
20 it. But I think there's some ground to begin.
21 They're just leveraging other reference points showing
22 that honestly most of the gram-negative drugs -- I'm
23 guessing if you do a study internally controlled,

1 because some of the methodology is so dicey for
2 measuring pulmonary levels, you'll find out they're
3 kind of all the same because it's physics; it's just
4 how the body operates. And if we can show that, then
5 we can show the physiology for one drug predicts the
6 other. Because these patients that are crashing, it's
7 fluid volume, it -- you know, obviously we're pushing
8 extra water in. The drug dissolves in water. We
9 could probably translate a lot of results from
10 different drugs to each other as long as they share
11 similar physical properties.

12 So the one thing I see lacking as a
13 scientist is even if in the end we still have to do
14 the exact same trial, it would be really refreshing to
15 hear us talk about here's the exact physiological
16 thing we're concerned about and why we need to go show
17 it just to make it feel more real.

18 HELEN BADER: Aaron?

19 AARON DANE: I was just going to echo
20 what Roger was saying. So what I'm going to try and
21 talk about tomorrow is this idea of these magical
22 criteria we have for inferential statistics. If we
23 know we can only get 50 or 100 patients, we know the

1 setting. Can we shift some of those? Can we do that
2 in an informed way so we don't just blindly do that?
3 But it feels like that's a way of rather than saying,
4 well, if we can't do 200 or 300 patients, then there's
5 no point in doing anything, which seems to be where we
6 are at the moment.

7 And so understand the risks, understand
8 the consequences of that, but certainly look at it in
9 that way and try and have a bit more of a broader view
10 on what we might be able to do with the numbers we can
11 get to.

12 HELEN BADER: Okay, we'll have a quite
13 note for question number three, which is some feasible
14 approaches to updating treatment guidelines more
15 frequently. Anybody want to have a stab at that? I'm
16 between everyone's dinner time. Dr. Sears, you've
17 been nominated.

18 CYNTHIA SEARS: Well, I tried to
19 present a structure in which we're considering -- and
20 I don't know if silence is, you know, okay, give that
21 a try or if there's other comments.

22 It is a complicated business and it is
23 definitely hard to rally all the forces needed to do

1 something like this. You can all think about it. My
2 email is readily available. And just send me any
3 thoughts. Because we are there. So if you want to
4 have some input, now is the moment.

5 HELEN BADER: Great. Kevin?

6 KEVIN OUTTERSON: So I was just
7 wondering, what do you think it costs? What is the
8 budget for IDSA? And then the second piece of that
9 is, you know, if you had a larger budget and you could
10 have a full-time person, a post-doc that, you know,
11 was on the budget for -- is there a way to increase
12 the quality and speed?

13 CYNTHIA SEARS: You know, I don't know
14 what it costs. I know that budgets are under
15 development. The IDSA budget is approved by the
16 Executive Committee and the Board in December. That's
17 flexible. You know, we're not static at all.

18 As just a comparison, the HCV guidance
19 was a \$400,000 project. And yes, more money always --
20 you know, to do this at the pace that I think I sense
21 the group would like, you know, takes really a big
22 investment. And then to keep it going, to keep people
23 -- we need a group of really engaged people who are

1 ready to move quickly. And, you know, that's
2 complicated, trying to figure out exactly how to put
3 that together to draw on those resources at the moment
4 you need them. But, you know, money always helps.

5 KEVIN OUTTERSON: So just to put the
6 question back. So you said \$400,000 for the hep C.
7 So would it be fair to say that a million dollars a
8 year for the next five years, you know, if that money
9 came from someplace else, that that would really just
10 transform your ability to do guidance?

11 CYNTHIA SEARS: I think the short
12 answer is yes.

13 KEVIN OUTTERSON: And Amanda had a
14 little proviso.

15 AMANDA JEZEK: I was just doing to add
16 it depends on if that money comes with any strings.

17 KEVIN OUTTERSON: It could not come
18 from any company at all.

19 AMANDA JEZEK: Right. Well, or if it
20 came from a federal agency, what would be the
21 requirements around that. If we wound up having to
22 invest the majority of those funds and simply
23 reporting back to a federal agency and not actually

1 developing a guideline. Just as an example, not that
2 that would ever happen.

3 KEVIN OUTTERSON: That's never happened
4 in the history of...

5 HELEN BADER: Okay. Aaron, did you
6 want -- okay.

7 MANOS PERROS: Thank you. It's also a
8 question more than a comment. Guidelines are
9 important, but well-informed infectious disease
10 physicians can put two and two together and from the
11 published data and molecular data they can often make
12 the right choice as infectious disease pharmacists as
13 well.

14 From a company perspective, the
15 constituency that we do influence goes well beyond
16 that. Guidelines, for instance, influence hospital
17 administrators, so payors (indiscernible) as an
18 example.

19 HELEN BADER: Great. All right, well,
20 I'm very aware of the hour and just want to say thank
21 you to everybody. I think the talks today were
22 outstanding, as was the discussion. Really appreciate
23 everyone's really respectful, engaged, spirited

1 dialogue.

2 I just want to remind everyone to take
3 all of their things. Just leave your tent cards if
4 you would, panelists, but take all your paperwork and
5 everything. Because I think we may even be in a
6 different room in the morning. Same time tomorrow.
7 Registration starts at 7:30. The meeting starts
8 promptly at 8:30. And we will see you soon. Thank
9 you.

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I, MICHAEL FARKAS, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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