

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH
3
4

5 ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC)
6
7

8 Thursday, December 4, 2014

9 8:30 a.m. to 4:24 p.m.
10
11
12
13
14
15

16 The Marriott Inn and Conference Center
17 University of Maryland University College (UMUC)
18 3501 University Boulevard
19 East Hyattsville, Maryland
20
21
22

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and Consultant
Management

Office of Executive Programs, CDER, FDA

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

Ellen M. Andrews, PhD

(Consumer Representative)

Executive Director

CT Health Policy Project

New Haven, CT

Lindsay R. Baden, MD

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Boston, MA

1 **Alan J. Magill, MD**

2 Director, Malaria

3 Bill and Melinda Gates Foundation

4 Seattle, WA

5
6 **Luis Z. Ostrosky, MD**

7 Professor of Medicine and Epidemiology

8 Division of Infectious Diseases

9 University of Texas Medical School at Houston

10 Houston, TX

11
12 **CAPT Monica E. Parise, MD**

13 ***(Chairperson)***

14 Chief, Parasitic Diseases Branch

15 Division of Parasitic Diseases and Malaria

16 Center for Global Health

17 Centers for Disease Control and Prevention (CDC)

18 Atlanta, GA

1 **Marc H. Scheetz, PharmD, MSc**

2 Associate Professor of Pharmacy Practice

3 Midwestern University Chicago College of Pharmacy

4 Downers Grove, IL

6 **ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBER**

7 **(Non-Voting)**

8 **Patrick Robinson, MD**

9 **(Industry Representative)**

10 Deputy International Therapeutic Area Head-Virology

11 Boehringer-Ingelheim

12 Ridgefield, CT

14 **TEMPORARY MEMBERS (Voting)**

15 **Diane M. Cappelletty, PharmD**

16 Associate Professor of Pharmacy Practice

17 The University of Toledo College of Pharmacy

18 Toledo, OH

1 **John P. Dekker, MD, PhD**

2 Co-Director, Bacteriology, Parasitology & Molecular
3 Epidemiology

4 Department of Laboratory Medicine

5 Clinical Center

6 National Institutes of Health (NIH)

7 Bethesda, MD

8
9 **Dean Follmann, PhD**

10 Assistant Director for Biostatistics

11 Chief Biostatistics Research Branch

12 National Institute of Allergy and Infectious
13 Diseases (NIAID)

14 NIH Bethesda, MD

15
16 **Nicole Mayer Hamblett, PhD**

17 Director, Core for Biomedical Statistics

18 Seattle Children's Hospital

19 Associate Professor, Department of Pediatrics and
20 Biostatistics

21 University of Washington

22 Seattle, WA

1 Debra McCall, BS, MBA

2 *(Patient Representative)*

3 Murrieta, CA

5 Thomas A. Moore, MD, FACP, FIDSA

6 Clinical Professor

7 Department of Medicine

8 University of Kansas School of Medicine

9 Wichita Campus

10 ID Consultants of Kansas

11 Wichita, KS

13 L. Barth Reller, MD

14 Professor of Medicine and Pathology

15 Division of Infectious Diseases

16 Duke University School of Medicine

17 Durham, NC

1 **Paul C. Schreckenberger, PhD, D(ABMM), F(AAM)**

2 Director Clinical Microbiology Lab

3 Acting Director Molecular Pathology Lab

4 Loyola University Medical Center

5 Maywood, IL

6
7 **Paige E. Waterman, MD**

8 LTC, MC

9 Pillar Chief, Antimicrobial Resistance

10 Global Emerging Infections Surveillance and

11 Response System

12 Deputy Director, Multidrug-resistant Organism

13 Repository & Surveillance Network

14 The Walter Reed Army Institute of Research

15 Silver Spring, MD

16
17 **FDA PARTICIPANTS (Non-Voting)**

18 **Edward Cox, MD, MPH**

19 Director

20 Office of Antimicrobial Products (OAP)

21 Office of New Drugs (OND), CDER, FDA

1 **Katherine Laessig, MD**

2 Deputy Director

3 DAIP, OAP, OND, CDER, FDA

4
5 **Lisa LaVange, PhD**

6 Director

7 Office of Biostatistics

8 Office of Translational Sciences, CDER, FDA

9
10 **Sumati Nambiar, MD, MPH**

11 Director

12 Division of Anti-Infective Products (DAIP)

13 OAP, OND, CDER, FDA

14
15 **Joseph Toerner, MD, MPH**

16 Acting Deputy Director for Safety

17 DAIP, OAP, OND, CDER, FDA

| | | |
|----|---|------|
| 1 | C O N T E N T S | |
| 2 | AGENDA ITEM | PAGE |
| 3 | Call to Order and Introduction of Committee | |
| 4 | Monica Parise, MD | 12 |
| 5 | Conflict of Interest Statement | |
| 6 | Moon Hee Choi, PharmD | 15 |
| 7 | FDA Presentations | |
| 8 | FDA Introductory Remarks | |
| 9 | Edward Cox, MD, MPH | 19 |
| 10 | History of Antibacterial Drug Development | |
| 11 | Katherine Laessig, MD | 28 |
| 12 | Clinical Development Issues for | |
| 13 | Antibacterial Drugs for Patients with | |
| 14 | Unmet Medical Need for the Treatment of | |
| 15 | Serious Bacterial Diseases | |
| 16 | Joseph Toerner, MD, MPH | 39 |
| 17 | Statistical Considerations in Evaluating | |
| 18 | Products for Unmet Medical Need | |
| 19 | Daniel Rubin, PhD | 47 |
| 20 | Trial Considerations for Unmet Need | |
| 21 | Sumati Nambiar, MD, MPH | 59 |
| 22 | Clarifying Questions | |

| | | |
|----|--|------|
| 1 | C O N T E N T S (continued) | |
| 2 | AGENDA ITEM | PAGE |
| 3 | Presentations by Professional Organizations | |
| 4 | American Thoracic Society | |
| 5 | Clinician/Clinical Investigators's | |
| 6 | Perspective | |
| 7 | Richard Wunderink, MD | 109 |
| 8 | Infectious Diseases Society of America and | |
| 9 | Pediatric Infectious Diseases Society | |
| 10 | (IDSA and PIDS) | |
| 11 | Antibiotic Development for Patients with | |
| 12 | Serious Infections and Unmet Need | |
| 13 | Jason Newland, MD, MEd, FPIDS | 123 |
| 14 | Biotechnology Industry Organization (BIO) | |
| 15 | Clinical Development Issues with | |
| 16 | Antibacterial Drugs for Unmet Medical | |
| 17 | Needs - Patients, Pathogens, and | |
| 18 | Streamlined Drug Development | |
| 19 | Jeff Alder, PhD | 140 |
| 20 | Balancing Expectations | |
| 21 | Dataset Size vs. Feasibility | |
| 22 | John Rex, MD, FACP | 152 |

| | | |
|----|---|------|
| 1 | C O N T E N T S (continued) | |
| 2 | AGENDA ITEM | PAGE |
| 3 | Clarifying Questions | 167 |
| 4 | Open Public Hearing | 183 |
| 5 | Questions to the Committee and Discussion | 241 |
| 6 | Adjournment | 338 |
| 7 | | |
| 8 | | |
| 9 | | |
| 10 | | |
| 11 | | |
| 12 | | |
| 13 | | |
| 14 | | |
| 15 | | |
| 16 | | |
| 17 | | |
| 18 | | |
| 19 | | |
| 20 | | |
| 21 | | |
| 22 | | |

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

CAPT PARISE: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Stephanie Yao. If you are here, please stand.

The first thing we're going to do is to go around the table for the members, consultants, and the FDA panel and all to state your name into the record.

DR. ROBINSON: Patrick Robinson with Boehringer-Ingelheim. I'm the industry representative.

DR. HAMBLETT: Nicole Hamblett, University of Washington.

DR. SCHRECKENBERGER: I'm Paul Schreckenberger, Loyola University, Chicago.

MS. MCCALL: Debra McCall, patient

1 representative.

2 DR. ANDREWS: Ellen Andrews. I'm the
3 consumer representative.

4 DR. SCHEETZ: Marc Scheetz, Midwestern
5 University and Northwestern Medicine.

6 DR. WATERMAN: Paige Waterman, Department of
7 Defense.

8 DR. RELLER: Barth Reller, Duke University.

9 DR. DEKKER: John Dekker, NIH Medical
10 Center.

11 CAPT PARISE: Monica Parise, Centers for
12 Disease Control.

13 DR. CHOI: Moon Hee Choi, designated federal
14 officer.

15 DR. CAPPELLETY: Diane Cappelletty,
16 University of Toledo.

17 DR. MAGILL: Alan Magill, Bill and Melinda
18 Gates Foundation.

19 DR. OSTROSKY: Luis Ostrosky, UT at Houston
20 Medical School.

21 DR. MOORE: Dr. Tom Moore, University of
22 Kansas in Wichita.

1 DR. BADEN: Lindsay Baden, Brigham and
2 Women's Hospital and Harvard Medical School.

3 DR. LAVANGE: Lisa LaVange, director, Office
4 of Biostatistics, CDER, FDA.

5 DR. TOERNER: Joe Toerner, acting deputy
6 director for safety in the Division of
7 Anti-Infective Products, FDA.

8 DR. LAESSIG: Katy Laessig, deputy director
9 of Division of Anti-Infective Products, CDER, FDA.

10 DR. NAMBIAR: Sumati Nambiar, director of
11 Division of Anti-Infective Products, CDER, FDA.

12 DR. COX: Ed Cox, director of Office of
13 Antimicrobial Products, CDER, FDA.

14 CAPT PARISE: For topics such as those being
15 discussed at today's meeting, there are often a
16 variety of opinions. Some of them are quite
17 strongly held. Our goal is that today's meeting
18 will be a fair and open forum for discussion of
19 these issues and that individuals can express their
20 views without interruption. Thus, as a gentle
21 reminder, individuals will be allowed to speak into
22 the record only if recognized by the chairperson.

1 In the spirit of the Federal Advisory
2 Committee Act and the Government in the Sunshine
3 Act, we ask that advisory committee members take
4 care that their conversations about the topics at
5 hand take place in the open forum of the meeting.

6 We are aware that members of the media are
7 anxious to speak with the FDA about these
8 proceedings. However, FDA will refrain from
9 discussing the details of this meeting with the
10 media until its conclusion. Also, the committee is
11 reminded to please refrain from discussing the
12 meeting topic during breaks or lunch. Thank you.

13 Now I'll pass it to Moo Hee Choi, who will
14 read the Conflict of Interest Statement.

15 **Conflict of Interest Statement**

16 DR. CHOI: The Food and Drug Administration
17 is convening today's meeting of the Anti-Infective
18 Drugs Advisory Committee under the authority of the
19 Federal Advisory Committee Act of 1972. With the
20 exception of the industry representative, all
21 members and temporary voting members of the
22 committee are special government employees or

1 regular federal employees from other agencies and
2 are subject to federal conflict of interest laws
3 and regulations.

4 The following information on the status of
5 this committee's compliance with federal ethics and
6 conflict of interest laws covered by, but not
7 limited to, those found at 18 USC Section 208 is
8 being provided to participants in today's meeting
9 and to the public.

10 FDA has determined that members and
11 temporary voting members of this committee are in
12 compliance with federal ethics and conflict of
13 interest laws. Under 18 USC Section 208, Congress
14 has authorized FDA to grant waivers to special
15 government employees and regular federal employees
16 who have potential financial conflicts when it is
17 determined that the agency's need for a particular
18 individual's services outweighs his or her
19 potential financial conflict of interest.

20 Related to the discussions of today's
21 meeting, members and temporary voting members of
22 this committee have been screened for potential

1 financial conflict of interest of their own, as
2 well as those imputed to them, including those of
3 their spouses or minor children and, for purposes
4 of 18 USC Section 208, their employers. These
5 interests may include investments, consulting,
6 expert witness testimony, contracts, grants,
7 CRADAs, teaching, speaking, writing, patents and
8 royalties, and primary employment.

9 Today's agenda involves the discussion of
10 issues related to clinical development programs and
11 clinical trial designs for antibacterial products
12 for the treatment of patients with serious
13 bacterial infections for which there are limited or
14 no therapeutic options. This is a particular
15 matters meeting during which general issues will be
16 discussed.

17 Based on the agenda for today's meeting and
18 all financial interests reported by the committee
19 members and temporary voting members, no conflict
20 of interest waivers have been issued in connection
21 with this meeting. To ensure transparency, we
22 encourage all standing committee members and

1 temporary voting members to disclose any public
2 statements that they have made concerning the topic
3 at issue.

4 With respect to FDA's invited industry
5 representative, we would like to disclose that
6 Dr. Patrick Robinson is participating in this
7 meeting as a nonvoting industry representative,
8 acting on behalf of regulated industry.

9 Dr. Robinson's role at this meeting is to represent
10 industry in general and not any particular company.
11 Dr. Robinson is employed by Boehringer-Ingelheim
12 Pharmaceuticals.

13 We would like to remind members and
14 temporary voting members that if the discussions
15 involve any other products or firms not already on
16 the agenda for which an FDA participant has a
17 personal or imputed financial interest, the
18 participants need to exclude themselves from such
19 involvement, and their exclusion will be noted for
20 the record.

21 FDA encourages all other participants to
22 advise the committee of any financial relationships

1 that they may have with the firm that could be
2 affected by the committee's discussions. Thank
3 you.

4 CAPT PARISE: Thank you. We will now
5 proceed with the FDA's introductory remarks from
6 Dr. Cox.

7 **FDA Introductory Remarks - Edward Cox**

8 DR. COX: Thanks, Dr. Parise.

9 Good morning, everybody. I'll just make a
10 few introductory remarks about today's discussions.
11 I thought it might be helpful to provide some
12 context around the discussion.

13 Today we will be discussing antibacterial
14 drug development for areas of unmet need. These
15 are patients with serious infections who have few
16 or limited treatment options. We've seen that over
17 time -- and this is no surprise to the folks that
18 are here today -- that our antibacterial drug
19 armamentarium is essentially eroded by resistance,
20 so we essentially are losing some of the drugs that
21 we rely upon to treat patients.

22 We know where we are now. We can expect

1 that in the future that resistance will further
2 erode our therapeutic armamentarium, even with our
3 best efforts at stewardship. We also know that
4 developing a new antibacterial drug is a very
5 challenging endeavor. There are considerable
6 scientific challenges in developing a new
7 antibacterial drug, from discovery all the way
8 through clinical trials; that the patients in whom
9 these drugs are studied are acutely ill, a very
10 difficult area to actually conduct a
11 well-controlled trial.

12 We also know there are considerable economic
13 challenges in studying an antibacterial drug.
14 There have been a number of reports on this. One
15 of the more recent ones is that done by the Eastern
16 Research Group that looked at the economic
17 challenges of antibacterial drug development for
18 HHS.

19 Despite these challenges, we have seen,
20 encouragingly, some minor uptick in the degree of
21 antibacterial drug development if we look at where
22 we are now compared to where we were four or five

1 years ago. But we have to be careful because this
2 is a very fragile field, and this modest uptick,
3 it's still within a state of fragility at this
4 point.

5 Some other factors to keep in mind, too, is
6 that it really takes a number of years to develop a
7 new antibacterial drug. And if we look at
8 development programs, only some of the drugs that
9 one starts out developing will actually make it all
10 the way through. If we think about antibacterial
11 drug resistance, we think about the time frame that
12 it takes to develop a new antibacterial drug -- can
13 be 5 to 10 years -- it's really hard to respond to
14 resistance once it's occurred.

15 Ideally, you have ongoing development. You
16 have options that are already out there and
17 available on the shelf to be able to reach back to
18 when a new resistance mechanism pops up.

19 Drugs with new mechanisms of action, drugs
20 paired with resistance inhibitors, drugs that have
21 chemical modifications that will remain stable to
22 existing resistance mechanisms are probably the

1 answers to turn to as far as new therapeutics.
2 It's always important that stewardship is always
3 part of this equation, too, but we need the new
4 options. We don't want to find ourselves playing
5 catch-up and trying to chase resistance mechanisms
6 after they've occurred.

7 We at FDA have been working on feasible
8 scientifically-sound, clinical trial design
9 pathways for development of new antibacterial
10 drugs. I think about this in terms of two
11 different prongs. One is general development, sort
12 of the ongoing development for standard infections,
13 whether they be skin infections, community-acquired
14 pneumonia, hospital-acquired pneumonia,
15 ventilator-associated pneumonia and such.

16 The second prong, and what we're here to
17 talk about today, is development of drugs in the
18 area of unmet medical needs. So again, these are
19 patients with serious infections who don't have
20 much in the way of options.

21 If we think about development approaches for
22 areas of unmet need, a key factor here is balancing

1 benefits and risks. So we're talking about more
2 streamlined development programs, so there will be
3 greater uncertainty around safety and efficacy.
4 But if we think about the need here and balancing
5 benefit/risk, it's appropriate in this particular
6 area for patients with serious infections who don't
7 have options to be able to balance those
8 benefits/risks, to be able to facilitate
9 development of new drugs for antibacterial drugs
10 that patients need.

11 If we look at our IND regulations in
12 subpart E, this is actually recognized. It talks
13 about balancing benefits and risks in areas where
14 patients don't have much in the way of treatment
15 options, and they have serious diseases.

16 Folks may know, too, we published a guidance
17 document in July of 2013 on developing
18 antibacterial drugs in the area of unmet need for
19 patients with serious infections. That came out in
20 July of 2013, and we've continued our thinking.
21 Proposals have come forward with regards to
22 particular development programs. I think we are

1 continuing to learn, continuing to develop,
2 consistent with the statutory deadline, and we're
3 working towards finalizing that document towards
4 the end of this month.

5 So this is really a challenging situation.
6 The economic and scientific challenges of
7 antibacterial drug development are considerable.
8 And our efforts really are intended to achieve the
9 best outcomes here for patients in public health to
10 have the options that we need to be able to treat
11 patients.

12 If you step back and think about this for a
13 minute, you can see, given the economic and the
14 scientific challenges, that there are really
15 inherent trade-offs here; very precise
16 characterization of safety and efficacy. If it's
17 not really feasible, if it's not practical to
18 achieve, that may mean very few drugs are
19 developed.

20 If there is a balance between risk and
21 benefit, that may lead us to a situation where we
22 get quality information, but characterization may

1 not be quite as precise. But it may allow for new
2 options to be developed, and those new options may
3 be very important for patients. So that, you'll
4 see, will be part of the discussion today as we go
5 through this.

6 Really, what we're talking about here is
7 balancing benefits and risks at an appropriate
8 level while still maintaining scientific quality
9 and the data. And we'll be looking for your
10 comments on that as we work through the day.
11 Really, beyond what we can cover in detail here
12 today, we're talking mostly about development
13 pathways, clinical trial designs and such.

14 Some of the other things that have been
15 talked about that are important to field, folks may
16 recall the meeting from this past summer where
17 there were discussions about common clinical trial
18 or master protocols, clinical trial networks,
19 development of rapid diagnostics, other things that
20 are really important to the development of new
21 antibacterial drugs and really beyond the scope of
22 what we can do here in the area of unmet need,

1 important other factors and components in this
2 overall equation of how we get needed antibacterial
3 drugs to patients.

4 One other comment, too, something also
5 beyond the scope of today's discussion. Something
6 we're working on, too, is how to label these
7 products. It's very easy and common discussions on
8 medical wards to talk about resistance in general.
9 What we're finding a little more challenging is
10 actually how to accurately describe this in product
11 labeling given the tremendous number of resistance
12 mechanisms that are out there. That's just a point
13 that we will continue to work on.

14 Final thoughts. The other thing that has
15 come up, too, is that if we have drugs that are
16 developed using streamlined pathways, it would be
17 really important to have tools available to
18 communicate these products, their development
19 pathway, risk/benefit, and uncertainty that
20 surrounds the development pathway to healthcare
21 providers so that they are aware of the nature of
22 the drug and use it in appropriate benefit/risk

1 scenarios.

2 Folks may be aware of the idea of the IDSA's
3 LPAB proposal, very much in line with these
4 thoughts; identification of such products; the
5 affirmative recognition of such a pathway; and then
6 also the opportunity for premarket review of the
7 promotional materials, given the critical
8 importance of communicating clearly the development
9 pathways for such drugs so that they are used
10 appropriately out there.

11 One comment on stewardship because this
12 oftentimes comes up. Stewardship is something
13 that, really, all antibacterial drugs need to be
14 part of, in essence; that we need to use all of our
15 drugs carefully. So it's not just the new ones,
16 but it's all the drugs and the potential of
17 cross-resistance, the selector pressure that drugs
18 do apply.

19 So we're working to put forth proposals to
20 really address -- and you'll hear some of these
21 proposals discussed today -- pathways that will
22 allow for the development of antibacterial,

1 particularly for patients with serious infections
2 who don't have much in the way of options. And we
3 look forward to your discussion on these topics and
4 your input, and we value your willingness to join
5 us here today for these discussions. Thank you.

6 CAPT PARISE: Thank you, Dr. Cox.

7 Before we move to the FDA presentation, we
8 do have a new member who's joined us.
9 Dr. Follmann, can you introduce yourself and your
10 organization for the record?

11 DR. FOLLMANN: Yes. Thank you. I'm Dean
12 Follmann, head of biostatistics at NIAID. Sorry
13 I'm late.

14 CAPT PARISE: Thank you. We'll now proceed
15 with the FDA presentations. Dr. Laessig?

16 **FDA Presentation - Katherine Laessig**

17 DR. LAESSIG: Good morning, everyone. I'm
18 tasked with laying some additional groundwork for
19 the committee's discussions today about unmet need
20 products and development programs. I'll start off
21 with something light, statutes and regulations.
22 Then I'll move to antibacterial drug development

1 through the years, particularly how clinical trial
2 designs for infectious disease indications evolved
3 and also understanding of infectious diseases
4 themselves became more sophisticated, diagnosis,
5 management, and outcomes changed.

6 I'll cover highlights from some recent
7 guidances, particularly those that are relevant to
8 unmet need products. I won't cover the unmet need
9 draft guidance itself, as that will be -- the
10 particulars of that will be discussed by
11 Dr. Toerner, and then some brief conclusions.

12 As a regulatory body, we have to bear in
13 mind that approved drugs must meet the statutory
14 standards for effectiveness under the Food, Drug,
15 and Cosmetic Act. As stated in Section 505(d)(1),
16 "Substantial evidence is evidence consisting of
17 adequate and well-controlled investigations,
18 including clinical investigations, among other
19 things."

20 Then in 21 CFR 314.126(b), adequate and
21 well-controlled studies are further described.
22 Here I'm just highlighting something of particular

1 interest for unmet need trials, and that is the
2 control arms, which may include placebos, dose
3 comparisons, no treatment, active treatment, or
4 historical external control.

5 In the Food and Drug Modernization Act, in
6 Section 115(a), it allowed for data from, one,
7 adequate and well-controlled clinical investigation
8 accompanied by confirmatory evidence to establish
9 effectiveness of a drug.

10 So there is some flexibility within the
11 statutory standards, and this is discussed in more
12 detail in the guidance for industry providing
13 clinical effectiveness, evidence of effectiveness,
14 for human drugs and biological products, again
15 which discussed evidence of effectiveness may come
16 from a single study and supportive evidence such as
17 phase 2 data. And since we're dealing with
18 infectious diseases, we are fortunate to have the
19 benefit of microbiology information, which may be
20 in vitro information, animal models of infection.

21 As Dr. Cox just mentioned, there's 21 CFR
22 312.80 subpart E, which discusses drugs intended to

1 treat life-threatening and severely debilitating
2 illnesses, which is the subject of today's meeting;
3 and again, the recognition that physicians and
4 patients are generally willing to accept greater
5 risks or side effects from drugs that treat
6 life-threatening and severely debilitating
7 illnesses than they would accept from drugs that
8 treat something less serious. And as we do with
9 all drugs, the benefits need to be evaluated in
10 light of the severity of the disease being treated.

11 Now I will walk through some antibacterial
12 drug development through the decades. In the 1960s
13 through the 1980s, the trials generally enrolled
14 subjects with a variety of infections at different
15 body sites into the same trial. The objectives
16 were generally to demonstrate comparable point
17 estimates to an active control for a clinical cure
18 endpoint for each of the different infection types.

19 For some of these trials, there was no
20 formal statistical inference testing, or if they
21 had it, they may have had noninferiority margins
22 that weren't supported, or there were other design

1 limitations. In general, the indications were
2 based on these subsets of body sites of infections
3 from within these trials.

4 The indications themselves tended to be less
5 specific, such as just respiratory tract, which
6 later became lower and upper. Lower respiratory
7 tract included bronchitis and pneumonia, and upper,
8 sinusitis among other things. A broad indication
9 of skin infections is another example.

10 The next decade, 1990 through 2000, trials
11 became more specific to the body site because there
12 was a recognition that the natural history of
13 diseases at different sites may differ. Endpoints
14 and treatment duration may differ. Drug efficacy
15 may differ at different sites, as well as dosing
16 regimens may need to be different.

17 This was captured in great detail in the
18 1992 Infectious Disease Society of America
19 Guidelines, as well as in the 1992 FDA Points to
20 Consider document, Clinical Development and
21 Labeling of Anti-Infective Drug Products.
22 Recognition of these differences and better

1 understanding of the disease processes resulted in
2 more sophisticated clinical trial design
3 recommendations.

4 Again, there was a clear need to improve the
5 design of studies and conduct of trials for
6 anti-infective drugs by providing a clear
7 definition of the disease states and their clinical
8 and microbiologic endpoints, as well as taking into
9 account changes in the diagnosis and management of
10 specific infectious diseases.

11 From 2000 through today, the last 14 or so
12 years, trials generally use an active control. So
13 there was greater emphasis on the evidence base for
14 noninferiority trials. For various reasons, there
15 was public concern about the scientific validity of
16 these trials because the noninferiority margins may
17 not have had a large justification.

18 Another consequence of the noninferiority
19 trial design was that they generally required
20 larger trials. More patients had to be enrolled.
21 There was the evolution towards the more specific
22 indications, upper respiratory tract infection.

1 Acute bacterial sinusitis and acute
2 bacterial otitis media were upper respiratory tract
3 infections. Lower respiratory tract infections
4 became community-acquired bacterial pneumonia,
5 acute bacterial exacerbation of chronic bronchitis,
6 and nosocomial pneumonia was divided into
7 hospital-acquired bacterial pneumonia, and then
8 later associated-bacterial pneumonia.

9 This was scientifically reasonable because
10 if you do a study in acute bacterial exacerbation
11 of chronic bronchitis, it doesn't inform you at all
12 about how the drug's going to perform for
13 hospital-acquired bacterial pneumonia or
14 ventilator-associated bacterial pneumonia.

15 Now I'll step quickly through some of these
16 recent guidances so you can keep in mind what the
17 recommendations are. And this is based on the work
18 in the agency and with other stakeholders to
19 develop trial recommendations. Some concepts
20 underlying these guidances are that the goal is to
21 recommend trial designs that are scientifically
22 well grounded as well as feasible.

1 Some of the ways that we've attempted to
2 increase the feasibility is through allowing some
3 prior use of antibacterial drugs and treatment
4 often that's empiric; use of the intent-to-treat
5 population for certain indications; use of a
6 comparator drug that's standard of care but may not
7 necessarily have a labeled indication, such as for
8 HABP/VABP. Noninferiority margins larger than
9 10 percent are possible for some indications such
10 as community-acquired bacterial pneumonia.

11 A big point in these guidances is also to
12 make sure that patient populations with the disease
13 are actually enrolled. This has been a problem on
14 occasion with other NDA packages, where review has
15 revealed that it was questionable whether patients
16 actually had the infectious disease that we were
17 interested in; also, endpoints that reflect a
18 benefit to the patients, and then noninferiority
19 margins that are based on historical evidence of
20 sensitivity to drug effect, as well as on clinical
21 judgment.

22 The first one is the guidance on

1 hospital-acquired bacterial pneumonia and
2 ventilator-associated bacterial pneumonia. It
3 recommends enrolling hospitalized subjects with new
4 onset of worsening pulmonary signs or symptoms with
5 hypoxemia or need for acute ventilatory changes.
6 They should have at least one: a fever,
7 hypothermia, elevated or depressed white cell
8 counts, and bandemia, plus a chest radiograph
9 showing new or progressive infiltrates suggestive
10 of bacterial pneumonia.

11 The recommended primary endpoint is
12 all-cause mortality alone or with no
13 disease-related complications at day 14 through 28.
14 The primary analysis population will depend on the
15 spectrum of activity of the product, so it's the
16 microbiological intent to treat when you have a
17 narrow spectrum product and the ITT for a
18 broad-spectrum agent. The recommended margin,
19 since we have a mortality endpoint, is 10 percent.

20 Complicated urinary tract infection,
21 guidance recommends enrolling subjects with
22 conditions associated with risk for cUTI plus at

1 least two signs and symptoms. Risks include an
2 indwelling urinary catheter, urinary retention of
3 greater or equal to 100 milliliters of residual
4 urine after voiding, neurogenic bladder,
5 obstructive uropathy, azotemia, or a diagnosis of
6 pyelonephritis.

7 I'm just mentioning intravenous drug here,
8 not oral. The primary endpoint is resolution of
9 symptoms and less than 10 to the 4th colony-forming
10 units per milliliter of the pathogen, isolated at
11 baseline by day 5. So this is in part of micro
12 endpoint. The primary analysis population is the
13 microbiological intent-to-treat population, and the
14 margin is 10 percent.

15 Next is complicated intra-abdominal
16 infection. The guidance recommends enrolling
17 subjects with one or more systemic signs or
18 symptoms, who've been hospitalized and have an
19 operative procedure completed or scheduled to occur
20 within 48 hours; have a variety of complicated
21 intra-abdominal infectious processes, including
22 intra-abdominal abscess, appendicitis or

1 diverticulitis complicated by perforation or
2 abscess, cholecystitis with perforation or empyema,
3 intestinal perforation with abscess or fecal
4 contamination, also perforation or peritonitis with
5 fecal contamination.

6 For this indication, the primary endpoint is
7 resolution of baseline signs and symptoms at day 28
8 with no failures. Again, in this case, the primary
9 analysis population is the microbiological intent
10 to treat, and the margin is 10 percent.

11 Just to wrap up here before I turn it over
12 to Dr. Toerner, when you're considering these unmet
13 need development programs, obviously bear in mind
14 the statutes and regulations and recall how the
15 drug development became more sophisticated over the
16 decades, trial designs improved, our understanding
17 of the diseases became more sophisticated.

18 Then also bear in mind the recently issued
19 guidances for the indications that are relevant, in
20 particular, patient populations, endpoints, and the
21 NI margins. And as Dr. Cox elaborated, obviously
22 the benefit/risk for unmet need patients. Thank

1 you.

2 CAPT PARISE: Thank you, Dr. Laessig. We'll
3 now move on to Dr. Toerner for the next FDA
4 presentation.

5 **FDA Presentation - Joseph Toerner**

6 DR. TOERNER: Hi. Good morning. I'll be
7 going through an overview of recommendations for
8 the streamlined clinical development of
9 antibacterial drugs for unmet need. As Dr. Cox had
10 mentioned, in July of 2013, we issued a draft
11 guidance document on antibacterial drug development
12 for unmet medical need. We've reviewed the
13 comments to the docket and response to the draft
14 guidance while we're working on finalizing that
15 guidance document.

16 Meanwhile, in preparation for this advisory
17 committee, we included in the background package a
18 general overview of recommendations for streamlined
19 drug development programs for antibacterial drugs
20 for unmet need, and Subpart E is our recurring
21 theme here today. We turn to the regulations, and
22 this particular regulation gives us some

1 flexibility in our recommendations for a more
2 streamlined drug development, in particular, for
3 patients with unmet need.

4 We define unmet medical need as patients who
5 have a serious bacterial disease for which
6 effective antibacterial drugs are limited or
7 lacking. This includes patients who have
8 antibacterial diseases in which in vitro
9 susceptibility testing shows resistance to several
10 antibacterial drugs.

11 Characteristics of new antibacterial drugs
12 that are likely to be candidates for unmet medical
13 need are drugs that have a new mechanism of
14 antibacterial action; or drugs that have an added
15 inhibitor that neutralizes a mechanism of
16 resistance; or a drug that has an alteration in the
17 structure such that a particular mechanism of
18 resistance does not affect the activity of the new
19 drug; or some other characteristic of the drug that
20 can enhance effectiveness.

21 Drugs that are intended to treat a single
22 species of bacteria can also be a candidate for

1 streamlined drug development programs for patients
2 with unmet need. However, there are some important
3 issues to consider for a drug that treats a single
4 species of bacteria: the frequency with which the
5 infection occurs; the use of a rapid diagnostic to
6 reliably and promptly identify patients with the
7 particular infection that would enable study of the
8 drug in a clinical development program; as well,
9 the issue of the use of the rapid diagnostic in
10 clinical practice and issues of co-development of
11 the rapid diagnostic, along with the
12 investigational drug.

13 I'm just going to provide a general overview
14 of antibacterial drug development in a streamlined
15 fashion for unmet medical need, and Drs. Rubin and
16 Nambiar are going to focus on statistical issues
17 and clinical trial design issues. I'll first
18 provide a general overview of nonclinical
19 considerations.

20 In a clinical development program that is
21 going to have smaller, shorter, or fewer clinical
22 trials, the nonclinical data, relative to the

1 clinical data, may take on a more important role in
2 the overall data submitted for review to
3 demonstrate safety and effectiveness. Therefore,
4 the nonclinical evaluations should not be
5 streamlined or smaller.

6 In nonclinical evaluations, the
7 characterization of properties to assess a new
8 drug's potential to address an unmet medical need
9 is important. Its mechanism of action should be
10 characterized.

11 In terms of the nonclinical toxicology
12 evaluations, there are guidance documents available
13 on the FDA website, and sponsors can avail
14 themselves of these guidance documents when
15 planning for nonclinical toxicology studies. This
16 should be completed before an IND submission as
17 well as during drug development.

18 I wanted to focus on nonclinical
19 microbiology considerations. It's important that
20 the in vitro activity of the investigational drug
21 is evaluated. This can be done by showing activity
22 in animal models of infection. And as well, among

1 samples of target bacterial pathogens, the minimum
2 inhibitory concentration can be characterized.

3 There are many mechanisms of resistance, and
4 these should be characterized in nonclinical
5 evaluations. Whether it's an enzymatic resistance,
6 permeability issues, an altered target site, or an
7 efflux of the drug, it's important to characterize
8 in a nonclinical development. As well, the issue
9 of cross-resistance can be characterized in
10 nonclinical evaluations.

11 The pharmacokinetic and pharmacodynamic
12 characteristics of an investigational drug should
13 be evaluated in nonclinical studies. There are
14 in vitro models that evaluate pharmacokinetic and
15 pharmacodynamic relationships of an investigational
16 drug and animal models, the target value of PK/PD
17 index, and can be evaluated.

18 It depends on the mechanism of action of the
19 antibacterial drug, whether it's the AUC over the
20 MIC, the Cmax over the MIC, or time above MIC. It
21 could be one of those indices or another PK/PD
22 index.

1 As well, appropriate levels of antibacterial
2 drugs and certain tissue sites can be evaluated in
3 nonclinical animal models of infection. And then
4 you can compare them. As you're starting to gather
5 human PK data, you can compare these data and begin
6 to understand the activity of the drug in unmet
7 medical need.

8 In early clinical development, PK/PD in
9 human studies can be important, and the drug
10 distribution in relevant tissue sites is an
11 important area for consideration, for example,
12 epithelial lining fluid for a drug that is intended
13 to treat pneumonia.

14 Because patients with unmet need often have
15 comorbid conditions, it would be important to
16 characterize pharmacokinetics in patients who have
17 renal impairment or hepatic impairment that could
18 guide dosing recommendations so that these patients
19 can be included in the pre-approval clinical
20 development program, so that with the first
21 approval, there will be dosing recommendations for
22 such patients.

1 A sparse sampling strategy can be important
2 in clinical development, and it may be helpful to
3 answer questions that arise when there may be
4 decrements in efficacy or a safety issue may occur.
5 A sparse sampling strategy can be very useful to
6 help evaluate those issues that occur in drug
7 development.

8 We also wanted to address labeling. The
9 indications in the usage section of labeling should
10 include an appropriate level of detail on the
11 population for whom the drug is intended. There
12 should be a statement included if the drug should
13 be reserved for certain clinical situations and
14 also recommendations to include a limitations of
15 use statement; for example, in certain patient
16 subgroups for whom the drug is indicated.

17 As well, for antibacterial drugs, there is
18 the first list of bacterial pathogens. And these
19 are the bacterial pathogens that are evaluated in
20 the clinical trials that show efficacy. As well,
21 there are regulations in labeling that there should
22 be a statement about resistance.

1 In the microbiology subsection of labeling,
2 there is included a second list of bacterial
3 pathogens. And these are bacterial pathogens that
4 may not have been included in the evaluation of
5 efficacy in the clinical trials but are felt to be
6 important target bacterial pathogens. And there's
7 guidance available on the approach to select the
8 pathogens to be included on the second list.

9 The mechanisms of resistance in
10 cross-resistance should be included in this
11 section, and currently, it's important to describe
12 susceptibility test methods and interpretative
13 criteria. While nonclinical evaluations can
14 provide very useful information on a single
15 resistance mechanism, for example, it's very
16 important that susceptibility testing be described
17 because bacteria often have the presence of more
18 than one resistance mechanism.

19 For the clinical study section of labeling,
20 our regulations state that any clinical study that
21 is discussed in prescription drug labeling, that
22 relates to an indication for or use of the drug,

1 must be adequate and well controlled as described
2 in the Code of Federal Regulations 314.126(b).

3 There was also guidance that FDA has issued
4 on the clinical study section of label, and
5 clinical studies that provide the primary support
6 for effectiveness should be included. Other
7 important supporting evidence of effectiveness can
8 be included, and studies that have a prospective
9 evaluation of the safety endpoint can be included
10 in the clinical study section of product labeling.

11 I thank you, and I'll turn the podium over
12 to Dr. Rubin.

13 CAPT PARISE: Thank you. We'll have
14 Dr. Rubin give the next FDA presentation.

15 **FDA Presentation - Daniel Rubin**

16 DR. RUBIN: Thank you. This presentation
17 will discuss evaluating new antibacterial drugs
18 meant to address the unmet needs of patients with
19 serious or life-threatening infections, who
20 currently lack safe and effective therapy due to
21 resistance. I will cover statistical properties of
22 various development pathways.

1 The most direct method of establishing
2 safety and efficacy of a new antibacterial drug
3 would be to conduct a randomized superiority trial.
4 In a superiority design, the objective is to
5 determine whether the new therapy leads to better
6 outcomes than a control regimen.

7 The utility of the superiority design is
8 that it addresses the most relevant hypothesis in a
9 setting of unmet need, which is whether the new
10 therapy improves upon existing therapies. It also
11 provides the most statistically reliable answer to
12 this question in that it does not depend on the
13 type of unverifiable assumptions required to
14 interpret a noninferiority trial.

15 Possible inducements we have discussed for
16 facilitating superiority designs are pooling of
17 subjects with infections at different body sites;
18 use of a statistical significance level less
19 stringent than the standard, one-sided, 0.025 alpha
20 level; and allowance for cluster randomization to
21 streamline enrollment.

22 The main challenge of a superiority design

1 relates to feasibility. In particular, it is
2 necessary to wait until there is a sufficiently
3 large group of patients with sufficiently defective
4 therapy that is plausible to evaluate superiority.
5 You can see from the sample size table that unless
6 treatment effects are in the range of 15 to
7 20 percent on the absolute difference scale, sample
8 sizes can exceed what industry sponsors have told
9 us are feasible trials to conduct.

10 I'll next discuss noninferiority trials. In
11 a noninferiority design, the objective is to
12 determine whether the new antibacterial drug is
13 unacceptably worse than a control regimen,
14 according to a selected noninferiority margin.

15 Noninferiority trials are used when it would
16 be unethical to randomize subjects to a placebo
17 control due to the existence of an already
18 effective therapy for a serious disease. They have
19 been the traditional method for developing
20 antibacterial drugs. However, they necessarily
21 provide less direct evidence of efficacy than
22 superiority trials.

1 Related to the external control approach
2 I'll soon discuss, the interpretation depends on
3 certain non-testable assumptions, such as whether
4 the control regimen itself is more effective than a
5 hypothetical placebo, or whether the trial has the
6 sensitivity to detect differences between
7 interventions that are in fact different.

8 The 2013 draft guidance on unmet need
9 discusses the development pathway whereby a sponsor
10 would conduct a noninferiority trial in patients
11 who do have acceptable options. The noninferiority
12 margin could be wider than normal so as to
13 indirectly show a benefit over a hypothetical
14 placebo, but not necessarily show the new therapy
15 tightly preserves the benefits of existing therapy
16 in patients for whom the existing therapy is
17 thought to be effective. Efficacy would then be
18 extrapolated to the group with unmet needs for whom
19 existing therapy is considered ineffective.

20 One challenge of this extrapolation is that
21 patient factors can differ between those with
22 drug-sensitive infections and those with

1 drug-resistant infections. These factors can be
2 prognostic of outcomes and can modify antibacterial
3 treatment effects.

4 To illustrate differences in patient
5 factors, this table compares baseline
6 characteristics between those with drug sensitive
7 infections and drug resistant infections at an ICU
8 in Virginia. You can see from the p-values that
9 nature doesn't randomize resistant pathogens to
10 patients.

11 I'll now discuss considerations for studies
12 that combine patients with infections at different
13 body sites. The motivation for pooling over body
14 sites is to increase sample size in scenarios where
15 it may be difficult to conduct fully powered
16 studies in each specific site.

17 It's important to note that trials already
18 pool over many subgroups such as those defined by
19 pathogen, region, or demographic factors. The
20 indications were originally separated based on
21 clinically determined heterogeneity regarding which
22 patient groups make sense to combine rather than

1 statistical considerations.

2 Pooling of infections have mainly been
3 internally discussed in the context of major
4 Gram-negative indications such as hospital-acquired
5 and ventilator-associated bacterial pneumonia,
6 blood stream infections, complicated
7 intra-abdominal infections, and complicated urinary
8 tract infections.

9 There are several ongoing antibacterial
10 trials in the unmet setting that pool patients with
11 life-threatening pneumonia and bloodstream
12 infections, which you can read about from the
13 clinicaltrials.gov identifiers on this slide.

14 In a trial pooling over body sites, some
15 statistical methods, such as Bayesian hierarchical
16 models, could attempt more principled estimation.
17 Model-based methods form estimated treatment
18 effects for each subgroup and reduce the noise
19 inherent from very small sample sizes by smoothing
20 these estimates using data from other subgroups.
21 This is an area under continued internal
22 investigation at FDA, and Dr. LaVange and I could

1 provide more details during the discussion.

2 The main challenge of a trial pooling over
3 body site subgroups is that it might not be able to
4 precisely characterize efficacy in each disease.
5 Likewise, it could have little power for detecting
6 efficacy differences across diseases. If one
7 assumes going in that the body sites are
8 combinable, it might not be possible to test this
9 assumption with small sample sizes.

10 There are also several relatively recent
11 examples of antibacterial drugs, which I will
12 summarize on the next few slides, for which there
13 may be efficacy decrements in patients with
14 respiratory infections or who are more severely
15 ill.

16 This slide shows mortality results from the
17 FDA meta-analysis that yielded a warning for
18 tigecycline. Observed that the meta-analysis
19 showed a statistically significant increased risk,
20 point estimates for mortality went against
21 tigecycline for every disease, and the largest
22 mortality difference was in ventilator-associated

1 pneumonia, where tigecycline was not given FDA
2 approval.

3 Similarly, doripenem is FDA approved for
4 several indications such as complicated
5 intra-abdominal infections and complicated urinary
6 tract infections. It was not given FDA approval in
7 2008 for nosocomial pneumonia, in part due to a
8 signal for increased mortality during intravenous
9 therapy. The sponsor began a new study in
10 ventilator-associated pneumonia with an increased
11 dose, but, as shown on this slide, it was halted
12 for futility with excess mortality and numerically
13 worse clinical cure rates.

14 I'll now discuss the use of external
15 controls. The rationale for an external control is
16 to increase power when resistant pathogens are
17 scarce. An external control group also allows a
18 more methodologically rigorous analysis than a
19 descriptive single-arm case series.

20 Controlled comparisons are needed for
21 antibacterial drugs not only because of regulations
22 but because even patients with resistant pathogens

1 do not uniformly fail, as I'll illustrate on the
2 next slide. Discussing external controls, we still
3 recommend conducting a randomized trial, possibly
4 with disproportionate randomization, but augmenting
5 the control arm with external data.

6 This slide provides the selected summary of
7 literature reports of pandrug-resistant,
8 Gram-negative infections, meaning resistance to all
9 antibiotics, including colistin. The table
10 illustrates the necessity that I mentioned for a
11 control group, which is that patients without the
12 new treatment cannot necessarily be assumed to
13 uniformly die or fail to recover. The quote,
14 "survival rate" from these series was approximately
15 60 percent.

16 Challenges we've encountered putting
17 external controls into practice include the exact
18 details of how to select the control group and how
19 to ensure comparability between the treatment and
20 control groups on factors other than the
21 interventions being tested.

22 Another challenge is how to prespecify the

1 analysis, particularly with retrospective data and
2 ensure patients are not included in the analysis on
3 the basis of their outcomes. Other challenges are
4 that outcomes across resistant pathogen cohorts are
5 heterogeneous, and outcomes are influenced not only
6 by drug effects but by underlying comorbidities
7 that would need to be controlled in a
8 non-randomized comparison.

9 I will now briefly summarize lessons from
10 three published randomized-controlled trials in the
11 unmet need setting. These trials were conducted in
12 patients with carbapenem resistant blood stream
13 infections to the *Acinetobacter baumannii*. They
14 compared colistin monotherapy to colistin
15 combination therapy with rifampicin or intravenous
16 fosfomycin.

17 The trials were conducted because in vitro
18 synergy suggested that the combinations improved
19 bacterial killing. If this translates to improved
20 patient outcomes, then the combinations could
21 provide beneficial new options. Conversely, if it
22 does not translate into improved patient outcomes,

1 then the benefit to risk profiles would presumably
2 be unfavorable. Rifampicin, for instance, leads to
3 many drug-drug interactions.

4 The three trials were conducted in Italy,
5 Turkey, and Thailand, and together enrolled
6 approximately 350 total subjects. This slides
7 shows that the majority of enrolled patients had
8 pneumonia but that these resistant pathogen trials
9 did pool over body sites.

10 Here are the mortality results. In the
11 largest trial, which was the Italian study with
12 approximately 100 subjects per arm, there was no
13 mortality difference seen between the randomized
14 groups.

15 The Turkish and Thai trials showed numerical
16 trends favoring combination therapy, but these did
17 not approach statistical significance. The
18 synthesized data do not provide evidence of a
19 mortality benefit from combination therapy relative
20 to monotherapy, but the confidence intervals are
21 wide enough that they did not exclude a meaningful
22 benefit.

1 What lessons can be drawn from these
2 results? In terms of bias, the mortality rate
3 significantly fluctuated over trials. Hence,
4 non-randomized cross-study comparisons of
5 interventions, like monotherapy, combination
6 therapy, or new drugs would need to match or
7 otherwise statistically adjust for baseline factors
8 in order to control confounding. With this in
9 mind, there may be utility and an anti-infective
10 trial networks that collect natural history data at
11 study sites that would then prospectively enroll
12 patients in future studies.

13 In terms of variance, despite almost 350
14 subjects in these completed trials, we currently do
15 not have a definitive answer for whether
16 combination therapy should be given rather than
17 monotherapy.

18 If basing decisions on very small data sets,
19 it will be difficult to make statistically reliable
20 conclusions unless treatment effects are fairly
21 dramatic. Consequently, there is a need for
22 leveraging or augmenting varied data sources in a

1 principle manner.

2 Here are my references. Thank you. I'll
3 turn it over to Dr. Nambiar.

4 **FDA Presentation - Sumati Nambiar**

5 DR. NAMBIAR: Thank you and good morning,
6 everybody. In my presentation today, I'll try to
7 touch upon some trial considerations for
8 antibacterial drugs being developed for patients
9 with unmet need and build upon the statistical
10 framework that Dr. Rubin has already laid out.

11 I'll briefly discuss some general trial
12 design considerations as they are applicable to
13 antibacterial drugs being developed for unmet need.
14 And then we thought it would help to actually work
15 our way through some examples, which put the
16 discussion in context.

17 Most of the examples -- in fact, the first
18 four examples -- really relate to drugs being
19 developed for Gram-negative infections, which is
20 where we have the greatest need at this point. And
21 the last example certainly are applicable to both
22 Gram-positive and Gram-negative drugs.

1 I think we have stated this at multiple
2 different fora as well. We do think that well
3 conducted noninferiority trials of antibacterial
4 drugs are very important to maintain a robust
5 pipeline of antibacterial drugs so that we have
6 options before new mechanisms of resistance emerge.

7 As Dr. Cox mentioned in his presentation,
8 waiting for resistance to develop and then trying
9 to develop drugs is not in the best interest of
10 public health because you're really behind
11 resistance at that point.

12 A well conducted noninferiority trial will
13 provide adequate evidence of a drug's efficacy in
14 the particular body site of infection in which it
15 is studied. In such a noninferiority trial,
16 patients could be enrolled who either have the wild
17 type or the multidrug resistant phenotype pathogen
18 of interest.

19 In general, these trials are limited to
20 situations where the baseline pathogen is
21 susceptible to both the test and comparator drug.
22 And as a result, these trials often enroll few or

1 no patients who are infected with an MDR phenotype.
2 The activity against the MDR phenotype organisms
3 comes from in vitro data or from animal models of
4 infection.

5 If an antibacterial drug is being developed
6 for unmet need and the option is to conduct a
7 noninferiority trial, our recommendation is that
8 one adequate and one well-controlled, phase 3
9 noninferiority trial will suffice. And every
10 attempt should be made to enroll patients with
11 severity of illness or comorbidities, which are
12 similar to those seen in patients with unmet need.

13 In these trials, we're willing to accept a
14 wider noninferiority margin than that used for
15 traditional development programs. Necessarily
16 labeling from such a program will include a limited
17 use statement.

18 We've thought about pooling across body
19 sites for noninferiority trials. We think it can
20 be challenging for many reasons. And I think
21 Dr. Rubin has already outlined this in his
22 presentation. You do see potential deficit in

1 treatment effect across infection types.

2 If you pool across body sites, you may not
3 notice the deficit. The treatment effect does vary
4 across infection types. The endpoints also vary by
5 infection types. But again, this is one topic we
6 would really like discussion on and welcome the
7 committee's thoughts on this concept.

8 Superiority trials certainly provide a very
9 clear finding of efficacy, however, the ability to
10 rely on superiority is likely time limited because
11 as new therapies become available, ongoing trials,
12 which are designed to demonstrate superiority over
13 standard of care, will become unethical and will
14 need to be stopped, and all subsequent trials will
15 have to be noninferiority trials.

16 For superiority trials, we are more
17 comfortable. Again, there are caveats, but pooling
18 across body site is acceptable. We do recommend
19 that every attempt be made to enroll a larger
20 fraction of patients who have more serious
21 infections, such as hospital-acquired pneumonia or
22 ventilator-associated pneumonia, where we have seen

1 deficits in performance of antibacterial drugs.
2 Dr. Rubin walked you through a couple of examples,
3 tigecycline and doripenem.

4 Superiority trials for test drugs can be
5 compared to an active comparator. And as I've
6 already stated, it is usually dependent upon the
7 comparator arm of the trial representing suboptimal
8 treatment. It's very infrequently that we come
9 across an antibacterial drug that actually provides
10 additional benefit or active standard of care.

11 Superiority trials can be performed using
12 external controls, and there are shortcomings with
13 using external controls. Every effort should be
14 made that these controls be as similar as possible
15 to the study population. Another option would be
16 an add-on design, where the test drug plus standard
17 of care is compared to the standard of care plus
18 placebo.

19 Nested noninferiority/superiority trial
20 design is another option, which is essentially a
21 noninferiority trial, and you try to demonstrate
22 superiority in a subset of patients who have

1 baseline microorganisms, which are resistant to
2 comparator. Now, in this study, design of
3 superiority is not demonstrated in the subgroup.
4 It does not impact on the conclusion of
5 noninferiority. And no multiplicity adjustments
6 are needed to control for overall type 1 error.

7 I'll just walk you through a few examples
8 and some of the discussion we've had internally
9 about potential pathways for these types of drugs.
10 The first example is an antibacterial drug that
11 works against most members of the
12 Enterobacteriaceae family and also has activity
13 against *Pseudomonas aeruginosa*.

14 Its activity includes several
15 extended-spectrum beta-lactamases, including some
16 of the carbapenemases. Activity of the drug has
17 been demonstrated in relevant animal models of
18 infection, and human PK studies have also been
19 done. And the drug does achieve adequate levels in
20 epithelial lining fluid.

21 So what might be some options for such a
22 drug? It could be a single noninferiority trial at

1 one body site, a nested NI superiority option, or a
2 superiority trial.

3 If one would to pursue a noninferiority
4 trial, it could be done at any of these body sites.
5 Our first reference would be that such a trial be
6 done in patients with hospital-acquired bacterial
7 pneumonia or ventilator-associated bacterial
8 pneumonia, given the spectrum of activity of the
9 drug. But we do understand that these trials are
10 difficult to do.

11 As an alternative, the first trials could be
12 done in patients with complicated intra-abdominal
13 infections or complicated urinary tract infections.
14 And we would be willing to accept a wider
15 noninferiority margin, and as I've stated, it would
16 result in a limited use labeling.

17 Such an NI trial could be supplemented with
18 data from a study pooling across body sites in
19 patients with unmet need. Such a trial would
20 provide PK data in sicker population who are likely
21 to have more comorbidities.

22 We'll also provide some clinical experience

1 in patients with infections due to organisms of a
2 certain resistance profile. And this is something
3 we've heard from clinicians, that this information
4 would be very useful to them. And if the study is
5 designed such that there is some inference testing
6 around it, then it could potentially support a
7 labeling, a limited-use labeling as well.

8 The same drug can also be tested in a
9 superiority trial testing where you could pool
10 across body sites. And typically it would be
11 pooling intra-abdominal, complicated UTI and
12 HABP/VABP. But to be able to demonstrate
13 superiority, the trial would have to enroll
14 patients with infections due to certain resistant
15 phenotype, and in this instance an example would be
16 carbapenemase production.

17 The comparator could be best available
18 therapy only or one could use best available
19 therapy and leverage some external control data
20 using disproportionate randomization. The endpoint
21 could be all-cause mortality or could be a
22 disease-specific definition of clinical success.

1 And as Dr. Rubin has mentioned, a one-sided alpha
2 of .05 would be acceptable.

3 I think Dr. Rubin went over these numbers.
4 The point of the slide, really, is if the treatment
5 difference is huge, then obviously the sample sizes
6 are much smaller. But if the treatment difference
7 is in the 10 percent range, then certainly these
8 trials are going to be fairly large, at least close
9 to 500 and, hence, the issue of feasibility of some
10 of these trials.

11 The second example -- and I apologize; in
12 your handouts, this would say example 3 -- is very
13 similar to the previous drug. The only difference
14 here would be that the drug does not have activity
15 against *Pseudomonas aeruginosa*.

16 Again, here the options are very similar to
17 the previous example. But rather than pursue a
18 HABP/VABP indication, we would recommend that
19 complicated UTI may be the first indication to
20 pursue, because for HABP/VABP, one would need to
21 address the issue of overlapping activity of other
22 antibacterial drugs, which are used to treat

1 Pseudomonas and whether or not they would overlap
2 with the spectrum of this drug.

3 So in this instance, we would be comfortable
4 if the first indication being sought or pursued is
5 complicated UTI. And then similar to the previous
6 example, nested NI superiority or superiority is an
7 option.

8 The third example is rather challenging
9 because this is a drug that's only active against
10 Pseudomonas aeruginosa, Acinetobacter. But the
11 message here is that this drug does not have a
12 broad spectrum of activity and really focuses on
13 one or maybe two pathogens. So we picked
14 Pseudomonas as an example, and we do acknowledge
15 it's difficult to study such a drug in the given
16 paradigm.

17 Pseudomonas does not occur at a high
18 frequency in any one particular body site; it's on
19 the lower side for most of the common indications
20 we study. And some of these infections are
21 polymicrobial and necessitating the use of
22 concomitant therapy, which has an overlapping

1 spectrum of activity. Currently, we don't have
2 rapid diagnostics at our disposals, but if they do
3 become available, they could help some, but
4 certainly will not obviate all the problems.

5 One option we've considered -- and it is
6 fraught with difficulties -- is whether an NI trial
7 could be done at a single body site, say HABP/VABP.
8 Some of the issues we're dealing with is this test
9 drug would then need to be co-administered with a
10 second antibacterial drug to cover other
11 Gram-negative organisms because this test drug only
12 acts against Pseudomonas, but at the same time not
13 obscure the treatment effect of the test drug was
14 Pseudomonas aeruginosa.

15 The second issue is often there is a need
16 for double coverage, or at least that's the
17 clinical practice, for treatment of Pseudomonas
18 aeruginosa, which could then further obscure the
19 treatment effect. And even Pseudomonas is
20 identified as the only pathogen, we often see there
21 is great reluctance to de-escalate, and we've had
22 experience in other clinical trials where the rate

1 of de-escalation has been rather dismal. Lack of
2 rapid diagnostic makes it difficult to broach the
3 trial population.

4 So again, we would welcome the committee's
5 thoughts on whether such a drug could be studied
6 for HABP/VABP, and also if there are any other
7 potential sites of infection that could be suitable
8 to study such a drug. We've been thinking about
9 complicated UTI; would burns be another indication?
10 But again, each of these have their own sets of
11 problems.

12 The other option would be to do a
13 superiority trial pooling across multiple body
14 sites, where the test drug would have to beat best
15 available therapy. But again, to be able to do so,
16 one would need to enroll patients where the
17 organisms are multidrug resistant. You could use
18 concurrent external control data. Something else
19 we've been thinking about and not sure if it would
20 work out is, is it possible to leverage some
21 historic control data from untreated *Pseudomonas*
22 infections. We really need to go back and look at

1 the literature; haven't gotten that far.

2 One other question we have, would welcome
3 the committee's thoughts on this, is could studies
4 be done in populations who are more likely to have
5 infections due to *Pseudomonas aeruginosa*. An
6 example would be cystic fibrosis or bronchiectasis,
7 and if the answer is yes, what might the indication
8 look like. Would it be treatment of pulmonary
9 exacerbations, and would we encounter some of the
10 same difficulties as we are in patients with
11 HABP/VABP?

12 The fourth example we have is a new
13 beta-lactamase inhibitor, which is being combined
14 with an approved beta-lactam antibacterial drug.
15 For this example, the beta-lactam is a carbapenem.
16 It's an approved carbapenem, and the indications
17 it's approved for are complicated UTI,
18 intra-abdominal infections, and HABP/VABP.

19 Under Section 505(b)(2) of the Food, Drug,
20 and Cosmetic Act, we can rely in part on the
21 agency's finding of safety and effectiveness for
22 the approved indications for the carbapenem. This

1 information can provide some of the evidence needed
2 for the development of this new carbapenem BLI
3 combination. And this combination -- either you
4 could use the (b)(2) approach, which I'm going to
5 discuss in the next slide, or certainly can be
6 studied using more traditional approaches where one
7 does a full-fledged NI trial or superiority trial,
8 as I discussed previously.

9 I'll spend just a couple of minutes talking
10 about 505(b)(2) applications. Section 505 of the
11 Food, Drug, and Cosmetic Act describes three types
12 of new drug applications. Applications under
13 (b)(1), they contain a full report of
14 investigations of safety and effectiveness of the
15 product. For 505(b)(2), some of the information
16 required for approval comes from studies which are
17 not conducted by or for the applicant and for which
18 the applicant has not obtained the right of
19 reference. And (j) covers generics. I'll talk
20 about that.

21 The kinds of information that one can rely
22 on in the 505(b)(2) paradigm, as I've stated, could

1 be the agency's finding of safety and effectiveness
2 for a previously approved drug product. It could
3 be the published literature: clinical trials or
4 animals studies. And this information is necessary
5 for the approval of the application if the
6 applicant has not obtained a right of reference.

7 If there is right of reference to the raw
8 data, then it's a (b)(1). In some instances, the
9 applicant could rely on both literature and upon
10 the agency's finding of safety and effectiveness
11 for a previously approved drug.

12 Using the 505(b)(2) approach, if the new
13 drug -- the carbapenem plus the new BLI, a data
14 package could look like this. We could accept
15 clinical data from phase 2 trials in patients with
16 cIAI, cUTI, or HABP/VABP. So these are the
17 indications for which the carbapenem is approved.

18 We would like some clinical data from
19 patients who have infections due to the beta-
20 lactamase producing microorganism that this BLI is
21 active against. The evidence for activity against
22 the beta-lactamases is available from in vitro

1 studies and animal models of infections.

2 We know that by adding the BLI, there is the
3 additive benefit. We would need adequate safety
4 both for the BLI alone and for the combination
5 product. Such a data package would result in
6 limited use labeling for the indications, which are
7 studied in the phase 2 trials with the new
8 carbapenem and BLI combination.

9 This is my last example. This is a product
10 being developed as an adjunctive therapy to
11 standard of care, and these are just some examples.
12 It could be an inhaled antibacterial drug being
13 developed for ventilator-associated pneumonia
14 patients, where it's given in conjunction with
15 standard of care antibacterials. It could maybe be
16 immune modulators, or it could be a monoclonal
17 antibody targeting a specific microorganism. In
18 this context, we would recommend a superiority
19 trial where the test drug plus standard of care is
20 compared to standard of care.

21 So to summarize, here are some options for
22 clinical trial designs or data packages for these

1 drugs being developed for patients with unmet need.
2 One option is to do a noninferiority trial at a
3 single body site. We are willing to accept a wider
4 noninferiority margin. And as an option, one could
5 certainly include the nested superiority trial
6 design.

7 A superiority trial could be done where we
8 are willing to accept pooling across body sites.
9 The comparison is made against best available
10 therapy. It's acceptable to leverage external
11 control data. And if the test drug is adjunctive
12 therapy, then test drug plus standard of care would
13 have to be compared to standard of care.

14 If it's a new beta-lactamase inhibitor being
15 developed that's being combined with an approved
16 beta-lactam drug, one could rely in part on our
17 previous finding of safety and effectiveness of the
18 approved beta-lactam as spelled out in
19 Section 505(b)(2). Thank you.

20 CAPT PARISE: Thank you, Dr. Nambiar.

21 Are there clarifying questions for the FDA?
22 Please remember to state your name for the record

1 before you speak. If you can, please direct
2 questions to a specific presenter. Dr. Follmann?

3 DR. FOLLMANN: I have a couple of questions
4 I'd like to bring up to Dr. Laessig and also to
5 Dr. Rubin. The first one, you talked about 21 CFR
6 312.8, which talks about how you're willing to
7 accept greater risk or side effects in unmet need
8 populations who are at risk of dying, basically.

9 I understand that. I guess the way I would
10 interpret that is you're willing to accept a drug
11 that has a higher toxicity profile like colistin or
12 something like that to treat people who are in dire
13 need. But it doesn't say anything about reducing
14 the level of evidence or having less than
15 substantial evidence for approving drugs for such
16 people. It's just allowing that the drug could
17 have a greater toxicity profile.

18 Is that correct?

19 DR. LAESSIG: Yes, that's correct.
20 Certainly, the examples would be oncology products,
21 chemotherapy. This obviously can be fairly toxic,
22 but if you have terminal cancer, you're willing to

1 accept that. Earlier in the days of antiretroviral
2 treatment, those products tended to be more toxic.
3 But, yes. You do have to still meet the
4 substantial evidence of efficacy standard.

5 DR. FOLLMANN: Thanks. The next question I
6 have is for Dan Rubin. On slide 10, and also
7 Dr. Nambiar talked about this design, where
8 basically there's discussion about one of the
9 approaches where you have a noninferiority trial, I
10 guess, where you study that in people, not with the
11 unmet need but a similar population.

12 So I assume that's people who have
13 drug-sensitive organisms instead of drug
14 resistance. You studied in a different group, and
15 then you also allow for a wider margin, and then
16 extrapolate to the group that you really didn't
17 study very much, which is those with drug resistant
18 pathogens.

19 Is that correct as one of the designs the
20 FDA's considering?

21 DR. RUBIN: So that type of design is
22 discussed in the 2013 draft guidance on unmet need

1 and is a design that we're considering.

2 DR. FOLLMANN: All right.

3 DR. NAMBIAR: Dr. Follmann, let me just add
4 to that. So yes. The focus is really not on the
5 resistant phenotype of the organism because here
6 the resistance is to the other existing therapies.
7 It's not resistance to the test drug. And so what
8 we're trying to, again, understand here better is
9 whether the drug works at a given body site of
10 infection. The fact that it works against a
11 certain resistance phenotype would be known from
12 in vitro studies. We would have the animal models
13 of infection.

14 DR. FOLLMANN: Right. So that's all very
15 clear to me and supportive, but ultimately you're
16 not really studying the drug in the population for
17 which it's met, right? I mean, you're developing a
18 drug that will work against a drug-resistant
19 phenotype. It seems logical to try and study it in
20 that population and not study it in a different
21 population.

22 DR. NAMBIAR: Generally, we'll differentiate

1 a patient who has a drug-susceptible versus and
2 drug-resistant infection, usually comorbidities and
3 other coexisting conditions. So we do try to
4 encourage that these trials enroll patients who
5 have comorbidities. We want drugs to be studied
6 ahead of time for patients with renal impairment
7 and hepatic impairment, so such patients that
8 aren't excluded from the trials. The only piece
9 that's missing is does the test drug work against a
10 certain resistance phenotype, and that information
11 does come from in vitro and animal studies.

12 DR. FOLLMANN: Okay. And then the final
13 question, there was discussion about external
14 controls and also augmenting 4 to 1 or 3 to 1
15 randomization, where you would have 4 people on
16 test drug and one person on the control. So you're
17 talking about bringing in external controls to
18 evaluate therapy. I'm curious about the thinking
19 behind that because there's a long history of why
20 we're very hesitant about using historical controls
21 to evaluate therapies reliably.

22 So what's the thinking behind bringing that

1 in, either directly or in through the backdoor,
2 where you're augmenting the randomized control
3 group with this external control data?

4 DR. LAVANGE: I'll take that one. This is
5 something we've been discussing as an alternative
6 to a single-arm study. We get proposals sometimes
7 to just have the non-randomized, single-arm study,
8 and we feel like it would be an improvement to have
9 at least some randomization. That's the first
10 part.

11 But if it's a limited sample size or
12 patients are reluctant to enroll because they don't
13 think there's an alternative therapy other than the
14 test drug, then we could potentially facilitate
15 enrollment -- sponsors could -- with an imbalanced
16 randomization, 2 to 1 and 3 to 1, or even higher.

17 If there were external data that we felt
18 were reasonable, which probably won't be very
19 historical because of the change particularly in
20 resistant pathogen settings -- but maybe case
21 studies, chart pulls, if you had a trial network in
22 place that the NIH has been talking about, for

1 example, that could be a resource where these types
2 of data could be pulled from.

3 Then if you had some amount of
4 randomization, you could look at your control group
5 as concurrent in the trial with your hopefully
6 concurrent external controls -- concurrent in
7 calendar time -- and then assess whether there's a
8 big difference. If there is, you drop the external
9 controls. If there isn't, you could even further
10 reduce randomization.

11 This is something that we've tossed out
12 there as an idea. It's not been latched onto yet.
13 And it has a lot of difficulty. It gets to
14 the -- Dr. Laessig talked about the risk. You've
15 seen us talk about wider noninferiority margins,
16 relaxing alpha to one-sided .05 instead of our
17 usual criteria of one-sided .025.

18 I think in this area of unmet need, part of
19 the risk is that we're willing to accept more
20 uncertainty about the effectiveness side of the
21 equation in addition to the risk that you mentioned
22 about toxicities. So that's where the external

1 controls might come in, maybe improve over a
2 single-arm proposal.

3 DR. FOLLMANN: Just to finish up with a
4 final comment, you talk about being willing to
5 accept more uncertainty about the benefit. I have
6 to question that. I understand there's this
7 concern about an unmet need and about resistance
8 pathogens developing.

9 If we really had a lot of resistant
10 pathogens, we could study it directly. And so we
11 don't have that, but we anticipate there's an unmet
12 need that will be substantial soon. And then the
13 thinking is we'll have a robust armamentarium of
14 drugs to attack it when it actually happens, when
15 it really does widespread with resistant pathogens,
16 so it's pre-planning.

17 But if you're preplanning and your
18 armamentarium is filled with these drugs that
19 really haven't undergone rigorous testing and maybe
20 they're not so effective, but you think they are
21 because you approved it, I don't know if that's
22 necessarily in the best interest of the public

1 health either.

2 So there's a different perspective on this.
3 I know the urgency seems to be coming and so on,
4 but we do certainly want effective drugs that we
5 approve.

6 DR. COX: Thanks, Dean. That's getting to
7 the core of the issue that we're interested in
8 hearing the committee's opinion on. You can tell
9 from my opening comments and the comments being
10 made by folks, we really are trying to balance
11 feasibility and practicality here and recognizing
12 the need for new agents now and in the future.

13 This is the heart of the issue, and we're
14 very interested to hear folks' opinions on it. And
15 you can tell that we think there is a need out
16 there. In order to have new drugs developed to
17 address patient needs, we think this is important.
18 But we want to hear more from you on this, and
19 that's why we're here today.

20 CAPT PARISE: Next was Dr. Hamblett.

21 DR. HAMBLETT: Hi. Clarification question
22 for Dr. Nambiar. In your presentation, the designs

1 that you presented, is there an implicit assumption
2 that the active control would be blinded? And how
3 does that affect the choice of the active control
4 in terms of steering it towards generics versus
5 standard of care changes? It's less feasible to
6 compare against, newly approved therapies.

7 DR. NAMBIAR: There is no assumption that
8 these will be open-label trials. Certainly, we
9 prefer blinded trials as much as possible, but in
10 the nested NI superiority, I think that can become
11 a concern because if you are now having -- once you
12 have the resistant phenotype back, and you know
13 that it's not susceptible to the comparator, at
14 that point you have to change. So we have to work
15 that into the design and see at what point the
16 design could be broken, who could break through,
17 who would know the treatment assignment.

18 I think we are still -- every attempt is
19 being made to keep these trials blinded. Sometimes
20 they are challenging because of the kind of
21 comparators you choose and whether or not it's
22 feasible to blind given that the dosing regimens

1 are very different. It's very difficult to require
2 placebo infusions in these patients who are very
3 critically ill and will have problems with fluid
4 overload.

5 So I think it just depends on each
6 development program. Whenever possible, we still
7 prefer that the trials be blinded.

8 CAPT PARISE: Dr. Moore was next.

9 DR. MOORE: Thank you. Just a quick word
10 about Dean's point about external controls. And
11 that is that there is some precedence for this in
12 looking at fluconazole for the treatment of
13 disseminated coccidioidomycosis. When it was
14 compared against amphotericin B, they used external
15 controls. The external control was used for that
16 particular study. The supporting efficacy was the
17 Natural History trials.

18 Again, different for this population we're
19 looking at for bacterial infections and resistant
20 bacterial infections. But nevertheless, the
21 precedent is there and seems to have done well in
22 the past.

1 CAPT PARISE: Dr. Robinson?

2 DR. ROBINSON: Yes. Actually, for
3 Dr. Nambiar or Dr. Toerner. There's one risk
4 assessment that I haven't heard in the discussion
5 thus far, and I wonder how that figures into the
6 calculus of approvability of the drug. And that's
7 the ease or speed of which pathogens may develop
8 resistance to the new test drug. Where would you
9 put that, in terms of your evaluation of an
10 approvable drug, and how important is that?

11 DR. NAMBIAR: Certainly, a
12 pre-approval -- there are a battery of microbiology
13 tests done, which do look for the potential for the
14 development of drug resistance beyond. Since the
15 passage of FDAAA in 2007, whenever a new
16 antibacterial drug is approved, there is a
17 postmarketing requirement that surveillance studies
18 be done and those data be reported to us on an
19 interim basis, which, generally, we are looking for
20 development of resistance all the time. So we can
21 do that as a postmarketing requirement.

22 CAPT PARISE: Dr. Andrews?

1 DR. ANDREWS: Just as a comment, and then I
2 have a couple of questions, and I have no idea who
3 they go to. I work around a lot of different kinds
4 of policy tables, and I have to tell you that this
5 is incredibly thoughtful, and the data that's being
6 used here is really refreshing. Too many times
7 policies are made based on one constituent. I
8 think this is amazing, and never does anybody
9 anticipate things happening and make changes to
10 address them. So I think that you should be
11 applauded for that.

12 My questions are about labeling. Does
13 labeling include a -- when you say that doctors and
14 patients with an unmet need and facing death are
15 more likely to take risks, that's true. And the
16 aggregate, not necessarily true for every
17 individual patient. And I'm wondering if there is
18 anything in the labeling that goes to patients to
19 explain to them that this might have higher risks
20 for -- or that the risks are not as well known as
21 something that had a more rigorous testing.

22 Also, because the sample sizes are so small,

1 there are clues to things that aren't significant.
2 But are those still included in the labeling, if
3 you're saying that it's not significant but there
4 was -- at this particular site, there was less
5 effectiveness?

6 That was one question. And the second one
7 is, also, how confident are you that these changes
8 will actually end up with more drugs being
9 developed, that these will really work?

10 DR. COX: To the first question about
11 labeling, in the clinical study section, we do
12 describe the key studies that supported approval.
13 Now, you asked more specifically would there be
14 some cautionary wording in there about that. It's
15 probably going to be more in the data itself.
16 You'll be able to see the size of the trial, the
17 trials that were conducted.

18 There is also information for patients that
19 would be in there. But again, I really think that
20 the information about risks or uncertainty will be
21 in the other parts of the label that describe the
22 adverse effects of the drug, describe the overall

1 evidence that was used to support the drug, the
2 size of the trials, the confidence intervals and
3 the uncertainty around them. So it is going to be
4 a little more technical, I think, than what you're
5 describing.

6 Some of the ideas that have been brought out
7 by groups, like IDSA for their LPAD proposal, do
8 get to this issue of trying to identify such drugs
9 so that healthcare providers have a quick and easy
10 way of identifying drugs that are approved on a
11 more limited basis.

12 Remind me of your next question. I'm sorry.

13 DR. ANDREWS: [Inaudible - microphone off.]

14 CAPT PARISE: Could you put your microphone
15 on just so people can hear?

16 DR. ANDREWS: Sorry. The labeling question
17 about non-significant findings, and then also how
18 confident are you that this will lead to faster
19 drug development.

20 DR. COX: On the issue of non-significant
21 findings or other smaller things, it depends upon
22 the nature of the finding as to whether that would

1 appear or not. As we get to more and more granular
2 information that's less clear, it tends to be the
3 sort of thing that would be less likely to be
4 included.

5 If it's a safety finding and there are
6 reasons to be concerned, such as you saw it in
7 animals, in the animal studies, and then you're
8 seeing some in the clinical trials, that would be
9 the sort of information that would be included. So
10 it depends a little bit on the type of information.

11 DR. ANDREWS: [Inaudible - microphone off.]

12 DR. COX: So the question of is this going
13 to help. The situation that we've been in is that
14 there really has been a significant reduction in
15 the number of antibacterial drugs in development.

16 Where we sit and see these drugs coming
17 through, there was really a significant decline in
18 the amount of development going on. A number of
19 factors I think contributed to that, the field is
20 maturing, economic issues; scientifically, it's
21 difficult, the alternative uses for -- alternative
22 areas where drugs may be developed.

1 Clearly, one of the things that we've heard
2 through scientific meetings and discussions on
3 antibacterial drug development over the last
4 several years are really the significant challenges
5 of developing such drugs. And from where we sit,
6 we think those challenges are real. We are trying
7 to do what we can to develop approaches that will
8 address some of the challenges that are out there.

9 It goes back to Dean's question and I think
10 the comments that we're making, that there is a
11 recognition that there are trade-offs we bring to
12 you today and what those trade-offs are, and trying
13 to balance the trade-offs of patient needs,
14 benefit/risk in order that new drugs are developed.
15 I don't know that there are specific guarantees,
16 but these are the types of changes that we expect
17 will help to address some of the challenges that we
18 are aware of that are out there in the field today.

19 DR. LAESSIG: Certainly, in general, when
20 there's a clear regulatory pathway for development
21 of products, that helps a great deal. There are
22 other issues -- economics -- that are beyond the

1 agency's ability to change, so those things also
2 need to be addressed. But again, that's beyond our
3 capacity to deal with, such as incentives and other
4 things like that. A clear regulatory pathway
5 definitely does help.

6 DR. COX: Thanks, Katy. And I did try to
7 mention some of that, too, the idea of clinical
8 trial networks. Master protocols for development,
9 rapid diagnostics, could also help the field, could
10 help drug development. Things like rapid
11 diagnostics may also help with appropriate use once
12 a drug is out there, too.

13 So thanks, Katy. That's an important point
14 to bring up as part of this overall equation of how
15 we positively impact upon antibacterial drug
16 development. Those things will take time. The
17 problem is here, it's now, and we're trying to
18 respond to it.

19 CAPT PARISE: Dr. Magill?

20 DR. MAGILL: Just a couple of comments and
21 two, hopefully, straightforward questions. The
22 comment is, I certainly very much welcome and

1 applaud the FDA for coming forward with this kind
2 of what I call a very flexible and personalized
3 approach to antibacterial drug development.

4 I think the key here would be to allow our
5 FDA colleagues, the professionals at this, the
6 flexibility to engage with applicants and sponsors
7 to actually come up with a plan for that particular
8 product and indication, and I think that's probably
9 the intent. And I think it's well done.

10 The concept that a randomized-controlled
11 trial with a superiority endpoint is the answer to
12 every question is clearly not true, so I think
13 that's welcomed.

14 The issue about controls continually comes
15 up. That's why we have ICHE-10. There are various
16 control groups and things one could use.
17 Historical controls are not appropriate for some
18 studies, but they may be appropriate for others,
19 and I think that's the flexibility that one needs.

20 There is somehow a sense that once a drug is
21 FDA approved, all learning stops, and that's a
22 mistake. Of course, learning is a continuous

1 process as you go through. And if drugs are
2 approved based on a certain urgency and
3 risk/benefit and less robust effectiveness data,
4 then maybe a learning phase needs to be built in,
5 in phase 4, that is taken forth. So I think all
6 that can allow flexibility.

7 A couple of questions. One, there is a bit
8 of a reliance on microbiologic endpoints such as
9 in vitro susceptibility testing, which may or may
10 not actually predict clinical outcome. And the
11 issue of what those breakpoints are, how they're
12 set, and do they actually predict anything of value
13 in the patient continues to -- it's a difficult
14 area. And I appreciate a little bit more -- maybe
15 your thoughts on how that would be applied in these
16 settings.

17 The other one is I like the concept of a
18 limited-use indication. And what I'm wondering is,
19 once a drug is FDA approved, how do you translate a
20 limited-use indication into limited use and is that
21 a concern going forward.

22 DR. NAMBIAR: Maybe I'll start with the

1 second question. We do share the concern. Even
2 though it's a limited-use statement, whether
3 actually there will be limited use once a drug goes
4 out, and that's why we would depend on our clinical
5 colleagues to exercise good stewardship. We really
6 don't control the practice of medicine.

7 So our hope is that once we spell out
8 everything in the labeling in terms of what we
9 could and couldn't learn from the study, we do rely
10 really on practitioners at that point to exercise
11 good judgment in terms of stewardship.

12 That's one of the big risks we are taking.
13 These development programs are going to be very
14 small. So there is uncertainty both from an
15 efficacy standpoint; there's an uncertainty from a
16 safety standpoint. We may unfortunately come upon
17 a situation where there will be some unidentified
18 safety signals that you may see for the first time
19 post-approval.

20 So yes, there is going to be a great
21 reliance on stewardship, but there's also going to
22 be a great reliance on healthcare practitioners to

1 be very vigilant in terms of any kind of untoward
2 safety findings.

3 Your first question I think related to
4 in vitro activity and breakpoints. I wasn't as
5 much referring earlier to susceptibility and
6 interpretive criteria. It's more does the drug
7 have activity when you're interested in a certain
8 resistance phenotype. Does it cover certain
9 carbapenemases? Does it cover the ESBLs? I think
10 that's the intent.

11 The actual breakpoints, we will have
12 to -- interpretive criteria, we will set once we
13 have the clinical trials and we have clinical PK
14 and micro data, putting all that into context, and
15 we would set the breakpoints.

16 DR. MAGILL: So it's almost like an
17 inclusion criteria for entering -- for use of the
18 drug in a clinical trial to show that it has
19 in vitro activity.

20 DR. NAMBIAR: Right. I think as Dr. Toerner
21 had in his presentation, this is part of the
22 nonclinical or the preclinical development program

1 for these drugs, that you actually have to show it
2 has activity.

3 CAPT PARISE: Just a reminder before I call
4 the next panelist, the session now is mainly for
5 clarifying questions. We will have plenty of time
6 this afternoon for discussion. So let's limit it
7 to clarifying questions for now. Dr. Ostrosky,
8 you're next.

9 DR. OSTROSKY: I'd like to second Alan's
10 comment. This is a very well thought-out approach,
11 very progressive, addressing a problem that is not
12 academic or theoretical. It's a real problem we
13 are facing right now.

14 My question is for Dr. Nambiar. When we're
15 talking about best available therapy as controls,
16 are we talking about drugs that may not have an FDA
17 approval for that particular indication but are
18 widely considered the standard of care in the
19 community for those infections?

20 DR. NAMBIAR: I'm sorry. I missed the first
21 part of the question. Was it standard of care?
22 Can you restate your question?

1 DR. OSTROSKY: Yes. So when we talk about
2 best available therapy as a control in these
3 trials, are we including drugs that may not be FDA
4 approved for that indication that are widely
5 considered a standard of care?

6 DR. NAMBIAR: Sure. Yes, I think that would
7 be acceptable.

8 DR. OSTROSKY: I think that's a very
9 progressive approach.

10 DR. NAMBIAR: Yes, very hard. If they're
11 all of the approved, then probably you're not
12 putting together a best available therapy regimen
13 at that point.

14 DR. OSTROSKY: I think that's a very well
15 thought-out approach.

16 CAPT PARISE: Dr. Baden?

17 DR. BADEN: Thank you for a wonderful set of
18 presentations framing an incredibly important
19 issue. My question is for Dr. Nambiar. In
20 thinking about the noninferiority design versus
21 superiority design and the threats to validity,
22 when one looks at the ITT versus the per protocol

1 or as treated, I think they have different risks
2 for the different designs. With the ITT in a
3 noninferiority design, does that increase the
4 potential to demonstrate non-noninferiority?

5 DR. RUBIN: So the question was about
6 analysis populations, and in particular the per
7 protocol population and the intent-to-treat
8 population, and whether an intent-to-treat
9 population would be less appropriate for a
10 noninferiority design than a superiority design
11 because of the possibility of essentially biasing
12 toward the alternative of not showing a difference.

13 That is an inherent limitation of
14 noninferiority design, and those designs, we always
15 look at the per protocol or evaluable population.
16 In our guidances, we generally still recommend that
17 the primary analysis population is an
18 intent-to-treat population or a microbiological
19 intent-to-treat population consisting of those
20 randomized subjects who have the relevant pathogen
21 because there are other trade-offs.

22 In particular, the intent-to-treat

1 population preserves the integrity of randomization
2 and minimizing confounding between the two compared
3 groups on factors other than what's being tested,
4 whereas the per protocol or evaluable can exclude
5 patients based on post-randomization events, which
6 impacts the integrity of randomization. But
7 certainly that is relevant limitation and
8 consideration of noninferiority designs, and
9 compliance or lack of compliance can bias you
10 toward the alternative rather than the null and is
11 always part of the review.

12 DR. BADEN: So getting to the open comments
13 in the discussion session, the substantive efficacy
14 or activity, both the ITT PP would be used as
15 evidence given the intrinsic weaknesses -- in this
16 setting of unmet need and complicated populations.

17 DR. RUBIN: Right. So the considerations
18 that I mentioned really applied to both prongs that
19 Ed mentioned in his first talk, the unmet need
20 setting and the more general development. Sorry.
21 For the record, I'm Dan Rubin.

22 CAPT PARISE: Dr. LaVange.

1 DR. LAVANGE: This is Lisa LaVange. I'm
2 worried that you're asking if you have to win on
3 both populations.

4 DR. BADEN: I was not suggesting winning on
5 either, nor a preference as much as -- the
6 challenge here is we'll have limited data in the
7 target population, with the target organism, with
8 other complexities, including medication
9 compliance.

10 The ability to establish or convince
11 ourselves of substantive efficacy I think requires
12 the ability to look at these different kinds of
13 populations within a study, because it's hard to
14 believe that a patient who never receives the
15 medicine or receives one dose at day 10 or 14 may
16 reflect the same activity as someone who receives
17 the full course.

18 But I do share the concern that
19 randomization takes into consideration unmeasured
20 factors that we have to be careful not to discard.
21 But I think the totality of the evidence will be
22 important in assessing the activities.

1 CAPT PARISE: Dr. Scheetz, and then
2 Dr. Reller.

3 DR. SCHEETZ: Like everybody else, I'd like
4 to applaud the Center's efforts here. The draft
5 guidances have been very helpful. Specifically, I
6 want to ask about the M1 estimates. I think
7 they've done a very admirable job of trying to
8 define M1.

9 When we're talking about pooling across
10 sites -- and this question is probably for
11 Dr. Rubin. When we talk about pooling across
12 different sites of infection, on different
13 infections, M1 changes. So when you pool across
14 these different sites, and you have a changing M1,
15 are there methodologies to compare the differences
16 between M2 and M1?

17 DR. RUBIN: Right. Dr. Nambiar actually had
18 some information written down on the different M1s
19 for different sites of infection. I don't know
20 whether she wants to go through that or not, but
21 let me take a stab at your question.

22 First, we do think that a noninferiority

1 trial, the logistics of this would be more
2 difficult for a pooled body site trial than a
3 superiority design because of the considerations
4 that you mentioned. And that was one issue that we
5 wanted to bring forth for the committee today.

6 You would essentially, in terms of M1, have
7 to argue that the overall effect across sites of
8 the active control had a difference of a
9 substantial magnitude relative to the overall
10 effect of placebo across sites, which really gets
11 to the issue of clinical heterogeneity and how much
12 sense it makes to combine these sites.

13 The other consideration I would say
14 regarding pooling of body sites in superiority
15 versus noninferiority is that the reason we've been
16 talking about pooling body sites is basically as a
17 last resort when resistant pathogens, or patients
18 with resistant pathogens, are difficult to find.
19 Noninferiority is generally reserved for situations
20 where there are active comparators with substantial
21 efficacy that are options for patients. So we
22 think it would be less challenging to conduct

1 site-specific noninferiority trials.

2 CAPT PARISE: Dr. Reller?

3 DR. RELER: My question is also for
4 Dr. Rubin. Barth Reller.

5 Dr. Rubin, on your slide 10, the second
6 bullet, the challenges of extrapolation for
7 noninferiority designs, the two subsets of that
8 both had to do with patient factors that could
9 affect the outcome and the striking differences on
10 your next slide between the kinds of patients with
11 resistant susceptible organisms.

12 My question is, is there a statistical way
13 to tease this out in a meaningful way? If the
14 endpoint were mortality, one could get this with
15 different populations of attributable mortality.

16 Is there a concept of poor outcome, even
17 with an endpoint of mortality -- that or one of the
18 endpoints -- that could be attributable to the
19 resistant organism as opposed to not the resistant
20 organism? Is there a way to correct or modify or
21 adjust -- an adjustment factor that takes those
22 other influences on outcome that would separate it

1 to what could be attributable to the resistance
2 mechanism or the resistance organism?

3 DR. RUBIN: Thank you. That's an excellent
4 question, and it also gets to Dean's first question
5 about noninferiority trials conducted in patients
6 with sensitive infections, and then extrapolating
7 the results to a patient with resistant infections,
8 and the fact that these patients can differ on
9 their underlying covariates. And those differences
10 can be prognostic of outcomes and modify
11 antibacterial treatment effects.

12 Now, there are statistical methods that
13 attempt to perform that correction, propensity
14 score matching, weighting, and so on, which
15 basically amount -- if you think about
16 stratification, if patients in the resistant
17 pathogen cohort are more severe, then you would
18 compare those patients to patients in the sensitive
19 pathogen cohort with greater underlying severity.

20 The challenge is that all these statistical
21 methods basically require extrapolation or leaps of
22 faith, reliance on assumptions that are far less

1 pristine than you would obtain in a direct
2 randomized comparison within the resistant pathogen
3 cohort.

4 DR. RELLER: So in follow-up to that, it may
5 be that it's a matter of how much -- what kinds of
6 leaps of faith one would be willing to make. I
7 mean, to some extent, it's a leap of faith that a
8 neutropenic mouse thigh is alone, or as Dr. Magill
9 pointed out, the plus or minus dilution or
10 millimeter here or there. All of these are, to
11 some extent, a leap. It's which leaps are more
12 plausible or consonant with the clinical outcome.
13 That's our challenge.

14 DR. RUBIN: Right. In this case, the
15 measured covariates that can be used to adjust or
16 correct between different populations are often
17 only a tip of the iceberg of differences between
18 these populations. So it is a very challenging
19 problem. And I can't say statistically that we
20 have the solution or that we can give you the type
21 of answer that would be as reliable as the first
22 option that I mentioned, of conducting a

1 superior trial in a resistant pathogen cohort.
2 There are unverifiable assumptions that go into
3 this, but I'd welcome comments from my clinical
4 colleagues as well.

5 DR. COX: Just one more thing. Again, we
6 actually have this in the draft guidance document,
7 and it talks about -- if you're going to use it in
8 another trial design, one of the things we do
9 strongly encourage is trying to enroll sicker
10 patients, patients that have the comorbidities that
11 are likely to be as representative as possible as
12 the resistant pathogen population.

13 Again, to guarantee that they're the same is
14 something that is beyond what can be done, but
15 certainly steps can be taken to enroll patients
16 that are more like those that have resistant
17 organism infections to try to decrease the degree
18 of leap of faith as one is extrapolating to that
19 patient population.

20 Also, too, within these development
21 programs, there's also the idea that if the NI
22 trial does not enroll a fair proportion of patients

1 with a particular resistance phenotype, again that
2 resistance phenotype is resistant to some other
3 drugs, not the test drug that you're using, there
4 may also be additional work done, an additional
5 study done in patients with the resistant pathogens
6 of interest, not so much to study the resistant
7 pathogen per se, not so much to study that
8 particular resistance phenotype, but to understand
9 the patient characteristics of that patient
10 population, to gather PK data to see if there are
11 other events that are happening in that patient
12 population.

13 That study may not be powered, but it would
14 provide some information that may help one to
15 bridge the differences, what those differences may
16 be between an NI trial that's designed their own
17 separate patient populations and the patient
18 population with a resistant phenotype of interest.

19 CAPT PARISE: Are there any other clarifying
20 questions from the committee?

21 (No response.)

22 CAPT PARISE: We'll now take a 15-minute

1 break. Panel members, please remember, there
2 should be no discussion of the meeting topic during
3 the break amongst yourself or with any member of
4 the audience. I have 10:20 now, so for 15 minutes.
5 We'll come back at 10:35. Thank you.

6 CAPT PARISE: We're going to get started
7 again. Please take your seats. We will now
8 proceed with the presentations by the professional
9 organizations, starting with the American Thoracic
10 Society.

11 **Presentation by Professional Organization**

12 **Richard Wunderink**

13 DR. WUNDERINK: Thank you for the
14 opportunity to present here. I'm going to be
15 representing the American Thoracic Society. Our
16 members are predominantly pulmonary and critical
17 care physicians, and we're often the primary care
18 physicians for many of the patients who develop
19 these MDR and XDR pathogens. Many of our members
20 are also actively involved in clinical research in
21 pneumonia and sepsis.

22 These are my conflict of interests that

1 include many of the people here. And this is the
2 clinical scenario that I have to deal with on a
3 regular basis. This is a 69-year-old patient who
4 is initially admitted to our ICU with a
5 community-acquired pneumonia, the left lower lobe,
6 had bad COPD, a short ventilator run. Went out to
7 the floor, and then came back with respiratory
8 failure and hypotension. It would seem that this
9 looks like a straightforward case of new
10 hospital-acquired pneumonia. The problem is that
11 the patient also had a central line in for seven
12 days. It hadn't been pulled when he initially left
13 the ICU.

14 For the clinicians in here -- and I can't
15 see very well from here -- but if you look at his
16 NG tube, it actually goes down and then heads back
17 north. So one of the considerations was that this
18 was actually an aspiration pneumonitis. So I'm
19 sitting here with a patient who could have sepsis
20 from central line and early ARDS. He's got a
21 changed X-ray. It could be aspiration. It could
22 be new ARDS. And yet, this looks like a great

1 patient to put in one of our clinical trials of
2 pneumonia.

3 So that's the kind of patients that we deal
4 with on a regular basis, and you sometimes forget
5 the complexity of these patients.

6 I'm going to try and address at least three
7 of the discussion points that were put forward by
8 the FDA here on trial design options for a product
9 with limited spectrum of activity, the
10 acceptability of some smaller safety databases, and
11 some issues about the trial design, especially a
12 control group for inference testing and best
13 available therapy.

14 The first point is about trial design for a
15 drug with a limited spectrum of activity. And the
16 points is, been there and done that. We've
17 actually done this in the past for MRSA. That's a
18 very limited spectrum of treatment with vancomycin
19 or linezolid. And I think it's illustrative to see
20 what this is going to mean when you have a trial
21 that looks for a very narrow group of patients.

22 This trial took 5 years and 3 months,

1 multiple institutions in six continents, to get an
2 adequate number of patients. This is the flow
3 diagram. And what you see is that we started with
4 1200 patients.

5 Now, all of these were supposed to have very
6 high risk of MRSA pneumonia when they were enrolled
7 in the study, and yet what we ended up with in the
8 microbiologic intent-to-treat populations were a
9 couple hundred patients in each group. That was
10 still sufficient to actually show the superiority
11 that this trial was designed to show in clinical
12 outcome, and it was consistent across these
13 different subgroups or different assessment points,
14 but it didn't show a mortality difference.

15 Now, I'll remind you, at the time when we
16 originally started doing linezolid studies, there
17 was an unmet need of mortality difference compared
18 to vancomycin. The point about this is when you
19 got to this trial, the difference here in this
20 latest phase 4 trial versus these two phase 3
21 trials earlier was that, in fact, linezolid was on
22 the market, and so there's salvage therapy for

1 vancomycin failures.

2 When you're doing a phase 3 trial or an
3 initial trial, if there's no salvage therapy,
4 you're going to see a mortality difference. If you
5 have some sort of salvage therapy, that mortality
6 difference may go away. So that's going to be an
7 important issue. If we get one drug on the market
8 for some of these MDR Gram-negative pathogens, it's
9 going to be very important that maybe only one
10 study is going to be able to show us superiority,
11 and then every one after that is going to have to
12 show equivalence.

13 I think this issue of salvage therapy is
14 critically important to understand. We in the
15 intensive care unit do everything we can to not let
16 a patient die, and that includes all sorts of
17 salvage therapy that is non-FDA approved.

18 What about this smaller safety database of
19 300 to 400 patients? I'll take you through
20 Pseudomonas since that's one of the important
21 pathogens that we're talking about here. This is
22 probably the largest randomized controlled trial

1 that included Pseudomonas patients. In their
2 intention-to-treat population, there were 44
3 Pseudomonas cases treated with imipenem and 47 with
4 ciprofloxacin.

5 This was the original ciprofloxacin phase 3
6 registration trial, and that's the largest database
7 that we have on treatment. That was before cipro
8 or imipenem were routinely available, and therefore
9 routinely had selective pressure; and yet we're
10 seeing resistance developing already here.

11 If you look at best study of combination
12 therapy and how many Pseudomonas cases they
13 included, 20 and 22 in each of the arms. And here,
14 looking at the most recent trial of a comparison of
15 two carbapenems, the Pseudomonas group was 17
16 patients and 10 patients. And yet even with this
17 clinical response difference and this mortality
18 difference in those studies, it was statistically
19 significant.

20 So the bottom line is we don't have a big
21 database for Pseudomonas, Acinetobacter, CREs, any
22 of these. Even retrospective studies only have

1 about 183 cases here that we can make some
2 conclusions on as far as treatment and also safety
3 issues in these patients. I'll point out that
4 inappropriate initial therapy, even when corrected,
5 is always associated with worse outcome. The
6 acceptability of a smaller safety database of 300
7 to 400 patients, I'd love it. I'd love you to be
8 able to show me a database that has 300 *Pseudomonas*
9 cases, or 300 *Acinetobacter* cases, or 300 CRE
10 cases. That would be very acceptable to
11 clinicians.

12 Now, what about the superiority trial design
13 and selection of the control group for inference
14 testing, especially this issue of best available
15 therapy? And this is my interpretation of best
16 available therapy. I don't know what it is. We
17 can't see the forest for the trees clinically
18 because these patients are so complex, you don't
19 know whether that fever is in fact a failure of
20 your drug or whether it's something else.

21 So we had some hope about the use of the
22 Clinical Pulmonary Infection Score, which is

1 nothing really fancy. It's putting numbers on what
2 clinicians look at all the time: what the fever
3 is, are the secretions down, is the oxygen
4 improving. And I'll point out, in this carbapenem
5 study, where they compare doripenem to imipenem,
6 where there was a clear difference in clinical
7 response rates and even a trend toward a mortality
8 difference, the CPIS score, the median or mean here
9 was exactly the same until you started to stop
10 antibiotics, and then they started to separate.

11 So on therapy, CPIS doesn't mean very much,
12 and it also illustrates that a lot of the signs and
13 symptoms that we follow can be suppressed even with
14 not totally adequate antibiotic therapy.

15 One of the critical things to remember is
16 something that we drive into the heads of all of
17 our trainees, is that time to first antibiotic dose
18 is critically important to outcome. And many of
19 our trials of adjunctive agents, actually when you
20 look at time to first appropriate antibiotic dose,
21 there effect goes away. So we cannot tolerate not
22 giving broad spectrum, empiric antibiotic therapy

1 up front.

2 Now given that, we still have issues of what
3 if that's inappropriate? What if we have one of
4 these carbapenem Enterobacteriaceae? In initial
5 inappropriate empiric therapy, if you look at PF
6 ratios or fever, if you start a Pseudomonas that's
7 initially inappropriate versus Pseudomonas that's
8 appropriate with initial therapy, what you see is
9 that for both fever and oxygenation, starting wrong
10 significantly affects your subsequent response
11 rates.

12 In these very common clinical criteria, if
13 you start wrong, it looks like MRSA, which looks
14 like treatment is bacteriostatic. If you start
15 right, you get a very rapid drop-off and
16 improvement in these clinical symptoms. And that's
17 going to have a clear effect in a clinical trial.

18 We can't forget the fact that antibiotics
19 kill bacteria. And in fact, I think we
20 underutilize microbiologic response in a lot of
21 these studies. If you have non-responders, you're
22 going to have persistent positive cultures. We

1 just don't do them often enough, particularly in
2 ventilated patients where there is relatively easy
3 access.

4 This is an important endpoint to look at,
5 but it's not the be-all and end-all. If we make
6 bacteria disappear and still the patient is in
7 septic shock or ARDS and dies, it's sort of like
8 the surgeon who says the surgery was a success but
9 the patient died. So it has to be complemented
10 with other things.

11 There is some increasing emphasis clinically
12 in the use of biomarkers, probably procalcitonin,
13 and this is now all off-label use of procalcitonin.
14 Procalcitonin does predict outcome here at day 3,
15 nice ROC curve on predicting patients who would
16 fail therapy or die. At day 7, slightly different
17 criteria but same very good ROC curve. And there's
18 actually randomized controlled trials of duration
19 of antibiotic therapy based on biomarkers.

20 So basing how long you treat a patient on
21 procalcitonin has shown to significantly decrease
22 antibiotic therapy, and this actually offers the

1 first evidence of the timing of duration of
2 antibiotic therapy to be 7 days, other than the
3 fact that God rested that day. So this is one of
4 the things that I think is also underutilized and
5 is used more and more clinically to determine, is
6 the patient responding? Can I stop antibiotics?
7 And I think that that's one of the critical things
8 that we need to look at, is stopping antibiotics.

9 This is data on early discontinuation in
10 culture-negative cases. And what you see, if you
11 follow the symptoms, if you stop early when your
12 cultures are negative versus continuing
13 antibiotics, you actually have less fever. So some
14 of the symptoms that we are treating, thinking the
15 patient's not responding are actually drug fever.

16 The importance, though, is if you stop, you
17 have less super infection overall, less infection
18 of pneumonia, less super infection with MDR
19 pathogens. So one of the critical things that we
20 need to follow as we look at these new agents is
21 are they actually selecting for super infections
22 because that's what really kills these patients.

1 One of the things that I think is important
2 to include that I haven't heard a discussion about
3 is the actual duration of antibiotic therapy. This
4 is one of the few randomized controlled trials in
5 critical care medicine that we actually have to
6 answer a clinically relevant question. And this
7 is, antibiotic duration of 8 days versus 15 days.
8 And for those of you that are a little bit limited
9 as far as your distance vision, that's actually two
10 lines. It looks like one, but there are two lines
11 there. That's absolutely no difference between 8
12 days versus 15 days.

13 People look at this study and are
14 particularly concerned about the nonfermenter
15 group, where there seems to be a slightly higher
16 recurrence rate, and so have suggested longer
17 duration of treatment in those patients.

18 When you actually drill down on it, it turns
19 out that the 8 days was associated with less
20 emergence of MDR pathogens, and it was actually
21 associated with a lower mortality, even in that
22 specific subgroup, and associated with

1 significantly greater antibiotic free days.

2 This is just a problem with Pseudomonas.
3 There's recurrence. Here, an old study that shows
4 basically 50 percent of everybody who survives a
5 first episode of Pseudomonas pneumonia gets a
6 second episode. Fifty percent of those that
7 survive that second episode get a third episode,
8 and nobody survives that third episode.

9 So recurrent Pseudomonas and probably
10 Acinetobacter is a problem. There's a mathematical
11 error here. You just have a longer observation
12 time in the 8-day treatment because they were
13 looking at recurrence within 28 days.

14 If you actually look at the relapses, in
15 both groups it's one per day. Wit this increased
16 emergence of MDR pathogens and no effect, possibly
17 even slightly lower mortality, there's no reason to
18 not go longer than 8 days. And 8 days actually
19 represents failure of therapy, and that needs to be
20 incorporated into some of our studies that have
21 this very nebulous 7 to 21 days of treatment. And
22 I think that we really need to call those failures

1 and change the regimens.

2 From a clinician investigator perspective, I
3 think that rapid accurate diagnostic testing will
4 make trials of specific pathogens more feasible.
5 It was easier for MRSA than it will be for CRE or
6 Pseudomonas unless we get some rapid diagnostic
7 testing. And that's not a Gram stain. I think the
8 safety database of 300 to 400 in patients who are
9 most likely to get this antibiotic would be
10 wonderful, would be fantastic.

11 Much more robust outcomes measures are
12 really needed for these smaller clinical trials.
13 The clinical response from a clinician is just not
14 reliable enough, and I think we need to define what
15 the best available therapy is better because that's
16 very heterogeneous between different groups. And I
17 think the FDA should encourage antibiotic
18 stewardship by limiting duration in clinical trials
19 and tightening up that requirement. Thank you very
20 much.

21 CAPT PARISE: Thank you, Dr. Wunderink.

22 We will now proceed with the IDSA PIDS

1 presentation.

2 **Presentation by Professional Organization**

3 **Jason Newland**

4 DR. NEWLAND: Good morning. My name is
5 Jason Newland, and I'm a pediatric infectious
6 disease physician at Children's Mercy Hospital in
7 Kansas City. And I'm here to represent the
8 Infectious Diseases Society of America, as well as
9 the Pediatric Infectious Disease Society. I'd like
10 to thank the committee as well as the presentations
11 earlier today from the FDA. I appreciate the
12 opportunity to learn in this setting and to provide
13 you our views in regards to this very, very timely
14 and important topic.

15 The IDSA membership, as well as the
16 Pediatric Infectious Diseases Society membership,
17 is over 10,000; the Pediatric Infectious Diseases
18 Society if probably around 2,000. As you can see,
19 we are primarily clinicians, over 50 percent, and
20 you'll see we're also involved in basic research,
21 epidemiology, and administration.

22 I like to think of us that as infectious

1 physicians, we touch a lot of folks in the
2 hospital, in the community, and public health, and
3 therefore we are a very important part. But
4 obviously, most of us, if not all of us, are
5 clinicians at heart, and this is what got us into
6 this field and why it's so important, and why this
7 topic is so important to all of us.

8 This is why. The IDSA, as well as PIDS, has
9 been focusing on this tragedy of ineffective
10 antibiotics over the past decade and seen this.
11 And you see the names, and the deaths, and the
12 life-altering disabilities here on this slide and
13 can be seen on the website of idsociety.org. But I
14 also have my personal story about this, and it was,
15 actually, probably over four or five years ago when
16 I was on service in my hospital, at Children's
17 Hospital, about 300 beds, in the neonatal intensive
18 care unit, with an ex-24-week preemie who at
19 4 weeks of life developed a Pseudomonas infection,
20 and actually had been doing well. As hard as it is
21 to believe, our medical community has developed
22 amazing strategies to keep these children alive.

1 But at 4 weeks of life, developed a
2 bloodstream infection with Pseudomonas. As we've
3 heard, Pseudomonas is one of those scary bacteria,
4 as you all know, and it was susceptible to
5 cefepime. We treated it with cefepime, stopped the
6 treatment, and after a short time after that,
7 developed that Pseudomonas infection again. And as
8 you know where the story's going, that Pseudomonas
9 was now resistant to cefepime.

10 So what did we use? We used a carbapenem,
11 and our carbapenem of choice in our hospital is
12 meropenem. So we used that meropenem and treated.
13 And again, after that treatment, the child
14 developed another Pseudomonas infection. And as
15 you can imagine where this story is going, that
16 Pseudomonas infection was resistant now to
17 meropenem.

18 So you wonder four or five years ago what a
19 pediatric infectious disease physician was deciding
20 what they were going to use. And as many of you in
21 the audience know, we all thought colistin, and
22 that's what we gave the child. And unfortunately,

1 the child end up passing away in the midst of the
2 colistin therapy.

3 I don't think my dad, who's a family
4 physician in Oklahoma, would have ever thought that
5 we'd be in an era where you wouldn't be able to use
6 an antibiotic, nor I as a new, young practicing
7 pediatric infectious disease physician would have
8 already come on to a case where you thought, "Wow.
9 We didn't have an antibiotic to treat a neonate,"
10 one of our most vulnerable.

11 So what are those unmet needs? And this is
12 what we see from the Infectious Disease Society of
13 America, the major unmet needs. One of those,
14 which I just illustrated you a story, which is not
15 an uncommon story across the country, even in our
16 children's hospitals, are antimicrobials to treat
17 Gram-negative infections.

18 But we also need better antimicrobials to
19 treat Gram-positive infections, like our MRSAs that
20 can even become resistant to linezolid, especially
21 in those cystic fibrosis patients, where we've
22 already seen that happen. And then there's no

1 truly oral option for these children or these
2 adults.

3 Also, oral antibiotics for complicated UTIs,
4 sexually transmitted infections, especially
5 gonorrhea, as we've all seen the increase in
6 resistance; respiratory infections, step-down
7 therapy, so that we can get off some of our
8 intravenous therapies and go home on orals to
9 prevent some of the complications of our central
10 lines and other things needed to give these
11 medications.

12 Finally, and why I'm so glad to be here and
13 appreciate all the work that's being done to help
14 address this, is to develop a robust and
15 sustainable pipeline of anti-infective drugs to
16 provide for our patients now and for those future
17 generations yet to come.

18 So what are the realities? Well, I gave you
19 that story. I gave you that story to set up this
20 aspect. Really, the only antibiotic remaining to
21 treat many Gram-negative infections is colistin;
22 also, polymixin is brought up because it's in the

1 same class. But it's toxic, especially in the
2 adult population. It can cause kidney failure.
3 And colistin has not been used in 30 years. And so
4 when we saw this resistance, we go back and pull it
5 out, and it can work, but obviously it has its
6 negative consequences.

7 After colistin -- and we asked the residents
8 who don't even really know that colistin's in the
9 armamentarium -- we usually stop at meropenem.
10 There's nothing after meropenem, but we all say,
11 "Look. We have colistin." I don't want you to
12 know about that yet, but the reality is they do
13 know about it. And in certain parts of the world,
14 they really know about it because that's all they
15 can use, like in places like Greece, where
16 50 percent of their *Klebsiella pneumoniae* is
17 resistant to carbapenems, if not more.

18 What do you have, that alternative as you
19 see in that green box? Current alternatives for
20 these patients, do you want to die or be in
21 dialysis for the rest of your life or you can get a
22 kidney transplant? Not an easy decision and

1 obviously why we need the new drugs.

2 So what do we do? What do we do? What did
3 I do? What do all my colleagues do when they come
4 into this situation where you have resistance and
5 you're trying to come up with other strategies to
6 treat these infections? We saw the nice slides
7 around combination therapies to try to help utilize
8 that, but, really, we rely on libraries. We rely
9 on animal studies, case reports, small series. We
10 rely on our colleagues.

11 We have listservs. We sent out the
12 questions on how do you treat these infections. We
13 also look at the label and hoping it contains that
14 good information that can help us make that
15 decision. And even some older labels, having that
16 PK data is important for the sites; brain and bone,
17 that's very useful.

18 Just this week, literally, just this week,
19 on Sunday, while this is an antiviral, I was
20 looking into the literature about making sure also
21 tamivir will get into the bloodstream enough for a
22 patient that was seriously ill with influenza

1 because we were giving it by NG. I had to make
2 sure to know if I was going to have to go to an
3 experimental drug to be able to treat these
4 patients.

5 These patients can now survive because of
6 folks like Dr. Wunderink, who can keep them alive
7 on ECMO, and have them extubated and talking to you
8 while on ECMO. And it would be a tragedy to think
9 that we don't have an antibiotic like we had in the
10 past to be able to treat these complications that
11 can occur from these serious infections.

12 What kind of information do we really have?
13 Well, if you look at this, we rely upon data that's
14 in that tier B or C, or even tier D, that animal
15 data. In infectious diseases, we have the
16 pathogens. I think we can get these measurable,
17 minimum, inhibitory concentrations to know, and we
18 can get that pharmacokinetic data to allow us to
19 know if those drugs can reach a level into the
20 areas we need to treat. That's an important aspect
21 for us.

22 When we have the pharmacokinetic data and we

1 have the pharmacodynamic data, that can be
2 predictive for us. And with that, we can make some
3 good decisions, and often we have to do that.
4 Often we have to utilize that information. I talk
5 to my pharmacist. I talk with my colleagues about
6 this sort of data frequently. And I think as
7 infectious disease physicians, we really rely on
8 this, and we utilize around these really hard cases
9 that need to be treated with these infections.

10 I don't think there's anybody in this room
11 that doesn't agree with this initiative that has
12 been set forth in 2010, and that's the 10 by 20,
13 meaning 10 New Antibiotics by 2020 Initiative. And
14 that's fabulous because we have that public
15 support. We have the FDA. We have everybody
16 really trying to work on doing this. We have the
17 industry trying to work this.

18 But if you look at that number, it's only
19 four, and in a short 26 days, we'll be into 2015,
20 and we'll be six behind. And if you look at the
21 four drugs that are there, they're all
22 Gram-positive agents for the most part, And not a

1 single one of them goes against the resistant
2 Gram-negatives that meropenem and the carbapenems
3 can't treat.

4 So we need more help, and that help is going
5 to be in the form of -- the regulations could be
6 one of those ways in which we can do that, making
7 that somewhat better and more helpful to bring
8 these drugs to market. It's a very hard balance.
9 I get that. But definitely, we need to be making
10 changes; again, why I'm so appreciable of what's
11 being done here today.

12 So what can we do? Obviously, this session
13 is being focused on the regulatory pathway, but
14 there are others that were mentioned earlier around
15 economic incentives, building on the GAIN Act, such
16 as tax credits, increasing our funding, and
17 improving our reimbursements. But really, we need
18 to work on that regulatory pathway, and obviously
19 the discussion today -- it's hard for companies.
20 It's hard to populate these traditional large-scale
21 clinical trials for new drugs that currently occur
22 in just a small number of patients.

1 I gave you one patient name. Obviously,
2 there's many. But this is across the country. We
3 don't have a lot of these, thankfully. We don't
4 have that thing we saw with the Turkey slide, where
5 they had a number of patients where you could have
6 colistin versus colistin and fosfomycin.
7 Thankfully, we don't have that yet. I don't want
8 to have that. I don't want to be testing this for
9 that reason.

10 But there also many barriers to our patient
11 enrollments in these clinical trials. Again, small
12 patient population. The second one that was
13 brought up, lack of diagnostics, rapid diagnostics.
14 If I have Sally come into the intensive
15 care -- into the ED with a very serious illness,
16 and they're trying to die, I'm going to give them a
17 therapy right away, empirically.

18 I might not know or have thought about this
19 new experimental drug at that time, and they're
20 going to get put on vancomycin at my institution,
21 likely cefepime. If they're super sick, maybe
22 meropenem. And I'm not going to really know what

1 that infection is for 36 hours or at least what the
2 susceptibility is until 36 hours later. That makes
3 it difficult. Now you've had someone already on
4 antibiotics, and now, how does that impact our
5 trials? As we know, that can be a sticking point.

6 Finally, it's been discussed here, is that
7 superiority trials are really typically impossible
8 for the most resistant infections that we have.
9 And I think this has been discussed. You can't
10 really give a placebo in these cases because of the
11 risk. And for some of these highly resistant
12 pathogens, there's really no comparator. There was
13 no comparator for that neonate I had that was sick.
14 It was resistant to everything. It wasn't
15 colistin. And I think again, it's unethical to use
16 an antibiotic to which it is bacteria resistant as
17 a comparator.

18 So as you've heard, as Dr. Cox mentioned,
19 the Antibiotic Development to Advance Patient
20 Treatment Act has been put forth by the Infectious
21 Diseases Society of America. And this establishes
22 a limited population antibacterial drug-approval

1 pathway to address serious or life-threatening
2 infections where an unmet medical need exists.

3 So these drugs would be approved based upon
4 smaller, faster, and less expensive clinical
5 trials. Drugs must still be demonstrated to be
6 safe and effective for indicated populations based
7 upon the current FDA evidentiary standards. This
8 labeling, then, must make clear -- be
9 transparent -- to the healthcare community that
10 these drugs are approved for a limited population
11 and must be used appropriately.

12 Finally, and I think it's been brought up,
13 is around stewardship. I've cut my teeth in
14 stewardship. That's what I first did when I came
15 to Children's Mercy Hospital. We have to steward
16 these drugs. And with that, these drugs used would
17 be monitored by the CDC's National Healthcare
18 Safety Network, and especially with the fact that
19 they now have that drug use module that many
20 hospitals are starting to give to. I think that
21 it's in place that we can do this.

22 We're not the only ones asking for this.

1 We're not the only one pushing this. Obviously, in
2 September of 2014, the President's Council of
3 Advisors on Science and Technology stated the
4 following: "FDA should use existing mechanisms to
5 facilitate approval of drugs based on demonstration
6 of safety and efficacy in specific patients
7 infected with antibiotic resistant bacteria, while
8 discouraging use in other patient populations. In
9 parallel, the Administration should support the
10 passage of legislation that explicitly authorizes
11 the FDA to establish a full, Special Medical Use
12 pathway for antibiotics." Definitely needed and
13 wanted and appreciated.

14 So in the label, what do we want to see?
15 Well, we hope to see in vitro/in vivo data, the
16 activity, that mechanism, how is that
17 mechanism -- how does it work on those resistant
18 pathogens? What's the pharmacology? What's those
19 drug interaction data?

20 As I mentioned, the pharmacokinetic data;
21 what those drug levels are in relevant tissue sites
22 of infection. What's the prior human experiences?

1 What are those case series? Our colistin case
2 series in pediatrics is of 30 patients that was
3 published by a group of us so that we can say, hey,
4 here's what it is. Here's what you can see. We
5 use that. We pass that around to our colleagues
6 when they have to use colistin. So again, I think
7 those are helpful and can be utilized in the label.

8 Also, optimal, obviously, to include the
9 patients from the U.S. Small randomized trials in
10 multiple body sites may be useful. I think we've
11 talked about the historical controls being useful.
12 And then studying of these drugs in the less
13 severely ill patients will be useful to understand
14 them further.

15 Finally, and not to ever under-appreciate
16 this, but the safety data is key, and we have to
17 note that and realize that that is in there. And I
18 really appreciate that comment that even after
19 approval doesn't mean you don't quit learning about
20 these drugs. That has to continue to happen.

21 Clinicians, we do understand this stuff more
22 than we probably sometimes act like we do, but we

1 do. We know the difference between these
2 randomized trials and the small case series. We do
3 understand, and we look at that, and we take that
4 into account. And we understand that aspect, there
5 are small responses and recovery to severe
6 diseases, but we need to see that.

7 We need to see that across sites, across the
8 different comorbidities. We need to see it in the
9 pneumonia, the brain, the abdominal infections, the
10 pediatrics, the children that can be infected by
11 these.

12 Obviously, anything with bloodstream
13 infections is helpful. Without these things in the
14 label, our patients are at risk when we are forced
15 to use toxic drugs like colistin with little to no
16 guiding information and when they can develop
17 syndromes that have not yet been studied.

18 So we're at a crossroads, and I'd like to
19 take you back to the 1930s when Dr. Domagk had
20 identified that sulfa drugs could be used as an
21 antibiotic. And the irony of it is that Dr. Domagk
22 had a child that developed a cellulitis of the leg,

1 and that cellulitis was so severe, they were
2 contemplating amputation.

3 Now, they had antibiotics early on, and she
4 was able to receive that and saved her leg and
5 saved her life. And not just two and a half years
6 ago, my own daughter had orbital cellulitis, an
7 infection of the eye, and so did one of her friends
8 about six weeks earlier. And if she had been born
9 in the 1920s, she could have lost that eye, if not
10 something worse.

11 So prior generations gave us the gift of
12 antibiotics. Today, we have a moral obligation to
13 ensure that this global treasure is available for
14 our children and future generations. We must
15 appropriately balance the risk of allowing smaller,
16 more feasible clinical trials against the far
17 greater risk of prohibiting the development of
18 urgently needed new antibiotics and entering the
19 post-antibiotic era, or what it was like prior to
20 the use of antibiotics. Thank you.

21 CAPT PARISE: Thank you, Dr. Newland. We'll
22 now proceed with the bio presentations. Dr. Adler

1 is first.

2 **Presentation by Professional Organization**

3 **Jeff Adler**

4 DR. ADLER: Good morning. I'm Jeff Alder.
5 I'll be speaking on Patients, Pathogens, and
6 Streamlined Drug Development. Here are my
7 disclaimers, a special thanks to John Rex, Mark
8 Goldberger, and Barry Eisenstein for their advice.

9 The issue is that finding the right patient
10 and the right pathogen in modern drug development
11 will invariably and directly lead you to a
12 discussion on streamlined drug development and
13 their, of course, smaller data sets. And we should
14 say actually finding the right severe patient leads
15 you to the discussion of streamlined drug
16 development and small data sets.

17 So overall, our goal is that trials are
18 clearly needed in more severe patients. Those are
19 the patients most likely to have a resistant
20 pathogen. Those are the patients, however, that
21 also have the most complications, and the more
22 severe the patient, the more difficult they are to

1 enroll in a clinical trial.

2 As an example of severe patients, ventilated
3 pneumonia. Ventilated pneumonia is a disease with
4 20-plus percent mortality, depending on some of the
5 variations. I consider that unmet medical need.
6 There are at least seven clinical studies ongoing
7 in ventilated pneumonia currently.

8 Most of these trials have similar goals,
9 that is to enroll severe patients, severe patients
10 which occasionally, depending on the trial design,
11 could be enriched for resistant pathogens. But
12 importantly resistance is not a requirement for all
13 but one -- only one of these trials requires
14 resistant pathogens. The rest are enrolling, by
15 and large, susceptible pathogens.

16 However, one thing that's common amongst
17 them is that enrollment is quite slow in all of
18 these trials. Why? Ventilated pneumonia, as
19 you've just heard, is not a unique disease. It's
20 not a rare disease. But here's an example of how a
21 1000-bed hospital will quickly reduce to zero. A
22 1000-bed hospital, you may have 20 ICU beds. That

1 means you've eliminated 98 percent of the beds from
2 consideration a priori.

3 Of that, perhaps 5 patients will be on a
4 vent and have pneumonia, and this is without regard
5 to did the pneumonia develop plus 48 or minus 48
6 intubation; just pneumonia and a patient on a vent.
7 Of those, 1 to 2 patients will grow the correct
8 Gram stain classification for your drug, assuming
9 you're targeting either Gram-positive or
10 Gram-negative. Then start to apply the typical
11 inclusion/exclusion criteria: renal impairment;
12 hepatic; Apache II score being too high or too low;
13 immunosuppression.

14 Why do we apply all these
15 inclusion/exclusion criteria? Well, the reason is,
16 the more severe the patient, the greater the early
17 range of responses. A ventilated pneumonia patient
18 at 72 hours could either die of fulminating disease
19 or be showing significant improvement in clinical
20 signs and symptoms. And a way to try to limit that
21 variation is through inclusion/exclusion to try to
22 exclude some of the patients that are most valuable

1 for study: renally impaired, dialysis, hepatic,
2 immunosuppressed, et cetera.

3 Then apply the prior effective antibiotic
4 limitation 24 to 48 hours. That is the number one
5 criteria that knocks most patients out. They've
6 been on prior antibiotics too long to get all of
7 the tests done. And oh, try to get informed
8 consent during this period, during what's typically
9 a pretty stressful time, either for the patient or
10 more often for family members.

11 What all of this boils down to, then, in
12 ventilated pneumonia is an enrollment rate of one
13 patient per site/per year. Yes, per year. So if
14 you're at one patient per site/per year in
15 ventilated pneumonia, that causes a raft of
16 secondary problems. Just as an example, sites lose
17 interest or they certainly lose experience and
18 expertise in executing the protocol if they're only
19 enrolling one patient per year.

20 Are these severe patients unique? Are
21 trials with severe patients unique? Yes, they are.
22 If you want an example of less severe, there are

1 lots of examples to look for: complicated
2 intra-abdominal, complicated UTI, acute bacterial
3 skin and skin structure infection. And you see a
4 list there of some of the drugs that have gone
5 through these development pathways recently. All
6 of them enroll typically one to one and a half
7 years.

8 For the more severe infections, you've got
9 pretty much two choices if you want to engage that
10 patient population. You could go for ventilated
11 pneumonia, or if you're a real glutton for
12 punishment, you could try bacteremia endocarditis,
13 but nobody's done that in probably more than
14 10 years. On the ventilated pneumonia, the current
15 estimates are 3-plus years for the global trial,
16 and a big emphasis on the plus part of that, 3 or
17 more years to execute a ventilated-pneumonia trial
18 in severe patients. And here, we're not demanding
19 resistant pathogens, just any pathogen.

20 The most recent example -- there's no
21 examples of ventilated pneumonia, but Rich
22 Wunderink gave you the linezolid versus vanco

1 trial, which enrolled about 1200 patients in 5 and
2 a quarter years. That did not require
3 ventilated -- they included ventilated pneumonia,
4 but that was not a requirement. So in effect, the
5 patient pool was bigger. And of those 1200
6 patients, it boiled down to 448 mITT. That is,
7 they actually grew a pathogen.

8 So this brings us to streamlined drug
9 development. Most of you have seen this graphic
10 before. Tiers A and D are familiar. Tiers B and C
11 are meant to bridge the gap between the two phase 3
12 adequate well-controlled trial and the Animal Rule.
13 In tier B, what we're talking about is a single
14 phase 3 trial. It's in susceptible pathogens,
15 probably in severe patients much like the
16 ventilated pneumonia. You may be able to include
17 resistant pathogens if your trial structure permits
18 treatment of these pathogens. And you're naturally
19 going to have a smaller data set.

20 Tier C is when it's not even possible to do
21 a phase 3 adequate and well-controlled trial. Here
22 we're focused most likely on resistant pathogens or

1 on just a couple genus species, such as Pseudomonas
2 and Acinetobacter, possibly pooled across body
3 sites. There's no or unlikely limit. It's
4 unlikely to have inferential statistical testing,
5 or there might be some level of testing, but it's
6 certainly not to the level of an adequate, well-
7 controlled phase 3 trial.

8 However, tier C is what's needed if we
9 really want to engage the most severe patients. If
10 we want to get the mild to moderate, you can run a
11 complicated UTI, enroll in some resistant
12 pathogens. The severe patients, we really need a
13 tier C codified, which would help us to develop
14 drugs in this patient population.

15 Superiority was touched upon a couple of
16 times, potentially could this be the answer. And
17 we're running a couple of superiority trials at
18 Bayer. And if you assume a large superiority
19 effect, you can dramatically reduce the trial size.
20 But to assume a large superiority effect, you are
21 further limiting yourself to the most severe of the
22 most severe patients because that's the group most

1 likely to show a large superiority effect. And
2 those most severe patients are even more difficult
3 to enroll.

4 If you assume a more modest superiority
5 effect, the trial size quickly grows to 700, which
6 is basically a noninferiority trial. And you saw
7 this morning from the FDA presentation, as an
8 example, if you assume a failure rate of 50 percent
9 in control and only 40 percent in the experimental
10 agent, you come to 385 patients per arm or
11 basically a 700-plus patient trial, and that's with
12 a 10 percent assumed real differential.

13 Labeling and streamlined development. The
14 labeling could be based on the indication. That's
15 the standard. It's pretty direct, drug X indicated
16 for infection Y, and then you list the bugs you
17 successfully treated in the trial. Or it could be
18 based on the pathogen. No known examples of this
19 yet, but it would read something like drug X is
20 indicated for infections caused by, and then list
21 the pathogen.

22 Clearly, that's a much broader label, and

1 that would therefore then come with a disclaimer.
2 And you see an example of a disclaimer listed
3 there, where limited or no alternative therapies
4 are available. So that would be the trade-off for
5 a pathogen-specific type labeling.

6 There are data limitations in labeling, and
7 you've heard several talks lamenting the
8 limitations on a label. Basically, labeling in the
9 indications and usage section and the clinical
10 studies section is limited to data that directly
11 supports an approved indication; or the other way
12 to say that is the data must not imply or suggest
13 alternative uses.

14 What does that mean to not imply or suggest
15 alternative uses? On the label, what it means is
16 that the data is excluded if it's PK data that's
17 not directly related to the body site, other than
18 the standard blood PK, and then pulmonary PK if you
19 have a pulmonary indication, et cetera. And then
20 efficacy and safety data for body sites that are
21 unrelated to the approved indication. And I've
22 heard many physicians lament that the older labels

1 are really better because they actually had some
2 useful data outside of the standard indication.

3 Now, there are some latitude within the
4 label. There is some ability to put other data,
5 and it comes in the clinical pharmacology section
6 in the microbiology portion. It's divided into
7 what's commonly termed the "indication section" and
8 the "potency section." The indication section is
9 very simple. It basically states that the drug has
10 activity both in vitro and in clinical infections,
11 referring you back to the indication. And then
12 there's a list of the bugs that you successfully
13 treated in the approved indication.

14 But there's also latitude. And in the
15 potency section, it's quite interesting, and I
16 think a quite good section. The potency section is
17 important in that it shows in vitro potency against
18 those pathogens that you did not encounter in the
19 approved indication. So there are a list of
20 pathogens for which there's good potency, and
21 that's based on the breakpoint, which is a whole
22 different discussion. But those pathogens are not

1 encountered in sufficient numbers to go into the
2 indications section.

3 Now, this potency section is bracketed by
4 two disclaimers. The first, clinical significance
5 has not been established. The second disclaimer,
6 efficacy has not been established in an adequate
7 and well-controlled trial. The question is, why
8 put this data in the label bracketed by two
9 disclaimers? The reason is because it's valuable
10 to physicians, and physicians understand that
11 potency does not comply a clinical indication, but
12 it is indeed valuable and important to clinicians.

13 The wording here is quite good, the two
14 disclaimers especially in red. And with some minor
15 modifications, as shown here, I think could be used
16 to show the clinical data that physicians have been
17 calling for, which is unrelated to the approved
18 indication. Some examples are here, but the type
19 of data that could be shown would be
20 pharmacokinetic data unrelated to the primary
21 indication. For example, bone PK, if you don't
22 have an osteomyelitis indication, or CSF PK.

1 Efficacy and safety data, unrelated to the
2 approved indication, and that could be where all of
3 these smaller, supportive studies that are called
4 for in the backgrounder that was put out for this
5 meeting -- the question is, what do you do with
6 these smaller, supportive studies? With the
7 appropriate disclaimer, the data could be valuable.
8 This could also be a place for discussion of
9 resistant pathogens. Whether you do the phenotype
10 or the genotype of the resistant pathogens is a
11 whole different discussion.

12 In summary, the patients and pathogens, the
13 more severe the patient, which is what we all want
14 to engage, the more difficult it is to enroll them.
15 This means streamlined drug development if we're
16 going to go into this patient population, and that
17 means smaller data sets, tier B and tier C.
18 Codifying tier C especially would be helpful. And
19 informational labeling that could include
20 additional clinical data unrelated to the primary
21 indication would be particularly helpful.

22 I'm going to close with just a bit of hockey

1 philosophy because developing a drug has been
2 compared to scoring a goal in hockey. Steve Jobs
3 was a big hockey fan, and he was interested in
4 breakthroughs and how do you have a breakthrough.
5 So he consulted Wayne Gretzky, and he asked Wayne,
6 "How do you know when to shoot?" Because in modern
7 NHL, the goaltender will stop 90 to 95 percent of
8 the shots.

9 So how do you, the greatest scorer of all
10 time, know when to shoot? And Wayne Gretzky said,
11 "That's simple. You miss a hundred percent of the
12 shots you don't take." And I think a lot of
13 discussion today is going to be should we do
14 something a little bit different than we have been
15 in order to be able to engage this patient
16 population, i.e., should we take the shot? Thank
17 you.

18 CAPT PARISE: Thank you, Dr. Alder. We'll
19 now have Dr. Rex's presentation.

20 **Presentation by Professional Organization**

21 **John Rex**

22 DR. REX: Thank you. Thanks to the

1 committee for the opportunity to present today. My
2 focus is going to be on balancing expectations,
3 data size and feasibility. My disclaimers are
4 shown on the slide.

5 The big picture here is that if we want a
6 diverse, vibrant, antibiotic pipeline focused on
7 present and future unmet need, the regulatory
8 paradigm needs to permit two things: registration
9 based either on a single standard prospective,
10 comparative phase 3 trial of a standard size or
11 small comparative trials that use wider confidence
12 limits, and labeling that describes the limitations
13 of all the available data, provides all the
14 available PK data for various body sites, and
15 supports rational extrapolation of potential
16 activity when a physician is faced with a
17 challenge.

18 We've actually made a lot of progress
19 towards these goals. I could put green check marks
20 next to a number of these things. And I hope that
21 today we will take another step forward because
22 we're not entirely yet -- I can't put green check

1 marks next to everything.

2 I'm going to cover initially a section I
3 call the Rules of the Road, and I'm going to bring
4 together a number of ideas you've heard this
5 morning because I want you to hear them kind of in
6 tight juxtaposition. And I'm going to use that as
7 a springboard into a critical question: What is an
8 adequate and well-controlled noninferiority trial?
9 And then we'll have some exam questions.

10 So adequate and well controlled, critical
11 concept defined in 314.126. It's the primary basis
12 for substantial evidence that leads to approval. A
13 number of requirements for adequate and well
14 controlled, but the core one for today is that you
15 have to have a valid comparison with a control;
16 comparison with control. Five types of controls
17 are defined -- it makes perfect sense -- ranging
18 from no treatment to active treatment. And you
19 have to say some kind of comparison you're going to
20 do, and you have to do it, though there's not a
21 specific recommendation about how you do it.

22 Next rule of the road, 201.57, part of the

1 labeling regulations. The structure of the drug
2 label is defined, and 201.57 makes comments on the
3 content. So for indications and usage, it says
4 that all indications must be based on adequate and
5 well-controlled studies. And there's a reference;
6 there's a boilerplate indication there: drug X is
7 indicated for the treatment of infection 1.

8 It also says that you can't have an
9 indication or usage implied somewhere else in the
10 label that's not in this section. Let's look at
11 clinical studies, where we're told exactly the
12 mirror of that, which is that you can't put
13 something in clinical studies that implies an
14 indication that's not in indications and usage, so
15 it makes good sense. It all ties together.

16 Taken at face value, this implies clinical
17 information not linked to an indication, and in
18 particular, it appears to exclude PK at body sites
19 for which there's not an indication, like CSF
20 penetration data in the absence of a meningitis
21 indication. There is a specific cut-out for
22 in vitro susceptibility testing data. There's a

1 specific disclaimer that's provided, so you can put
2 that in. So it has a distinct cut-out here.

3 Finally, there's some debate on this, but
4 one way to read 201.57 would also seem to preclude
5 the use of a pathogen-focused indication, where you
6 just say drug X is indicated for infections due to
7 organism Y. I think this latter indication is very
8 important, and I think it's important that we think
9 about how to get at this concept, as Dr. Alder also
10 said.

11 Next rules of the road have to do with trial
12 designs. There's been a lot said about superiority
13 versus noninferiority. I'm going to put my
14 comments in perspective here by saying superiority,
15 when you can do it, is very compelling. But I'll
16 also tell you that when you can do it, you're very
17 unhappy. Right now, it would be possible to do a
18 superiority study for Ebola because there are no
19 active therapies.

20 That mere fact is causing us a lot of
21 unhappiness. You don't want to be able to do
22 superiority studies because in order to be able to

1 do them, you have to be randomizing to potentially
2 ineffective or toxic therapy. Instead, be grateful
3 for noninferiority, where we have drug X versus
4 drug 6, both at meaningful doses.

5 Now, we have to exclude if the pathogen is
6 resistant to either agent. It doesn't mean the
7 pathogen is not resistant to other things. So in
8 studies of Gram-negatives right now, the comparator
9 is almost always a carbapenem because the
10 carbapenems still work most of the time. But the
11 carbapenems are the last thing. When they go,
12 we're done.

13 So the fact that we're doing a
14 noninferiority study against a carbapenem doesn't
15 make it a bad study, and we can actually enroll
16 very sick patients here. We can study very
17 difficult pathogens here. But it's noninferiority,
18 and we're protecting the patients in both arms, and
19 there's really no rationale expectation of
20 superiority in this study.

21 So in what sense, then, is the new drug
22 better? Well, the superiority's in the

1 microbiology, which is the hedge against current
2 and future resistance. And you're going to have to
3 get your data on pathogens that are resistant to
4 almost everything via other means. So in the
5 future, phase 3 for most drugs is going to look
6 like this, after the usual phase 1 and phase 2, and
7 with a substantial PK/PD based dose justification,
8 lots of preclinical data. It was commented by the
9 FDA. You do not want to short-change that.

10 You will do, if possible, trial number 1, in
11 which you do a standard size and site body study:
12 complicated intra-ab, UTI, one of those. No
13 expectation of resistance to the comparators in the
14 study. Remember, that doesn't mean it's an easy
15 bug. It just means that you happen to be able to
16 do noninferiority because you still have a
17 comparator that works. And this study provides
18 clear data on efficacy and safety, and leads to an
19 indication for that body site.

20 Then finally, you do trial number 2 in which
21 you go out looking for the worst of the worst. You
22 find very difficult pathogens. For any given

1 patient, you identify a therapy you think might
2 work, and then you do a prospective randomization
3 to whatever you identified or your test agent.
4 This study will almost invariably be small viewed
5 in noninferiority terms, that we use large NI
6 limits and have wide confidence intervals. It may
7 be necessary to use data from several body sites.
8 This kind of data across several body sites is how
9 you get at the pathogen-focused indication.

10 Final rules of the road. The notion of
11 developing drugs for serious, life-threatening
12 illnesses gets a fair bit of air play in the
13 regulations. And it's because of the common-sense
14 thing in the middle of the slide: physicians and
15 patients are generally willing to accept greater
16 risk from patients that treat life-threatening,
17 severely debilitating illnesses. And they think
18 about those risks in light of the severity of the
19 disease being treated.

20 So understand that this underpins our
21 conversation today, and it's part of how the
22 structure that we use comes together. This is a

1 critical element.

2 The next thing is that the statutory
3 requirements, they're good. They're what we need.
4 But there are a lot of situations out there in the
5 world. And so helpfully, the regs say FDA is
6 required to use its scientific judgment in thinking
7 about the situation at hand to determine the kind
8 of quantity of data required. And also, FDA's
9 application of the statutory standards shall
10 recognize the need for a medical risk/benefit
11 judgment. This is built in as well. So we are
12 permitted to use these tools. So these are the
13 rules of the road.

14 Now, I want to turn now to asking the
15 question, what is an adequate and well-controlled
16 noninferiority trial? It's helpful to get
17 concrete, so I'm going to take an indication that
18 will be often studied, complicated intra-abdominal
19 infection, well-defined, life-threatening. And
20 very helpfully, the FDA has done an exhaustive data
21 review, and they have available to us an estimate
22 of the response rate on placebo and an estimate of

1 the response rate from a series of trials with
2 modern comparators, 61 percent versus 82 percent;
3 there the 95 percent confidence intervals.

4 M1 is the difference between the red
5 underlined numbers, and then we reduce M1 to M2,
6 which will be the margin we actually use in the
7 trial. And we reduce it -- it is somewhat
8 arbitrary. We reduce it to adjust for uncertainty
9 in the estimation of M1, and also to ensure that we
10 don't drift too far away from the active control.
11 In practice, M2 comes out at 10 to 12 and a half
12 percent.

13 Let's look at this visually. I plotted here
14 on this graph. The Y-axis is arbitrary probability
15 against the units, and I plotted those 95 percent
16 confidence intervals. The entire confidence
17 interval is shown, and the 95 percent is the solid
18 interior core. And if you look really closely, you
19 can see the little clear white spaces on either
20 side that are the 2 and a half percent tails to the
21 left and the right of the 95 percent central
22 density.

1 M1 is the space between the two solid
2 blocks. Let's do a standard 10 percent
3 noninferiority margin trial. It requires 620
4 evaluable patients, probably closely to 700 by the
5 time you deal with the fact that you're going to
6 lose some along the way. I'm going to assume the
7 control drug does exactly what the control drugs
8 did in the FDA's estimate, an 82 percent response
9 rate. And I plotted the confidence, the 95 percent
10 CI, for that response rate for 310 patients.

11 In green, is the worst case result for a
12 test agent that is within a 10 percent margin. If
13 the green is any further to the left, your trial
14 has failed. This is as far to the left as you can
15 go. And you can see -- it's quite obvious -- the
16 control and the worst case test are well separated
17 from historical placebo.

18 Now, let's double the size of the margin.
19 It sounds like a big number, but it also shrinks
20 the trial by 75 percent. I now only need
21 78 patients per arm. Control response rate, I'm
22 assuming it's in the same place, but the confidence

1 interval's now wider because I've only got 78
2 patients. Here's the worst case result for test
3 that's within a 20 percent margin. And despite the
4 fact that the margin's 20 percent, it's tighter,
5 but there's still little overlap with these
6 95 percent confidence limits, and the central
7 tendencies are very well separated.

8 I know the margin of 20 percent sounds like
9 a huge number, but, as I've shown you, the worst
10 case result is still well separated from historical
11 placebo. And I should say that that placebo in the
12 intra-ab data is really a pretty conservative
13 number as well.

14 So it's one thing to require 620 evaluable
15 subjects when the drug is active across multiple
16 species and can easily be studied in a single
17 complicated intra-ab study. And if you can do that
18 study, you should. But what do you do when a large
19 data set is not possible in a non-geologic time
20 frame? And that's really where you are with
21 *Pseudomonas* and *Acinetobacter*. And if you want to
22 insist that all the cases of *Acinetobacter* come

1 from one body site, you've made the problem even
2 worse.

3 So the heart of the matter -- and this is
4 the point of my entire talk -- is that adequate and
5 well controlled is the regulatory standard for the
6 data and label, and none of us want to change that.
7 But adequate and well controlled is also, to some
8 extent, a matter of judgment. And when you look at
9 these margins, you have to think about the slides I
10 just showed you, and also realize that you have
11 more than just those phase 3 data. You also have
12 all the PK/PD backing for that dose. You know why
13 that exposure of that drug is working in that human
14 being. So the totality of the data at this point
15 is enormous.

16 Now, please understand me. I am not calling
17 for small trials just for convenience, but we have
18 got to learn to live with smaller trial programs in
19 order to have some of the kinds of drugs we want.
20 Further, the label needs to contain all of the
21 available PK data from all of the body sites. That
22 can be invaluable. I really want to know if it

1 gets into the CSF because one day I might need to
2 use that. And where appropriate, we need to
3 indicate it for infections broadly, and maybe
4 that's actually a way to enable us to include the
5 other PK data.

6 Finally, some exam questions. This
7 afternoon, you guys are going to be posed some
8 questions by the FDA. Here are my answers. Is a
9 streamlined program acceptable? Yes, absolutely,
10 particularly when the choice is no drug.

11 Is a larger M2 acceptable? You now know
12 what M2 is. Yes, absolutely, and I've shown you
13 why. And it's going to be required for products
14 with a spectrum limit of less common organisms.
15 And remember, you don't just have the phase 3
16 trial. You've got all the other stuff behind it.

17 Is pooling acceptable? I think this is
18 going to be something that we are going to figure
19 out how to do. We're going to figure out how to do
20 data sharing across indications. I think this is
21 possible both for noninferiority and superiority,
22 and I'd love to have some more conversations about

1 that.

2 Finally, how big should the safety database
3 be? Three hundred is good, but based on what you
4 know from the preclinical and what you've seen in
5 your phase 1 and phase 2, you might be willing to
6 register on a little bit less, particularly for a
7 drug that's only going to be used in a few
8 patients.

9 So I'm going to close by saying that this
10 needs to happen. Industry interest in this area is
11 fragile. As of the beginning of this year, the
12 number of companies doing work in this field was
13 the same as it was in 1960. We've lost an enormous
14 number of companies over the last two decades. An
15 enormous amount of insight has gone away.

16 What companies are looking for -- and you
17 ask is this going to make -- somebody earlier
18 asked, will this make a difference to industry? My
19 answer to that is yes. Even the possibility that
20 these things might change has lit off a fair bit of
21 interest in this area. I'm seeing more companies
22 turn up at these events than I have seen in the

1 past 10 years. And I have spent the last 10 years
2 working to try to get to this day where there are
3 this many companies in this room.

4 I want to close by just paraphrasing
5 something that Ed Cox once said that I just love.
6 "By acting quickly to create approaches to describe
7 and manage the uncertainty of small data packages,
8 we will provide patients with timely access to
9 urgently needed life-saving antibiotics, and we
10 will avoid the paradoxical situation of being
11 forced in the future to accept even greater degrees
12 of therapeutic uncertainty as AMR progresses." We
13 do not want to get behind the eight ball. Be
14 grateful for noninferiority instead of angered with
15 it. Thank you.

16 **Clarifying Questions**

17 CAPT PARISE: Thank you, Dr. Rex.

18 Are there any clarifying questions for any
19 of the professional organizations? Please remember
20 to state your name for the record before you speak.
21 And if you can, please direct questions for a
22 specific presenter. Dr. Dekker?

1 DR. DEKKER: This is a question for
2 Dr. Newland, IDSA. On your slide 11, you talk
3 about a limited population antibacterial approval
4 pathway, and the third bullet point talks about
5 labeling these products. And you say labeling must
6 make clear to the healthcare community that these
7 drugs are approved for a limited population and
8 must be used appropriately.

9 Of course, the flipside of that -- and this
10 is something that was pointed out by another panel
11 member -- is how do we turn a limited use labeling
12 indication into true limited use? What is the
13 opinion of IDSA on that?

14 DR. NEWLAND: No, I think it's an important
15 aspect of this, and obviously something that we in
16 IDSA and Pediatric Infectious Diseases Society are
17 working on diligently, just outside these
18 limited -- in this drug approval pathway in regard
19 to all of our stewardship efforts that we have
20 worked on.

21 I think it's going to take that partnership
22 with CDC to have that, being able to be monitored

1 closely in that aspect, because I think we all see
2 it. We all know it. Many of us have probably
3 walked to our physician's office and heard about
4 someone that's gotten a Z-PAK for something that
5 they didn't need. And I think that's what I hear.

6 So I think that pathway and the fact that
7 the CDC has been engaged in this effort and with
8 those -- will have to be built in so that we see
9 when those are used; that we monitor that exact
10 use, and that those indications are being followed
11 as they should be. Because if not, then you're
12 right. It doesn't matter, and all we've done is
13 created the next kill everything -- antibiotic
14 that's being used inappropriately, and then we're
15 finding these toxicities that are much worse to our
16 patients and kids.

17 CAPT PARISE: Dr. Moore?

18 DR. MOORE: Just to follow up that point,
19 one concern, Dr. Dekker. A good illustration would
20 be something that this panel, this committee, met
21 about a couple of years ago when bedaquiline was
22 being discussed for the treatment of multidrug

1 resistant and extremely drug resistant
2 tuberculosis. And the concern was, of course, at
3 that time, that this was the first drug that had
4 been approved for treatment of tuberculosis since
5 Nixon invaded Cambodia in '72, and we really wanted
6 to preserve that; how do we stop clinicians from
7 using it for non-tuberculous microbacteria. And a
8 partnership was discussed at that time with the CDC
9 and public health agencies to try to restrict and
10 protect that particular drug, and I think that
11 there are examples of precedents like that where
12 that can be done.

13 CAPT PARISE: Other panel members have
14 clarifying questions? Dr. Follmann?

15 DR. FOLLMANN: One question for Dr. Alder.
16 On slide 9, you talk about tier B and how this
17 could be a streamlined path to licensure, including
18 a phase 3 study and some other stuff. I wanted to
19 have you comment a little more on what you mean by
20 supplemented with small studies, persistent
21 pathogens, and patients excluded from the typical
22 phase 3 trial. Do you mean case studies by that or

1 do you mean like an additional study for
2 superiority focused entirely on resistant
3 pathogens? Or just what do you mean by that?

4 DR. ALDER: Tier B is typically when we can
5 still do a single phase 3 study with all the
6 inferential statistical testing, probably
7 noninferiority, but also supplemented during
8 clinical development. So we're not talking about
9 case studies post-approval but during development,
10 smaller studies that probably would focus on either
11 resistant pathogens or on the most severe patients.

12 That might be open label. It could be
13 patients that would fail because of, say, renal
14 dialysis. How many times have we heard that we
15 would really want to see how drug X works in a
16 dialysis patient? So it's to capture those
17 patients that would not qualify for the phase 3.
18 And it becomes part of the submission package
19 reviewable by the FDA.

20 DR. FOLLMANN: So open label means just a
21 description of a sequence of patients who's gotten
22 the drug presumably with a resistant pathogen. So

1 it's like a series of case studies in a way, but
2 under an umbrella protocol --

3 DR. ALDER: Not necessarily a series of case
4 studies. No. It's a legitimate, bona fide trial
5 negotiated with the FDA. It could be randomized in
6 comparator or it could be single agent and open
7 label.

8 DR. FOLLMANN: Thank you.

9 DR. ALDER: All to be negotiated depending
10 on the disease and the patients.

11 DR. FOLLMANN: Thanks.

12 CAPT PARISE: Dr. Baden?

13 DR. BADEN: A question for Dr. Rex. I'm
14 trying to understand the application of the
15 indication, drug X for infections due to
16 organism Y. So the implications of that is
17 wherever organism Y is, we can use drug X? That is
18 a bit broad-sweeping.

19 DR. REX: Correct. It's a broad statement.
20 But the whole indication is infections due to
21 organism Y in patients with limited treatment
22 options. And the last part is important. And I

1 think that -- if you think about this medically, if
2 you have seen some evidence of activity in a
3 series -- in a collection of -- I'd like it to be
4 prospective and randomized, even if small, but some
5 pneumonia cases, some intra-abdominal cases, and
6 maybe a skin infection or two.

7 If you have that collection of information,
8 you can approach it like a Bayesian viewpoint and
9 say I've seen this drug work in a variety of
10 subjects. I understand its pharmacology. I
11 understand the exposure that is required to produce
12 this effect. And it's useful in some fashion to
13 say that this drug is useful for infections due to
14 these organisms when you're out of options.

15 I can't say all the rest of it in the
16 indication, which is and be sure you've thought
17 about the PK, and be sure that you've exhausted all
18 your other options. In fact, it's what you and I
19 do as clinicians. We're backed up with somebody.
20 We're out of choices. And we start digging around
21 saying, "Well, what might work?"

22 Notionally, this is in effect what we do

1 anyway with a drug right now, is that filter exists
2 at the back end of any given drug, that you're
3 thinking, "Well, I might have to apply for
4 meningitis one day, and that's why I would like to
5 know about CSF penetration. I don't want to use it
6 because I'd rather use something that I understand,
7 but I might have to use it." And it could be that
8 that's the kind of wording that allows us to get at
9 the notion of being able to provide the information
10 on these other body sites.

11 DR. BADEN: I agree that the issue of
12 limited treatment options is critical. It's
13 predicated on that. But this would then mean that
14 drug X would be indicated for infection by
15 organism Y in the CNS, or with a prosthetic, since
16 the indication follows the bug as opposed to many
17 of the other factors that we all have been
18 discussing.

19 DR. REX: That's right. And we do it from
20 time to time. Linezolid has an indication for
21 treatment of VRE, and it's just what's indicated
22 for infections due to VRE. Now, it's not because

1 that's the first place you go, and it's not because
2 there was a huge amount of data. But it was at
3 some point deemed relevant to say that.

4 The difficulty is how to capture this. And
5 the reason I went through those rules of the road
6 was to try to help you understand why the
7 regulatory agency is thinking about this and the
8 constraints that they face in putting the
9 information in the label right now that you and I
10 want to use; so the notion that you can't put in
11 the PK data for the CSF.

12 I understand that you don't have a
13 meningitis indication, but surely the sponsor, the
14 drug developer, is the company that knows the very
15 most about the best quality data. And if they have
16 any estimate at all, I'd rather have that in the
17 label so I can find it than have to go to library
18 land and maybe find it, and maybe not be as
19 comfortable about the caveats around it as the drug
20 company would be.

21 So the question of that indication could be
22 one that has to do with how do you -- flip it

1 upside down and say, maybe it's not that indication
2 that I care about. Maybe what I care about is
3 having the data where available, even in small data
4 sets on the other body sites where it's been
5 explored. And it will be almost a complimentary
6 way of saying we're interested in that kind of an
7 indication. Does that make sense?

8 CAPT PARISE: Dr. Hamblett?

9 DR. HAMBLETT: This is again a question for
10 Dr. Rex. In your discussion of widening the
11 noninferiority margins, I'm just curious as to your
12 thoughts of how this might depend on the severity
13 of the endpoint. We're talking about lots of
14 different indications and different endpoints,
15 ranging from mortality to resolution of symptoms.
16 Does that play into your comfortability in terms of
17 how wide you should go with those margins?

18 DR. REX: In a sense, the answer really
19 probably is not a lot, but not the reason you
20 expect. When I'm thinking about these infections,
21 we have a lot of confusion about severity versus
22 seriousness. Somebody -- and I'll give you an

1 example of distinction between those two things.

2 If you present with streptococcal
3 pneumonia -- with pneumococcal pneumonia, an adult
4 presents with pneumococcal pneumonia, a young
5 person might turn up with pneumococcal pneumonia
6 and have a normal blood pressure, and just feel bad
7 and have a fever. An elderly person might turn up,
8 and at the moment I see them be hypertensive in the
9 ICU. But that young person, you might say, well
10 his infection isn't so severe because he doesn't
11 look so sick yet. You can put him in an ambulatory
12 bed.

13 He still is at risk of dying. And so the
14 fact that my endpoint for -- so that young person
15 has a very life-threatening illness. The endpoint
16 I use in that trial is one of improvement of his
17 symptoms. I can study did his chest pain go down,
18 did his cough go down, did his fever go down.

19 So you might say, well, that's not a serious
20 endpoint, but in fact it is a serious endpoint
21 because that young man, if I did not give him an
22 adequate therapy, he would wind up dead. We can go

1 back through all the data on the death rates for
2 pneumococcal pneumonia, but in a healthy young
3 adult, it's 1 in 6 will die. So the fact that
4 we're using -- you might say, well, that's a soft
5 endpoint. No, it's actually not. It's a very hard
6 endpoint because it's on the way to an awful
7 endpoint that I really don't want to measure. So
8 again, you should be grateful for the fact that you
9 can measure something less than all-cause mortality
10 as the endpoint.

11 CAPT PARISE: Dr. Scheetz?

12 DR. SCHEETZ: This question is also for
13 Dr. Rex, as well as widening the margins, which I
14 think is a very interesting concept. Now, if you
15 widen the margins, and your measure of central
16 tendency for your test treatment is worse than the
17 standard of care, but you're still not inferior,
18 you have the potential that you'll have a drug out
19 there on the market that is potentially worse.
20 Physicians will be using a potentially worse drug.

21 What do you foresee is the role of mandatory
22 phase 4 follow-up testing to ensure that if we

1 approve drugs on wider inferiority margins,
2 noninferiority margins, that we can actually
3 gravitate back to saying the standard of care was
4 in fact better?

5 DR. REX: A couple of questions buried in
6 that. Every drug should have a postmarketing
7 pharmacovigilance program. The kind of data you
8 can acquire there, though, is not as good as you
9 can do during the registration phase. You've done
10 the best studies you're going to be able to do in
11 the registration phase. Dr. Wunderink put up a
12 good discussion of why it becomes more difficult as
13 drugs become registered in order to do clinical
14 studies in the future.

15 But pharmacovigilance includes
16 safety -- sorry, includes efficacy, safety data
17 collection. Efficacy, I guess I'm
18 concerned -- when I think about this problem, I
19 think about the question of, well, is a BIO creep
20 thing going to go on? Is this new thing going to
21 get out there, and somebody's going to use it as a
22 comparator?

1 I don't think that's going to happen because
2 I think that now that we have regrounded on
3 placebo, with all the work that we've done in
4 rethinking noninferiority studies, we understand
5 both the relative and the absolute magnitude of the
6 response is to expect -- I think we're going to
7 know that, that a new drug can't come in with a
8 placebo-like effect rate.

9 So I guess I'm not -- I feel like we need to
10 do the pharmacovigilance that we've been doing, but
11 I don't think there is an easy way to do a whole
12 lot more than that. And if there was, we'd do it.
13 For a lot of these things, the studies you wish
14 for, we wish for them, too. If it were possible to
15 them, we'd do them. But as you've heard, we can't
16 get better data.

17 I feel I may not be answering the heart of
18 your question. You might want to try stating it
19 again if those ideas don't cover at least some of
20 the topics.

21 DR. SCHEETZ: I think it certainly answered
22 portions of the question. I think the biggest

1 concern is that you would approve a drug that would
2 fall somewhere in between placebo and standard of
3 care. So the new drug would not be quite as good
4 as standard of care but would still be approved. I
5 echo the concerns of some of the other reviewers.

6 Currently, our stewardship efforts are just
7 not good enough. We know that if we leave people
8 their own devices, prescribing patterns are not
9 great. And hopefully one day, we'll have some
10 thing more regimented in terms of oversight, making
11 sure that people are in fact doing the right thing.
12 But in the current environment where that doesn't
13 necessarily exist, what do we do in that case when
14 we have approved a drug that's not quite as good as
15 standard of care, but it's already been approved?

16 DR. REX: I don't have a good answer for
17 you. I think that case could well occur, and I
18 think that's why we label it for patients with
19 limited treatment options. And if that's the only
20 drug that's left here -- colistin is an example of
21 a drug like that right now. Are we grateful for
22 colistin right now? You bet. Are we cranky about

1 colistin? Yes, you bet.

2 I think you've got to recognize here that
3 the perfect in some ways is the enemy of the good
4 and having the option available could be really
5 important. So I can't go any further than that.
6 It becomes very much an application of common sense
7 and risk/benefit, and do you want to have some
8 choices versus no choices?

9 CAPT PARISE: Does the committee have any
10 other clarifying questions?

11 (No response.)

12 CAPT PARISE: We'll now break for lunch.
13 We'll reconvene again in this room at 1:00. Please
14 take any personal belongings you may want with you
15 at this time. Committee members, please remember
16 there should be no discussion of the meeting during
17 lunch among yourselves, with the press, or with any
18 member of the audience. Thank you.

19 (Whereupon, at 11:57 a.m., a luncheon recess
20 was taken.)

21

22

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

(1:00 p.m.)

Open Public Hearing

CAPT PARISE: We're going to get started again and start the open public hearing, everybody.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To

1 ensure such transparency at the open public hearing
2 session of the advisory committee meeting, FDA
3 believes that it's important to understand the
4 context of an individual's presentation. For this
5 reason, FDA encourages you, the open public hearing
6 speaker, at the beginning of your written or oral
7 statement to advise the committee of any financial
8 relationship that you may have with any company or
9 group that may be affected by the topic of this
10 meeting.

11 For example, the financial information may
12 include a company's or group's payment of your
13 travel, lodging, or other expenses in connection
14 with your attendance at the meeting. Likewise, FDA
15 encourages you at the beginning of your statement
16 to advise the committee if you do not have any such
17 financial relationships. If you choose not to
18 address this issue of financial relationships at
19 the beginning of your statement, it will not
20 preclude you from speaking.

21 Will speaker number 1 step up to the podium
22 and introduce yourself. Please state your name and

1 any organization you are representing for the
2 record.

3 MR. FRATTI: Hello. My name is John Fratti.
4 I do not represent any organization. I do not have
5 any financial conflicts of interest. I appreciate
6 the opportunity to provide my testimony here today
7 and for all the work the FDA has done in attempting
8 to improve noninferiority clinical trials.

9 I am a former pharmaceutical sales
10 representative. I worked in industry for seven
11 years and sold the antibiotic Ceftum. I speak
12 before you today, however, as a patient, a patient
13 whose life has been dramatically altered by an
14 antibiotic.

15 Over nine years ago, I was prescribed
16 Levaquin, a potent antibiotic in the
17 fluoroquinolone drug class. I suffered severe
18 injuries to my central and peripheral nervous
19 system, along with damage to my tendons. Prior to
20 my disability, I was healthy, active, and had
21 earned my MBA degree. Today, nine years later, I
22 require multiple pain medications in order to be

1 somewhat functional.

2 On the basis of noninferiority trials,
3 Levaquin received FDA approval in December of 1996.
4 Many of the Levaquin clinical trials submitted to
5 the FDA, upon which its approval was based, were
6 considered significantly flawed in protocol design
7 and protocol implementation, and this is noted on
8 the FDA website.

9 Noninferiority trials often fail to make
10 basic quality criteria, report biased and
11 misleading conclusions, and are often unduly
12 influenced by commercial sponsors. FDA approved
13 over 60 new drug applications for sinusitis,
14 bronchitis, and ear infections in children based on
15 noninferiority trials, which could not
16 differentiate the new drug from placebo. Yet these
17 same drugs increase side effects for patients and
18 spread antibiotic resistance.

19 In addition, as a former drug rep, I believe
20 certain antibiotics have the potential to be
21 promoted off label for indications not approved by
22 the FDA. It is important to also note that more

1 than 3,000 fluoroquinolone associated deaths have
2 been reported to the FDA since 1997. And more than
3 half of the fluoroquinolones that were once on the
4 market have now been removed due to various
5 toxicities.

6 In Levaquin or other widely prescribed
7 fluoroquinolones, such as cipro or Avelox are the
8 only available antibiotic class to keep people
9 alive, then they should show superiority and
10 effectiveness to older less effective drugs.
11 However, for patients with other safer options for
12 serious infections that do not cause the potential
13 severe and long-term disability associated with
14 fluoroquinolones, there's no need for patients to
15 accept increased risks.

16 As often stated by pharmaceutical companies
17 and others, that patients with unmet medical needs
18 are willing to take risks to try new drugs without
19 knowing whether they will be effective or not, are
20 these patients giving their informed consent in the
21 case of noninferiority trials to possibly taking a
22 drug that may be 10 to 20 percent less effective

1 than currently available drugs. Do they know they
2 are being put at risk for some potential, untested,
3 and hypothetical future benefit.

4 In closing, I stand before you as one who
5 could have taken a better tested drug with fewer
6 side effects. And I can assure you I would not
7 choose nor would I recommend any other patient
8 choose to be in such a trial. I made this
9 difficult trip here today to raise awareness about
10 noninferiority clinical trials and to possibly
11 prevent other people from suffering my fate. Thank
12 you for your time and consideration.

13 CAPT PARISE: Thank you. Will speaker
14 number 2 step up to the podium and introduce
15 yourself? Please state your name and any
16 organization you are representing for the record?

17 DR. DAYHOFF-BRANNIGAN: Hi. My name is
18 Dr. Margaret Dayhoff-Brannigan, and I am a senior
19 fellow at the National Center for Health Research.
20 Our research center scrutinizes scientific and
21 medical data and provides objective health
22 information to patients, providers, and

1 policymakers. We do not accept funding from drug
2 companies, and I therefore have no conflicts of
3 interest. Thank you for the opportunity to speak
4 here today.

5 I completed my PhD in biochemistry and
6 molecular biology at the Johns Hopkins School of
7 Public Health. A few years ago, I lost my
8 grandfather to a hospital-acquired antibiotic
9 resistant infection. I bring a perspective as both
10 a researcher and as someone personally affected by
11 the need for safe and effective antibiotics today.

12 Antibiotic resistance and the inability to
13 treat common infections is an increasingly urgent
14 public health crisis, which affects everyone,
15 especially some of the most vulnerable in our
16 society. Finding treatment options for unmet
17 populations is urgently important, but ineffective
18 antibiotics lead to an increase in antibiotic
19 resistance.

20 Noninferiority trials provide limited
21 information, not enough to provide the best
22 treatment for patients and certainly not enough to

1 reduce resistance. Unfortunately, the benefits of
2 new antibiotics over existing antibiotics are not
3 well established by clinical trials such as those.

4 Many drugs approved on data from
5 noninferiority trials are subsequently withdrawn
6 from the market. Examples include fluoroquinolones
7 and cephalosporins, many of which were withdrawn
8 for safety concerns, as we just heard. In fact,
9 among 61 new antibiotics approved between 1980 and
10 2009, 43 percent were later withdrawn for safety or
11 efficacy reasons. This rate is three times as
12 often as the 13 percent of non-antibiotic drugs
13 approved over the same time period.

14 Withdrawn antibiotics pose risks for
15 patients receiving them and increase the risk of
16 developing resistant pathogens that could spread.
17 We must ensure that proper clinical trials are
18 performed to reduce the number of antibiotics that
19 are unsafe and ineffective. Ten new antibiotics by
20 2020 will not help us if they're withdrawn later
21 for safety or efficacy reasons.

22 Superiority trials are the best way to test

1 new antibiotics for use in patients with unmet
2 needs. New antibiotics need to be tested in
3 patient populations like those that will be getting
4 the drug, not in healthy populations. This is
5 important because often bacterial infections can be
6 self-resolving in healthy populations, therefore
7 biasing the results; also, patients with resistant
8 infections that do not react to treatment the same
9 as patients with susceptible infections.

10 The health of the patient and whether they
11 have other co-infections or diseases plays a large
12 role in the effectiveness of the treatment, so
13 studying the right type of patients is critically
14 important. The proposed streamline approach, which
15 would increase the noninferiority margin in order
16 to do smaller trials, means that patients would
17 take on more risk and will not benefit from the
18 drug. This is not ethical since other options
19 already exist.

20 To avoid delays in treating populations with
21 resistant infections, we need to develop better
22 methods for accurate diagnosis of particular

1 pathogens. Better diagnostic tools will improve
2 the ability of industry to design clinical trials
3 in appropriate populations.

4 In conclusion, we want to provide the best
5 treatment for patients and reduce the number of
6 patients put at risk by taking antibiotics that are
7 later withdrawn from the market due to their lack
8 of safety or efficacy. The best way to accomplish
9 both of these goals is to improve the standards for
10 clinical testing. Superiority trials are critical
11 because they will require that these drugs show
12 effectiveness in the population most likely to
13 benefit from the drug. Thank you.

14 CAPT PARISE: Thank you. Will speaker
15 number 3 step up to the podium and introduce
16 yourself? Please state your name and any
17 organization you are representing for the record.

18 DR. MOLCHAN: I'm Dr. Susan Molchan. I'm
19 not representing any organization today, and I
20 don't have any conflict of interest. Today I'm
21 speaking as a physician in practice, though I spent
22 much of my career at the NIH in clinical research

1 and five years at the FDA. So I do have a lot of
2 respect for the work and people at the agency.

3 While we always have preclinical
4 evidence -- all the good things listed on this
5 first slide; a leap, as some people say, from
6 animal and test-tube studies -- that a drug has
7 activity against targets, or our discussion at hand
8 today, microbes, time after time, we've seen that
9 this doesn't always translate into our hopes for
10 treating disease in people.

11 Recent examples of antibiotics that have
12 looked promising from preclinical and early small
13 studies in human, but then failed when used in six
14 patients, include the six antibiotics listed on the
15 slide here, and we have heard about some of the
16 earlier today. The first three examples,
17 daptomycin, doripenem, tigecycline, are all
18 approved drugs for infections in skin, the urinary
19 tract, and the abdomen. In trials at another site,
20 though, in the lung to treat pneumonia, they didn't
21 work.

22 This makes the point about one of the

1 discussion points for this meeting, pooling various
2 body sites into a single study of a drug. Why were
3 these drugs ineffective for pneumonia? In the case
4 of daptomycin, later animal studies performed after
5 the trials showed that the drug interacted with
6 surfactant, inhibiting its bactericidal activity.

7 Not only may the dose of a test drug be
8 different in the lung or the abdomen or skin
9 structures, but so may the dose of a comparator.
10 Pooling outcomes across different body sites,
11 combining infections with different natural
12 histories and patient populations could well
13 create, as articulated in this review article I
14 like on composite outcome measures, an exaggerated
15 perception of how well interventions work.

16 Tigecycline was granted priority review as a
17 new antibiotic to treat MRSA and other resistant
18 organisms. It was approved in 2005. The black
19 boxed warning came in 2010, indicating that it
20 increased the risk of death compared to older
21 drugs. The drug may have been noninferior in
22 trials, but when used in really sick patients who

1 weren't included in pivotal trials, it was more
2 likely to be fatal. A point coming from this is
3 that noninferiority in less sick patients doesn't
4 translate into superior or adequate outcomes in
5 sicker patients with resistant disease.

6 Tigecycline was approved based on trials
7 with noninferiority margins of 15 percent, wider
8 than the more traditional 10 percent. Later,
9 analyses of the data indicated that if larger
10 trials with smaller margins had been used, its
11 mortality disadvantage and higher non-cure rates
12 would have been revealed sooner. Once approved,
13 tigecycline itself was used as a comparator in a
14 noninferiority trial, potentially perpetuating a
15 downward spiral of standards for efficacy, along
16 with perhaps an undesirable spin-off of more
17 post-approval, perhaps, black boxes. There's that
18 little guy down in the corner digging a hole. A
19 point about him is coming.

20 What about the results of decades of
21 noninferiority studies? One is that over a 20-year
22 period, from 1980 to 2009, half of the antibiotics

1 approved -- and this was alluded to earlier -- were
2 discontinued. Of 61 new molecular entities during
3 these years, 26 were withdrawn, 6 of them for
4 safety. The others were essentially me-too drugs.
5 They simply weren't selling. We've been digging a
6 hole so to speak, and we need to stop digging and
7 change course in some of the ways recommended in
8 the National Strategy on Combating
9 Antibiotic-Resistant Bacteria report, for example.

10 Across clinical research, too, an increasing
11 emphasis is being put on patient-centered outcomes.
12 Patients and physicians look to the FDA to center
13 on what matters to patients as well. And since I
14 have a minute, I want to congratulate Drs. Cox and
15 Temple on their New England Journal article,
16 published yesterday, calling for randomized trials
17 for drugs to potentially treat Ebola. No one would
18 argue the urgent need there. Patients with
19 bacterial disease deserve no less. Thanks.

20 CAPT PARISE: Thank you. Will speaker
21 number 4 step up to the podium and introduce
22 yourself? Please state your name and any

1 organization you're representing for the record.

2 DR. FRIEDLAND: Good afternoon. My name is
3 Ian Friedland, and I'm the chief medical officer at
4 Achaogen, which is a small biotech company
5 developing plazomicin and new amino glycoside. And
6 we are one of the few companies pursuing a
7 pathogen-based development program.

8 I would like to focus on what constitutes
9 substantial evidence of efficacy as required by
10 current regulation. Traditionally, for antibiotics
11 active against Gram-negative bacteria, sponsors
12 have followed an indication-based development plan,
13 usually including complicated urinary tract
14 infection and/or complicated intra-abdominal
15 infection. These are conducted with all-comer
16 pathogens that the inevitable consequence of this
17 is little direct clinical data on the most
18 important target pathogens that are usually the
19 basis for developing the antibiotic in the first
20 place.

21 Thus, for sponsors developing antibiotic
22 targeting specific resistance profiles, it would be

1 preferable to conduct a pathogen-focused clinical
2 development plan if this were feasible. However,
3 these types of studies can be very challenging to
4 design and enroll. Reasons for this include
5 overestimation by a fairly wide margin of the
6 numbers of patients suitable for enrollment in
7 registrational trials, based on epidemiological
8 resistance rates.

9 Also, in the absence of a reliable and
10 widely available rapid diagnostic test, there are
11 inevitable delays in confirming a specific
12 resistance pathogen, and patients with these
13 resisting infections frequently receive confounding
14 prior and concomitant antibiotics. Further, other
15 pathogens, either prior to or following enrollment
16 in the trial, confound reliable therapy. There are
17 many other reasons, which unfortunately I don't
18 have time allotted to go into.

19 In addition, the FDA currently requires such
20 pathogen-focused trials to demonstrate statistical
21 superiority over existing therapies. If a
22 pathogen-focused development plan is to be a more

1 desirable approach for sponsors, I believe greater
2 flexibility in trial design is essential and that
3 smaller clinical databases should be allowed.

4 Trial designs for pathogens that involve several
5 hundreds of patients are challenging to complete in
6 a reasonable time frame.

7 I therefore request that the committee
8 please consider the following two questions in
9 their deliberations:

10 One, follow resistant-pathogen study
11 development approach. Can flexibility and database
12 sizes be tailored commensurate with the urgency of
13 the unmet need and the infrequency of the
14 resistance pathogen being studied? So for example,
15 colistin-resistant and carbapenem-resistant
16 Enterobacteriaceae is an emerging problem for which
17 there is no accepted, reliable therapy.

18 Although these infections are a growing and
19 urgent need, the incidence varies widely by region.
20 The design of these trials needs to be especially
21 flexible, both in terms of indications included and
22 what is considered evidence of benefit, i.e., the

1 quantity of data and the definition of superiority.

2 My second question relates to supplementary
3 new drug applications. If initial approval was
4 based on an indication approach, say cUTI or cIAI,
5 can the requirements for substantial clinical
6 evidence against special pathogens be lowered in a
7 subsequent submission? Requiring sNDAs that focus
8 on unmet need pathogen be based on the same data
9 size and powered inferential statistics as the
10 initial approval is a significant deterrent in
11 seeking important clinical data against resistant
12 pathogens.

13 Furthermore, should the FDA consider an
14 orphan-drug type approach where much greater
15 flexibility is extended? This approach appears to
16 be acceptable in other therapeutic areas, where
17 following an initial approval, subsequent approvals
18 had been based on smaller databases, and in some
19 cases substantially smaller.

20 In summary, please allow me to repeat the
21 two additional questions I'm asking the committee
22 to consider in the context of targeted resistant

1 pathogen studies. One, for an initial approval,
2 can the amount of data required for approval be
3 tailored according to the incidence and clinical
4 consequences of the infecting pathogens? In other
5 words, a one size does not fit all approach.

6 Two. If an original approval was based on
7 an indication approach, can subsequent approvals
8 for resistant pathogens be based on smaller and
9 non-statistically powered studies? Thank you.

10 CAPT PARISE: Thank you. Will speaker
11 number 5 please step up to the podium and introduce
12 yourself? Please state your name and any
13 organization you're representing for the record.

14 DR. ECHOLS: My name is Roger Echols. I'm
15 an infectious disease consultant with more than
16 30 years experience developing anti-infective
17 drugs. I'm here today representing the viewpoints
18 of Shionogi and Company. Shionogi is a 136-year-
19 old Japanese pharmaceutical company with a strong
20 commitment to antibiotic drug discovery, including
21 such drugs as sulfamethoxazole, moxalactam,
22 ceftibuten, and doripenem.

1 The company is currently developing a
2 siderophore cephalosporin with potent activity
3 against carbapenem-resistant, Gram-negative
4 bacteria, including Enterobacteriaceae,
5 Pseudomonas, and Acinetobacter, which produce
6 serine or metallo-carbapenemases. The company's
7 had numerous discussions with the FDA and oversees
8 regulatory agencies regarding the appropriate
9 development pathway for this compound.

10 Shionogi agrees with the 2013 FDA draft
11 guidance that there must be a streamlined
12 development pathway for addressing the lack of
13 treatment options for patients with multidrug
14 resistant bacteria. And additionally, Shionogi
15 fully supports the tenets of antibiotic
16 stewardship, including limited use for patients
17 with these target pathogens.

18 Importantly, our understanding of
19 microbiology and PK/PD provides a rationale for
20 dose selection, and advances in rapid diagnostics
21 allow for precise pathogen-targeted, patient
22 selection, both for clinical trials and in clinical

1 practice.

2 There are several important areas, which
3 need to be resolved, regarding both the development
4 pathway and the indication for product labeling.

5 While the EMA guidance of 2013 clearly states that
6 a pathogen-focused study would not be powered for
7 inferential testing and that descriptive statistics
8 would be acceptable, the FDA appears constrained by
9 its definitions for substantial evidence of
10 efficacy, which require interpretable data from
11 inferential testing, i.e., an hypothesis-driven
12 clinical trial.

13 A pathogen-focused superiority study would
14 be preferred, however, a superiority study where
15 mortality is the primary endpoint remains
16 unattainable since only a small proportion of
17 all-cause mortality can be attributed to the
18 infection. Antibiotics alone do not determine the
19 mortality of patients. These are, after all,
20 largely nosocomial infections in very ill patients.

21 Alternatively, an infection-specific,
22 empiric treatment noninferiority trials require

1 large numbers of patients, only a small percentage
2 of which are infected with the target pathogens. A
3 pathogen-focused noninferiority study is
4 problematic because there's no established standard
5 of care, and justification of the noninferiority
6 margin is not possible.

7 Furthermore, Shionogi strongly believes that
8 the product label should accurately reflect both
9 the rationale for and how the drug was developed,
10 namely a pathogen-focused indication for patients
11 with limited treatment options. The product
12 indication should clearly reflect how the drug
13 should be used once marketed. In other words, its
14 use should be restricted to patients with target
15 multidrug-resistant infections.

16 The FDA's current position that the product
17 label indication must be for a site-specific
18 indication can only result in inappropriate or
19 off-label use. This would impair the ability of
20 the pharmaceutical company to appropriately market
21 the product.

22 The committee is being asked to discuss two

1 options regarding study designs, a noninferiority
2 study, which is infection-site specific, and a
3 superiority design, which is pathogen focused
4 involving multiple infection sites. Shionogi
5 believes that there's a third option, a pathogen-
6 focused study that includes infections at different
7 body sites caused by carbapenem-resistant,
8 Gram-negative bacteria, which will assess efficacy
9 based on meaningful clinical and microbiologic
10 endpoints analyzed with descriptive statistics.

11 This study would include a secondary
12 objective to test efficacy on a site-specific
13 infection, however, this inferential test would not
14 be as robust as found in traditional trials. This
15 randomized study using best available therapy as
16 the active control could provide substantial
17 evidence for the approval of an urgently needed
18 antibiotic.

19 To conclude, Shionogi believes that there
20 must be a continuum of thought and deed from the
21 time a drug candidate is selected to address an
22 unmet medical need to the targeted clinical

1 development of a product, which is then reflected
2 in a clear label that supports the most appropriate
3 use of the product. To achieve this, we must
4 accept a lower burden of proof to establish
5 efficacy for urgently needed treatments, and thus,
6 even adjust our expectation for product labeling to
7 better reflect how these drugs should be used.

8 Thank you.

9 CAPT PARISE: Thank you. Speaker number 6,
10 step up to the podium and introduce yourself.
11 Please state your name and any organization you're
12 representing for the record.

13 DR. EISENSTEIN: Good afternoon. Barry
14 Eisenstein, infectious disease physician and
15 microbiologist from Cubist Pharmaceuticals. The
16 topic of today's meeting is Antibiotic Development
17 for Patients with Serious Bacterial Diseases and
18 Unmet Medical Need. These unmet needs are mainly
19 infections caused by resistant organisms that can't
20 be addressed adequately by current approved
21 therapies.

22 Antibiotic resistance has rightly garnered

1 attention as a significant public health threat and
2 a focus of policymakers worldwide. One only needs
3 to look at today's New York Times, "Super Bugs Kill
4 India's Babies and Pose and Overseas Threat." The
5 GAIN Act of 2012 in the Obama Administration's
6 recent executive order are welcomed acknowledgments
7 of the need for urgent action to tackle resistance
8 and stimulate the development of much needed
9 treatments.

10 We applaud FDA's efforts to streamline the
11 regulatory pathway and approval process for
12 antibiotics, including the draft unmet need
13 guidance that we're focused on today. While the
14 draft outlines acceptable clinical trial designs,
15 it does not provide guidance on how to convey in
16 the label a drug's possible effectiveness against
17 resistant pathogens.

18 Although good policy has emerged regarding
19 how best to capture information about Gram-positive
20 resistance, such as MRSA, we fear that is not the
21 case for resistant Gram-negative pathogens. Labels
22 must be smart, providing physicians with critical

1 information on the most appropriate use of the
2 drugs and the potential value they provide to
3 patients. For the antibiotics we're talking about
4 today, labels must adequately describe the unmet
5 needs that the drugs address, mainly the resistant
6 mechanisms they target.

7 It's important to have a conversation about
8 labels in the context of what is valuable to
9 prescribing physicians. In the virtual absence of
10 rapid diagnostics, almost all antibiotic treatment
11 for serious infections is initially empiric.

12 Today physicians receive causative pathogen
13 and susceptibility information only after a patient
14 has started therapy. Until that information is
15 available, a doctor must select appropriate
16 treatment using IDSA or other guidelines and based
17 on the best local information available about what
18 is causing an infection.

19 The antibiotic label is the best source for
20 useful information about the performance of a new
21 antibiotic and the context of local and regional
22 antibiotic resistance patterns. Ideally, labels

1 would capture the best available data about an
2 antibiotic's effectiveness against organisms with
3 different resistance mechanisms to guide individual
4 patient treatment and support good stewardship. We
5 will never have the perfect solutions of labeling
6 antibiotics, but we can try to map out what an
7 informative label should include. Access to
8 information about resistance mechanisms is better
9 than no information at all.

10 What might such a label include? As I
11 prepared for today, the Hippocrates quote,
12 "Declare the past, diagnosis the present, foretell
13 the future" came to mind. I think it applies here.

14 First, we can declare the past by informing
15 physicians of the specific clinical performance of
16 an antibiotic as observed in trials. For example,
17 the clinical program enrolled a sufficient number
18 of patients with pathogens harboring resistant
19 mechanisms such as ESBLs, KPCs, or metallo-
20 beta-lactamases, and the antibiotic is effective.
21 This information should be included in the
22 indication section of the label.

1 Given the complexity of antibiotic
2 resistance, providing clinical outcome data, when
3 available, along with in vitro data against
4 resistant pathogens would provide physicians more
5 complete information for treatment decisions for
6 the individual and support good stewardship.

7 Second, we can diagnose the present by
8 strongly reinforcing in the label the importance of
9 susceptibility testing. To complete the picture,
10 we must foretell the future, explicitly
11 acknowledging the limitations of our knowledge
12 about potential resistance mechanisms, including
13 those that are yet to be discovered or the presence
14 of multiple resistance factors that may render an
15 antibiotic ineffective.

16 It is imperative to juxtapose what we know
17 from the past, that is how the antibiotic has
18 performed against no mechanisms, both in vitro and
19 in the clinic, with what is unknown because the
20 only certainty is that pathogens will adapt and
21 evolve.

22 For Cubist and others on the short list of

1 companies interested in this therapeutic area, to
2 make investments in efforts worthwhile, the label
3 needs to capture the value of the new antibiotics
4 by describing their activity against resistant
5 mechanisms in a relevant way. The FDA has the
6 power to include this language in prescribing
7 information for future therapies, and we urge the
8 FDA to do so. Thank you.

9 CAPT PARISE: Thank you. Will speaker
10 number 7 please step up to the podium and introduce
11 yourself? Please state your name and any
12 organization you're representing for the record.

13 MR. BRODINE: My name is Joseph Brodine, and
14 I am representing myself, and I don't have any
15 conflict of interest to declare. At its inception,
16 in the Pure Food and Drug Act of 1906, the FDA's
17 first purpose was to protect the American public
18 from unsafe medical treatments. Providers and
19 patients are more than just grateful to the FDA
20 preserving this function. We are dependent on the
21 FDA to, above all, protect patients' safety.

22 My name is Joe Brodine, and I'm a medical

1 student who took one of my exams a day early so I
2 could be here today to advocate on behalf of my
3 future patients. I'm also a former registered
4 nurse with more than a decade of clinical research
5 experience. I came because I'm alarmed by the
6 trajectory of changes to antibiotic approval
7 standards. The need for the FDA to expedite
8 innovation is clear, but efforts to accelerate the
9 approval process may imperil patients.

10 Clearly, the agency is being pushed by
11 recent legislation to fast-track drug approvals to
12 combat problems of drug resistance. It would be
13 prompted further if Congress passed the antibiotic
14 development to advance the Patient Treatment Act
15 that would allow surrogate endpoints, such as
16 mathematical modeling and in vitro studies to
17 substitute for clinical outcomes of real patients.
18 Such measures would undoubtedly diminish the safety
19 assured by their review process, much as the
20 current prevalent use of noninferiority trial
21 designs may have already posed a risk to current
22 study participants and future patients.

1 Today the committee is discussing clinical
2 trial designs for patients with infections for
3 which there are limited or no therapeutic options.
4 As a future clinician, I urge the FDA to keep the
5 patient at the core of their approval process.

6 Are patients who serve as study participants
7 in drug trials being asked to test an appropriate
8 hypothesis in a noninferiority trial? As we know,
9 in a noninferiority design, an unknown study drug
10 is tested against the known comparator in order to
11 determine if the study drug is noninferior to an
12 unacceptable extent.

13 Is it ethical to expose a study patient to
14 the harms of an unknown drug when there's no chance
15 of deriving added benefit? The patients I enrolled
16 in HIV and brain tumor treatment trials invariably
17 asked me if the study drug would help them. It is
18 a fundamental concern of a sick person seeking to
19 be well that participating in drug research will
20 have the added benefits for them, a concern that
21 FDA leadership must keep foremost in their guidance
22 to the industry.

1 It seems that noninferiority studies not
2 only ask the wrong question but may have provided
3 answers that cannot be appropriately applied to the
4 patients with the greatest unmet medical needs.
5 Study sample populations should represent the
6 intended recipients of the approved therapy. If
7 new drugs are studied only in patients with
8 susceptible disease who are less critically ill
9 than patients with resistant disease, how will
10 physicians know what to expect from a drug when
11 considering its use in a critically ill patient?

12 A meta-analysis of 14 comparative clinical
13 trials published last year showed a 50 percent
14 mortality rate in patients with
15 ventilator-associated pneumonia who received
16 tigecycline versus 7.7 percent in the comparator
17 group. Tigecycline was approved based on
18 noninferiority studies despite increasing mortality
19 compared to older drugs.

20 New drug research and approval should aim
21 for superior efficacy compared to standard
22 treatments in order to address antibiotic

1 resistance. History shows this to be possible.
2 When I worked with HIV patients, they would recount
3 the limitations of therapy at the advent of HAART.
4 AZT was administered, 400 milligrams every 4 hours
5 day and night. Improvements in quality and
6 quantity of life were gained from research built on
7 superiority trials in the sickest patients.

8 The FDA should streamline and augment its
9 approval process for greatly needed novel therapies
10 in ways that actually add more effective and safer
11 drugs to our armamentarium. We need innovation,
12 and innovation should mean that drugs are superior,
13 not noninferior. We need studies that focus not
14 just on surrogate endpoints but on patient-centered
15 endpoints, like overall survival and functional
16 improvement with meaningful quality of life.

17 We must develop rapid diagnostics to
18 identify drug susceptibilities. We must establish
19 data sets for sharing clinical trial data so that
20 these data sets are public and treatment decisions
21 can be based on the most complete information.
22 Finally, we should encourage comparative efficacy

1 designs that aim to demonstrate superiority. Drugs
2 that are truly superior actually require fewer
3 study patients than those used in noninferiority
4 studies.

5 These suggestions originated from
6 stakeholders, academia, and the FDA's own guidance
7 for industry documents. Most importantly, these
8 mechanisms are consistent with the FDA's mandate to
9 guarantee safety and effectiveness for the many
10 patients of today and the countless patients of
11 tomorrow.

12 CAPT PARISE: Thank you. Will speaker
13 number 8 please step up to the podium and introduce
14 yourself? Please state your name and any
15 organization you're representing for the record.

16 MS. SCOTT: My name is Drusilla Scott. I
17 work in regulatory affairs at Cembra
18 Pharmaceuticals, and I'm speaking on behalf of the
19 company today. We wanted to present some
20 considerations for trials for small population
21 indications in patients who have refractory bone
22 and joint infections and are in need of additional

1 oral options because they're not candidates for
2 definitive surgery.

3 As with most uncommon conditions, clinical
4 trials of related infections in small,
5 non-homogeneous populations -- innovative trial
6 design endpoints and statistical methodology, and
7 you've certainly been discussing that today.
8 Osteomyelitis and prosthetic joint infections are
9 increasing in number as the population ages, with
10 increasing incidence of diabetes and peripheral
11 vascular disease. The prevalence is still quite
12 small, and in adults in the U.S., it appears to be
13 less than 100,000 for both types of infections.
14 And there's actually published data on the internet
15 that prosthetic joint infections is less than
16 20,000 per year.

17 Most treatment of bone and joint infections
18 involves definitive surgery when that's possible to
19 remove the infective bone sequestration or foreign
20 materials, along with a follow-up course of
21 antibiotics. And when possible, for example in
22 knee replacement, you would undergo a two-stage

1 revision in which the infected prosthesis is
2 removed and replaced with a new joint.

3 However, there is a subset of patients with
4 these types of infections, whether associated with
5 foreign material or not, who simply cannot undergo
6 the definitive surgery because of their poor
7 health, age, or other comorbidities. These
8 patients might undergo more limited surgery,
9 including debridement and irrigation, placement of
10 intra-articular antibiotics via beads or spacers,
11 and an initial course of IV antibiotic of some
12 weeks, followed by 3 to 6 months of antibiotics,
13 oral when possible, and even longer in some cases.

14 Patients whose infections relapse after the
15 completion of their course of oral antibiotics can
16 get additional courses, but often times they again
17 fail on these and must be once again hospitalized
18 for additional cycles of debridement, irrigation,
19 and antibiotics. While these patients do not have
20 no options, they can be hospitalized again, and in
21 the worse cases, there can be amputation, we
22 believe there's a clear need for additional oral

1 options for these patients.

2 Some of the things we've been thinking about
3 in terms of study design recognize that the
4 population is not going to be homogeneous. They
5 may need a new oral treatment for a number of
6 reasons. One, they're frankly failing. They're
7 just not responding to the drugs that are
8 available, or they may not be able to receive or
9 continue to receive the available oral therapies
10 that they've been on for safety or new tolerability
11 concerns.

12 Their sources of infections are going to be
13 different. They may be associated with foreign
14 material or post-traumatic osteomyelitis, and their
15 overall health and underlying comorbidities may be
16 quite different. So these may certainly show
17 differences in how people are going to respond to
18 treatment. However, we think that it may be
19 feasible to study new oral treatments in a
20 comparative trial by employing composite endpoints
21 that are objectively measurable and clinically
22 meaningful.

1 Some things we are thinking about is
2 defining a population as refractory if they have
3 relapse for either efficacy or safety from at least
4 two prior courses of oral antibiotics. A
5 noninferiority design would be very difficult. And
6 even if practical, even if possible would be
7 impracticable because of the sample size. So while
8 there, again, are other options, we think a
9 superiority design may be very reasonable given
10 that the people will have relapse from their prior
11 oral regimens, at least two.

12 We think you can do what you can to
13 normalize and standardize the study arms. For
14 example, you would give them the same duration of
15 IV antibiotic treatment once they've enrolled but
16 before they've been randomized into the study.
17 Then you would debride. You would obtain a culture
18 to see if their pathogens are sensitive to the
19 tests and standard of care drugs that the physician
20 might employ, then they would receive the test drug
21 or standard of care that they were randomized to.

22 We believe that while endpoints clearly have

1 subjectivity to them, you can make objective
2 measurements that are clinically meaningful and
3 define failure and success by measures such as
4 things as hospitalization to treat the infection,
5 whether joint mobility improves. So you can put
6 this constellation together and we think define
7 failure and success, and potentially bring some new
8 products to the market for these patients.

9 CAPT PARISE: Thank you. Will speaker
10 number 10 please step up to the podium and
11 introduce yourself? Please state your name and any
12 organization you're representing for the record.

13 DR. DUDLEY: Good afternoon. My name is
14 Michael Dudley, and I am senior vice president in
15 Infectious Disease Global Innovation Group, and I'm
16 responsible for research and development of
17 anti-infectives at The Medicines Company. I'm
18 serving as its representative today.

19 The mission of The Medicines Company is to
20 save lives, alleviate suffering, and to contribute
21 to an improved economic performance of the
22 healthcare system. The Medicines Company remains

1 one of the few companies actively conducting
2 internal antimicrobial research and development. I
3 have worked in antibacterial and antiviral drug
4 development for over 30 years, in both academia and
5 industry, as well as practiced in the clinical
6 setting, what is now known as antimicrobial
7 stewardship. And thus, I hope to provide a
8 perspective as both a clinician and drug developer.

9 I would like to make the following four
10 points this afternoon. First, we support recent
11 legislative initiatives, PCAST recommendations, and
12 the resulting executive order calling for the
13 development of a new regulatory pathway as well as
14 use of existing mechanisms to streamline the
15 development and approval of urgently needed
16 antimicrobials for use in patients where existing
17 choices are limited or not appropriate.

18 These LPAD pathways may include pathogen or
19 resistance-directed programs that are consistent
20 with stewardship principles and provide clinical
21 data in patients with a pathogen and resistance
22 mechanisms of interest.

1 Secondly, we believe that in fulfilling the
2 order of point 1, the totality of data,
3 particularly PK/PD data that bridge to clinical
4 observations, can play an increasingly important
5 role.

6 Thirdly, clinical data, including those from
7 appropriately sized, perhaps relatively small data
8 sets from patients with infections due to the
9 pathogen and resistance mechanism of interest are
10 important and can support approvals for new agents
11 for use in patients with limited treatment options.

12 Finally, the results from clinical studies
13 on treatment of infections due to antimicrobial
14 resistance threat pathogens, including the
15 experience from small or clinical trials, should be
16 included in product labeling.

17 Now, let me unpack these ideas in the
18 following points. Point 1, develop new regulatory
19 pathways. Conduct of clinical trials in patients
20 with target pathogens and resistance mechanisms is
21 challenging. These patients may be complicated nor
22 are they readily enrolled in traditional

1 indication-based clinical trials. Alternative
2 trial designs that are pathogen and resistant
3 directed can provide important data sets to support
4 regulatory decisions and inform on risk/benefit in
5 patients where existing treatments are limited or
6 not appropriate.

7 Moreover, we believe that indication-based
8 comparative studies typically conducted to support
9 FDA approval for broad indications -- where the
10 pathogens are susceptible to both the test and
11 control drugs and, thus, don't include patients
12 with pathogen resistance mechanisms of
13 interest -- do not represent a pathway for
14 substantive innovation, nor do they serve the
15 interest of antimicrobial stewardship.

16 Point 2, use the totality of data from
17 clinical and nonclinical investigations. As noted
18 in FDA's briefing document, we agree that PK/PD and
19 pharmacometric analyses of both nonclinical and
20 clinical data are important and serve to improve
21 the estimate of treatment effect for new
22 antimicrobials. These analyses embody the

1 learn/confirm approach to drug development
2 introduced by Drs. Sheiner and Peck that were so
3 effectively used for early HIV drug development
4 over two decades ago.

5 Thirdly, clinical data from patients with
6 infections due to the target pathogens and
7 resistance mechanisms are important. It is
8 important that clinical data be generated in
9 patients with the pathogen and resistance
10 mechanisms of interest.

11 We agree with the concepts outlined in FDA's
12 proposal on the briefing document and draft
13 guidance that these data could be derived from
14 smaller clinical data sets from comparative trials,
15 for example, with best available therapy. In order
16 to provide timely information, these trials need
17 not always be powered for formal inferential
18 testing. Formal confirmation of effects may need
19 to come later with more potentially post-approval
20 studies.

21 Finally, labeling. Communicate the results
22 in the label. We believe it is important to

1 communicate the information and product labeling on
2 the results of all relevant data from a streamlined
3 development program. Communication of these data
4 and its limitations in product labeling would
5 benefit clinicians, stewardship practitioners and
6 payers in making judgments about the risk/benefit
7 for use of these new drugs in patients with limited
8 treatment options.

9 We applaud FDA's considerations for product
10 labeling in the current CFRs and further suggest
11 that many elements of an adequate and well-
12 controlled investigation can be built into smaller
13 studies, including dose control, which is embodied
14 in a pharmacometric analysis, and concurrent
15 treatment controls. Moreover, if the statutes
16 won't allow this information in product labeling,
17 let us pursue changes in them rather than accept
18 limitations on informing those who must make
19 risk/benefit decisions in the care of infected
20 patients with limited choices.

21 So in closing, we have been called to action
22 in this crisis. We can learn from lessons learned

1 decades ago, and the successful development and
2 approval of drugs for HIV and AIDS can be reapplied
3 today. And we urge application of those learnings
4 in the current threat of multidrug resistance
5 bacterial infections. Thank you.

6 CAPT PARISE: Thank you. Will speaker
7 number 11 step up to the podium and introduce
8 yourself? Please state your name and any
9 organization you're representing for the record.

10 MS. RAMACHANDRAN: Hello. My name is Reshma
11 Ramachandran. I'll be speaking on the behalf of
12 the National Physicians Alliance FDA Task Force. I
13 have no financial conflicts of interest and serve
14 as a task force co-chair.

15 The National Physicians Alliance is an
16 independent, multi-specialty physician organization
17 dedicated to providing evidence-based medicine and
18 advocating, first and foremost, for our patients
19 and public health. I'm also a final year joint
20 medical and public policy student at Brown Medical
21 School and Harvard Kennedy School. Thank you for
22 this opportunity.

1 I echo my colleagues in saying that the FDA
2 must not compromise safety and efficacy in favor of
3 a streamlined or expedited antibiotic approval
4 process. Doing so would only undermine the FDA's
5 mission in protecting the public health by assuring
6 us as clinicians and our patients of the safety,
7 efficacy, and security of all drugs, including
8 antibiotics. We agree that new antibiotics are
9 needed, but the bottleneck is not regulatory.

10 Dating back to 1964, antimicrobials have had
11 the highest rates of regulatory agency approval
12 compared to any other therapeutic class. Data from
13 the pharmaceutical industry has also shown that
14 there's only a 7 percent yield from screening
15 promising antimicrobial drug compounds, which is
16 less than one-tenth of the yield for finding
17 promising drugs in all other therapeutic areas.

18 This only indicates that the bottleneck is
19 well before clinical trial testing. Not only that,
20 but the time in clinical development for
21 anti-infectives is among the shortest compared to
22 other therapeutic classes.

1 Additionally, shortening clinical trials
2 will not stimulate antibiotic innovation. The
3 Eastern Research Group modeled various incentives
4 for the U.S. Department of Health and Human
5 Services and found that shortening trials or
6 changing approval standards would not make a
7 difference economically for drug companies unless
8 they cut clinical trial links by 75 percent. This
9 would not be possible without severely compromising
10 patient safety.

11 As noted by the examples in Dr. Susan
12 Molchan's talk earlier, standards of approval of
13 new antibiotics are already low and already use too
14 few patients in clinical trials. This has resulted
15 in FDA approval of these new drugs actually causing
16 more deaths in patients than existing treatments.
17 As a physician in training, I cannot advocate in
18 good faith for this sort of uncertainty, especially
19 if it may cost my patients' lives. Also, these
20 regulatory mistakes could instead have a chilling
21 effect on drug R&D.

22 Instead, we ask the FDA to provide

1 incentives only for antibiotics that address unmet
2 medical needs, studied in patients with these unmet
3 medical needs, and actually demonstrate added
4 benefits for these patients. Both patients and
5 clinicians want drugs that will improve efficacy
6 and/or decrease harm.

7 Current legislation in Congress, namely the
8 ADAPT or Antibiotic Development to Advance Patient
9 Treatment Act, fails to target incentives to
10 developing truly novel antibiotics rather than
11 me-too products. The withdrawal rates of
12 antibiotics from the market is already more than
13 three times as high than that of non-antibiotics,
14 as these drugs appear to be just not effective
15 enough to compete with existing regimens.

16 The FDA approval process should not be
17 undermined but rather strengthened. In regards to
18 the tiered approval approach, we agree with the FDA
19 that tier C and tier D are not sufficient to meet
20 FDA's requirement for demonstration of safety and
21 effectiveness.

22 We also think that the tier B approach of

1 one phase 3 body site trial, with inference testing
2 demonstrating effectiveness and safety and not body
3 site, along with descriptive studies, receiving
4 investigational drug would not be sufficient
5 either.

6 Extrapolating noninferiority in one patient
7 group to show superiority in another patient group
8 is not valid. There have been many examples of
9 drugs, including ones already mentioned today, that
10 were shown to be noninferior in less ill patients,
11 but then showed mortality in sicker patients. This
12 clearly shows that patient factors are equally as
13 or even more important than organism factors.
14 Besides this, using descriptive studies are not
15 adequate or well-controlled themselves and will not
16 become so just because of noninferiority trials in
17 another group of patients.

18 In 1970 in the case Upjohn versus Finch, the
19 court actually rejected the standard of case
20 studies as being substantial evidence for drug
21 efficacy in addition to relying on in vitro animal
22 data. Instead, we ask that the FDA approve

1 antibiotics based on a single superiority study
2 with patient-centered outcomes in patients with a
3 single type of disease. If the drug is effective,
4 fewer patients are needed.

5 Additionally, the FDA should remove
6 financial conflict of interest in setting standards
7 for antimicrobial susceptibility. The process for
8 determining these standards should be transparent
9 independent of financial conflict of interest and
10 be based on patient-centered outcomes such as
11 survival, function, and mortality.

12 Only three of the current members of the
13 Clinical and Laboratory Sciences Institute
14 Antimicrobial Susceptibility Subcommittee reported
15 no financial conflict of interest. In 2010, this
16 committee lowered antibiotic resistant breakpoints
17 for ceftriaxone, which would have led to a
18 300 percent increase in the number of infections
19 that are classified as antibiotic resistant. This
20 would have led to physicians prescribing newer
21 broad-spectrum antibiotics for these cases, even
22 those studies have shown that this change would not

1 have offered any improvement in clinical outcomes.
2 Changing these standards for antibiotic resistance
3 could lead to greater resistance from
4 inappropriately prescribed and increased use of
5 broad-spectrum antibiotics that should be reserved
6 for infections for which they are effective.

7 The NPA asks that the FDA continues to
8 uphold its mission to provide us as clinicians and
9 our patients assurance that the drugs the agency
10 continues to approve are truly safe and effective.
11 Thank you so much.

12 CAPT PARISE: Thank you. Will speaker
13 number 12 please step up to the podium? Please
14 state your name and any organization you represent
15 for the record?

16 DR. AMBROSE: Hi. My name is Paul Ambrose.
17 My potential conflicts include I'm a special
18 government employee of the U.S. FDA. The opinions
19 I'm about to express are mine, not the U.S. FDA or
20 any pharmaceutical company or biotechnology
21 company, and no one has paid me to be here today.

22 The elephant in the room. I think what we

1 have here is a failure to communicate, guys.
2 Multidrug resistant bacteria are just bacteria. We
3 choose to act as if there are different species of
4 bacteria. They're not. This results in us putting
5 together regulatory pathways that do not serve the
6 needs of patients. In reality, MDR pathogens are
7 just isolates with elevated MIC values to some
8 drugs and not to others. From a pharmacological
9 perspective or a PK/PD perspective, MDR bacteria
10 and wild type bacteria respond to drug exposure in
11 the exact same way. Crazy you say? Well, let's
12 follow the science.

13 These are data from Dr. Bill Craig's
14 laboratory. You're looking at exposure/response in
15 neutropenic mice. Time above MIC on the X-axis,
16 change in log CFU on the Y-axis. The red symbols
17 represent ESBL-producing bacteria; the blue,
18 non-ESBL bacteria. The dashed line in the middle
19 is net bacterial stasis. Positive numbers on that
20 Y-axis are growth; negative numbers on that Y-axis
21 are bacterial killing.

22 What do you see? You see it doesn't matter

1 whether it was an ESBL or not? If you've got
2 enough drug exposure measured as time above MIC for
3 these cephalosporins, you've got the exact same
4 effect. You might be saying, "You're crazy.
5 That's animals. We're treating patients."

6 Well, I'm going to share with you some data
7 for gatifloxacin in the treatment of typhoid fever.
8 In multivariable logistic regression analyses that
9 were carried out on a data set developed with the
10 Wellcome Trust, MDR was not a predictor of response
11 even though 60 percent of these patients had MDR.
12 But guess what was? You've got it. Drug exposure
13 index to MIC, that's what predicts response.

14 So if you get the dose right to cover your
15 MDR pathogens, everything shakes out just fine. It
16 is true you have to get bigger exposures to cover
17 some MDR pathogens, but it's the same time above
18 MIC -- or AUC, that's important -- relative to wild
19 type.

20 So you might say, "You're crazy. You're
21 crazy, Ambrose. There are lots of papers in the
22 literature. They all say MDR is a risk factor for

1 failure." Well, I'll tell you -- remember, check
2 those emotions. The people who get MDR pathogens
3 are different. They suffer from many more
4 comorbidities. They receive multiple courses of
5 antibiotic; oftentimes, the wrong antibiotic first.
6 And they've been in the hospital a lot longer.

7 MDR is hopelessly confounded with this. The
8 reality is, it's the patients who get MDR that are
9 different, not the fundamental interaction between
10 microorganism and bug. And Dr. Follmann, the
11 reason you see -- well, if you get your dose right,
12 if you get the dose right, the other drivers of
13 outcome are the reason why people with MDR
14 pathogens do worse than others. You've got the
15 drug right. Everything's going to be okay.

16 So what are the keys for the puzzle today?
17 Well, if you remember, from a PK/PD perspective,
18 MDR are not different than wild type bacteria. And
19 if you can remember that it's the patient
20 population that's different, I urge you to study
21 new drugs in the patient population of interest
22 that matters irregardless of susceptibility to a

1 pathogen.

2 Don't run around the world searching for
3 dragons to slay. Don't look for left-handed
4 patients with polymyxin-resistant,
5 gentamicin-susceptible CRE. It's going to take you
6 forever. And as we show with the preclinical
7 models, and if you even look in clinical data when
8 you index the drug exposure, that's not what's
9 important.

10 So, what are the implications of this? If
11 you can accept these two, what I believe, simple
12 truths -- here's a mythical drug that's been
13 developed. The green histogram represents the wild
14 type distribution for this pathogen. We'll call it
15 *Pseudomonas aeruginosa*. The red part of that
16 histogram is resistance mechanism A, and the blue
17 is resistance mechanism B. Pretend some sponsor
18 ran out and enrolled a whole mess of patients, and
19 they got that first distribution. Almost everybody
20 has got the wild type pathogens, and there's a
21 smattering of people that have the red resistance
22 mechanism, but no large number of them.

1 The reality is the product should say,
2 "Ambrosicillin [ph]" -- and I named it after
3 myself; it's really a good drug -- "is indicated
4 for the treatment of pneumonia caused by
5 susceptible *Pseudomonas aeruginosa*, including those
6 that express resistance mechanism A," because we
7 can show in the preclinical models, and we know
8 from clinical experience with other drugs, it
9 doesn't matter, as long as the MIC captures what
10 you need to know, as long as you index that MIC to
11 drug exposure. If you want to cover resistance
12 mechanism B, you're going to have to use much more
13 intensive dosing to make sure you can cover that
14 pathogen.

15 So as I wind up, please recognize that MDR
16 bacteria are just bacteria. It's the patient
17 populations that are different. And please
18 recommend pathways that can provide patients timely
19 access to urgently needed medication, and I stress
20 timely. It's a time for choosing, ladies and
21 gentlemen. We either descend into a future, a dark
22 future, without effective antibiotics, or we make

1 decisions starting today that assure we have
2 effective antibiotics in the future. Thank you.

3 CAPT PARISE: Thank you.

4 The open public hearing portion of this
5 meeting has now concluded and we'll no longer take
6 comments from the audience. The committee will now
7 turn its attention to address the task at hand, the
8 careful consideration of the data before the
9 committee, as well as the public comments.

10 I think before we get into discussion,
11 Dr. Nambiar is going to make a few comments.

12 DR. NAMBIAR: Thank you, Dr. Parise. So as
13 you've heard from discussions today, the field of
14 antibacterial drug development is challenging to
15 say the least. There is an urgent need for new
16 therapies to address the present unmet need and
17 also to ensure a robust pipeline for the future.
18 Streamlined development programs carry uncertainty
19 with regard to safety and efficacy, which we have
20 to balance with the feasibility of conducting such
21 trials.

22 So with that in mind, we have four

1 discussion questions for you today. There are no
2 voting questions. Your comments and thoughts will
3 be of tremendous value to us as we continue to make
4 these trials scientifically sound and feasible to
5 meet patient needs.

6 The first question is, please discuss the
7 acceptability from a clinical perspective of a
8 streamlined development program that has greater
9 uncertainty about the safety and efficacy of a new
10 drug because of the smaller size of the clinical
11 studies.

12 The second question has two parts. The
13 question states, please discuss the following
14 options for trial designs for streamlined
15 development programs. The first one relates to
16 noninferiority trials, and we would like you to
17 discuss noninferiority trials at a single body site
18 of infection. We've given you some examples, cUTI
19 or cIAI, using larger than usual noninferiority
20 margins.

21 The second discussion point is regarding
22 superiority trials and your thoughts on pooling

1 across different body sites of infection and also
2 selection of the control group for inference
3 testing, be it best available therapy or the use of
4 external controls.

5 The third question is please discuss trial
6 design options for a product that has a spectrum of
7 activity limited to one or two microorganisms. We
8 have two examples, *Pseudomonas aeruginosa*,
9 *Acinetobacter baumannii*.

10 Question number 4 is please discuss the
11 acceptability of a smaller safety database; for
12 example, 300 to 400 patients exposed to the
13 investigational drug at the dose and duration of
14 therapy. We look forward to the discussion. Thank
15 you.

16 **Questions to the Committee and Discussion**

17 CAPT PARISE: We'll now proceed with the
18 questions to the committee and the panel
19 discussions. I'd like to remind public observers
20 that while this meeting is open for public
21 observation, public attendees may not participate,
22 except at the specific request of the panel.

1 I'm going to now read the first question
2 that we're going to discuss now, is to please
3 discuss the acceptability from a clinical
4 perspective of a streamlined development program
5 that has greater uncertainty about the safety and
6 efficacy of a new drug because of the smaller size
7 of the clinical studies.

8 Are there any issues or questions, first,
9 about the question that people need clarified?
10 Yes, Dr. Andrews?

11 DR. ANDREWS: Does the question assume that
12 there would be just a range of options, and one of
13 the options would be each drug trial would
14 only -- you wouldn't change the margin and pooling
15 body site, and a smaller size on a particular drug,
16 or just using one of those as an option?

17 DR. NAMBIAR: Certainly, if you have other
18 options that you would like to discuss, we're open
19 to suggestions. These are just some thoughts we
20 had, but if you have any other ideas, we'd
21 certainly welcome those.

22 DR. ANDREWS: No, no. My question was

1 you're only going to do one at once, right?

2 DR. NAMBIAR: Sorry?

3 DR. ANDREWS: You wouldn't do multiple
4 changes to the standard for a particular drug. I
5 think the question -- I'd like to know whether
6 you're talking about these are options, and you
7 would use one of them in any given trial, or maybe
8 two if it's appropriate. But you wouldn't make
9 all -- I don't know, maybe five or six of these in
10 any given drug trial.

11 DR. NAMBIAR: It's any given development
12 program or any given trial. Any given trial would
13 either be a noninferiority trial or a superiority
14 trial. But in a development program for a product,
15 you could use either of the trials or you could use
16 both, depending on what your overall development
17 program is. I hope that answered the question.

18 DR. ANDREWS: I don't know whether I mean
19 trial or --

20 DR. COX: I think this question is really
21 just getting at the bigger picture issue, so not so
22 much to the granularity of particular things that

1 you might do in a particular trial. It's a little
2 bit more of that level of detail in the subsequent
3 questions. But this one I think is getting more
4 the idea of -- given the issues that are out there
5 with resistance, the challenges of antibacterial
6 drug development, from a big picture standpoint,
7 streamlined development is one approach to try and
8 address that. So we're interested in hearing
9 folks' comments on that and your perspectives.

10 DR. ANDREWS: I guess my question was just
11 how big are you talking about going.

12 DR. COX: I think that you'll get a little
13 more granularity in the next questions, but I
14 really think this is at a higher level. The
15 particular maneuvers that you might consider in
16 specific settings are probably a little bit more
17 detailed than we could ever really even hypothesize
18 for this higher level question.

19 CAPT PARISE: The question's open for
20 discussion. Dr. Moore?

21 DR. MOORE: As been mentioned by other
22 speakers before, this really takes me back to the

1 days when HIV therapy first became introduced. On
2 the one hand, you had individuals who wanted to
3 make sure that the drugs were very, very safe. On
4 the other hand, you had a large number of patients
5 that were dying and needed access to drugs, which
6 may or may not have been proven to be completely
7 safe.

8 Although we're not in that situation right
9 at the moment, the anticipation is that with the
10 ongoing spread of multidrug resistance and
11 completely drug resistant organisms, we may find
12 ourselves in that situation. It's an unenviable
13 position I think for the FDA to be in because you
14 really can't please everyone.

15 The way I would view this is I would
16 definitely support the FDA's discretion in
17 streamlining clinical trials or coming up with
18 streamlined programs for drug approval that relies
19 upon a looser margin of inferiority for drugs, not
20 broadly, but just drugs that would anticipate
21 meeting an unmet need. And to that end,
22 Dr. Ambrose's point is well taken.

1 I was thinking about this at lunch earlier
2 today, that the way the world works is not by
3 organism but by clinical presentation. Patients
4 present with a particular condition. You can't
5 predict what organism they have necessarily, and I
6 think the clinical trials would have to be done not
7 by selecting for a particular organism but by
8 mining the data of a clinical trial, looking for
9 resisting organisms upon which the FDA could make a
10 recommendation about approving a particular drug,
11 or within reason, establishing a recommendation
12 based on safety and efficacy of a smaller subset.

13 I think that's ultimately the way that it's
14 going to have to be done. Because really, with the
15 progression of resistant organisms, there is -- my
16 personal opinion -- and I think it's paramount to
17 try to encourage pharmaceutical companies to get
18 back into the business of developing antibiotics,
19 which are drugs you take for a short period of time
20 rather than the drugs -- most of the drugs that are
21 coming on the market, which are drugs people take
22 forever. These are critical needs that have to be

1 met, and any way to encourage that, particularly
2 for highly drug-resistant organisms, needs to be
3 encouraged.

4 CAPT PARISE: Thank you. Dr. Ostrosky?

5 DR. OSTROSKY: Again, I'd like to emphasize
6 that this is not a theoretical or academic
7 discussion. This is affecting real people today in
8 the United States. I have a patient in my hospital
9 that has had VRE bacteremia for 35 days. He's on
10 five antibiotics. I don't think he's going to make
11 it. And we need to do something about this, so
12 something has to give. We need to be able to bring
13 more antibiotics into the market, and we need to
14 use them very wisely. And we need to make sure
15 they're safe.

16 It's a very complicated question today. I
17 think I'm, in general, very supportive of a
18 streamlined development program, but what I would
19 also like to see is in the backend a much more
20 robust postmarketing pharmacovigilance framework,
21 where it's not just voluntary reporting through
22 MedWatch or post-regulatory commitments. It needs

1 to be something very systematic, where we
2 periodically look at the efficacy and safety of
3 things that have been approved.

4 Finally, I think trial design is not the
5 only program that needs to be addressed. There are
6 a whole bunch of regulatory issues with data
7 management, data security, informed consent. We're
8 making people sign 15 pages of informed consent
9 that's [indiscernible] clinical research. And
10 there really needs to be a multipronged approach to
11 this issue, not just trial design.

12 CAPT PARISE: Dr. Follmann?

13 DR. FOLLMANN: Yes. I'd like to make a few
14 comments. I thought the FDA's presentations were
15 very interesting. I thought they had a lot of nice
16 ideas in them, so I won't go into detail about the
17 things that I agree with, but I'll just mention a
18 few things that I might have questions about.

19 Fundamentally, I think, as some of the
20 speakers mentioned, it makes sense to me to
21 study -- if you're interested in blood-resistant
22 pathogens, you should study the drug and patients

1 who have drug-resistant pathogens. I'm
2 uncomfortable with the idea of studying drugs
3 susceptible only, and then making a leap of faith
4 based on clinical judgment or PK/PD data, or other
5 bits of evidence that fall short of a comparative
6 study of the drug in question and the population of
7 interest. So that's a fundamental point with me.
8 I think strongly we should still try and do that.
9 To me, it seems self-evident.

10 Having said that, I'd like to talk a little
11 more about Dr. Rex's tier B study, which I thought
12 was interesting. And I think there might be a kind
13 of tweak of that, where it would be more acceptable
14 in the unit. It also hearkens to a comment that
15 Dr. Moore made. With the tier B study, you have a
16 phase 3 study, so a large study, which could be
17 noninferiority in a population of interest.

18 But then in addition, I want additional data
19 that would look and show for evidence of
20 superiority in patients who have resistant
21 pathogens. And this could be combined across
22 different body sites, and we can use different

1 statistical methods to allow combinations across
2 different body sites. But really, I'm just looking
3 for some subgroups, some evidence somewhere that
4 the drug shows superiority.

5 As we understand, this is a drug that's
6 meant to be effective against drug-resistant
7 pathogens. It's meant to address the unmet need.
8 That's why we're here today. And so why not have
9 evidence that it actually does what it's supposed
10 to do in a human population.

11 A couple of other comments. I don't really
12 like the idea of using non-randomized controls. I
13 think that's a big step backward. Unless there's a
14 specific proposal where you, I guess, have a census
15 of everyone who has an infection or something that
16 I haven't seen yet in terms of broad coverage, I
17 wouldn't be in favor of historical controls.

18 A comment about the PK/PD data. I think
19 important work has been done in that. They've
20 shown interesting results that I think can be used
21 to identify drugs that won't be promising in a
22 particular population. But in my mind, PK/PD data,

1 MIC data is really essentially observational type
2 data, and so it can presumably identify an enriched
3 population where a new drug could show its largest
4 benefit. But then why not study it in a clinical
5 trial or a subgroup of patients to show superiority
6 in that group that shows such promise in terms of
7 the PK and PD.

8 Just another comment I guess. People have
9 talked about doing studies that aren't powered for
10 formal inferential testing but have descriptive
11 statistics. I really don't know what that means.
12 To me, it sounds like it could be we'll look at
13 10 people or 5 or 15 and have a feeling about the
14 data. But to me, it's just a license to make
15 inference that's really not supported by data.

16 Then finally, people have talked about
17 phase 4 type studies that could maybe catch
18 ineffective or harmful drugs that are approved
19 after they're out there. I'm skeptical of that as
20 well. If there is a phase 4 type mechanism that
21 could identify harmful drugs that have gotten
22 through reliably, I'd like to see what it is and

1 see a proposal for it. But the idea of lowering
2 the bar essentially now, and then hoping we can
3 develop new methods of pharmacovigilance to correct
4 our errors I think is misguided.

5 CAPT PARISE: Dr. Magill?

6 DR. MAGILL: If I look at that question on
7 face value, just a simple question, and it's a yes
8 or no answer, then my answer would be yes. I think
9 there is an acceptability to have a more
10 streamlined development program, but that leads to
11 a couple of additional questions.

12 One line of discussion here has been in
13 essence what I call the off-label use. You develop
14 a product. You test it, whether it's in a large
15 population or small population. But you test it in
16 a population that has some boundary or definition.
17 And then as it gets used more in clinical practice,
18 it gets outside of that comfort zone. I think that
19 would even be more important in a setting like
20 this, where you had a streamlined approval process.
21 Essentially, how can you ensure that the indication
22 that it's been tested for is the one that has

1 actually been used, and then how do you take that
2 forward.

3 The medical community has to step up and do
4 a better job than it currently does. And I'd just
5 use some -- maybe I've added examples, but if you
6 are an obstetrician, and you ask to be credentialed
7 to do knee replacements, I don't think you would.
8 That would not be allowed.

9 If you're a primary pediatrician stepping up
10 and wanting to do induction chemotherapy on a
11 leukemic, well, I don't think you'd ever be
12 credentialed. You couldn't do that. So why would
13 anybody just be able to prescribe one of these new
14 antibiotics and not be credentialed to do so?

15 I think this needs a far more thoughtful
16 interaction going forward because that will help.
17 Again, if you're going to approve these on a more
18 streamlined package, then you're going to have to
19 have a much more tailored window by which these are
20 administered and how you capture the data.

21 I like this concept of once the drug is
22 approved, we stop learning. That just can't be.

1 So how can we enforce that learning process that
2 goes forward? I know I'd like to hear more about
3 what the FDA thinks it can do in terms of a
4 regulatory package; can you have a REMS-like
5 strategy or something that's adapted from REMS to
6 take it forward so you can actually look at what
7 may be the suspected adverse events are as you
8 start opening up and using this in large numbers of
9 patients?

10 CAPT PARISE: Dr. Schreckenberger?

11 DR. SCHRECKENBERGER: My background is
12 clinical microbiology, so I have a little bit more
13 to say when we get to question 3. But with regards
14 to this question, after reading the information and
15 hearing the presentations this morning, I would say
16 yes to this question, that a smaller size for
17 clinical studies seems okay.

18 I don't know that the size of the study is
19 so important. Isn't it the difference in
20 treatment? As we learned this morning, the
21 difference in treatment affects what power the
22 study has to have in terms of a measure of

1 significance. So if there's a narrow difference,
2 to show significance, you might have to enroll a
3 lot more patients. So it's not really the size of
4 the population but the difference in treatment that
5 you see.

6 In terms of the safety, I don't know that
7 we're ever going to have really confidence from a
8 clinical trial anyway. Even if you enrolled a
9 thousand patients -- even if you enrolled 3,000
10 patients, it's just a -- if the drug gets legs and
11 it really becomes a widely used drug, that's such a
12 small fraction of the number of patients that are
13 going to be treated.

14 So it's really the postmarket analysis that
15 I think needs to be followed closely for any drug
16 in order to know its safety when it's used broadly
17 across a large population base. So I think just a
18 smaller size study is not counter-productive. I
19 think it's -- I would answer yes to this question.

20 CAPT PARISE: Dr. Baden?

21 DR. BADEN: In reading this question, I also
22 would say yes. However, it has great depth to it

1 as to how to operationalize. And I read this in
2 the context of limited treatment options. So to
3 me, that's the predicate upon which this question
4 is to be interpreted. And then that requires an
5 understanding of the definition of limited
6 treatment options, and that will be a great
7 struggle; as well as establishing the efficacy or
8 other aspects also has many layers to it as to the
9 kinds of endpoints that might be utilized, given
10 the variability of the populations that have these
11 problems.

12 But I think we need to keep in mind that it
13 is both the issue of we don't want to put patients
14 at risk for drugs that are not effective and have
15 side effects. We also don't want to not have
16 treatment for patients who have these infections
17 that we are unable to treat. So there are two
18 sides to this problem that have to be weighed,
19 which is why I think we're all here. But I think
20 this question is easy on the face of it and very
21 hard when you get to the definitions of the
22 implicit terms.

1 CAPT PARISE: Dr. Cappelletty?

2 DR. CAPPELLETY: This particular one I
3 would also say yes on the streamlining for all the
4 reasons that have been stated so far. And I would
5 like to reiterate some of the postmarketing needs
6 with not only this but in general.

7 I just recently was in conversations with
8 some of my colleagues regarding streptococcal
9 infection and toxin production, should you or
10 should you not add clindamycin to the
11 penicillin-based therapy? And they were split as
12 to whether they did or did not do that in their
13 practice simply because of the limited number of
14 toxin-based strep infections that they had
15 encountered in their career path.

16 Once the article had come out of Australia
17 using a larger national database, indicating that
18 there was a positive outcome when the clindamycin
19 was added has now got them thinking, okay, across
20 the board, maybe we need to be doing this. And
21 getting that information is going to be where we're
22 going to get greater power, but getting it in a

1 database that is not cumbersome, that is readily
2 accessible, and that the data goes in as meaningful
3 data so that you can mine meaningful data out is
4 really going to be problematic. But it's something
5 that no one agency I think can tackle, but I think
6 many agencies need to come together in order to
7 define that and make that something that we
8 actually start contributing to have that data
9 postmarketing on a more powerful basis.

10 CAPT PARISE: Dr. Robinson?

11 DR. ROBINSON: Without taking a count, I
12 guess there seems to be a developing point of view
13 that in the situation of limited options, greater
14 risk is reasonable to take. I'd like to add a
15 little granularity to that question, though, and
16 come back to a point that one of the public
17 speakers raised. And that is, is this going to be
18 an either streamlined package or full package, or
19 can the level of risk that's acceptable be
20 calibrated so that in a situation where perhaps the
21 benefit is greater -- that is more severe
22 infections, more highly resistant organisms, or the

1 size of the available database, and the rarity of
2 these infections are smaller -- are my colleagues
3 willing to consider some variation in the level of
4 risk that should be taken on by allowing a larger
5 M2, for example?

6 CAPT PARISE: Dr. Scheetz?

7 DR. SCHEETZ: I think we're hearing a lot of
8 the same things, and everybody seems to be coming
9 back to balancing efficacy and safety because you
10 really -- to effectively treat patients, some
11 patients at the end of the day are going to be
12 harmed, and we have to decide how much harm we're
13 really willing to accept.

14 I agree with others that the current
15 mechanisms for stewardship are not good enough,
16 that simply approving the drug and hoping that
17 people do the right thing will lead to patients
18 that end up with bacterial sinusitis being treated
19 with these therapies. We've already heard some
20 interesting ideas, something such as a registry,
21 something such as credentialing. I would support
22 those means.

1 We also heard Dr. Dudley talk about learn
2 and confirm. I think that's a very interesting way
3 to be thinking about this problem. We also should
4 be thinking about learn and deny. So I think we
5 should have some prespecified time points that we
6 should be looking, some prespecified endpoints that
7 we can say things aren't going the way that we want
8 them to be going. It's time to shut this drug
9 down. So once something is approved, we hope that
10 it won't be out there for perpetuity.

11 One final comment. I've been very excited
12 to see that the Center is really starting to look
13 more at the pharmacokinetic/pharmacodynamic
14 interactions with efficacy. I think while there is
15 some discussion about how beneficial this is, I
16 think the majority of evidence shows that when you
17 look at things in the right way, if you capture the
18 amount of drug exposure appropriately, you can make
19 predictions.

20 One thing that I do see as noticeably absent
21 here will help us set our therapeutic window. We
22 also should be looking at

1 pharmacokinetic/pharmacotoxicity. So just as we
2 set the endpoints for efficacy, we also should be
3 thinking about the endpoints for toxicity such that
4 clinicians will be able to know how much dose can I
5 give.

6 When resistance happens and the initial
7 approved dose is no longer effective, how high can
8 I push my dose safely for my patient because we
9 don't have time to go back to a clinical trial.
10 The patient is in front of us and dying, and
11 sometimes we have to give them double the dose,
12 triple the dose. And those are discussions that
13 we'll have with patients, but we really do need the
14 full totality of information.

15 CAPT PARISE: Dr. Hamblett?

16 DR. HAMBLETT: I echo those of the last
17 speaker. Really, I think any guidance towards
18 streamlining this drug development program has to
19 be paired with the guidance for the aftermath in
20 terms of the postmarketing requirement. And not
21 only looking at outcomes and prespecified safety
22 outcomes with a particular drug, but a mechanism to

1 look across therapies for a particular pathogen.

2 It does also come to data sharing of these
3 drugs so that we can do pooled analyses and look
4 more broadly at resistance patterns in the absence
5 of perhaps an observational registry to look at
6 epidemiologic resistance pattern. We may be
7 relying on these marketing data sets to
8 miraculously summarize that and have our finger on
9 the pulse of how quickly resistance may be
10 developing.

11 CAPT PARISE: Dr. Andrews?

12 DR. ANDREWS: I like your idea of learn and
13 deny. I was actually thinking of provisional
14 approval. I don't know if that's possible or if
15 that's done. But something that could be approved
16 and then when you do these further studies that
17 coming to a consensus should be in, you'd look at
18 it again and decide whether that should stay in
19 place. It wouldn't have to be -- it would be a bar
20 that they'd have to pass again. And it could be
21 exactly the bar that is there right now, so you're
22 not disadvantaging them relative to where we are

1 right now. And they would be able to recoup costs
2 through that time period at least, for sure.

3 That ought to give an economic incentive to
4 move forward, but I think it would -- certainly, in
5 terms of patients' safety, it would make people
6 feel better that that's not just a hope and a
7 prayer that we're going to look at things going
8 forward. We have to. At a certain point, there's
9 a sunset.

10 CAPT PARISE: Dr. Reller?

11 DR. RELER: These questions are always so
12 complex because of the way they're worded, but I'd
13 like to dissect this and still keep on the larger
14 picture. What to me is important in discussion of
15 this topic is the flexibility. It's embedded in
16 this susceptibility; that is the flexibility of the
17 agency looking at the whole picture because there
18 are some pitfalls.

19 For example, there are agents that one could
20 discuss that cover what are perceived to be
21 multidrug resistant organisms, that in fact they do
22 that. But they add a little bit more to cover

1 those. It's not as if there is no drug out there
2 that's available. You'd like to spare that class
3 of drugs perhaps.

4 For example -- and I could give specific
5 drugs that one could think about in these terms.
6 What a pitfall is, is that a new drug that does
7 cover resistant organisms would be subjected to
8 less rigorous consideration than another drug
9 that's already approved that covers most of the
10 same organisms, but maybe one little hole; that you
11 would have a possibility of a new comparator and
12 that the standards would become less rigorous.

13 Dr. Laessig's talk this morning, if one
14 looks at the big picture of drug development and
15 relationship with FDA, it's been one of increasing,
16 over time, specificity, rigor, and trial design,
17 and what is required for approval. And I think it
18 would be very important not to have the message
19 portrayed that one is loosening the standards of
20 safety and efficacy. And then coming to that
21 coupling of the safety and efficacy in this
22 question, I think they need to be separated, and

1 I'll give you a specific example.

2 If one had a drug that is used only when
3 things are desperate -- colistin for
4 example -- that's highly toxic, and there was
5 nothing else; and you had a drug that covered that
6 same organism, resistant organism, that was even
7 similarly effective or marginally better, but it
8 was much less toxic, that would be a
9 reasonable -- an important contribution; that is,
10 something that is safer than what is currently
11 available for a drug that's used in desperation.
12 If it were better than that drug, that would be
13 dynamite.

14 So I think this question, safety versus
15 efficacy balance, part of it is being explicit, the
16 physician with the patient, what you are infected
17 with is not treatable with anything else, and we
18 don't know as much about the safety, is a much
19 more -- is much more important than simply making
20 a -- there isn't a flexibility of the agency to
21 make different determinations rather than you
22 approve that drug with those limited studies, and

1 why is our drug any different? So that there's the
2 possibility of not necessarily having exactly the
3 same criterion because there are going to be
4 differences in this balance, is what I'm trying to
5 get at.

6 CAPT PARISE: I think I'll just add my
7 comments since I haven't said anything yet. My
8 answer, I don't think I have a lot to add other
9 than the points that have already been made. My
10 answer to this is pretty strongly a yes. And I
11 think -- I view that mostly because I do think the
12 unmet medical need that we're talking about are
13 really patients who have their back against the
14 wall. And I think in those cases, we do have to
15 streamline.

16 Any other discussion from the panel on this
17 question? I'm sorry. Alan?

18 DR. MAGILL: This was prompted by a few
19 comments by the fellow panel members. I agree. I
20 think the word "streamline" and "noninferiority"
21 and such, it just leads to a reaction of a lowering
22 of standards. And I think it's certainly not the

1 way I see it. I think it's really more of
2 right-sizing. You have an indication -- all the
3 interactions I've had with the FDA over the years,
4 it's about presenting an appropriate plan based on
5 efficacy and safety with a risk/benefit for the
6 indication at hand.

7 I guess I'm not seeing a lot of difference
8 here. That's what's being proposed in my mind. So
9 maybe it's a bit of a language issue. I think that
10 puts a much higher burden on FDA, to be honest, to
11 personalize approvals as opposed to have just one
12 CFR standard that everyone has to meet. But again,
13 I think we have to give some discretion to our FDA
14 colleagues and responsibility to the sponsors of
15 these products to come forward with exceedingly
16 high-quality plans and high-quality dossiers.

17 CAPT PARISE: Ms. McCall?

18 MS. MCCALL: I'd just like to dovetail on
19 Dr. Magill's comments and also Dr. Reller's. I've
20 sat on multiple cardiac drug and device ADCOMs, and
21 this kind of reminds me of some of the discussions
22 we've had. There was a device that was

1 streamlined. The company worked very closely with
2 the FDA, and they worked to make sure that the
3 numbers were robust and that the statistics were
4 solid. And it went through the pipeline a little
5 bit more quickly than most other devices. This
6 device has now been out for several years. Many of
7 the patients on my patient forum have this device
8 and just adore it. It's so wonderful.

9 Also, with what Dr. Reller mentioned about
10 the safety and the efficacy between similar drugs
11 doing similar bugs, we almost have that within
12 NOACs, the novel oral anticoagulants. We now have
13 three that have been approved, a fourth one that's
14 pending. And they're all segmenting almost the
15 same market now that we have another choice beyond
16 warfarin for blood thinners for atrial
17 fibrillation.

18 I think that comes to my big point, is I
19 think clinicians, and I know patients, really want
20 to have options. We do want safe and effective
21 options, but we like having options. We're all
22 individuals. We like to be treated individuals.

1 So this gives the clinician an option of going,
2 "Well, I know your history and I know how you react
3 to things, so I'm going to choose this drug for
4 you." And I'm hoping in the long run that the
5 majority of prescribing physicians for these
6 antibiotics will take that into account and not
7 just hand it out.

8 What I mean by hand it out is this happened
9 in my primary care's office just last month. I was
10 sitting in her waiting room to have a chat with
11 her, and there were two young mothers and there
12 were several young children amongst them. They all
13 had ear infections, so they're all coming in. One
14 mother said to the other, "Well, just ask for
15 cipro. It works for anthrax, so it will be really
16 good for your kid's ear infection." So I'm kind of
17 biting my tongue not saying anything. But
18 hopefully, the physicians that will be prescribing
19 these will be cautious and use them only when
20 they're supposed to be used.

21 CAPT PARISE: Thank you. Other comments?

22 (No response.)

1 CAPT PARISE: Okay. I'm going to try to
2 summarize this discussion before we move on to the
3 next. I think there were a few points that we
4 heard repeatedly. The panel by in large did
5 support the streamlined development program in the
6 areas of unmet medical need. There were a few
7 points that were raised with respect to that. But
8 the important caveat are limited treatment options
9 and that the agency should have the flexibility in
10 determining what the bar is for different -- and
11 treat different drugs and indications in different
12 ways.

13 Another theme that came up multiple times
14 was the need for attention to phase 4, the
15 importance of phase 4, how can we get better data
16 in phase 4 and data sharing and such. And another
17 point that was raised by several panel members was
18 the importance of stewardship and the medical
19 community doing a better job, including using these
20 drugs that may have very narrow indications in the
21 proper way.

22 There were also a variety of other points

1 raised. I'll just mention them quickly because I
2 think they may come up in the next questions. One
3 opinion was this should be done by site as opposed
4 to by pathogen, the trial design. Trial design
5 issues need attention, including, for example,
6 informed consent. One opinion was raised that
7 there should be studies that included that these be
8 done in patients with resistant organisms. I think
9 that may come up a little bit later as well. We're
10 going to discuss non-random controls as well later.
11 That was mentioned; and then the issue of PK
12 endpoints with respect to toxicity and is that
13 something that could be thought about.

14 We're going to move on to the second
15 question. Please discuss the following options for
16 trial designs for streamlined development programs:
17 a) noninferiority trials at a single body site of
18 infection, for example, complicated UTI or
19 complicated intra-abdominal infections using
20 largely than usual noninferiority margins, for
21 example M2 closer to M1 than is usual in
22 traditional development programs; and superiority

1 trials, including issues related to pooling across
2 different sites of infection and with respect to
3 selection of the control group for inference
4 testing, for example, best available therapy and
5 external controls.

6 The floor is open for discussion among the
7 panel. Dr. Hamblett?

8 DR. HAMBLETT: Well, I do have some concerns
9 about widening the noninferiority margins, although
10 I would say if that were to be done, I think the
11 importance on the supportive data becomes much more
12 critical. And so, what does that supportive data
13 look like? It can either be -- as we heard this
14 morning, it could be superiority data among the
15 resistant pathogens, maybe not statistically
16 significant but strong evidence showing superiority
17 in that subgroup.

18 It could be the nonclinical data, as was
19 mentioned, were the microdata, although that has
20 caveats in that we know that some of these
21 endpoints, such as MICs, don't accurately predict
22 response. But the third element that hasn't really

1 been discussed is patient-reported outcomes and if
2 there's a role here for PROs, in particular, to
3 bolster the comfort with providing a clinically
4 meaningful benefit to the patients. Also, we do
5 look at safety and efficacy along two different
6 dimensions, and our PRO is a way for us to better
7 capture risk versus benefit to the patient for some
8 of these therapies.

9 CAPT PARISE: Dr. Follmann?

10 DR. FOLLMANN: I'd like to talk about the
11 margin as well. I think the exchange we had
12 earlier between Dr. Rex and Dr. Scheetz I think
13 really laid out what the consequences of a larger
14 margin are. To crystallize this, we traditionally
15 use, say, a 10 percent margin at a single body
16 site. What are the ramifications of setting it to
17 20 percent?

18 Well, as Dr. Rex pointed out, you get a much
19 smaller sample size. You get maybe one-fourth of
20 the sample size, which is nice. The sample size is
21 smaller. But as Dr. Rex pointed out, this is at a
22 cost of potentially letting through drugs that are

1 inferior to the comparator.

2 Just to report a calculation I did, let's
3 suppose that the comparator has an 80 percent
4 success rate and the new drug has a 70 percent
5 success rate. So we do a study with a margin of
6 20 percent, and about a third of the time, we'll
7 say that they are noninferior; this drug that has a
8 worse success rate will be approved. Dr. Rex
9 recognized that this is the cost of having a larger
10 margin, more things will get through. And it
11 depends on whether you're willing to accept that
12 cost or not.

13 It's appealing to think that phase 4 studies
14 somehow will be able to correct these mistakes for
15 drugs that get through with a large margin, which
16 is I think the concern of all of us. But I just
17 have seen many times where it seems as if the
18 appeal to phase 4 studies is like mom and apple
19 pie, that it will fix things without really getting
20 into the details of how it will do so. Phase 4
21 studies are purely observational. They just report
22 events and they have substantial problems in terms

1 of identifying signals.

2 If someone can come up with a better phase 4
3 program than what I'm aware of, I think that would
4 be great. But just to hope that it will cure or
5 fix these problems, I just don't see it, really.
6 So it's something we should do and so on, but I
7 don't know that it's the remedy for a paradigm
8 where the bar is widened, and you have potentially
9 inferior drugs getting through.

10 CAPT PARISE: Dr. Ostrosky?

11 DR. OSTROSKY: I'm a little bit
12 uncomfortable as well with wider noninferior
13 margins. To me, it sounds a little bit more
14 attractive to look at larger superiority trials
15 where you can pool across body sites, yet your
16 routine elevated to get signals from the different
17 body sites.

18 I do think the choice of controls is the
19 most important aspect here, where we can't be
20 expecting to be comparing to older, FDA-approved
21 therapies that are not necessarily in clinical use
22 at this point. It makes the trials very messy,

1 very difficult to interpret going forward. I like
2 this concept of best available therapy, which
3 recognizes postmarketing knowledge and common
4 practice. So my preference would be superior
5 trials with pooling.

6 CAPT PARISE: Dr. Reller?

7 DR. RELER: To follow up on the statements
8 just made, I too, I'm cautious about the wider
9 margins on part A. The part B, particularly for
10 resistant organisms with a mechanism of resistance
11 that is recognized, and a compound, a putative new
12 compound, that renders that, for practical purpose,
13 is irrelevant. And if the MIC, by that mechanism,
14 the resistance is 64, and it comes down to .5, with
15 this new compound, that's very important.

16 I don't have as much a problem with pooling
17 across body sites as long as that extra information
18 is available that gives me confidence that it's
19 scientifically, biologically plausible. Specific
20 examples. If you can demonstrate the new drug gets
21 into lung tissue, is not inactivated by surfactant,
22 crosses the -- penetrates and is bioavailable in

1 CSF, is not protein bound to the extent that it's
2 not -- when one has all of the PK/PD information,
3 distribution of the antimicrobial, then I'm less
4 concerned because of the small numbers that one
5 would combine across body sites.

6 In fact, as has been pointed out in the
7 discussion earlier today, that's what clinicians
8 do. Currently, the best available therapy for some
9 of these infections is with agents that don't have
10 any approval and sometimes not even much known
11 about them as what we would be requiring in this
12 rigorous streamlined approach. And I'm attracted
13 to the idea because that's the reality.

14 The clinician wants to know what people are
15 using now, sometimes in near desperation, is this
16 new drug as efficacious and ideally, with the
17 superiority trial, is better than that drug with a
18 safety record at this point that is not
19 intolerable? And that I think is what clinicians
20 want to have available.

21 CAPT PARISE: Dr. Dekker?

22 DR. DEKKER: I want to agree with Dr.

1 Reller. I too would feel a little bit cautious
2 about the noninferiority trials with the wider
3 margin for the possibility that we might approving
4 drugs that are truly inferior by arbitrarily
5 manipulating that margin.

6 With the superiority trials, I understand
7 there are many problems with pooling from body
8 sites, and we all know about the daptomycin
9 example, but I do think it's possible to mitigate,
10 to some extent, the statistical problems there by a
11 greater reliance on preclinical mechanistic
12 information, which I really do think is -- we are
13 in a new era, and I think that in the 1960s, we
14 didn't have whole genome sequencing of organisms.
15 We didn't have large databases of sequences. And
16 we can now supplement our thinking about mechanisms
17 with data that wasn't really available before. And
18 I think that we're thinking about new drug
19 development and approval in a different kind of
20 environment.

21 CAPT PARISE: Dr. Follmann?

22 DR. FOLLMANN: I just wanted to comment

1 briefly on discussion point B. I agree with what's
2 been said before about superior trials and pooling
3 across different body sites of infection. I think
4 nonclinical data and so on can inform us as to
5 whether it's reasonable, a priori, to combine these
6 different sites in a single superiority analysis
7 where all the different sites are contributing
8 patients who have drug-resistant pathogens.

9 Something we're not going to get in today,
10 the statistical technical aspects to this because
11 you don't want to just lump all the patients
12 together necessarily and say, "Oh, I don't care
13 what site it is." You can do methods similar to
14 what's called meta-analysis, where you will take
15 different studies, get estimates of the treatment
16 effect across those different studies and
17 statistically combine them. You can do a similar
18 kind of method here for body sites, and there are
19 other more technical ways to do this I'm sure the
20 FDA knows about, but I won't get into at this
21 point.

22 Selection of the control group for inference

1 testing, I would favor randomization to the new
2 drug and best available therapy as an option rather
3 than an external control, which to me means a
4 non-randomized study.

5 CAPT PARISE: Dr. Baden?

6 DR. BADEN: I think that the noninferiority
7 trial question is quite complicated, in that the
8 10 percent, trying to understand the magic of the
9 10 percent, let alone the 20 percent. And I think
10 it does depend a bit on the consequence as to what
11 one can learn about activity against a resistant
12 pathogen that might have clinical meaning,
13 depending upon the consequence of if you undertreat
14 that person for a period of time.

15 So it gets into the granularity of the study
16 design or the circumstance that you're assessing to
17 gain information about the activity of the agent
18 and its potential use. So it's hard for me to say
19 yea or nay to 20 percent or to 10 percent,
20 depending on what the circumstances are of the
21 particular issue being considered. I think it's
22 worth re-reflecting on the 10 percent because I'm

1 not convinced it's magic.

2 Regarding the superiority trial question,
3 the pooling across different body sites, it's very
4 complicated, in my mind. We know about surfactant
5 and interaction with certain antimicrobials now.
6 I'm not sure we appreciated the significance of
7 that beforehand. So I'm not sure I'm aware of the
8 problems that we might run into with a new agent,
9 in the new site of interest, with an organism that
10 we may not have as much familiarity with because
11 it's an emerging -- if it's an organism that's
12 highly prevalent, that might be different than some
13 of the ones that I think we're talking about, which
14 are MDRs that are emerging, that we are gaining
15 experience and trying to rapidly scale up to
16 responding to the need.

17 So I think that there has to be some caution
18 in how to think about that CSF bone, potentially
19 lung, might be different than some other sites.
20 This would, again, have to be considered case by
21 case.

22 I think the most important issue that hasn't

1 already been touched on in the current discussion
2 on this question is the issue of the control.
3 There's the control in relation to the bug. As has
4 already been alluded to throughout the day, the
5 host is so important. And without controlling for
6 the host in terms of concomitant therapy, the prior
7 treatment history, organ insufficiency, potential
8 vulnerabilities and inability to tolerate therapy
9 or instability, make it very hard to easily
10 understand how external controls can be directly
11 applied.

12 So that would have to -- and again, it's
13 case by case because I can imagine so many
14 different scenarios where an unmet need is being
15 approached. So I strongly advocate for the agency
16 having flexibility in assessing these scenarios
17 case by case because I think the differences are
18 probably substantive in how one may frame the
19 design, and therefore inference of activity, and
20 what level of toxicity can tolerate. But I think
21 the ability to control for the host being similar
22 between treatment allocation A and B is a very

1 important element. And historical external
2 controls in that setting are fraught with great
3 difficulty.

4 CAPT PARISE: Dr. Magill?

5 DR. MAGILL: So that actually partially
6 answered one of the questions I had as well. Just
7 on the pooling across different sites, it certainly
8 makes me nervous. I don't think the sites are the
9 same; they never are. Bone, CSF, cysts, whatever,
10 they tend to be different. And this is very
11 much -- as one of, I think, the public speakers
12 noted -- a PK issue.

13 So if one were to choose that as a way to
14 address the particular question, I think you'd have
15 to be pretty convinced that that was the right
16 answer to that question. You'd have to have some
17 data based on whatever nonclinical and clinical
18 experience you had that that actually would be
19 useful. But a priori, I'd be pretty nervous.

20 The second question on the selection of the
21 control group, I'd be curious to have a sense,
22 actually, from the FDA as to what defines best

1 available therapy and who defines that. Does the
2 sponsor come to you with their definition of best
3 available therapy? Does FDA have a viewpoint on
4 that? And then at some point, it seems like a
5 combination of the two would actually look at that
6 and could perhaps conclude that best available
7 therapy is really, we don't really know; that the
8 database on the comparator actually is so weak that
9 that would then feed back to make me very nervous
10 about using noninferiority.

11 So it's complex. And I think what I would
12 argue for there is the flexibility of the agency to
13 have the ability to look at this and make a
14 science-based judgment. But I would tend to agree
15 that a lot of times, the best available therapy
16 is -- sometimes we just don't know, and that would
17 concern me.

18 CAPT PARISE: Dr. Nambiar?

19 DR. NAMBIAR: Dr. Magill, we don't have a
20 specific definition of what constitutes best
21 available therapy. Typically, sponsors will
22 include that in their protocol. And usually there

1 would be a menu. It would be two or three options.
2 Sometimes it depends on institutions or regions,
3 depending on the resistance profile seen at that
4 particular institution. So that's how we do it.

5 CAPT PARISE: Dr. Moore?

6 DR. MOORE: Not much to really add other
7 than what Dr. Magill said. Making a decision by
8 pooling data across body sites is fraught
9 with -- really, with danger. Osteomyelitis is not
10 the same as pneumonia, nor is it the same as
11 peritonitis. We all agree. Anybody in clinical
12 medicine understands that.

13 Nevertheless, having said that,
14 surely -- well, I would strongly emphasize, in
15 these clinical trials, which, again, to emphasize,
16 are streamlined for very specific indications, or
17 the very specific organisms, ideally, we really
18 need to have some PK/PD data on which to make any
19 reasonable inference about success, or
20 safety -- well, safety, but certainly efficacy of
21 treatment in certain conditions for which a
22 clinical trial would not be able to specifically

1 answer; say, for example, osteomyelitis.

2 CAPT PARISE: Dr. LaVange?

3 DR. LAVANGE: Yes. I just wanted to make
4 clear that the word "pooling" is a little -- it can
5 be misinterpreted. So I want to make sure we are
6 all talking about the same thing. And Dr. Follmann
7 mentioned this as well.

8 Simple pooling of data, just throwing it in
9 and analyzing it together, is not what we're
10 talking about. It's whether you study more than
11 one site of infection in a randomized clinical
12 trial, possibly stratifying by the infection site.
13 But the analysis method would -- if you had enough
14 sample size in each site, you could either run a
15 separate study or you could study them together,
16 and only use the data in each site to make your
17 site-specific treatment estimate and test the
18 hypothesis.

19 So in that case, if there was adequate
20 sample size in each site, the only advantage to
21 running them all together is infrastructure
22 advantage. You could just run them separately.

1 But what we're talking about here is where you may
2 have enough patients in a few sites but maybe not
3 enough in other sites. Is there any -- is it
4 better to have some knowledge or some data on the
5 low-enrolling sites? And if things look good, you
6 could combine with meta-analytic methods. But
7 you're really taking averages of site-specific
8 effects in that type of analysis. You're not just
9 doing simple pooling. All kinds of bad things can
10 happen, Simpson's paradox and so forth, in addition
11 to the sites not being comparable.

12 Then finally, the more complex methods, the
13 model-based methods and some of the hierarchical
14 modeling, Bayesian hierarchical modeling methods,
15 they're data driven, so they're a little different
16 than what we usually use in a regulatory setting.
17 But we're exploring them for utility here, and they
18 could let the sites separate. So you could have
19 those sites that look like they work and the sites
20 that look like they don't work. But that's a very
21 oversimplification.

22 In the best sense, with these model-based

1 methods, the site-specific treatment effect in a
2 low-enrolling site might borrow some strength from
3 the other sites to reduce the uncertainty. We have
4 lots of variability with the small sites, so you
5 borrow strength from the other sites to reduce the
6 uncertainty, stabilize the estimate, but you don't
7 do that borrowing unless it makes sense to do that.

8 So we're not asking you about just simple
9 pooling, but studying them together with the idea
10 that there may be some similarity to borrow
11 strength. That's probably more technical. This is
12 the technical detail Dr. Follmann was trying to
13 avoid.

14 CAPT PARISE: Dr. Cappelletty?

15 DR. CAPPELLETY: As a follow-up question to
16 something that you mentioned, getting enough
17 individuals within those disease entities to make a
18 statement on, not being a statistician, I've always
19 been told you look at subset analysis with a very
20 large grain of salt because the study was never
21 powered to answer such a question.

22 So how do you distinguish, then, between

1 what is a meaningful number versus a subset
2 analysis that really isn't giving you all the data
3 that you need?

4 If I throw in my mind the example of
5 daptomycin out there, if daptomycin had gone
6 through a pooled analysis type of study design, and
7 we didn't go into that study knowing that
8 surfactant broke down the drug but it just didn't
9 perform well in the pneumonia arm of the study but
10 did well in others, how would that play out to say
11 that response rate within that subgroup is showing
12 us that there's a problem somewhere versus it
13 getting masked with all the other data that they
14 might have obtained through other disease processes
15 that they studied in that trial?

16 CAPT PARISE: Dr. Follmann?

17 DR. FOLLMANN: I'd like to comment on this.
18 To me, this is really not conceptually different
19 from deciding on inclusion criteria at the start of
20 the study. You might have a drug that you expect
21 works in, say, the sickest patients with poor
22 prognostic factors, but then it's a decision as to

1 what are the inclusion criteria. You might put in
2 sick patients and not so sick patients. And I'm
3 not talking just about anti-infectives now. But
4 a priori, you make a decision based on knowledge of
5 how the drug works, an analogy would be PK/PD data
6 here and how the drug penetrates to the different
7 sites.

8 In a simple way of thinking of this, those
9 preclinical data and other data would say, yes, I'm
10 going to look at these three sites, but the bone I
11 won't look at because it doesn't seem to make sense
12 with this drug. And so, a priori, you essentially
13 specify what you're going to do. And then the
14 technical detail is more about how you combine the
15 sites statistically. But to me it's just like
16 inclusion criteria.

17 CAPT PARISE: Dr. Reller?

18 DR. RELER: While in complete agreement
19 with Drs. Moore and Magill about the clinical
20 differences between infections in the different
21 body sites -- and every other clinician around the
22 table would concur with that -- nonetheless,

1 whether it's intra-abdominal infections, urinary
2 tract infections, lung infections, provided that
3 the drug gets there and is active and all that,
4 what I'm interested in with these infections,
5 mostly, is if I have an Enterobacteriaceae in any
6 of those sites that's got a mechanism of resistance
7 that is not met by any available antibiotic, and
8 there's a new antimicrobial that renders that MIC
9 of 64 down to .5. I'd like to know that because
10 that's the drug that I want to use, regardless of
11 the site of infection.

12 Now, I realize that the ultimate outcome and
13 relapses and so on, a lot of things are so
14 dependent upon the host, but you're lost from the
15 outset if the drug is not susceptible. I mean, if
16 you don't meet that mechanism of resistance -- and
17 we may want to have a lot of information about
18 osteomyelitis, intra-abdominal infection, and so
19 on, but the reality is it's been pointed out
20 repeatedly we're not always going to get that.

21 Just like we can't anticipate all the
22 mechanisms of resistance that are going to come

1 along other than knowing they're going to come
2 along, we can't anticipate all of the
3 idiosyncrasies of failure in advance. But we can
4 anticipate as many as we can anticipate, that the
5 drug penetrates in the CSF, that the drug is not
6 inactivated, all of the things that we know.

7 There surely will be, with the postmarketing
8 follow-up, new -- well, it looked like it worked,
9 but it doesn't work in this particular location
10 because of this host factor. That will come. But
11 at the outset, we want to have options and have as
12 much confidence in those options. And I think the
13 mechanistic part of it is especially important in
14 these multidrug resistance organisms because we
15 know why the drugs fail, and we should take
16 advantage of that.

17 As Dr. Dekker pointed out earlier, we know a
18 lot more about the mechanisms than was ever known
19 before. So it's more than just depending upon the
20 vagaries of a twofold delusion. I mean, these
21 mechanisms are delineated. And more over, some of
22 them can be identified very early on with molecular

1 techniques. If that beast is there, this is not
2 going to work, regardless of what the MIC is.

3 CAPT PARISE: Dr. Moore?

4 DR. MOORE: Yes. I would agree with that.
5 And of course, to that end, what I would recommend
6 to the FDA is that the product label, as much as
7 possible, should include that information, some
8 information about in the absence of any specific
9 studies or data, say, about osteomyelitis, some
10 information to which the clinician can refer to in
11 the product's insert about penetration into the
12 bone or penetration into vitreous humour or other
13 fluid, so that when you do get into a situation, a
14 situation where you have to treat the patient, you
15 make some sort of inference about their
16 likelihood of -- the ability of the drug to get
17 where you need it.

18 CAPT PARISE: I'm about to summarize what
19 I've heard, but I guess it struck me that there
20 was -- the one thing we didn't hear, and I don't
21 know if anybody else has anything else to say to
22 the FDA on this.

1 So what I heard this morning was, sometimes
2 you can't do a superiority trial. That works
3 whenever there is no other option, but sometimes we
4 have to revert to the noninferiority. And the one
5 thing that we're hearing in this discussion is a
6 lot of concern about widening the margin. I guess
7 one question, are there any other suggestions we
8 have to the FDA on what could be done about
9 noninferiority, any changes in the approach to
10 that? Dr. Scheetz?

11 DR. SCHEETZ: I wasn't going to speak. I'm
12 not sure that 10 is the magic number, looking at
13 Dr. Baden's comments. I'm not sure that 20's a
14 magic number. I'm not sure that p-value of .05 is
15 magic. I'm not sure that a p-value of .01 is
16 magic.

17 I think the one thing that we identified
18 universally as a group with the first question was
19 that there needs to be a step-wise approach. So if
20 in fact we go with the a 20 percent noninferiority
21 margin, that's just the first starting point.
22 There has to be another point at which you can come

1 back and say maybe we were wrong.

2 Some of our statistical colleagues can talk
3 about Bayesian inference and how we can start to
4 apply some of those better mathematical techniques.
5 For many of us, including myself that's often a
6 black box. But there are much better mathematical
7 ways to handle these data these days now that
8 computers are able to make calculations very, very
9 quickly

10 I'm not sure that I'm going against the
11 group, but I'm not sure that any of the numbers are
12 actually magic. I think that if you set it at 10,
13 you still need to look in the future. If you set
14 it at 20, you still need to look in the future.
15 And perhaps there needs to be some flexibility
16 there. The wider the noninferiority margin, maybe
17 the earlier you need to look. Maybe the harder you
18 need to look to see if you actually were correct
19 with your first estimate.

20 Of course this can all be flexible based on
21 how severe the infection is. We saw the medical
22 community very quickly coalesce around Ebola. Why?

1 Because it was an urgent need. So I hope we don't
2 get to that stage with many of our resistant
3 infections, but as Dr. Ostrosky points out, this
4 isn't academic. There's a nice paper published by
5 the CDC; 23,000 patients are dying attributable to
6 drug-resistant infections every year, 23,000
7 patients. So this is a very real entity, and we're
8 talking about ways that we can allow the FDA to
9 look at drugs more closely.

10 I'm not sure I've helped with anything. I
11 just think that the framework afterwards, the phase
12 4 really needs to be better defined because there's
13 really nothing -- at least I think -- that special
14 about whatever endpoint we make at phase 3.

15 CAPT PARISE: Dr. Andrews?

16 DR. ANDREWS: I wasn't going to speak
17 either, but I keep doing it. I agree with you
18 around -- there's a lot of uncertainty about all
19 these things, and we're adding more uncertainty.
20 And as a consumer advocate, I don't necessarily
21 have a problem with -- I agree with Dr. Ostrosky
22 that we need more tools in the toolbox. And there

1 will be some that will be gold standard and some
2 that maybe don't work quite as well, but for some
3 people they do because of the host, because they're
4 allergic to something, because they're pregnant,
5 because they're old, because they're young.

6 So if the margin increases and you choose
7 something that may not be -- for whatever study
8 group happens to be picked, given sample sizes, not
9 as effective, it may be a right thing for the
10 patient. I'm more concerned -- and I think the
11 more information we have, the more studies we do
12 after helps inform that doctor and patient decision
13 better and gives us less uncertainty into the
14 future.

15 So I would argue that you should maybe open
16 it up but study again and look at it again, and
17 give the most number of tools to providers and
18 patients to choose from. Really, the thing that
19 worries more than efficiency, when you were talking
20 about separating effectiveness and safety, safety
21 worries me a great deal as a patient advocate, a
22 great deal. And I think the further studies can

1 also look at that as well.

2 So all of these, I would say yes, but. I
3 wish there was a yes, but button here. I just
4 think that we need to learn more.

5 CAPT PARISE: Any other comments on this
6 question from the panel? Dr. Hamblett?

7 DR. HAMBLETT: I just want to comment to the
8 magic number of 10 percent or 20 percent. I think
9 for some indications, there has been quite a lot of
10 thought put into what that margin should be in
11 terms of reviewing the past literature in terms of
12 getting that treatment effect in, how much of the
13 treatment effect you want to preserve your M2,
14 whether it's 50 percent or 60 percent. And it is
15 subjective because of what trials -- what studies
16 go into that initial estimation. And there's been
17 different methodologies I think presented to widen
18 the span of how much study data contributes.

19 But I just wanted to make the comment that
20 I'm not -- that I think thought has been put in for
21 some of these indications why that 10 percent is
22 meaningful. So I just want to make that comment.

1 CAPT PARISE: Dr. Baden?

2 DR. BADEN: Just continuing along that line,
3 I think that's to me central to how these questions
4 are predicated. If these questions are predicated
5 on unmet medical need, then presumably, the
6 historical experience of penicillin may not work as
7 well in this population, even if we have an
8 efficacy number for penicillin for bug X, because
9 in the '50s, it was established well.

10 By definition -- and that's where these
11 questions are not in a vacuum, at least in my mind.
12 These questions are in an unmet medical need, which
13 even makes noninferiority hard for me to fully
14 understand because noninferiority means there is a
15 standard I have confidence in. And so if there's a
16 standard I have confidence in, then I can build on
17 that for noninferiority. If there's a standard I
18 don't have confidence in but we're kind of doing it
19 because the alternative is to do nothing, then it
20 blurs in my mind how to frame the noninferiority,
21 in part, because the standard is not as clear and
22 as established with the various margins, point

1 estimates, confidence intervals, et cetera.

2 So that makes this very complicated for me.

3 Even though we're dissecting out from a trial
4 standpoint, common trial designs, the circumstance
5 that this is being applied to -- or at least I
6 think it's being applied to -- doesn't fit as
7 neatly; hence, the different comments about let's
8 get the best information available such as PK/PD,
9 such as mechanism of action, such as intuiting what
10 it might do in the vitreous.

11 I think those are how practice works when we
12 have an unmet medical need in the context of a
13 merging resistance or pathogens that we don't know
14 how to treat. And so, I did not mean to infer
15 previously that the noninferiority margins were not
16 well thought out. They have been. I think it's
17 very circumstance-dependent, and I think the
18 context of these questions, for me at least, are in
19 the context of an unmet medical need, not we have
20 five options that are well established, and here's
21 the sixth that might have a slightly better flavor.
22 It's in the context of the unmet need, and there

1 standards are very hard to understand, either for
2 the bug for standard treatment or the host, because
3 all of those to me are an integral of why we're in
4 this circumstance.

5 CAPT PARISE: Any other comments?

6 (No response.)

7 CAPT PARISE: Okay. I'm going to try to
8 quickly summarize, and then we'll take a break.
9 What I heard was that the agency should have
10 flexibility in determining I think the answer to
11 both these questions as far as what might be most
12 appropriate. On the noninferiority, there was a
13 fair amount of concern about widening the margin.

14 The point was made that if that is the
15 decision that that is the appropriate tool, that
16 the agency needs to think hard about what is the
17 backup step, whether that be in phase 4, or how do
18 we ensure that if we're wrong and something that's
19 less effective comes out, how do we stop that if
20 needed. I guess the other point that was made is
21 this is a difficult concept to get to, to think
22 about. The 10 percent isn't set in stone and the

1 circumstances will vary, and that need for
2 flexibility.

3 With respect to the second part on
4 superiority trials, in the pooling question, I
5 think the discussion pointed in that pooling could
6 be acceptable if the appropriate statistical -- if
7 it uses the appropriate statistical methodology and
8 if there is -- the agency feels confident that the
9 other supportive evidence is there.

10 I think the other point that was made was
11 that if this is a patient that has no other options
12 and there is supportive evidence, for example, that
13 a drug does get into body fluids, clinicians need
14 that information because with patients that have no
15 options, knowing that can be very helpful and if
16 there's a way for that to be included in
17 information that clinicians have.

18 In terms of the controls in the discussion
19 of best available therapy in external controls,
20 et cetera, there were certainly concerns about
21 using the external controls. In one point that was
22 certainly brought out, was the issue of the host

1 factors, and that really makes external
2 controls -- is one of the reasons that they can be
3 problematic. I think another important point that
4 was made, in this modern day, we can better use
5 preclinical data, for example, from genomics; that
6 if the mechanism is known, that's something that
7 can be very useful, as well, to clinicians. I
8 think that is what I heard.

9 We're now going to take a 15-minute break.
10 Panel members, please remember that there should be
11 no discussion of the meeting topic during the break
12 amongst yourself or with any member of the
13 audience. We will resume at 3:35.

14 (Whereupon, a recess was taken.)

15 CAPT PARISE: We're going to get started.
16 Now we're going to work on question 3. And what
17 this is, is please discuss trial design options for
18 a product that has a spectrum of activity limited
19 to one or two microorganisms. For example,
20 *Pseudomonas aeruginosa* or *Acinetobacter baumannii*.
21 First, are there any questions or comments about
22 the wording of the question that people need for

1 clarification before we get into discussion?

2 (No response.)

3 CAPT PARISE: Okay. The floor is open for
4 discussion among the committee. Dr.
5 Schreckenberger?

6 DR. SCHRECKENBERGER: I guess the first
7 question I'd like to ask is the trial design.
8 Several times today it's been mentioned that for
9 this kind of a trial, it should be linked somehow
10 to a rapid diagnostic test so that you knew that
11 you had one of these targeted organisms. And I was
12 just wondering if anyone had any idea on how that
13 would occur.

14 I also would like someone to clarify what
15 they mean by rapid identification. If you're going
16 to develop a drug that's going to be targeted for a
17 specific organism, and you want to start a clinical
18 trial, and you say, well, it has to be linked to a
19 rapid diagnostic, what do you mean by rapid? What
20 time frame are we talking about?

21 We've seen some slides this morning that
22 showed that getting the right antibiotic started

1 and outcome can be a matter of hours. It's not
2 days; it's hours of getting the patient on an
3 effective antibiotic sooner. So if you're going to
4 design a clinical trial that is going to include in
5 its enrollment criteria that the patient has an
6 infection with one of these organisms, how rapidly
7 would you need to know that?

8 I'd be happy to respond about what I think
9 the lab can over, but I'd first like to know what
10 people are looking for in terms of a rapid result.
11 Are you talking about the next day? Are you
12 talking about 24 hours, 18 hours, 10 hours?

13 CAPT PARISE: Dr. Moore?

14 DR. MOORE: That's a great point. And of
15 course, in an ideal world, you'd have this test
16 that's available prior to the institution of the
17 antibiotic therapy. These diagnostic microbiology
18 tests are I think, in addition to antibiotics
19 available for multidrug resistant organisms, the
20 single greatest unmet need in infectious disease,
21 both practice and research, because you'd like to
22 know what it is that you're treating.

1 If you're going to be studying a particular
2 drug against an organism that's multidrug
3 resistant, as I said before, it's nearly impossible
4 to predict what the patient has when they come in.
5 You're going to be treating a condition
6 which -- patients present with conditions, and
7 you're going to be targeting conditions in which
8 you think the organism is likely to be causing a
9 problem.

10 That's kind of where this clinical trial
11 design is going to have to take place or how it's
12 going to have to look currently. I think at some
13 point in the future, if there were the development
14 of a rapid -- my personal inference about this,
15 Dr. Schreckenberger, would be that the rapid would
16 be less than 24 hours, certainly, actually just a
17 few hours or even sooner than 24 hours, to try to
18 identify it because obviously when these patients
19 come in, you want to start antibiotics right away.
20 And I personally don't see that happening. That
21 would be great, but it's one of those things that
22 might happen -- who knows when it would happen, but

1 it's not going to happen any time for the
2 foreseeable future.

3 Again, back to the point about this
4 particular question, I think the FDA will have to
5 embrace clinical trial designs that, again, are
6 targeted towards patients with conditions in which
7 these organisms are likely to play a role rather
8 than trying to design a clinical trial -- or insist
9 that companies design a clinical trial looking for
10 specific organisms, and then enrolling those
11 patients who have those organisms. That's just
12 going to be too difficult, as was pointed out in
13 the MRSA pneumonia study, which took 5 years and 6
14 comments and multiple locations.

15 CAPT PARISE: Dr. Magill?

16 DR. MAGILL: Well, just to follow up
17 on -- since that was the entry point into this
18 question, when you're really sitting there, the
19 question is, is it test and treat or treat and
20 test, and that decision is usually made within
21 minutes. And you've got syndromes like sepsis in
22 the ICU and such. I think it's going to be very

1 realistic. You're going to be very hard-pressed to
2 have any test that you have confidence in to allow
3 you to start a single antibiotic that has a very
4 narrow spectrum of activity. I just don't see it
5 happening.

6 So it's really treats and tests. And you're
7 going to use broad-spectrum antibiotics, whatever
8 combination de jour, and that that's going to go
9 for some period of time, and then the thought of
10 moving on. But one point here is are you really
11 confident, and what percentage of the time are you
12 really going to be confident that the person in
13 front of you is ill with a single pathogen and that
14 you're confident in using such a narrow spectrum.
15 I'm sure it occurs, but I bet it's pretty low
16 frequency.

17 CAPT PARISE: Dr. Schreckenberger, you had
18 another question, comment?

19 DR. SCHRECKENBERGER: I think that the
20 reality of what can be done right now is that we
21 don't have any tests that are sampled to answer.
22 In other words, you give me a sample, and in an

1 hour, I'll tell you what's there. Maybe someday,
2 not now.

3 What we do have are tests, for example, that
4 we can run from a positive blood culture bottle.
5 Now, most of our septic patients will signal
6 positive in 8 to 10 hours. And we have tests now
7 that we can perform right on that positive bottle
8 that might include one of the -- one of the tests
9 out there has 27 different targets. It covers
10 95 percent of all the agents of sepsis and a couple
11 of resistance markers besides. And so that would
12 be another hour. So in 8 or 9 or 10 hours, from
13 the time that sample was drawn, you could have that
14 answer.

15 It is *Pseudomonas aeruginosa*. It is
16 *Acinetobacter baumannii*. It is a KPC or an MRSA.
17 So I think that we do have that capability, but
18 right now that's really just pretty much for a
19 blood culture.

20 Everything else that's rapid, as far as ID
21 is concerned, has to come from an organism growing
22 on a cultured plate. So we have things like mass

1 spec that we can do right off of a cultured plate.
2 We can have a result in as little as a minute, but
3 we still need growth on a plate. So now we're
4 talking maybe 16, 18 hours, sort of minimum.

5 Just keeping in mind, if you're going
6 to -- so I agree with you that any study design
7 would mean that you probably have to start them on
8 some empiric cocktail, and then as the information
9 came back, you could switch them into this study
10 mode. But probably the earliest that's going to
11 happen is 12 to 24 hours into the study -- into the
12 treatment, I mean. So I don't know how that
13 affects this discussion.

14 As far as rapid detection of multiple
15 resistant organisms, I would say that's virtually
16 impossible by anything -- because even though we
17 have targets for specific genes, just because the
18 KPC gene is absent doesn't mean there's not a porin
19 mutation or an efflux pump or an MDM, a different
20 carbapenemase.

21 So there's no guarantee that you test for
22 one gene, that now that means the organism is

1 susceptible. It would mean, if you detect a gene,
2 that maybe it's resistant. But as was mentioned
3 this morning, the only way to know whether
4 something is susceptible is to do a phenotypic test
5 and see what it's susceptible to.

6 So markers for resistance are quite limited,
7 and they only test for that one marker that you're
8 looking for. It doesn't test for the hundreds of
9 other markers that could be there. So I don't know
10 how that affects this question, but I think that
11 the rapid diagnostics piece, we don't have what we
12 can tricorder medicine yet, those of you that are
13 Star Trek fans. Sample to answer is starting to be
14 looked at. We have some optimism that that's going
15 to happen, but it's a little bit away.

16 CAPT PARISE: Dr. Ostrosky?

17 DR. OSTROSKY: I like Dr. Magill's break out
18 of treat and test and test and treat. I think this
19 is where we need a little leeway and adaptive
20 design where if the two organisms or the organisms
21 fairly common -- Pseudomonas is starting to be very
22 common for ventilator-associated pneumonia or ESBL

1 E. coli for UTIs, and you treat and then test. I
2 think that that would be the design for that
3 particular scenario.

4 If the organism is more rare or the
5 resistance we're looking for is more rare, then you
6 probably need to get into test and then treat with
7 a much smaller data set. This is why I think you
8 almost start reaching orphan drug status. A
9 collection of fairly well-characterized cases would
10 be enough for that particular rare bug or mutation.

11 CAPT PARISE: Dr. Scheetz?

12 DR. SCHEETZ: So given the limitations of
13 what Dr. Schreckenberger just told us, it seems
14 inherent that a lot of times we are going to be
15 treating and then testing. I worry a little bit
16 about how much antecedent antibiotic therapy is
17 allowable for these trials. I think most of the
18 literature suggests that the first dose is the most
19 important dose, so that can have fairly large
20 implications. That's not to say that we should
21 throw those patients out because if you throw out
22 the patients that have had antecedent therapy,

1 we're left with no patients, as we saw in some of
2 the lectures this morning, as Dr. Wunderink showed
3 us.

4 So I think we are going to have to do a
5 better job of classifying exactly what the patients
6 received in advance because we don't have that
7 unbelievably rapid answer that, yes, this is
8 Pseudomonas. The first drug that we're going to
9 give the patient is going to be an
10 anti-Pseudomonal. Oftentimes these patients have
11 already received a litany of therapies prior to
12 that.

13 CAPT PARISE: Dr. Follmann?

14 DR. FOLLMANN: I don't have much to add.
15 But it seems like this is really an issue of
16 inclusion criteria, and maybe the approach would be
17 to test its strategy of broad-spectrum initial
18 antibiotic. And then as soon as you know you have
19 Pseudomonas, then randomize to the new agent that
20 has the spectrum for that versus whatever
21 comparator you have, and use that as your
22 inferential population. So you're essentially

1 testing a strategy of broad-spectrum first, and
2 then the targeted antibiotic and see if it works
3 relative to comparator.

4 CAPT PARISE: Dr. LaVange, then Dr. Baden.

5 DR. LAVANGE: A question back to
6 Dr. Follmann. Is that a test of the treatment
7 strategy? Because we would want to be able to
8 attribute benefit or risk to the new drug.

9 DR. FOLLMANN: In some sense, this is
10 semantics because we do have trials where patients
11 get prior antibiotic therapy. We still do our
12 noninferiority/superiority trials and effectively
13 attribute it to it. I said it, just baldly, that
14 it is a strategy trial, basically. And I called it
15 that. And that's in fact what you're doing
16 nowadays when you include patients with prior
17 antibiotics. So maybe it's semantics, and you'd
18 still have the issue of what's ascribable or not,
19 and good luck with that.

20 DR. BADEN: And I think along those lines,
21 some of the morning's presentations had the micro
22 ITT, where one has -- the microbiology is

1 prespecified as part of the assessment. And then
2 one can also look at this question in light of
3 earlier discussion about body of evidence. And one
4 could imagine certain populations, such as
5 bronchiectatics or cystic fibrosis patients, who
6 may not be in the extreme of illness, in the
7 emergency room or the ICU in severe illness, but
8 may have recurrent problems with organisms of
9 interest that one could, in a more structured way,
10 sort out some in vivo biologic activity that could
11 be meaningful and potentially be very supportive;
12 the behavior be antimicrobial with a pathogen in a
13 target population, though perhaps not in the most
14 severe illness. So there are a variety of ways one
15 could look at this.

16 CAPT PARISE: Any other comments on this
17 question? Dr. Schreckenberger?

18 DR. SCHRECKENBERGER: Well, another thing
19 -- your comment just triggered a thought -- is that
20 what if the infection's not monomicrobial? Because
21 even if we have a rapid test that has certain
22 targets, there could be organisms there that we

1 don't have targets from, and we won't know until
2 later that something else grew out of that
3 specimen.

4 So we have a lot of mixed infections,
5 including blood culture. But certainly in urines
6 and wounds and sputum, we see a lot of mixed
7 microbials. So again, you might not be able to
8 switch the patient -- due to inclusion and
9 exclusion criteria -- to a drug that has a targeted
10 organism in a lot of the studies because it's not a
11 pure culture. It seems like it's going to be
12 problematic trying to design these studies.

13 CAPT PARISE: Dr. Reller?

14 DR. RELLER: The urgent need that has been
15 alluded to multiple times today, I envision that as
16 the patient has infection with an organism that is
17 resistant to what the patient is getting, and it
18 may be with a Pseudomonas or Acinetobacter.

19 Perhaps a positive way of looking at
20 spectrum of activity limited to one or two
21 organisms, given the reality of not only the
22 urgency but the importance and efficacy of

1 empirical therapy, that if one had HAPB or VAPB or
2 complicated intra-abdominal infection, and a
3 traumatic extremity injury, and Acinetobacter was
4 there, and the coverage that was being used was not
5 effective, and that emerged, that to have an agent
6 that is targeted to the Acinetobacter or
7 Pseudomonas could be very useful adjunct therapy.

8 The positive aspect in terms of trial design
9 is that would be, as we talked about before, a
10 perfect opportunity for a superiority trial, of
11 adding a monoclonal antibody against Pseudomonas
12 aeruginosa in addition to what the patient was
13 already getting. And then it obviates the problem
14 of antecedent therapy. And I think the comment
15 that one dose and one cannot tell anything after
16 that is just not consonant with clinical reality.

17 These patients do not get better with one
18 dose of antimicrobial. Two doses at one day, two
19 days, I mean, somewhere in there, things would get
20 cloudier and cloudier in terms of one's confidence
21 that you're adding anything. I think that it's
22 worth looking at the exclusion criteria when you're

1 talking about drugs being developed for multidrug
2 resistant agents for which we have few or no other
3 options.

4 CAPT PARISE: Are there any other comments?

5 (No response.)

6 CAPT PARISE: Let me try to sum up.

7 Basically, the panel pretty much concurred that at
8 this point such a test does not exist. We don't
9 have a rapid test. Even if we did have some sort
10 of marker, there's barriers to that. Just because
11 a marker isn't there for resistance doesn't mean
12 that there couldn't be other markers that we don't
13 have and haven't looked at. So it wouldn't give us
14 confidence necessarily that the organism was
15 sensitive an that you could paradigm your therapy
16 and make it a more narrower spectrum. The reality
17 of the situation is that we test and treat.

18 One possible suggestion was, of necessity,
19 in these very sick patients, you're going to start
20 out broad. But one way to do it would be then once
21 you know what the infecting organism is, that you
22 could randomize at that point and then be testing

1 that strategy and testing the drug from that point
2 on. One of the questions that was raised, if this
3 is so rare, can orphan drug status be considered.
4 That was just raised as a possibility.

5 The main issue with this is -- the issue of
6 prior therapy is important, and we need to do a
7 better job thinking about exclusion criteria, and
8 excluding patients, we may be narrowing down -- we
9 may be narrowing down the patient database that's
10 useful if we can't think harder about the exclusion
11 criteria. The point was also made that if a
12 patient is on an antibiotic and failing, that's an
13 opportunity, then, to look at your new therapy that
14 may be targeted against that organism. An example
15 of monoclonal was an example that was given.

16 The other point was made that there could be
17 specific patient populations where you could gather
18 support of evidence; for example, from patients
19 with cystic fibrosis that are prone to Pseudomonal
20 infections, and that could be an opportunity to
21 gain some supportive evidence on that particular
22 microorganism.

1 I think that's about what I heard. So now
2 we're going to move on to question 4. Please
3 discuss the acceptability of a smaller safety
4 database, for example, 300 to 400 patients exposed
5 to the investigational drug at the dose and
6 duration of therapy.

7 First, are there any clarifying questions
8 that the committee has before we start the
9 discussion? Dr. Magill?

10 DR. MAGILL: I'm assuming that these are
11 antibiotic drugs that would be given in a standard
12 single-setting/multiple-setting dose, phase 1,
13 normal, healthy volunteer setting before you
14 entered into the efficacy. And 300 to 400 really
15 is talking about patients that are sick patients,
16 that are receiving it as part of the indication.

17 DR. NAMBIAR: That's correct, Dr. Magill.

18 CAPT PARISE: The question's open for
19 discussion from the panel. Dr. Magill?

20 DR. MAGILL: Just following on that, the
21 concept that you give this drug in these usually
22 very sick, hospitalized individuals, and trying to

1 pull out drug-related adverse events in the midst
2 of sickness and confounders, really hard to do. So
3 that's really important to pull out of the healthy
4 normals without really understanding what the
5 no-effect dose is, maximal tolerated dose, class
6 related, in a really high-quality MedDRA style
7 setting so that when you go into these populations,
8 you actually are specifically looking -- you have
9 some idea what you're looking for to see how that
10 may or may not be associated with this; because the
11 300 or 400, why not 200? Why not 500?

12 Perhaps the statisticians can give a sense
13 of what that is, but it's a small number. And
14 sever adverse events that are drug related may be
15 difficult to come by. Also, the carryover of the
16 PK and TK-related -- the drug measurements in this
17 setting and the PK parameters, when you carry that
18 over into these populations, I would think that
19 it's really important, again, to get therapeutic
20 drug monitoring in these individuals to really get
21 a sense of how the drug's performing in sick people
22 versus well people, and does this carry over -- are

1 any of these things you saw in the phase 1 setting
2 in healthy volunteers, are any of those things PK
3 or TK related.

4 So I think there's a lot of stuff you can
5 do, but it's not just 300 or 400 people and did
6 they live or die. It's what's the high content
7 that you can bring over and carry to those folks.

8 I was going to make this point at another
9 time, but it's probably a good one. These are very
10 sick, complex individuals. They also have ICU
11 polypharmacy, so they're often 10, 15 drugs on
12 board for various reasons. Anybody who thinks
13 there's any idea of what's going on in terms of
14 drug-drug interactions I think it's just fooling
15 ourselves.

16 So probably again, early on in the in vitro
17 and in vivo platforms, there should be some sense
18 of what is the potential DDI platform, if you will,
19 or profile of this drug. And then carrying it
20 over, that's why the TDM I think in these people
21 are really important because you get a sense of
22 what's happening in the sick people with all these

1 other drugs on board.

2 CAPT PARISE: Dr. Hamblett?

3 DR. HAMBLETT: I think answering this
4 question is very difficult without some parameters
5 around this question in terms of -- very rarely do
6 we prespecify what the toxicities are that we hope
7 to rule out. And so I think that there's an
8 exercise here -- that obviously we don't have time
9 here today to do -- that talks about how many
10 patients do you need to have, a precise estimate.

11 The other point really goes to the last
12 comment, that it's really hard to identify
13 drug-related toxicities toward these indications.
14 And I think if you're going to talk about accepting
15 a smaller safety database, then you need to be very
16 certain that the toxicities you're looking for are
17 actually being standardly collected across sites,
18 across investigators. It's very easy, in a setting
19 where you have a sick patient, to say, no, it's not
20 regulated. It's regulated to their underlying
21 condition.

22 So I think a lot of emphasis needs to be

1 placed on thinking in advance what you're trying to
2 look for and making sure that you're adequately
3 capturing it with the limited patient population
4 that you have.

5 CAPT PARISE: Dr. Cappelletty?

6 DR. CAPPELLETY: As we talk about the PK
7 importance in this patient population, something
8 that we don't do now that we would need to do to
9 meet this unmet patient population, would be some
10 more phase 1 PK data in these individuals. So
11 we're going to need patients on dialysis, people on
12 CRT, those with just reduced renal function or
13 liver function, so that we actually know what PK we
14 need to be applying to this patient population
15 because the stuff we get from the healthy
16 volunteers isn't even going to be close to what's
17 really going on in these individuals. So we need
18 to move some of that phase 1 up.

19 CAPT PARISE: Dr. Robinson, and then
20 Dr. Follmann.

21 DR. ROBINSON: One thought for
22 consideration, first to tighten up our level of

1 confidence about the side effect profile of the
2 drug, I think not only the numbers of patients is
3 important but also the character of the patients.
4 As Dr. Hamblett mentioned, the sickest patients are
5 the ones that are the most difficult to sort out
6 what is effective disease versus what's effect of
7 the drug.

8 So I wonder if augmenting, say, a 505(b)(2)
9 pathway with additional trial work patients who
10 would not be ultimately indicated would be
11 worthwhile; so the not so severe patients with
12 infections studied to augment the numbers and to
13 give a cleaner population against which you would
14 judge a safety profile.

15 CAPT PARISE: I just want to make sure I got
16 that right. So you're saying in addition to what
17 you need for a 505(b)(2), study some
18 additional -- augment that database with additional
19 patients to make you more comfortable that you're
20 looking with this safety issue.

21 DR. ROBINSON: Exactly. It would improve
22 the precision of the estimate of frequencies, and

1 it would also give a cleaner look at what the side
2 effect profile is.

3 CAPT PARISE: Dr. Follmann?

4 DR. FOLLMANN: I would agree with that
5 sentiment that if you want additional safety data,
6 and you can't study it in the drug-resistant
7 population, maybe because it's 300 to 400 to get it
8 in the drug-susceptible population or patients who
9 are somewhat augmented -- but I almost have a
10 philosophical perspective on this question because
11 we're not talking about efficacy. Usually, the
12 sample size driver is efficacy.

13 So if this was a study where 300 to 400 was
14 sufficient to show efficacy, maybe in the
15 superiority study or a noninferiority margin -- but
16 that seems pretty unlikely. But anyway, that
17 efficacy drives the sample size, and if 300 to 400,
18 where it's enough to show reliably that this was a
19 good drug, then I'd be happy with a smaller safety
20 database. That's usually what's done, really, a
21 power study for a certain sample size, which shows
22 it's efficacious; great. And then the safety data

1 is what you get out of that. You don't triple the
2 sample size to cover safety in greater detail
3 usually.

4 CAPT PARISE: Dr. Reller?

5 DR. RELER: To follow up on Dr. Follmann's
6 comment, if one had a superiority trial, and the
7 best available therapy were employed, and the new
8 compound was efficacious, and no more in a
9 randomized trial ill effects than the others, even
10 if the patient were getting 10 or 15 other drugs at
11 the same time, then it seems to me that those
12 factors, more than the absolute number, should see
13 what's acceptable for initial approval of a
14 valuable new addition, if it proved to be that.

15 CAPT PARISE: Dr. Baden?

16 DR. BADEN: Along those lines, I would
17 answer this question as yes, and it's hard to give
18 simple answers. If we had two phase 3 RCTs with
19 600 per study, 1200 subjects in it, I would still
20 argue that's inadequate to assess safety because
21 often safety effects are 10,000, 100,000, 1 in a
22 million, so that safety by its nature, which may be

1 eclectic or idiosyncratic, or associated with
2 variables that, a priori, we don't understand, has
3 to be a continuous issue.

4 So if we have a potential signal of efficacy
5 in 300 patients with a disease that doesn't
6 otherwise have adequate treatment, I think that's a
7 good safety database to build upon, and it seems
8 very reasonable as a starting place.

9 I think the issue of hw to get collateral
10 data in supported populations, such as dialysis
11 patients, without the pathogen, one has to think
12 carefully about putting patients at risk for
13 interesting data where they don't have benefit.
14 And that just comes to us having to think through
15 how we develop collateral data that can help
16 support metabolism, excretion, some of the other
17 things that we need to know. And I think creative
18 solutions for those issues are very plausible.

19 CAPT PARISE: Dr. Ostrosky?

20 DR. OSTROSKY: I'm also going to answer yes.
21 I think I'd feel comfortable with this size if we
22 had a very, very robust preclinical data set, an

1 enriched early clinical data set like we've been
2 discussing with appropriate populations. And
3 again, I'd like to qualify with my previous
4 comments, a very, very robust phase 4, where we're
5 really, really watching closely what happens after
6 the drug is released into the market.

7 CAPT PARISE: Dr. Andrews?

8 DR. ANDREWS: I would just echo the -- I
9 don't have any basis for knowing whether 300 to 400
10 is enough. I agree with you. It's probably not,
11 but whatever. But I like the idea of looking at
12 people with the kinds of problems, other associated
13 problems, that are likely to take this drug because
14 looking at healthy people doesn't necessarily tell
15 you a whole lot about what's going to happen with
16 people who have multiple other problems as well.

17 So I think if you're looking at 300 people
18 that are much more like the people who are going to
19 take this drug, that's a better comparison than 300
20 healthy, young 25-year-olds.

21 CAPT PARISE: Dr. Magill?

22 DR. MAGILL: I think one of the values of

1 doing this in terms of a traditional no effect or
2 MTD levels from healthy volunteers is it gives you
3 a pretty good idea of the drug, perhaps class
4 effect on organ systems. So if it's liver or
5 hematotoxic, you will start to see those signals,
6 and that just gives you a hint of what to look for
7 in the population of interest. So I think it is
8 important but, again, it's only in its use in the
9 population of interest.

10 One of the comments -- and this may fit best
11 under the safety rubric here -- is looking at these
12 antibiotics, not just in their microbiologic sense
13 but also in their collateral effects, especially
14 immune modulating.

15 I think in the world of infectious disease
16 and the drug-bug PK world, there's a sense that
17 people forget, that humans actually have an immune
18 system, and that's unfortunate because in many of
19 these effects -- for example, why azithromycin
20 seems to continue to work really well in COPC
21 exacerbations probably has little to do with this
22 microbiology, but it's a very potent immune

1 modulator, and we certainly see that with
2 doxycycline and all the -- tetracycline class.

3 We now understand this. We can look to TLR
4 agonist/antagonist panels, receptors, cytokine
5 stimulations, T cell. There are ways of looking at
6 this now that are standard actually in the industry
7 and were not available even 10 years ago.

8 So I think, again, it's about really
9 understanding your molecule, what it might do going
10 forward. There is a little bit of a risk here
11 because you can do those assays. You're get
12 results. And then what do those results actually
13 tell you? I would just think it's part of the
14 evaluation of a modern antibiotic. We should have
15 some sense of how it fits as an immune modulating
16 drug.

17 CAPT PARISE: Dr. Schreckenberger?

18 DR. SCHRECKENBERGER: I would like to just
19 agree with everything Dr. Ostrosky said about
20 safety. I think safety is a slippery slope. Who
21 wants to go on record as saying, yes, let's be less
22 safe? Let's lower our safety margin. I don't

1 think we're saying that, and we don't want to say
2 that. But what we recognize is if the phase 3
3 trials start having smaller numbers because we have
4 a larger margin for noninferiority trials or we do
5 more superiority trials, we may end up with lower
6 enrollments. And so, you're saying, well then,
7 we'll know less about safety in the sick patients.

8 So what I heard Dr. Ostrosky say, and I
9 agree with, is that's fine as long as it's coupled
10 with a robust preclinical safety study, as well as
11 a robust phase 4 collection of safety data.

12 CAPT PARISE: Dr. Scheetz?

13 DR. SCHEETZ: I won't reiterate what
14 everybody said because I agree with a lot of it. I
15 don't like the idea of a completely fixed number
16 saying that 300, 400. I do like the idea of
17 letting the FDA have some amount of flexibility.
18 And I guess that gets at the question of what's the
19 admission ticket to be able to be considered for
20 this? If it's a me-three drug that's still
21 addressing a drug-resistant pathogen, should we
22 maybe up the safety standard? If there already two

1 options that have already addressed the unmet need,
2 can we then say maybe 300's not enough. Maybe this
3 drug needs a thousand patients for a safety
4 standard.

5 So I do like the idea of not saying -- very
6 consistent with what Dr. Schreckenberger said.
7 Nobody wants to go on record and say this is the
8 least safe we can be. But I do think that there's
9 a growing need of people recognizing that we are
10 going to have smaller and smaller studies, and we
11 should move forward with those. But then as we
12 move forward with those, my opinion would be that
13 the bar should also move up.

14 CAPT PARISE: Other comments from the panel?

15 (No response.)

16 CAPT PARISE: I'm going to try to sum up.
17 The point was made that before we get to the
18 clinical work and before we get to the sick patient
19 population, preparatory work needs to be done, and
20 that's very important because it gets difficult to
21 sort out any adverse effects in very sick patients
22 who have many comorbidities. So your work in your

1 phase 1 in healthy people gives you a signal of
2 what body systems may be affected and what you want
3 to look for.

4 The question of how PK relates to that came
5 up because it can also give you a clue as to what
6 you're seeing, are there PK related effects that
7 you're seeing, that you saw when you did your
8 earlier work that may translate to help you
9 interpret data in the sick patients. In addition,
10 these patients are on many drugs in the ICU, and so
11 what you learn in the earlier studies in terms of
12 the DDI profile can be helpful in the
13 interpretation.

14 The point was made if we are going to have
15 smaller numbers in a safety database, the agency,
16 in conjunction with the sponsor, should be thinking
17 about, in advance, what you're going to potentially
18 be looking for and ensure that you have adequate
19 numbers to be able to look at those effects.

20 The point was made that PK information from
21 patients with, for example, impairments can be
22 useful as well because the patients that are

1 actually going to be getting the drugs will have
2 impairments such as renal impairment and hepatic
3 impairment.

4 Another suggestion was that 505(b)(2), drugs
5 being approved under that regulatory authority,
6 there the database mainly to be augmented with
7 additional numbers to ensure adequate safety data.
8 And that could potentially be obtained both in
9 patients with drug susceptible as well as drug
10 resistant, that had drug-resistant organisms.

11 There was fair amount of discussion on
12 efficacy is driving the sample size, and that's
13 typically what you're going -- the number that
14 you're going to get is the number that you have for
15 efficacy. That will be what you get on safety.
16 But as the agency may decrease the numbers needed
17 for approval under efficacy because of the
18 difficulty in doing these trials, the committee
19 wanted to emphasize we aren't saying we're having a
20 lower bar for safety. But if the trial size
21 decreases, that's just going to be the reality of
22 the situation on the safety side.

1 So there, we're okay -- I think there was
2 general thought that we're okay with that if that's
3 the reality of the situation, but then robust
4 preclinical -- robust support of data, both as far
5 as the preclinical and other data, as well as a way
6 to look closely in phase 4, both become more
7 important as these numbers on safety get lower.

8 The point was made that these antibiotics
9 can have immunomodulatory effects, and that should
10 be considered, those assays, as part of the whole
11 evaluation. Then lastly, the agency should have
12 flexibility on thinking about the numbers in the
13 safety database in terms of considering how limited
14 the options may be; for example, if it's a me-too
15 drug versus there's really no other option. So
16 that can affect where you set the bar. I think
17 that's what I heard there.

18 Before we adjourn, are there any last
19 comments from the FDA?

20 DR. NAMBIAR: Thank you, Dr. Parise. I just
21 wanted to thank all the committee members for a
22 very useful discussion today on a really difficult

1 and challenging topic. I would also like to thank
2 representatives from IDSA, BIO and the American
3 Thoracic Society for their presentations, and the
4 speakers of the open public hearing, for their
5 comments as well. For those of you who won't be
6 joining us tomorrow, we wish you safe travels. And
7 for the rest, we'll see you again at 8:00 in the
8 morning. Thank you.

9 CAPT PARISE: Before I adjourn, I think
10 Dr. Magill had a final comment.

11 DR. MAGILL: Thanks. It didn't come up at
12 all today, and I was actually a little surprised.
13 The whole driver of this is resistance, and I
14 actually didn't hear resistance come at all. So in
15 the development of the drugs is what's the ability
16 of the drug to actually induce resistance; and
17 there are many mechanisms in which to do that. And
18 in the clinical trials, in the clinical trial
19 design, what actually happens in treatment-emergent
20 resistance in the isolates that come up.

21 I would think this needs to be factored in
22 very clearly into the clinical trial design because

1 if monotherapy, which is what this may end up in
2 some settings, leads to treatment-emergent
3 resistant isolates coming up, then that to me would
4 signal the termination of that as a monotherapy,
5 and it would have to then move in to partner drugs.

6 So I just wanted to make sure that comment
7 was in for the record because I was surprised I
8 didn't hear it in the conversations today.

9 **Adjournment**

10 CAPT PARISE: Thank you. We will now
11 adjourn the meeting. Panel members, please take
12 all your personal belongings with you, as the room
13 is cleaned at the end of the meeting day. All
14 materials left on the table will be disposed of.
15 Please remember to drop your name badge off at the
16 registration desk so they can be recycled; that's
17 if you're not coming back tomorrow. Thank you.

18 (Whereupon, at 4:24 p.m., the meeting was
19 adjourned.)
20
21
22