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FOOD AND DRUG ADMINISTRATION (FDA)

PUBLIC WORKSHOP:
FACILITATING ANTI-INFECTIVE DRUG DEVELOPMENT FOR
NEONATES AND YOUNG INFANTS

September 15, 2016

Sheraton Silver Spring
8777 Georgia Avenue
Silver Spring, Maryland 20910

Reported by: Chaz Bennett

Capital Reporting Company

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

2 Session 1: Current State and Challenges Associated
3 With Neonatal Anti-infective Drug Development

4 Introductory Remarks

5 DR. NAMBIAR: So welcome to today's "Public
6 Workshop on Facilitating Anti-Infective Drug
7 Development in Neonates and Young Infants." My name
8 is Sumathi Nambiar, and I am the Director of the
9 Division of Anti-Infective Drugs at the FDA.

10 We do sincerely appreciate all of you taking
11 the time to attend today's workshop and look forward
12 to a very productive and fruitful discussion.

13 We are here today to discuss a very
14 important topic that lies very close to my heart as a
15 pediatrician and poses challenges on multiple fronts,
16 and we, as a group, have to work together to recognize
17 the challenges and find workable solutions so that
18 safe and effective therapies can be developed for
19 neonates and the neonate patient population.

20 So I think we'll start by introduction of
21 our panelists. So Dr. Mulugeta, maybe we can start
22 with you.

1 DR. MULUGETA: My name is Lily Mulugeta.
2 I'm a pediatric clinical pharmacologist at the FDA in
3 the Office of Clinical Pharmacology.

4 DR. MCCUNE: Good morning. I'm Susan
5 McCune. I'm the Deputy Director for the Office of
6 Translational Sciences in CDER, FDA, and I'm a
7 neonatologist.

8 DR. ALEXANDER: John Alexander. I'm the
9 Deputy Director for the Division of Pediatric and
10 Maternal Health. And I've previously been working in
11 the Anti-Infectives Division for many years.

12 DR. KOVANDA: Hi. Laura Kovanda, from
13 Astellas. I've worked on the anti-infective programs
14 for Astellas for many years.

15 DR. TURNER: Mark Turner. I'm a
16 neonatologist from Liverpool. I'm interested in any
17 phase drug development, particularly antimicrobials in
18 neonates, and also the number of international
19 collaborations.

20 DR. RUBINO: Hi. Chris Rubino, Executive
21 Vice President for Pharmacometrics at the Institute
22 for Clinical Pharmacodynamics. We are involved in

1 lots of different anti-infective drug development
2 programs. And I particularly have a specialized
3 interest in pediatrics.

4 DR. ZAJICEK: I'm Anne Zajicek. I'm a
5 pediatrician clinical pharmacologist, Chief of the
6 Obstetric and Pediatric Pharmacology Branch at NICHD.
7 And part of our program runs the Best Pharmaceuticals
8 for Children Act and the contract with Duke for the
9 Pediatric Trials Network.

10 DR. YASINSKAYA: Good morning. I'm Yuliya
11 Yasinskaya, Medical Officer from the Division of Anti-
12 Infectives Products, and I'm a pediatrician.

13 DR. SMITH: Good morning. I'm Tom Smith, a
14 clinical team leader in the Division of Anti-Infective
15 Products.

16 DR. FARLEY: I'm John Farley. I'm the
17 Deputy Director of the Office of Antimicrobial
18 Products at CDER.

19 DR. BRADLEY: I'm John Bradley, a pediatric
20 infectious disease doctor at the University of
21 California, San Diego, and have been studying drugs in
22 babies since the late '70s when we began to have

1 cefotaxime and probably didn't need it back then, but
2 now with all the new multidrug-resistant organisms,
3 it's critical that we study new drugs, and I'm not
4 sure that we know how, and I'm looking forward to
5 finding that out today. Thank you.

6 DR. BENJAMIN: I'm Danny Benjamin, Professor
7 of Pediatrics at Duke University, and I chair the
8 Pediatric Trials Network.

9 DR. NOEL: I'm Gary Noel. I'm a pediatric
10 infectious disease subspecialist, and I'm a founding
11 member of the Child Health Innovation Leadership
12 Department at Johnson and Johnson.

13 DR. HOPE: I'm William Hope. I'm an ID
14 physician from the University of Liverpool, and I run
15 a lab in antimicrobial pharmacodynamics and have a
16 special interest in neonatal and pediatric drug
17 development.

18 DR. SMITH: I'm Brian Smith. I'm a
19 neonatologist at Duke and work on a number of anti-
20 infectives as part of the Peds Trials Network.

21 DR. BAER: I'm Gerri Baer. I'm in the
22 Office of Pediatric Therapeutics at the FDA. And I'm

1 a neonatologist.

2 DR. NAMBIAR: Very good. So with that,
3 thank you all kindly for taking the time to be here.
4 We are also very happy that some of our colleagues
5 from EME will be joining us via phone and maybe by
6 WebEx as well. Hopefully, we don't have any more
7 technical difficulties.

8 So Dr. Radu Botgros, from EMA; Dr. Maria
9 Fernandez Cortizo, who is from the PDCU and
10 representing Spain; and Dr. Irmgard Eichler, from the
11 EMA pediatric team, will be participating remotely.

12 So just to remind you, today's meeting is a
13 workshop, it's really not an advisory committee, so it
14 tends to be much less formal. And we encourage active
15 participation from the audience members. So feel free
16 to interrupt, ask questions, provide comments. We
17 find that very helpful.

18 Broadly speaking, we have divided the day up
19 into two sessions. The first session will focus on
20 current state and challenges associated with neonatal
21 anti-infective drug development. And during the
22 second session, we will discuss some considerations

1 for potential path forward for studies in neonates and
2 young infants.

3 We'll take an hour for lunch break between
4 the two sessions. And as a reminder, prior to the
5 panel discussion in the afternoon, we have 15 minutes
6 for public comments if anybody could not get their
7 comments in during the Q&A session.

8 With that, a warm welcome again, and we look
9 forward to the presentations and discussions.

10 Our first speaker this morning is Dr. John
11 Farley. He is the Deputy Director in the Office of
12 Antimicrobial Products. Dr. Farley has been in the
13 office since 2009, and we, in the Division, were very
14 fortunate that he led our group for 2 years from 2011
15 to 2013.

16 With that, John, I will turn it over to you.

17 The Landscape of Neonatal Anti-Infective
18 Drug Development

19 DR. FARLEY: I'll see if this works: slide
20 up. No, it doesn't work.

21 (Laughter.)

22 DR. FARLEY: Oh, well. You can tell this is

1 not an industry event. Right? "Restart now
2 recommended," that can't be good.

3 PARTICIPANT: No.

4 DR. FARLEY: How about X'ing that and
5 "Norton Live Update" out?

6 PARTICIPANT: Let's just say, "Remind me in
7 24 hours."

8 DR. FARLEY: Oh, there's FDA slides. Oh,
9 there we go. Okay. Cool. Almost. Okay, I'll
10 manage. All right. Great. There we go. It worked.

11 Welcome, everybody. And I really appreciate
12 everybody being here in the middle of this rather
13 grueling September so far with kids back in school and
14 a number of us with favorite baseball teams and
15 pennant races. Sorry to all the Boston fans in the
16 room, but you'll probably make it anyway.

17 (Laughter.)

18 DR. FARLEY: All right. So I'm going to
19 talk a little bit about the landscape of neonatal
20 anti-infective drug development just to kind of get
21 everybody on the same page and kind of kick off the
22 day.

1 So talk a little bit about regulatory
2 overview, which you could expect. Talk a little bit
3 about anti-infective drugs developed during the last
4 decade and a half that have had a PREA requirement at
5 the time of their initial approval. Focus on anti-
6 infective drugs commonly used in the NICU. So what do
7 babies and neonatologists -- what are their
8 priorities? And then close with some thoughts for
9 today.

10 These are my views, not those necessarily of
11 the Food and Drug Administration. And I better not
12 have any disclosures.

13 So I think we're all here today because
14 we're really committed to two principles. One is that
15 pediatric patients, including neonates, should have
16 access to drug products that have undergone
17 appropriate evaluation for safety and efficacy; and,
18 secondly, that drug development programs ought to
19 include pediatric and, in fact, neonatal studies when
20 use is anticipated in those populations.

21 So I think it's a fair assumption that if
22 you got up and drove through traffic to get here this

1 morning, you're committed to those principles. And
2 I've been delighted to work with a variety of folks
3 over the past couple of years who are really firmly
4 committed to those.

5 So just to begin with a little historical
6 perspective, many of you were around then, but you'll
7 remember that in the 1990s, efforts on the part of
8 both the agency, academics, as well as care providers,
9 as well as industry, there were efforts made,
10 primarily through rulemaking, which is how regulations
11 are written in the United States, to encourage and, in
12 fact, mandate the study of drugs in children.

13 And in 1990, there were a series of rules
14 issues, or draft rules, ultimately challenged, as many
15 of you know. But in 1994, the FDA did issue a rule
16 allowing labeling of drugs for pediatric use based on
17 extrapolation of efficacy in adults in certain
18 circumstances, and Tom is going to focus on that in
19 his talk.

20 In 1997, FDAMA, or the Food and Drug
21 Administration Modernization Act, was passed, and that
22 was the first time that we had economic incentives for

1 pediatric studies.

2 That was renewed, those provisions were
3 renewed, in 2002 with the passage of the Best
4 Pharmaceuticals for Children Act, and, in fact, that
5 act provided mechanisms for studying both on- and off-
6 patent drugs in children, and the off-patent piece
7 becomes particularly important in the neonatal arena,
8 and it established the NIH Program for Pediatric Drug
9 Development, which is administered in collaboration
10 with NICHD even today.

11 In 2003, the Pediatric Research Equity Act
12 was finally passed, which required pediatric
13 assessments in certain circumstances. That was
14 retroactive for applications that were submitted on or
15 after April 1 of 1999, which I think was about the
16 time the FDA had issued a rule which had been stayed
17 by the court, so Congress stepped in and weighed in
18 strongly in that regard.

19 So let's sort of talk about kind of the
20 general regulatory perspective because labeling for
21 children, labeling for neonates, in terms of either an
22 indication per se or adding an indication really

1 requires the same standards, is required to meet the
2 same standards.

3 And as you know, in 1962, the Federal Food,
4 Drug, and Cosmetic Act was amended to establish the
5 substantial evidence of effectiveness standard,
6 substantial evidence of effectiveness through adequate
7 and well-controlled investigations, and that standard
8 holds for adding an indication or adding an indication
9 in an age group.

10 The Pediatric Research Equity Act, as I
11 mentioned, required assessments of safety and efficacy
12 for relevant pediatric subpopulations for new drugs,
13 and that included when there was a new active
14 ingredient, a new indication, a new dosage form, a new
15 route of administration. In those cases, PREA is what
16 we call kicked among regulators or applies.

17 But, in fact, we need to meet the efficacy
18 standard, and we can meet that two ways: through
19 adequate and well-controlled studies or through
20 extrapolation, and Tom is going to be talking about
21 that.

22 Two important points to keep in mind, which

1 you know: dosing is not a straightforward
2 extrapolation; and, secondly, we do not extrapolate
3 safety. We may have a lot of what we would call
4 priors for safety in terms of other age groups and
5 other populations, but we need to have safety studies
6 in children. And even revisiting that recently, other
7 folks who care for kids have made that quite clear,
8 that they really want that data.

9 So let's just review. We have the Pediatric
10 Research Equity Act, or PREA, it's amended Section
11 505(b) of the Food, Drug, and Cosmetic Act. That
12 requires companies to assess safety and efficacy of
13 certain products in pediatric patients.

14 And we have BPCA, or the Best
15 Pharmaceuticals for Children Act, which is Section
16 505(a), at least part of it, and the other part amends
17 Section 409 of the Public Health Service Act. Because
18 there are really two pieces of BPCA that are very
19 important. Okay?

20 So the financial incentives for BPCA is
21 basically exclusivity that attaches to patent life.
22 So that's very unique. So in order for that incentive

1 to apply, for most companies, the patent has to be in
2 effect, otherwise, there isn't an incentive. So these
3 are generally on-patent, recently developed drugs.
4 And that's very different than Hatch-Waxman or other
5 types of exclusivity that the agency awards.

6 So this has been in the past and I think
7 continues to be, depending upon the reimbursement
8 milieu in which the drug finds itself, very motivating
9 to companies. Certainly in the hepatitis C and HIV
10 arena, it's been a very big incentive.

11 However, BPCA also includes a provision for
12 off-patent drugs, which is very important. And the
13 FDA and the National Institutes of Health partnered to
14 obtain information, i.e., support the studies, to
15 support labeling of products used in pediatric
16 patients. So that's an important tool that we have.

17 So just to kind of review and compare the
18 two, PREA applies to drugs and biologics. So does
19 BPCA. PREA, there are required studies. Those are
20 publicly available to folks to look at because they
21 are included in the approval letters for drugs, which
22 are publicly available. It's on Drugs@FDA, fairly

1 easy to find.

2 BPCA is voluntary studies in response to
3 what's called a pediatric written request, which is
4 issued by the agency. Usually in response to some
5 dialogue with the company, they submit something
6 called a proposed pediatric study, but not
7 necessarily; the agency could initiate that on its
8 own.

9 For PREA, the studies may only be required
10 for the approved indications. For BPCA, the studies
11 relate to the entire moiety, and they actually may
12 expand indications. An example would be drugs that
13 were developed to treat acute bacterial skin and skin
14 structure infections, the agency might request a
15 pediatric study in osteomyelitis, for example.

16 For PREA, products with an orphan
17 designation are exempt from PREA requirements. Some
18 companies engage in those studies voluntarily, but
19 they are exempt if it's an orphan-designated drug.
20 For BPCA, we can request studies for products with
21 orphan designation. And in both cases, we want
22 pediatric labeling.

1 The study does not have to be successful.
2 Sometimes unsuccessful studies produce information
3 which is very valuable for pediatric care providers,
4 and we would like to include that in the labeling as
5 well.

6 So just to focus on antibacterials that had
7 a PREA requirement at the time of the initial approved
8 indication -- all right, weird things are happening.

9 (Laughter.)

10 DR. FARLEY: We have an urgent call to the
11 podium for a Millennial. All right. I'm just going
12 to move on, assuming that you guys have great vision.

13 So this is kind of the listing of drugs that
14 have been approved since 1999 in the antibacterial
15 space. And as many of you know, we would certainly
16 like there to be more of these.

17 But linezolid, which actually started their
18 work under BPCA because PREA hadn't yet been passed,
19 did a very nice development program and actually did
20 do CSF studies in neonates; unfortunately, not able to
21 achieve concentrations. So the labeling language is
22 cautionary.

1 You can come up and help me if you want.

2 Can you make this be full screen?

3 (Pause.)

4 DR. FARLEY: It's back. We're good. Okay.

5 I'm just going to do it with the arrow. Thanks.

6 Okay. Ertapenem, there were also some
7 concerns regarding CSF concentrations. I think this
8 illustrates some of the problems that happened in the
9 course of drug development because there were concerns
10 about use of some drugs in younger children because of
11 findings either in the adult population or older
12 children population or, in fact, in juvenile animal
13 studies, and daptomycin and telithromycin would be
14 good examples of that.

15 Ceftaroline did a very nice job with their
16 pediatric development program. And I considered that
17 to be fairly efficient. And just to give you some
18 idea, to get to labeling 2 months and older took about
19 5 years from approval. And others, we're still
20 waiting on some a very long time. And others are
21 simply too recent to have completed their pediatric
22 development to date.

1 Antifungals have been particularly
2 challenging, and you're going to hear a great case
3 study today about a company that really tried to work
4 very hard in the neonatal space and met a lot of
5 challenges, and so we'll talk through some of those.
6 But none of those actually have neonatal studies
7 completed to date, and I think that would be an
8 important thing to talk about and important to talk
9 about how we might get there.

10 This is a very nice paper. The senior
11 authors were two guys named Danny Benjamin and Brian
12 Smith, who are here today, but simply say this is a
13 great fellow project and hopefully maybe the next 5
14 years is underway.

15 This is the Pediatrix Medical Group database
16 for neonates, which is 305 NICUs. The original paper
17 was by Clark et al., looking at drug use in that
18 setting, and I think that was from 2000 to 2005; and
19 then this paper by Emily Hsieh, which was 2005 through
20 2010.

21 And I think what this highlights -- I'll
22 unpack this a little bit for you -- is how important

1 the off-patent drug studies are in the neonatal arena.

2 In terms of anti-infectives, which were
3 included in the top 50, some of these drugs are used
4 empirically a great deal, some when infection is known
5 to be present. So ampicillin, gentamicin, vancomycin,
6 cefotaxime, tobramycin, fluconazole, clindamycin,
7 acyclovir, ceftazidime, nafcillin/oxacillin, the amphi
8 B products, and amikacin. So those were in the top 50
9 from 2005 through 2010 in terms of frequency of use in
10 the NICU.

11 I highlighted those that are used in
12 extremely low birth weight infants. One of the --
13 (Slides malfunction.)

14 DR. FARLEY: All right. Well, I have it,
15 but they can't see it. For those of you who have
16 subsequent talks, you'll be happy that I'm sort of
17 working through all of the glitches that could
18 potentially happen. Okay. All right.

19 So for these commonly used drugs, we're
20 fortunate to have dosing information in the label in
21 neonates. I think the limitation is that as
22 neonatology has moved along and made progress, you

1 have lower and lower birth weight infants, so that's
2 certainly an issue and a consideration for today,
3 because there are premature infants, and there are
4 premature infants. And so that's a concern.

5 We don't actually have formal efficacy
6 established in the label. These were generally older
7 drugs. I think one could interpret that we do for
8 acyclovir because there's a nice adequate and well-
9 controlled trial that's described in the label, but
10 these are older labels that don't follow the current
11 format.

12 The other thing that was interesting that
13 Dr. Hsieh looked at was, what was the greatest
14 increase in drugs being used in neonates between 2005
15 and 2010? And they included azithromycin, you start
16 to see some of the newer drugs, linezolid, cefoxitin,
17 meropenem, pip/tazo, cefepime, and again fluconazole,
18 and cefazolin.

19 So I found that particular interesting, and
20 I'm hoping this a great fellow project to do 2010
21 through 2015 and perhaps you've even thought of that
22 already. But I think it's really very useful from

1 kind of a policy perspective and prioritization of
2 research funding. This was, I thought, a very
3 important paper.

4 So just to sort of turn to the off-patent
5 program, NICHD administers that program. There is a
6 priority list of needs in pediatric therapeutics that
7 is updated yearly. This is the 2015 list, and
8 presumably the 2016 list will be posted soon. The
9 website is up there. They have a very nice website,
10 which provides up-to-date information.

11 The criteria for updating the list are the
12 relevance to the BPCA mission and goals, that there
13 aren't disqualifying ethical concerns, what the level
14 of evidence available is currently and those current
15 gaps, consideration of different populations that
16 might benefit from the research, and the feasibility
17 and availability of the resources needed to conduct
18 the study.

19 Current research priorities listed in 2015
20 for infections in neonates were metronidazole in
21 abdominal infections; ampicillin, PK and safety in the
22 very low birth weight, so starting to address that

1 issue; fluconazole, again dosing and safety in very
2 low birth weight; and then meropenem, the PK safety
3 and safety in neonates with necrotizing enterocolitis.

4 A number of those studies are done through
5 the Pediatric Trials Network, which receives NICHD
6 funding through the BPCA program. We'll be talking, I
7 think about a number of studies that are open, and
8 we'll be hearing from Danny and Brian today about the
9 SCAMP study in intra-abdominal infections; the POPS
10 study, which is opportunistic sampling in children,
11 including neonates. They've completed a number of
12 studies, including ampicillin and meropenem.

13 One of the things to work through is just
14 kind of how neonatal labeling would happen for studies
15 conducted under that program. What happens is that
16 the data is submitted as though it were a supplemental
17 application, but it's submitted through a public
18 docket.

19 So as soon as the docket opens, other folks
20 can certainly take a look at that data, and the FDA
21 engages in that review through this public docket
22 process.

1 We then approach usually the innovator
2 company to try and get the labeling to happen. And
3 companies have usually been quite cooperative about
4 that.

5 So the meropenem studies were conducted in
6 infants less than 3 months of age with complicated
7 intra-abdominal infections. We'll probably talk a
8 fair bit about that today through the course of the
9 day. I think it highlights a number of issues,
10 particularly the issues about when one can extrapolate
11 efficacy and when one is not comfortable extrapolating
12 efficacy.

13 So just some thoughts for today. As you can
14 see, neonatal labeling for drugs approved since the
15 enactment of PREA is actually quite limited, and it's
16 like we do to the trial challenges that we're here to
17 discuss.

18 I think, as John mentioned, this is
19 particularly concerning as we seek to address unmet
20 needs, such as infections caused by carbapenem-
21 resistant Enterobacteriaceae. We don't want to
22 deprive kids of options to those products.

1 This is going really well from a technical
2 point of view. I'll just tell you what I'm thinking.

3 As I've tried to point out to you, and I
4 think you appreciate, the anti-infectives administered
5 most frequently to neonates are in fact off-patent.
6 And so the neonatal studies that are supported through
7 the NIH BPCA program have played a very important role
8 obtaining information for those drugs that are used
9 most frequently in neonates and will continue to do so
10 in the future.

11 And so one of the things to talk about today
12 is, what are the challenges? what are the successes?
13 what are the lessons learned from the studies to date
14 that have been conducted?

15 And, lastly, there are unanswered questions
16 that impact our progress. And one of the things that
17 we're particularly interested in hearing from you all
18 today is, what are the priorities for a regulatory
19 science research agenda for neonatal anti-infective
20 drug development? Regulatory science isn't glamorous,
21 but it makes a big difference in terms of public
22 health, and it makes a big difference in terms of

1 patient care. So we're keen to know, what are the
2 next things that we need to look at and what would
3 need support.

4 So thanks very much.

5 (Applause.)

6 FDA Perspective on Establishing Efficacy
7 for Common Indications
8 in the Neonatal Population

9 DR. SMITH: Okay. I'm going to talk a
10 little bit about some additional regulatory
11 considerations and lay the groundwork for some of the
12 talks and panel discussions to follow.

13 It's been a busy year for discussions on
14 drug development in pediatrics. Many of you attended
15 some of the meetings that are listed here.

16 In March, there was a Neonatal Scientific
17 Workshop held at FDA, and there was a session on
18 bacterial infections, and one of the questions that
19 came up was a vote on some priority projects, and the
20 leading candidates for projects turned out to be a
21 standard protocol for new studies in neonates and also
22 how to assess the efficacy of new antimicrobial drugs

1 on the central nervous system.

2 In the April CTTI meeting that was held at
3 this facility, there was a breakout session on
4 challenges in conducting neonatal studies. And I also
5 would like to put in a plug for the meeting next week
6 at FDA on Pediatric Master Protocols, which I know
7 many of you will be attending.

8 John has already mentioned our requirement
9 for substantial evidence. This evidentiary standard
10 applies to pediatrics as well as to adult populations,
11 and as he mentioned, the Pediatric Research Equity Act
12 requires assessments of safety and effectiveness for
13 all relevant pediatric subpopulations, and this
14 information can be obtained either through adequate
15 and well-controlled studies or through extrapolation.

16 As described in the CFR, where the course of
17 the disease and the effects of the drug are
18 sufficiently similar in adults and pediatric patients,
19 we may conclude that effectiveness can be extrapolated
20 from adequate and well-controlled studies in adults
21 usually supplemented with other information.

22 I want to emphasize here where the course of

1 the disease and the effects of the drug are
2 sufficiently similar. Studies may not be needed in
3 each pediatric age group if data from age group can be
4 extrapolated to another.

5 This is a diagram that's just on the FDA
6 website, and it describes some of the processes in
7 determining whether extrapolation is a reasonable
8 approach.

9 I think that certainly in the infectious
10 disease arena, the effects of the drug when you're
11 looking at an antibiotic to kill an organism, the
12 effects of the drug would be the same in pediatrics as
13 in adults.

14 And there are some issues that we'll talk
15 about in terms of whether we can extrapolate certain
16 indications to neonates, but I would also like to
17 point out from one of our guidances on providing
18 clinical evidence of effectiveness, some of the other
19 evidence that can be used to support extrapolation.
20 That includes common pathophysiology and natural
21 history of the disease in adult and pediatric
22 populations, common drug metabolism and similar

1 concentration response relationships in each
2 population, and experience with the drug or other
3 drugs in its therapeutic class in the disease or
4 condition or related diseases or conditions.

5 Now, this is something -- this will be one
6 of the discussion issues that we're having.

7 When you look at this list here, these first
8 four indications are areas where there has been a lot
9 of interest in recent antibacterial drug development.
10 Indications in adults tend to be organ-specific, and
11 you can see that these indications cover a variety of
12 Gram-positive infections, Gram-negative infections,
13 and anaerobic infections. I'll also touch a little
14 bit on areas where it's going to be much more
15 difficult for us to consider extrapolation. That
16 would be in the areas of neonatal sepsis and
17 meningitis and in invasive candidiasis.

18 Now, for acute bacterial skin and skin
19 structure infections, this is the definition that's
20 listed in our guidance. You can disregard the 75
21 square centimeters, but it includes infections like
22 cellulitis, erysipelas, wound infections, major

1 cutaneous abscesses. Generally these are caused by
2 Staph aureus and Strep pyogenes.

3 And in the recent approvals that we've had,
4 we've deferred PK and safety studies down to age zero.
5 We do think that it's possible for certainly a
6 significant segment of the pediatric age group to
7 extrapolate efficacy, and again we can have some
8 additional discussion about what to do with the
9 neonates.

10 For hospital-acquired bacterial --
11 (Technical difficulties.)

12 DR. SMITH: Okay, again, these are the
13 definitions, and we're looking at acute pulmonary
14 infections associated with some clinical signs and
15 symptoms and either hospital-acquired or ventilator-
16 associated, which probably is a little bit more
17 relevant to the neonatal population. The predominant
18 pathogens here are Enterobacteriaceae, Pseudomonas,
19 methicillin-resistant Staph. And although we haven't
20 had any recent approvals for this, this is something
21 that we think, again, potentially extrapolation can be
22 considered.

1 A couple of areas with more Gram-negative
2 infections include complicated urinary tract
3 infections. Again, you've got pyuria and a pathogen
4 from the urine accompanied by local and systemic signs
5 and symptoms.

6 The thing that's relevant to neonates is
7 that it would include pyelonephritis regardless of
8 whether there are underlying abnormalities in the
9 urinary tract. Again, this is an infection that for
10 the recent approvals, the PK and safety studies have
11 been deferred down to age zero.

12 The new drugs that are coming out all have
13 to have pediatric study plans that have been reviewed
14 by us and approved, and these plans need to address
15 all relevant pediatric age groups, and we've had a lot
16 more emphasis on trying to see our way to getting
17 information all the way down to the neonatal age group
18 with these plans.

19 Complicated intra-abdominal infections.
20 This is a little bit of a trickier area. When you
21 look at the way we've defined it in our guidance, it's
22 an infection that extends beyond the viscus into the

1 peritoneal space, and usually associated with abscess
2 formation or peritonitis. And when you look at the
3 clinical conditions that are associated with that, I
4 mean, generally, this requires a surgical procedure.
5 Predominant pathogens again are Enterobacteriaceae,
6 anaerobes, there are some Gram-negative organisms, and
7 these are often mixed infections.

8 As John pointed out with the meropenem
9 example, we do think that extrapolation is possible
10 for this infection, and again with the recent
11 approvals, PK and safety studies have been deferred
12 down to the neonatal age group.

13 Now, I do want to point out that surgical
14 necrotizing enterocolitis we think falls into this
15 category because you've got a perforation, you've got
16 surgical involvement, the organisms tend to be pretty
17 similar. Medical necrotizing enterocolitis is kind of
18 a different animal and really requires further
19 discussion and probably a separate workshop of its
20 own. There is really not an adult correlate to this
21 that we could consider for extrapolation.

22 Now, each of these infections, we do think

1 that extrapolation is probably the best approach to go
2 with to the extent that it's reasonable to do so. One
3 problem here is that each of these infectious
4 syndromes carries a risk of CNS infection in the
5 neonate. And I think Danny will be addressing some of
6 this, but the risk may vary somewhat depending on what
7 the inciting infection is.

8 When you look at neonatal sepsis and
9 meningitis, we don't really have a way to extrapolate
10 for that. The adult programs tend to be organ-
11 specific programs. There has not been recent
12 antibacterial development in the areas of sepsis or
13 meningitis, and this is an area where adequate and
14 well-controlled trials would be needed.

15 Invasive candidiasis we'll be hearing a
16 little bit more about shortly from Laura Kovanda. I
17 just want to point out by way of background with
18 micafungin, it was originally approved in 2005,
19 approved in 2008 for the treatment of candidemia and
20 acute disseminated candidiasis.

21 Studies were deferred initially for this,
22 and then in 2013, we were able to approve dosing for

1 pediatric patients up to 4 months of age -- or 4
2 months of age and older I mean.

3 This is another area where neonatal
4 candidiasis is just different, and there's a lot
5 greater likelihood of central nervous system
6 involvement and another area where you can't
7 extrapolate efficacy. We'll be hearing from her about
8 the program that Astellas had and the difficulties
9 that they had trying to get the information that we
10 wanted.

11 Regarding central nervous system, one of the
12 issues is, how do we assess the drug penetration into
13 the CSF, and how much information do we need about
14 this? This is obviously influenced by the state of
15 the blood-brain barrier, the presence of inflammation,
16 physical characteristics of the drug, PK
17 characteristics, which are affected by gestational and
18 postnatal age and renal maturation and hepatic
19 maturation.

20 And there are also, as you will hear about,
21 a lot of difficulties in obtaining samples in terms of
22 the simple availability of the samples and then the

1 timing of samples.

2 Lily Mulugeta, from FDA, will be speaking
3 and addressing some of these issues, and I think Brian
4 and Danny can weigh in about some of the issues with
5 trying to obtain samples in kids.

6 But the issues here again are, what
7 information do we need and how do we get it? And,
8 again, among the discussion points that you'll be
9 hearing about with the other speakers is, to what
10 extent will we be able to use information from animal
11 models or in vitro models, opportunistic sampling,
12 master protocols, pediatric networks to try to
13 supplement the limited information that we're likely
14 to be able to get from patients?

15 Thank you.

16 (Applause.)

17 CNS Dissemination in Neonatal Infections

18 DR. BENJAMIN: I'm Danny Benjamin. I'm
19 Professor of Pediatrics at Duke University.

20 As far as conflict of interest that I may
21 need to disclose, number one is far and away my
22 largest conflict is that I'm the Chair of the

1 Pediatric Trials Network.

2 Now, classically, people don't count
3 government funding as a conflict, but personally for
4 me, it's a large part of our research program, and so
5 I'm very, very, very, very, very invested in labeling,
6 since that's my one metric for success.

7 And the second conflict is if you're a major
8 pharmaceutical company and you have an anti-infective
9 therapeutic, you've probably come to Duke University
10 and talked to us about it, and knowing what I know
11 about Duke University, I'm confident that Duke, at the
12 very least, charged you for being there.

13 And what I'm going to -- Laura is nodding
14 her head yes.

15 So when you think about obtaining
16 cerebrospinal fluid in premature infants,
17 neonatologists are often very hesitant to do so
18 because as you roll the baby up either sideways or
19 front ways in order to obtain the cerebrospinal fluid,
20 you can actually cause them to develop apnea and
21 bradycardia, and it's possible to kill an infant from
22 doing the procedure because they'll brady down, and

1 the neonatologists, it's a feared complication in
2 doing the procedure.

3 So it's extremely variable by site whether
4 or not a lumbar puncture is obtained. In fact, the
5 strongest predictor of whether or not a lumbar
6 puncture is obtained when a sepsis workup is done and
7 a blood culture is obtained, the number one predictor
8 of whether cerebrospinal fluid is obtained is the last
9 name of the neonatologist. It varies tenfold between
10 sites, and then even within sites, it varies
11 considerably between neonatologists at the site.

12 So if you're a baby who's at Stanford right
13 now and you have a blood culture, you have a very,
14 very, very, very different probability of having
15 cerebrospinal fluid accessed from you than if you're a
16 baby at the University of San Francisco today.

17 And neonatologists often use the blood
18 culture to predict whether or not they need the lumbar
19 puncture. That is, they'll get the blood culture and
20 then get the lumbar puncture if it's positive.

21 And so first done by Wiswell and the United
22 State Army, he and colleagues showed that about one-

1 third of the time neonatologists, when they're getting
2 the lumbar puncture, will actually have a positive
3 lumbar puncture, and one-third of the time the blood
4 culture will be negative. So they would get a blood
5 culture and a cerebrospinal fluid culture, and about
6 one-third of the time the blood culture was negative
7 when the cerebrospinal fluid was positive. It's
8 frightening, so frightening that most people
9 disregarded it.

10 So Barb Stoll and colleagues, of the
11 Neonatal Research Network, repeated this study in a
12 cohort study published in 2006 in Pediatrics, and
13 again they found that about one-third of the time in
14 premature infants had negative culture or positive
15 CSF.

16 By this time, people were starting to think,
17 well, maybe this is not too much of a surprise because
18 babies don't localize infection well, but maybe it's
19 different for term infants.

20 So we then looked at that in term infants,
21 and it turns out about one-third of the time -- you
22 should be seeing a theme here -- about one-third of

1 the time they had positive CSF but negative blood
2 cultures, and there was actually some discordance
3 between the blood and the CSF sometimes when you got
4 both.

5 We looked at CSF parameters in an effort to
6 see if they would predict. Neonatologists would often
7 use CSF parameters. And there is in reference texts,
8 if you have greater than 25 white cells, that's
9 thought to be meningitis in a neonate rather than more
10 classic numbers for adults. That's based on some
11 single-site data and some magical thinking.

12 And it turns out the sensitivity there and
13 specificity is really not great; it runs in the
14 seventies or so. I looked at various combinations and
15 permutations of this; you really can't find it.

16 In preterm infants, it's really a mess.
17 This is just the white blood cell count. We looked at
18 all sorts of different things. And again there are
19 some babies that have a white cell count of zero and
20 will have positive organisms in their cerebrospinal
21 fluid. And then a week or so later you'll think, oh,
22 well, that's just a contaminant except you document 3

1 days later that it has cleared, and it hasn't cleared
2 yet, so it's not a contaminant.

3 So it's really imperfect. But what you can
4 do is that you can at least say with the combination
5 of blood culture, baseline incidents, you can at least
6 say that the baby with the combination of CSF
7 parameters and blood culture, the baby has a
8 probability of meningitis of much less than 1 percent
9 if everything falls into place for you, if you have an
10 unreliable culture. You can at least get down to less
11 than 1 percent probability.

12 We also looked at traumatic taps because
13 this has gone from one house officer to another and
14 sort of a lore of it depends on where you train,
15 whether it's 500 to 1, 1,000 to 1, observed to
16 predicted, the sign of the Zodiac multiplied by your
17 birthday, whatever it was you were going to correct
18 for white cells based on the number of red cells. It
19 turns out you shouldn't do that. It really does not
20 increase your test performance at all.

21 So given I've got an organism in the baby's
22 blood, now what's my probability of meningitis? Now,

1 we actually revised this slide -- and by "we," I
2 really don't mean me, I mean one of the assistant
3 professors -- revised this slide late last night for
4 us.

5 So ignore *Stenotrophomonas* because there are
6 only nine of those infants, and ignore *Acinetobacter*
7 for a moment. You'll see that about -- once you grow
8 something in the blood, the probability of growing it
9 in the CSF is about 10 -- oh, Gerri, don't do that,
10 these aren't peer-reviewed, taking pictures of that.
11 I'll give you the slide, but these aren't peer-
12 reviewed -- is about 10 to 15 percent. Okay?

13 Now, the lore that was in place, or the
14 myth, when I was training, was that *Staph aureus*
15 actually didn't cause meningitis in babies, or if it
16 did, it only did when there was a shunt in place, and
17 it turns out that's not true, it just occurs about 5
18 percent of the time when you have it in the blood.

19 So most common pathogens are typical late-
20 onset sepsis pathogens. Meningitis occurs in about 1
21 percent of infants who get a lumbar puncture. And in
22 order to diagnose it, you need the culture. No set of

1 clinical parameters or the presence of bacteremia is
2 really perfect.

3 You can get an estimate that the probability
4 of bacterial meningitis is less than 1 percent if you
5 use the combination of incidents, negative blood
6 culture, and several days later a helpful lumbar
7 puncture.

8 But infants don't localize infection well,
9 and so at the very least, we should be getting some
10 estimate of central nervous system penetration because
11 the last thing that we want is to give an infant that
12 clears it in the blood and makes the infant's signs of
13 infection go away -- these were classic cases with the
14 aminoglycosides -- would make it go away in the blood
15 but ultimately develop debilitating ventriculitis
16 because you didn't have reliable penetration into the
17 central nervous system.

18 So when we did the meropenem study, this was
19 how to get some cerebrospinal fluid samples. So I'm
20 going to change gears here a little bit. This is a
21 multi-center, multi-dose study. Your tax dollars paid
22 for it. Thank you for paying your taxes. NICHD

1 awarded it to us. Thank you, NICHD.

2 The infants, 20 mg/kg to 30 mg/kg every 8 to
3 12 hours. 200 babies. And Anne Zajicek really
4 deserves a lot of credit for this study because she
5 was the bridge between our group and the Food and Drug
6 Administration and really nursed this project along
7 for a couple of years. This is a really good example
8 of the FDA partnering with NIH, partnering with some
9 investigators. And Anne really was the bridge there.

10 So CSF will be collected from infants when
11 CSF is obtained as part of clinical care. And the FDA
12 allowed us to do that, and the NICHD allowed us to do
13 that, it was new at the time, to get that into an arm
14 of the study. We had 200 babies enrolled at 20
15 centers, enrollment took 16 months. And we had six
16 infants who gave nine CSF samples. So this should
17 give you some idea of the kind of lift if you're
18 actually going to get clinical samples from patients.

19 We're right now going with the Antibiotic
20 Safety in Infants with Complicated Intra-Abdominal
21 Infections, the so-called SCAMP study. Brian really
22 led, with Mickey, the meropenem study. Mickey is

1 leading the SCAMP study with Brian. This is open-
2 label, partially randomized, multi-center Phase 2/3
3 study, and it's got two -- it's got multiple arms.
4 It's got about five different arms because we're
5 studying multiple therapeutics at the same time in
6 almost a master protocol type format -- right? --
7 because these are all off-patents, so there is no
8 competition between companies, for example.

9 So the arms are amp, gent, metronidazole;
10 amp, gent, clinda; pip-tazo and gent; metronidazole in
11 babies, in late babies; and then older gestational age
12 infants for some dosing. And you can get
13 cerebrospinal fluid per routine medical care if it's
14 obtained, can occur on any day during the treatment
15 period, and from any source that you can get it, and
16 try to get blood within an hour of CSF collection, and
17 a maximum of five samples per infant.

18 The trial is still unrolling as of September
19 2016. The number of sites that are activated are 46.
20 We started enrollment almost 2-1/2 years ago now, and
21 at the moment, we've got 23 CSF samples. We don't
22 know yet, obviously, which arm and which -- well, we

1 know which arm, but which therapeutic number of
2 infants, number of samples per infant, how many
3 infants we've got, because these are interim data that
4 we've pulled down from our partnership with NICHD.

5 But suffice it to say you're going to be
6 enrolling 10 to 25 infants in a study in order to get
7 one sample, and that's if you nest your CSF study
8 within your open-label drug study.

9 So with that, I'll close. Thanks.

10 (Applause.)

11 DR. FARLEY: So we're going to take about a
12 5- to 10-minute break. Is that right? We've got to
13 flip out this computer.

14 (Break.)

15 Pharmacokinetic and Pharmacodynamic
16 Considerations in Neonates

17 DR. MULUGETA: So I'll talk about PK-PD
18 considerations in infants and neonates. And we only
19 have 15 to 20 minutes to discuss this topic, but this
20 can take a day to cover the entire range of
21 information on this topic.

22 So this is my disclaimer, that the opinions

1 that are presented in my slides today do not reflect
2 the opinions of the FDA.

3 And just to briefly go over the outline of
4 my talk, I'll talk very briefly about dose selection
5 in neonates and infants. And my talk will primarily
6 focus on impact of development on PK, so talking about
7 growth and maturation, a little bit on
8 pharmacogenetics, treatment modalities, and organ
9 function, and, lastly, the impact of development on
10 PD.

11 So from a dose selection standpoint,
12 especially for anti-infectives, the basis is that
13 there is a target effect that we're trying to achieve,
14 and we need a good understanding of the concentration
15 response relationship to be able to predict a target
16 concentration.

17 And once we have identified a target
18 systemic concentration, then really the goal is to
19 derive a dose that will achieve that concentration.
20 And in this population, understand the sources of
21 inter- and intra-patient variability both in PK and PD
22 will be important.

1 So from a PK variability standpoint, the
2 sources of PK variability differ in neonates and
3 infants as compared to older infants and children. So
4 in neonates and younger infants, age and size, so
5 maturation and growth, are the two major determinants
6 of variability.

7 Organ function also contributes to
8 variability, so talking about pathological processes,
9 such as sepsis, as well as treatment modalities, such
10 as ECMO, that are commonly used or that are specific
11 to this population.

12 Pharmacogenetics can contribute to PK
13 variability, but to a less extent than in older
14 children and in adults, and we'll talk about that as
15 well.

16 In older children, as opposed to neonates
17 and infants, size is the major determinant of
18 variability, and organ function and pharmacogenetics
19 contribute to a larger extent than in the younger
20 population.

21 So from a growth standpoint, we know that
22 there is an order of magnitude difference in body

1 weight when we go from neonates to adolescents or
2 adults, and even within the neonatal population, there
3 is at least one order of magnitude difference.

4 And we also know that the relationship
5 between body size and metabolic processes, such as GFR
6 and drug metabolism, is not linear. And this figure
7 demonstrates that concept. So on the X axis is
8 postnatal age, and on the Y axis is the morphine dose
9 in mcg/kg/h that achieves a target concentration, and
10 here it's 10 mcg/ml.

11 And as you can see, the morphine dose is
12 highest in patients 1 to 3 years of age and decreases
13 over the next several age groups, reaching adult rates
14 in adolescents. And this also demonstrates that
15 infants and neonates, so young infants and neonates,
16 required lower doses, demonstrating the impact of
17 maturation.

18 So talking about maturation -- and this
19 audience is very familiar with this, I'm sure -- age
20 is used as a surrogate for maturation. So gestational
21 age captures maturation before birth; postnatal age
22 captures maturation after birth; and postmenstrual age

1 is really the combination of the two, so maturation
2 before and after birth.

3 And PK parameters in neonates and young
4 infants need to be described both as a function of age
5 and body weight, for the reasons that I described
6 previously.

7 So this figure shows postmenstrual age in
8 terms of weeks on the X axis and percent adult
9 clearance for many drugs on the Y axis. And you can
10 see that the clearance of many drugs that are listed
11 here -- dexmedetomidine, acetaminophen, and morphine
12 -- change or can be described as a function of
13 postmenstrual age.

14 So talking about the different components of
15 ADME, and starting with impact of developmental
16 changes on absorption, drugs can have a slower rate of
17 absorption in neonates and infants because of the
18 prolonged gastric emptying time. Drugs can also have
19 lower drug absorption. Some lipophilic drugs can have
20 lower drug absorption because of the immature biliary
21 function as well as the immature activity of
22 pancreatic enzymes.

1 We can also have drugs with altered
2 bioavailability, so altered stability due to the
3 higher gastric pH for drugs that are more acid labile,
4 altered degree of ionization due to the higher gastric
5 pH as well for weak acids, as well as increased
6 bioavailability for some drugs that undergo extensive
7 intestinal metabolism.

8 Percutaneous absorption can also be altered
9 in this population as a result of the higher hydration
10 of the epidermis, the greater perfusion of the
11 subcutaneous layer, as well as the ratio or the
12 increased body surface area to body mass ratio.

13 So we know that volume of distribution
14 determines loading dose and half-life. This is a
15 basic concept in clinical pharmacology. And volume of
16 distribution is really determined by three factors:
17 tissue binding, plasma protein binding, as well as the
18 physicochemical properties of drugs.

19 So there are age-related changes that can
20 have drastic impact on PK in relation to body
21 composition. We know that total body water is
22 extremely high, around 80 percent in newborns, and

1 goes down to approximately 60 percent by 1 year of
2 age. In a similar fashion, body fat is very low in
3 preterm infants, so 1 to 2 percent, and increases to
4 10 to 15 percent in term neonates, and it's around 20
5 to 25 percent by 1 year of age. And depending on the
6 physicochemical properties of the drugs, this can have
7 a tremendous impact on PK.

8 So the biggest impact is really seen on
9 hydrophilic drugs, where the higher volume of
10 distribution results in decreased plasma
11 concentration, and we have seen this with gentamicin,
12 for example. The impact is less dramatic on
13 lipophilic drugs, but it can result in a decreased
14 volume of distribution, and as a result, it can result
15 in higher plasma concentration.

16 So another aspect that contributes to
17 changes in volume of distribution is plasma protein
18 binding, and this is an important consideration in the
19 neonatal population because it's really difficult to
20 extrapolate exposure response data based on total drug
21 concentration from data in adults or older infants,
22 especially for drugs that have high protein binding,

1 and the reason is because we do see lower protein
2 binding in neonates and infants for several reasons.

3 One is the lower circulating levels of
4 plasma proteins, both albumin and alpha-1-acid
5 glycoprotein, which are low in neonates. The other
6 one is the altered binding affinities of these
7 proteins. And, lastly, the higher concentration of
8 endogenous competing substances, which I have listed
9 here.

10 So this altered protein binding can result
11 in increased drug distribution from the plasma to
12 tissues, and we have seen this with phenobarbital, and
13 higher concentration of fraction unbound in the
14 plasma, and this is depicted for micafungin, which I
15 believe we'll be talking about today, where you see a
16 higher concentration of free drug in neonates as
17 compared to adults.

18 We can also see altered safety of drug
19 profiles because drugs can compete and displace
20 bilirubin from binding to albumin, and this can result
21 in an increased risk of having higher levels of
22 unconjugated bilirubin and risk of kernicterus in

1 neonates, and we have seen this with ceftriaxone.

2 And I think an important aspect in terms of
3 drug distribution for this particular topic is
4 distribution to the CNS. In terms of general concept
5 around what properties determine drug distribution to
6 the CNS, it really depends on the intracranial
7 compartment of interest, the molecular size,
8 electrical charge, lipophilicity, plasma protein
9 binding, affinity to active transport, as well as host
10 factors, so meningeal inflammation and CSF flow.

11 But it's really difficult to extrapolate
12 findings in adults in terms of CSF-to-serum
13 concentration ratios to younger infants and neonates,
14 and I'll talk briefly as to why.

15 So we have very limited data on ontogeny,
16 and the available data is really coming from non-
17 clinical studies. But even with the limited data, we
18 know that the blood-brain barrier has less myelination
19 and it's immature in neonates, so there is increased
20 permeability for some drugs, and we've seen this with
21 phenobarbital and amphotericin B.

22 There is also limited P-gp expression in the

1 brain at birth, so these are drug transporters that
2 efflux drugs from the CNS compartments. So P-gp
3 expression in the CNS increases postnatally but does
4 not reach adult levels till about 3 to 6 months of
5 age. So this decreases drug efflux back to the
6 systemic circulation, prolonging half-life within the
7 CNS.

8 And there are pathologic conditions that can
9 alter blood-brain permeability, including sepsis and
10 hypoxia, that are relevant to the population that
11 we're discussing today.

12 And I'll move to the second aspect of drug
13 disposition metabolism. And for the purposes of my
14 talk, I'll focus on liver metabolism, although
15 metabolism can occur in other sites of the body as
16 well.

17 So when we talk about liver metabolism,
18 we're predominantly talking about Phase 1, which is
19 mediated by CYP enzymes, so cytochrome P450 enzymes,
20 and Phase 2 enzymes, which are predominantly
21 glucuronidation, sulfation, and acetylation.

22 So for Phase 1 enzymes, there is delayed

1 maturation of CYP enzymes, and this can drastically
2 contribute to variability in drug clearance under 2
3 years of age, but definitely within the neonatal
4 population. And for each isoenzyme, there is a unique
5 pattern of maturation, and that relationship to age is
6 not necessarily linear. And really for most
7 isoenzymes, the adult levels are reached by 1 to 2
8 years of age.

9 Another aspect that's important to consider
10 in neonates is CYP isoenzymes that occur or that exist
11 just predominantly in the postnatal phase, and this is
12 CYP3A7. It's detectable as early as 50 to 60 days
13 gestational age and declines rapidly after birth, and
14 it's pretty much undetectable by 1 year of age. It's
15 pretty much localized to the hepatic tissues. And in
16 terms of its metabolic capacity, it's much lower than
17 CYP3A4 or CYP3A5.

18 So Phase 2 metabolism, in terms of
19 maturation, we have a lot less data as compared to
20 Phase 1, but even the limited data suggests that
21 sulfation is more pronounced in neonates, while
22 glucuronidation we know is very deficient in neonates,

1 and this can alter the relative contribution of each
2 enzyme, resulting in different concentrations of
3 metabolites, and if the metabolites are the active
4 drugs, then this can impact efficacy or it can impact
5 safety.

6 Similar to Phase 1 enzymes, the relationship
7 between clearance for drugs that undergo Phase 2
8 metabolism and age is nonlinear. And again similar to
9 Phase 1 enzymes, these enzymes are pretty much mature
10 by 1 to 2 years of age.

11 Transporters we have very limited data for
12 in terms of ontogeny. We have some data on P-gp, on
13 the ontogeny of P-gp in humans, and that shows that
14 it's very low at birth and increases during the first
15 few months of life and reaches adult values by 2 years
16 of age. The clinical significance of some of these
17 developmental changes as it relates to transporter
18 function is really unknown at this point.

19 I thought it would be important to touch
20 upon genetic polymorphism. So in addition to size and
21 maturation in older children, polymorphism can impact
22 drug clearance, so can contribute to variability. But

1 the extrapolation of the adult data may not
2 necessarily apply to neonates and infants because of
3 what I showed you in terms of maturation of these
4 enzymes.

5 So if the enzyme is mature, then, yes,
6 polymorphism may contribute to variability in PK, but
7 it has less of an impact on clearance for isoenzymes
8 that are very immature in the neonatal population,
9 because those patients pretty much act as poor
10 metabolizers.

11 So going on to renal elimination, three
12 different components contribute to renal elimination:
13 GFR tubular secretion and tubular reabsorption, GFR
14 being the component that we focus on the most when we
15 talk about drug elimination.

16 So GFR maturation really varies based on
17 degree of prematurity as well as postnatal age, and
18 that's depicted in the two figures that I'm
19 presenting. And it reaches adult values around 1 year
20 of age. Tubular secretion is also immature at birth,
21 so 20 to 30 percent, and matures by 15 months of age.
22 Tubular reabsorption is also immature at birth, and

1 reaches adult values by 2 years of age.

2 So moving away from pharmacokinetics,
3 talking about pharmacodynamics, here we have a lot
4 less data. We have extensive data now on PK but very
5 limited data on how developmental changes alter
6 pharmacodynamic response. But there are some cases
7 where we have seen such effects.

8 So, for example, for GABAA receptors, we
9 know that we see excitatory effects in neonates and
10 young infants, while these receptors have inhibitory
11 effects in older children and adults, as well as, for
12 example, vitamin K-dependent factors, which are really
13 low at birth but increase in older infants and
14 children.

15 In general, for anti-infectives,
16 developmental changes are not expected to impact PD
17 when the disease is similar to older children and
18 adults, and when systemic exposures can serve as a
19 surrogate for efficacy. So there I don't think
20 developmental changes would impact efficacy, but may
21 impact safety, and we've seen this with
22 aminoglycosides and the risk of nephro and

1 ototoxicity.

2 Another aspect that we have to consider in
3 this population is treatment modalities that are
4 specific to the neonatal population. So
5 extracorporeal membrane oxygenation, or ECMO, although
6 it's used in older children as well, it's commonly
7 used in neonates, and that can result in altered
8 volume of distribution of drugs.

9 It can also result in higher clearance for
10 drugs that absorb to the ECMO circuit, and these are
11 typically lipophilic drugs.

12 Hypothermia is also used in this population,
13 and this has been shown to reduce clearance for some
14 drugs.

15 And, finally, we have to consider how
16 diseases and other conditions may alter drug
17 disposition in this population, for example, sepsis
18 and renal failure.

19 So as a summary, developmental changes do or
20 can have an impact on absorption, distribution,
21 metabolism, and elimination. Growth and maturation
22 are the most important determinants of variability in

1 PK in infants and neonates as opposed to older
2 children. We do have extensive information on
3 maturational changes in PK for initial PK prediction
4 or dose estimation in this population, again when
5 systemic exposure can serve as a surrogate for
6 efficacy.

7 But we do have a lot of gaps in terms of our
8 understanding of maturation, and I have listed a few
9 here, both the drug distribution to the CNS in early
10 life, the impact of maturation on pharmacodynamics and
11 receptor function.

12 And, lastly, a lot of the data that I
13 described today and the information is based on
14 information that was derived for small molecules, and
15 we have very limited data on drug disposition of
16 therapeutic proteins in this age group, so our ability
17 to predict PK and estimate dosing in this population
18 for therapeutic protein is very limited.

19 Thank you.

20 (Applause.)

21 DR. FARLEY: Thanks, Lily. That was a great
22 talk.

1 Let's see. So next we have Laura Kovanda,
2 from Astellas. Do you need help with that?

3 DR. KOVANDA: We'll see.

4 DR. FARLEY: Okay. And she is going to be
5 speaking on lessons learned from the neonatal
6 candidiasis program conducted by Astellas.

7 Adequate and Well-Controlled Trials in Neonates:
8 Lessons Learned from Neonatal Candidiasis Program

9 DR. KOVANDA: Good morning. My name is
10 Laura Kovanda, and I am a director in the Global
11 Development Organization of Astellas. I've been
12 working in the anti-infectives programs for over 18
13 years at Astellas, and the project lead for Mycamine
14 pediatric clinical trials.

15 Today I would like to present to you our
16 experiences in neonatal candidiasis.

17 In my presentation today, I will provide a
18 short background on Astellas and Mycamine, and then
19 cover our steps in designing and conducting a Phase 3
20 study in neonates, and then provide some lessons
21 learned.

22 In my 18-year tenure at Astellas, we have

1 developed and commercialized three systemic
2 antifungals that have been licensed globally in the
3 three major classes. They include Mycamine, AmBisome,
4 Cresemba. And Mycamine and AmBisome have been studied
5 extensively in pediatric studies and have approvals
6 for pediatric patients, 1 month of age and 4 months of
7 age respectively. Cresemba has only recently been
8 approved, and no pediatric studies have been conducted
9 to date.

10 Mycamine is a member of the echinocandin
11 class of antifungals. It was approved in the U.S. and
12 globally. In the U.S., the label is approved for
13 adult and pediatric patients greater than 4 months of
14 age for the treatment and prophylaxis of invasive
15 candidiasis. You can see the indications on the
16 slide.

17 Pediatric patients were included in the
18 Mycamine development program prior to the initial
19 approval in 2005. However, emerging data about
20 invasive candidiasis in neonates necessitated further
21 investigation in this population.

22 Before proceeding into a pediatric

1 development program, one key question needs to be
2 answered: Is there something unique about the disease
3 state or pathogenesis of the condition in the intended
4 population compared to adults? And if the answer is
5 yes, simply matching drug exposures to efficacious and
6 safe exposures in the adults may not be adequate.

7 Around the time that Astellas began
8 designing the Phase 3 study in neonates, there were
9 important evolutions in the field. Research emerged
10 that showed that the pathogenesis in invasive
11 candidiasis in neonates and young infants is different
12 and that CNS involvement was a prominent feature,
13 requiring a unique strategy for appropriate dose
14 finding and adequate tissue penetration.

15 In order to determine the adequate exposure
16 in CNS disease for Mycamine, Astellas collaborated
17 with the NIH to conduct an in vivo rabbit model of
18 hematogenous Candida meningoencephalitis, which mimics
19 the pathogenesis of neonatal candidiasis. The target
20 AUC to achieve efficacy in the CNS for Mycamine is
21 approximately 170 mg h/L, which is higher than the AUC
22 to treat adults with invasive candidiasis, which has a

1 mean of around 100 mg h/L.

2 Once a target exposure was established, the
3 next question is whether the drug disposition in
4 neonates is different. To address the issue, Astellas
5 conducted a Phase 1 study of single-dose and multiple-
6 dose Phase 1 studies in neonates. This was done to
7 determine the PK and tolerability in the neonatal
8 population.

9 Plasma concentration data from the Phase 1
10 studies were combined with older children
11 concentration data to construct a population PK model.
12 The graph shows that Mycamine's weight-normalized
13 clearance is higher in patients less than 4 months of
14 age, as shown in the red square.

15 We then bridged to the efficacious rabbit
16 exposure by performing Monte Carlo simulations to
17 demonstrate that a dose of 10 mg/kg adequately
18 achieves the target exposure. As seen in the graph,
19 within the blue square, the maroon bar represents and
20 shows that greater than 85 percent of the simulated
21 population would be at or above the target exposure
22 with less than 10 percent represented in the lavender

1 bar at risk of reaching the range where non-clinical
2 toxicities were seen, notably, liver enzyme elevations
3 in neonatal rats, which are monitorable in patients.

4 Based on these findings, Astellas determined
5 that further investigation may be necessary for the
6 following reasons. First, Mycamine has a unique drug
7 disposition in neonates and young infants compared to
8 older children and adults. Second, CNS disease is a
9 prominent feature and requires higher target exposures
10 for treatment. And, finally, since there was limited
11 data on the safety and efficacy of these exposures in
12 this population, the FDA requested a Phase 3 study and
13 noninferiority study.

14 The design of the Phase 3 study in neonates
15 and young infants required close collaboration with
16 the FDA. We proceeded with FDA Special Protocol
17 Assessments and several Type C meetings to gain
18 agreement on the protocol and the dosage regimen for
19 the Phase 3 study. We also closely collaborated with
20 a scientific committee represented by experts in the
21 field.

22 In addition, it was important to all

1 involved to create a study design that followed the
2 standard of care as closely as possible so that there
3 was minimal impact and risk to the infant while still
4 gathering an important and informative dataset for
5 analysis.

6 Here is an overview of the Phase 3 study
7 design. This was a randomized, multi-center, double-
8 blind, non-inferiority study comparing Mycamine to
9 conventional amphotericin B. The primary endpoint was
10 fungal-free survival at 1 week after the last dose of
11 study drug.

12 We intended to enroll 225 patients with
13 proven invasive candidiasis. Randomization was
14 stratified by estimated gestational age and region.
15 We utilized two independent monitoring committees, one
16 for safety and one to confirm diagnosis and adjudicate
17 outcomes.

18 Two elements of the design were particularly
19 challenging: the sample size as well as the
20 comparator agent.

21 The table here describes key study
22 assessments intended to document the diagnosis of the

1 enrolling fungal infection, the extent of any end-
2 organ dissemination, and follow response to therapy.
3 While the table may seem extensive, the tests are
4 typically part of the standard of care at most
5 hospitals in infants suspected or diagnosed with
6 candidiasis.

7 To reduce unnecessary blood sampling, we
8 utilized a method called D-optimal design to define
9 the most informative sampling times for plasma PK, as
10 circled in the graph. This allowed for flexibility in
11 plasma sample acquisition and minimized the number of
12 samples required, again trying to reduce the impact to
13 the infant.

14 Getting started, we reached out to pediatric
15 clinical trial networks globally experienced with the
16 disease state. Several examples are included in the
17 slide.

18 We also established a scientific committee
19 to advise on the study, and several members are here
20 today.

21 Even with our prior experience with
22 pediatric fungal studies, finding investigative sites

1 for the study was extremely challenging. We
2 approached 597 sites in 70 countries. From those, 93
3 were selected for pre-study visits, and only 71 sites
4 from 23 countries were initiated and opened for
5 enrollment.

6 The primary reason for not being selected or
7 participating in this study was general lack of
8 interest. The other reasons include insufficient
9 patient population or insufficient staff or staff
10 experience. Several countries and sites could not
11 participate due to the age of the patients or the
12 choice of a comparator, amphotericin B, conventional
13 amphotericin B.

14 Once the 93 were selected, the main reasons
15 for not moving forward was several sites were declined
16 from health authorities or extreme delays from health
17 authorities or insurmountable site administrative
18 hurdles.

19 This was a global study with 23 countries
20 included. Interestingly, notice the distribution of
21 these countries and the obvious lack of participation
22 of western Europe. The majority of these countries

1 declined due to the comparator agent alone,
2 conventional amphotericin B, where the standard of
3 care is liposomal formulation.

4 Once the sites were selected, the other
5 challenge we faced was longer-than-expected protocol
6 approval times within certain countries. As you can
7 see from the graph, the blue bar represents the actual
8 protocol approval time, and the red bar represents
9 reported average approval times within a given
10 country. The time ranged anywhere from 1 to 17-1/2
11 months, and the range for U.S. sites was similar.

12 Delays were due to multiple rounds of
13 intensive question-and-answer, unlike any study I've
14 ever been involved with before. We had to provide
15 almost full literature reviews on why conventional
16 amphotericin B was our comparator and justify the
17 micafungin dose.

18 In addition, face-to-face meetings were
19 conducted with several agencies, and, rightly so,
20 health authorities and ethics committees questioned
21 every test and every blood draw.

22 And in one country, it was particularly

1 unfortunate where we expected very high enrollment,
2 but the health authority declined. We then appealed,
3 and they still declined.

4 The average monthly screening was
5 approximately eight patients overall. Enrollment
6 never exceeded five patients in an individual month.
7 Only 30 patients of our 225 target patients were
8 enrolled. In total, 51 percent of sites screened
9 patients, and 22 percent of sites enrolled at least
10 one patient.

11 The graph here illustrates that even with
12 participating sites actively screening, few patients
13 were eligible for enrollment. Each line here
14 represents 1 of the 36 sites that screened at least
15 one patient. The red dots represent a screened
16 patient, and the blue, an enrolled patient. Fourteen
17 percent of the screened patients were enrolled.

18 In summary, over the 2-1/2-year enrollment
19 period, 216 patients were screened, 31 randomized, and
20 30 received study drug; that is, 0.1 patients screened
21 per site per month, and 0.01 patients per site
22 enrolled per month. This is compared to our

1 anticipated enrollment rate of .12 patients per site
2 per month when we initially planned the study.

3 The main reasons for failing screening
4 primarily included the inability to confirm the fungal
5 infection either because it was not there or because
6 the diagnostics were too insensitive, or the infant
7 was greater than 4 months of age, received too much
8 prior systemic antifungal therapy, or the parents
9 declined consent.

10 To better understand these challenges, we
11 collaborated with Duke University, who was able to
12 analyze a large database from U.S.-based neonatal
13 intensive care units. The data showed that over a
14 period from 1997 to 2010, the incidence of invasive
15 candidiasis was declining, most significantly in
16 infants less than 750 grams. In addition, the same
17 data showed a paradigm shift in treatment practices
18 with increased use of prophylactic agents, especially
19 in high-risk neonates. This use falls right around
20 the time of the publication of the fluconazole
21 prophylactic study in the New England Journal of
22 Medicine, and several other studies followed.

1 You can see from the picture how this aligns
2 with the timing of our Phase 3 study initiation.

3 So now let's see how we did conducting the
4 study. Despite efforts to align the protocol with the
5 standard of care, compliance with protocol procedures
6 was challenging. While all 30 patients enrolled with
7 a confirmed infection, primarily candidemia, as you
8 can see from the graph or from the table, baseline
9 assessments were complete or near complete for almost
10 every patient. However, follow-up exams during the
11 treatment period were not consistently performed,
12 resulting in incomplete outcome assessments.

13 Also notice that the number of lumbar
14 punctures for CSF analysis were performed in 83
15 percent of patients at baseline, but only 53 percent
16 of patients had CSF cultures performed, primarily due
17 to insufficient sample volume.

18 Finally, CSF cultures during treatment were
19 rarely done. Let's look at CSF cultures more
20 specifically.

21 As I said, at baseline, 57 percent of
22 patients had CSF cultures. Nine patients had only

1 baseline cultures, and seven patients had both
2 baseline and post-baseline cultures, but only three of
3 the patients with follow-up exams were still on
4 therapy at the time, and the other four had follow-up
5 cultures drawn well after study drug discontinuation.

6 Of all the cultures drawn during the study,
7 there were a total of 30. None were positive, all
8 were negative, consistent with the low yield of CSF
9 cultures in this population.

10 There were three cases of CNS involvement in
11 the study, but all three were diagnosed based on head
12 ultrasounds.

13 Finally, as for PK sampling, 57 percent of
14 patients had plasma PK samples drawn, and only two had
15 CSF PK samples drawn. Both were amphotericin B
16 treated patients.

17 Now for our lessons learned.

18 At the onset of the neonatal program, the
19 evolving epidemiology was not fully defined until
20 later in the development program. And finding
21 eligible patients for the study was difficult due to
22 the low incidence. This program reinforced that well-

1 established PK-PD models with data rich PK bridging
2 studies provide valuable information to establish dose
3 regimens.

4 Importantly, regulatory acceptance of study
5 designs globally was a huge hurdle.

6 And there were differences in standard of
7 care globally, creating obstacles not fully
8 anticipated previously.

9 The neonatal patient population is
10 vulnerable, and parental consent is difficult. The
11 eligibility criteria increased the challenges in
12 enrollment and sites' ability to participate despite
13 efforts to mimic the standard of care. This was
14 primarily due to the stringent diagnostic criteria.

15 And, finally, we learned that data
16 requirements and efficacy definitions in the study
17 require careful consideration and that expectations
18 need to balance practical and logistical issues with
19 the need for the level of proof for regulatory
20 assessment. One example of this is two negative
21 cultures to define eradication.

22 So what are our thoughts on the future

1 direction of study in neonates? We think that a
2 combination of well-established in vivo PK-PD models
3 with data rich PK bridging studies and an open-label
4 trial or registry, leveraging comparisons to
5 contemporaneous historical controls may be an
6 appropriate development path and with recent
7 precedence with this approach.

8 Thank you.

9 (Applause.)

10 DR. FARLEY: Thank you so much, Laura, for
11 your willingness to share that level of detail. I
12 think there is a lot to talk about and a lot that we
13 might learn moving forward.

14 I think if it's okay with the audience, we
15 sort of had a mini break. Would it be okay to keep
16 moving? Are folks okay with that?

17 (Attendees in agreement.)

18 DR. FARLEY: Okay. So Brian Smith I've been
19 seeing a lot of lately working on a variety of
20 projects. And he is Professor of Pediatrics on the
21 Steering Committee of the Pediatric Trials Network,
22 and at Duke, and he will be talking with us about

1 clinical trial networks in neonatal studies.

2 Thanks, Brian.

3 The Role of Clinical Trial Networks in
4 Neonatal Studies

5 DR. SMITH: Thanks, John.

6 So, again, I'm Brian Smith. I'm going to
7 talk a little bit about my experience that I've had
8 with two neonatal networks, both funded by NICHD, the
9 Peds Trials Network and the Neonatal Research Network.

10 I've been much more heavily involved in the
11 Peds Trials Network in my career, but Duke has been an
12 active site in the Neonatal Research Network since I
13 was a fellow. I've consented parents for inclusion of
14 their babies in those studies and written a number of
15 papers with those investigators.

16 So those are my disclosures.

17 I'll talk mostly about the barriers that I
18 see to getting trials done in infants and how this
19 relates to networks, and then I don't have a lot of
20 solutions, but we'll talk a little bit about that.

21 There are lots of roadblocks to getting
22 trials done in infants in the U.S. Again, I won't

1 spend much time on the ones that are in black on this
2 slide, but there are not many really sick premature
3 babies. You can't give healthy babies a study drug.
4 Parents don't like 12-page consent forms. The consent
5 forms have these horrible risks of the drugs and the
6 study procedures.

7 You have really sick populations that have
8 really highly variable outcomes that make
9 interpretation of safety and efficacy endpoints really
10 tough.

11 A lot of the studies require the infant to
12 be sick or to get sick, and that affects the timing of
13 consent. You've got 48 hours, 72 hours, 12 hours to
14 get a patient in the study.

15 Neonatologists don't like giving placebos,
16 so kids get randomized to the placebo arm, and the
17 neonatologists start giving drug on top of that, and
18 it makes interpretation of the results really
19 difficult.

20 Long-term follow-up is important to do in a
21 lot of the studies that we do in babies. That
22 increases cost and time to do the study.

1 The roadblocks that I'll spend the most time
2 on in this talk would be looking at variability in
3 site enrollment. So it's something that, as a
4 coordinating center, we deal with a lot. There are
5 sites that we know are good sites for getting patients
6 in the study and giving us good data, and it's just
7 tremendously variable, even at NICUs that are similar
8 sized.

9 Getting buy-in from clinicians, and so the
10 clinician concerns about a protocol. Again, most of
11 these, in fact, almost all of our protocols are
12 developed in discussion with FDA, with experts at FDA.
13 They're reviewed by NIH. And if they've multi-
14 centered, they're approved by somewhere between 4 and
15 50 IRBs before they ever see a patient. And then
16 we'll have site investigators or their partners that
17 are concerned about study procedures or doses of study
18 drug.

19 And then when we do select NICUs, they have
20 competing priorities. So some of the NICUs that are
21 some of the most able to carry out clinical research
22 have other clinical trials that they're doing.

1 This is an example of one of the trials that
2 we did a number of years on anti-infectives looking at
3 enrollment by sites. This was a 20-site trial, so
4 each one of these quintiles is 4 sites, and you can
5 see that 4 sites enrolled almost half the patients in
6 the study, and that the worst 4 sites enrolled about 4
7 patients, I don't know if that's 3 or 4 patients.

8 So if you don't have a good idea going into
9 the trial of which sites can enroll and you end up
10 with a bunch of sites that are in quintiles 4 and 5,
11 you would never finish enrolling in the study.

12 This is again a similar study, anti-
13 infective in premature infants, 30 sites, 360
14 patients, and there are 4 or 5 sites that enrolled
15 less than 5 patients, and then there are several sites
16 that enrolled more than 20. And if I was able to
17 overlay here sort of the average daily census at these
18 NICUs, it would, I suspect, be a flat line going
19 straight across.

20 So some of the site characteristics that
21 we've recognized I think through the years that affect
22 enrollment is having an involved site PI and study

1 coordinator. It's probably the most critical thing,
2 that they have buy-in, that they're enthusiastic about
3 the protocol, and that can be damaged by the
4 relationship of that group of people at the site with
5 either the coordinating center or the sponsor. So if
6 they don't have a good relationship there or if every
7 time they enroll a patient it's really painful with
8 that relationship, then they're not going to enroll a
9 second patient.

10 Time to activation. So there are certain
11 sites that we know take forever at getting IRBs and
12 contracts through. Duke is probably the worst site in
13 the U.S., I think, for that.

14 (Laughter.)

15 DR. SMITH: Again, competing studies comes
16 up. It's something to ask about when you're
17 approaching sites, whether or not they can do a study,
18 or do they have studies that are either going to take
19 time away from the time they can spend on your study,
20 or will they not allow co-enrollment in certain
21 populations?

22 24/7 coverage is critical. Babies don't get

1 sick and get eligible for studies at 9:00 a.m. on
2 Monday morning; it's always Saturday night or Friday
3 night. And so the NICUs that have enough study
4 coordinators to cover 24/7 are going to enroll better.

5 And then this thing is harder to measure, it
6 often takes getting on the phone with every site, but
7 to make sure that that site PI has buy-in from all the
8 other neonatologists in their group because that site
9 PI is likely only on service 2 or 3 months out of the
10 year. The rest of the time you've got to have other
11 people there that are willing to put kids in the study
12 if they qualify.

13 I just want to give you a couple of examples
14 of where we have had pushback from sites around their
15 sort of beliefs about a molecule. One of the studies
16 that we've in Peds Trials Network is with furosemide,
17 so not an anti-infective, but neonatologists use it as
18 an antibiotic.

19 So all the most commonly used drugs in
20 neonates are antibiotics, but furosemide makes the top
21 5. It's behind amp and gent, which is essentially
22 given to every baby on admission. Caffeine, which

1 should be universally used in babies less than 1,000
2 grams. And then vancomycin is number 4. Furosemide
3 is number 5. There is almost no data available that
4 it works or is safe or what the right dose is.

5 And so when we decided to do this in the
6 Peds Trials Network, there was lots of pushback of
7 neonatologists that said, "We don't use it at all,"
8 and from here, it's the fifth most commonly used drug
9 in the nursery.

10 And then when the sites got around to
11 saying, "Well, maybe we'll study it, but the doses
12 that you're recommending are too high," and so high
13 would be greater than 1 mg/kg/day, what we found when
14 we looked across a large number of NICUs is that sites
15 do use high doses. So almost everybody uses 1/kg/day,
16 but over half the sites are using 4/kg/day, 8 if it's
17 PO, and then if you go about a quarter of the sites
18 are using 8/kg/day. And then another third of the
19 sites are using Bumex, which is 40 times more potent
20 and has zero evidence in the nursery.

21 Another example of this -- Danny touched on
22 this trial a little bit earlier, so I won't sort of

1 belabor the design of it, but it's the SCAMP trial.
2 We did some PK studies with a number anti-infectives
3 over the last several years, and then in discussion
4 with FDA, this trial came about to get safety data for
5 these anti-infectives. The study again is designed as
6 a randomized trial.

7 The dosing -- I don't want you to look at
8 these very small numbers, but these came from those PK
9 trials. So these PK trials are really the best
10 evidence as to what the right dose should be in
11 premature babies. The evidence that are in the
12 handbooks are from older children or adults or is
13 based on just a handful of neonates.

14 So these are the doses that are in the
15 protocol. A kid gets enrolled in the trial, they're
16 supposed to be on these doses because we want to know
17 the safety of the drugs in the population at this
18 dose.

19 And some of the things that we've heard back
20 from investigators is, "You want us to use 20 mg Q8,
21 but we use 30 mg Q12, and we really like that and we
22 want to go with that, so we're not going to put a kid

1 in the study," or, "Your dose is 15 or 20 percent
2 higher than we are comfortable with, so we're not
3 going to put a child in the study."

4 Often we've heard from sites where a child
5 is maybe randomized to amp, gent, and Flagyl, that
6 they think the kid is too sick to get amp, gent, and
7 Flagyl, that they should get Zosyn and gent, or the
8 kid is not sick enough. And so we've had to have a
9 number of discussions with sites around sort of what
10 their thoughts are what the evidence is for those
11 choices of drug regimens.

12 As you can see from this graph -- and this
13 graph we actually use in the protocol -- shows you
14 what neonatologists at different sites are using for
15 babies with intra-abdominal infections. And just sort
16 of the take-home message is it's really colorful, and
17 they use whatever. And, again, this is just a dozen
18 or so sites. This is not 100 sites. And, again, this
19 is like the top 10 most common regimens. Again, we
20 could have included a number more in this figure.

21 The other thing that we've heard, not just
22 with the SCAMP study, but a lot of our PK studies, is

1 the babies just don't get blood draws, and so we're
2 not going to be able to get the PK samples that you
3 need in the study.

4 And this is just a rough figure, this is
5 actually Duke data, on how often babies that are less
6 than 1,000 grams get stuck per week for unique lab
7 draws. And you can see the mean in the first few
8 weeks of life is 30 times per week. And even when the
9 kids are older, 2 or 3 months old, they're getting
10 stuck once a day. And almost all of our protocols
11 have sampling schemes that are way less intense than
12 this, and we're asking for seven samples max, and we
13 would love just to have three, and often we can't get
14 those samples, even when babies get stuck that often.

15 Another thing that you have to worry about
16 when you have a network of sites is the variability in
17 outcomes at a site. These data come from the Neonatal
18 Research Network we published a few years ago, and
19 these are the big outcomes. This is death, this is
20 death or NEC, death or late-onset sepsis, death or
21 neurodevelopmental impairment.

22 And the data come from babies that are 25 to

1 27 weeks old. So all these babies are resuscitated,
2 so there is no selection of some sites not
3 resuscitating a 25-weeker, they're all resuscitated.

4 And you can see the outcomes are somewhere
5 between three- and tenfold different between the best
6 site and the worst site. So it's probably not
7 dependent on what dose of ampicillin they're using or
8 what dose of meropenem or whether they're using
9 micafungin or amphotericin, it's just whether or not
10 -- you know, which ZIP Code the baby was born in.

11 I want to talk briefly about the two
12 networks that I have experience with. The NICHD's
13 Neonatal Research Network is about 15 centers now. It
14 represents about 40 nurseries, so most of the centers
15 are two or three nurseries make up a center. So
16 Duke's site is actually three Level 3 NICUs.

17 Their primary focus is doing randomized
18 trials in premature infants. And they haven't really
19 done antimicrobial studies, so despite the fact that
20 those are by far and away the most commonly used
21 medications in the nursery, they haven't done any
22 randomized trials with antibiotics.

1 They have 14 active studies, none of which
2 are evaluating antibiotics. And then there is a large
3 number of studies, approximately 20, that they have in
4 the queue waiting for some of these other studies to
5 finish up.

6 And the reason this network is somewhat
7 difficult to work with in terms of getting a trial in
8 is co-enrollment has been an issue. So we have
9 certainly tried to use some of these 40 NICUs that are
10 part of the Neonatal Research Network, and co-
11 enrollment has been an issue, and their studies take
12 priority at those NICUs, and so we either get really
13 poor enrollment or we have to use another site.

14 So for the Peds Trials Network, it's funded
15 by NICHD. The overall metric really is improving
16 pediatric labeling and child health.

17 Just a quick overview, we sit here, so FDAMA
18 started the care for pharmaceutical companies with
19 incentive, PREA is sort of the stick that FDA can
20 require the studies to get done, and we sit in really
21 the off-patent medicines where there is no incentive
22 to do those studies. And neonates end up being a

1 really huge component of the Peds Trials Network
2 because almost all of the medicines that we use are
3 off-patent.

4 And some of the lessons that we've learned
5 as a network is to figure out what FDA and NIH want.
6 There is no reason to do a huge study if it's not
7 going to help FDA make a determination about whether a
8 drug should be labeled for children or infants. You
9 have to keep the protocol simple. Enrollment is hard
10 enough when it is simple. If you make it hard, people
11 will not enroll.

12 You have to make the inclusion criteria as
13 inclusive as possible, and the exclusion criteria as
14 minimal as possible, again keeping in mind patient
15 safety, but if those lists get too long, it's going to
16 impair enrollment dramatically.

17 You can't stick the babies a lot because the
18 neonatologists won't get the labs. And the good thing
19 is, is they stick the babies all the time, so you can
20 just use the labs that they're already getting.

21 And then you have to work with experienced
22 sites. You can't go to brand-new sites or people that

1 don't have a track record of putting kids in trials.

2 A few of the other things that we've done to
3 hopefully improve enrollment, we have used a federated
4 IRB model. We're probably going to have to do this
5 more and more. I'm not sure we had a great experience
6 with it, but we have experience with it. We have
7 master contracts for almost all of our trials, so that
8 improves the contracting time.

9 And then we've done lots of neonatal
10 studies. We have taken advantage of sort of master
11 protocols or protocols that look like master protocols
12 to improve the efficiency of the network so that we
13 can study a number of drugs under one protocol.

14 We have about a little over 30 projects that
15 we've started. The majority of those are clinical
16 trials. We have over 5,000 children enrolled. And we
17 hope by the middle of next year we'll have 20 products
18 with data at FDA.

19 I just want to show you that our research
20 group, mostly through the Peds Trials Network, has
21 tried to impact the drugs that are the most commonly
22 used in the nursery, so these are antimicrobials that

1 are sort of in the top 50, and we have studied a
2 number of them. Some of the ones at the top of the
3 list that we haven't studied are therapeutic drug
4 monitoring, so the PK is pretty well described.

5 So despite all the things that we've done in
6 the Peds Trials Network to improve enrollment, in the
7 SCAMP study, it's 50 sites, the goal is 350 patients.
8 We estimate the number of eligible patients per site
9 per month as at 1.2, but we've only enrolled .2, so
10 we're enrolling less than 20 percent of the eligible
11 patients. And, again, this is with sort of our top
12 pick of the sites mostly in the U.S., and we're still
13 getting this enrollment rate.

14 If we look at the furosemide study, our goal
15 is to get to 25 sites. We need 120 participants. The
16 inclusion/exclusion criteria are more broad, so there
17 are more eligible patients per site per month, and the
18 enrollment is still really low. We're getting 4
19 percent potentially of eligible patients at those
20 trials. So despite sort of all of our tricks, working
21 with our best sites, identifying the best sites, we
22 still struggle with enrollment.

1 Thanks .

2 (Applause.)

3 Clarifying Questions from Audience/Panelists

4 DR. FARLEY: Great. So we're going to take
5 an early lunch, so I'm going to actually go ahead and
6 move right into clarifying questions from the audience
7 and the panelists for the different speakers, maybe
8 bring up some issues, lessons learned, ideas for a way
9 forward.

10 And, John, I'm going to invite you to kind
11 of co-facilitate this with me and hand you this
12 microphone because I'm going to stand up because I
13 actually can't see the left side of the room.

14 DR. ALEXANDER: Okay.

15 DR. FARLEY: So I think if the panelists
16 want to bring something up, just turn your tent card
17 on its side or put your microphone on, like Gary did.
18 And if someone from the audience wants to participate,
19 this is a pretty informal setting, feel free to walk
20 up to one of the mikes.

21 So thanks a lot.

22 Gary, do you want to go ahead?

1 DR. NOEL: John, actually the question I
2 wanted to ask was about your presentation, and I don't
3 know whether I heard it correctly or not. When you
4 are talking about how the Division looks at PREA, and
5 you say studies may only be required for approved
6 indications, you made a statement about osteomyelitis
7 and skin and skin structure infections. Were you
8 saying that with the skin and skin structure infection
9 indication in adults, the Division may require a
10 sponsor to study that drug in osteomyelitis?

11 DR. FARLEY: So that was an example of BPCA.

12 DR. NOEL: Okay.

13 DR. FARLEY: Okay. So that was an example
14 of what a pediatric written request might be like.

15 DR. NOEL: So the rules are, as we go
16 forward, the PREA-required studies, including those
17 being done in neonates, will need to follow the adult
18 approval in terms of a requirement. If it's approved
19 in skin, it needs to be studied in skin in newborns.

20 DR. FARLEY: That's our interpretation. I
21 invite John to jump in from the pediatric team.

22 DR. ALEXANDER: Certainly. So the idea

1 behind PREA is it's a requirement, but it only
2 addresses the indications for which the drug is
3 approved in adults. So the requirement for studies
4 can only address the indications for which the drug is
5 approved in adults.

6 The benefit of the BPCA program being
7 voluntary is that we can address other indications,
8 and that's where it does become complicated for
9 neonatal infections, for infections in general, where
10 we can start to sort of broaden the types of things
11 that we would ask for. So the osteomyelitis is an
12 example of where a drug that's seen to be effective
13 for Staph and Strep for treatment of skin infections,
14 osteomyelitis may be one of those types of studies
15 that would be of benefit to children to sort of
16 evaluate.

17 DR. FARLEY: Other questions and thoughts?

18 DR. BRADLEY: There is another level of
19 complexity that I would like to just share with
20 everyone and to have everyone think about as we move
21 from this morning's topics to this afternoon's topics.
22 And neonates are obviously a very special population.

1 Everyone in this room is very committed to figuring
2 out how to best care for this population.

3 The many neonatal workshops start off with
4 why babies are so difficult, why they have such high
5 mortality and high morbidity, because they're immune-
6 compromised.

7 And as the sophistication of extrapolation
8 from adults and older children gets better and we
9 understand the metrics of pharmacodynamics, time above
10 MIC, or AUC to MIC, and we begin to say, aha, this is
11 the bar we need to achieve, neonates are, again,
12 different, they're not just little children, they're
13 immune-compromised, so they have cellular immune
14 deficiencies, humoral, polymorphonuclear leukocytes
15 don't work as well.

16 And a couple of years ago there was an
17 award-winning lecture that was given at IDSA in which
18 the bodies, polys in a pneumonia model, were shown to
19 be modeled like an antibiotic. And once you've got
20 the load of organisms down at a certain point, the
21 white cells actually could take over. So short course
22 therapy once you dropped the inoculum was huge.

1 And I don't know that we've got that with
2 neonates. I think the antibiotics are called on or
3 antifungals or antivirals are called on to do more in
4 this particular population.

5 So not only are they immune-compromised and
6 perhaps will need greater exposures, higher doses, a
7 higher time above MIC or a greater AUC to MIC, but we
8 need to look at all these other different tissue
9 sites, which was beautifully elaborated earlier today.

10 And, of course, if you have more exposure,
11 in order to get the same clinical outcome, you have
12 more safety considerations because some of the doses
13 that you may need, each dose or the duration of
14 treatment is longer than we've ever done in children
15 or adults. And I absolutely get that, and this is the
16 population that you least want to put at risk of
17 safety.

18 And then there is an intangible, which was
19 touched on, "Babies make me anxious." And when you're
20 at the bedside and you're talking to the parents, and
21 a very sick baby, and they'll always say, "Is my baby
22 going to make it?" you are doing absolutely your best

1 to make sure that that baby survives and survives
2 intact.

3 And as we try to model what exposures you
4 need and the target attainment, like 90 percent target
5 attainment is sort of standard for predicting in a
6 population what percent of the group needs to meet
7 that PD target, 90 percent seems good, but when you
8 get to babies, to tell a parent, well, we're going to
9 use 90 percent, but -- there is a neonatologist
10 shaking her head -- but maybe for the baby, at least
11 my concern is 95 percent, maybe 99 percent, but then
12 if you do that, it's a greater exposure, more safety
13 considerations, and we're absolutely caught in this
14 bind.

15 So PK in and of itself is incredibly
16 complex, as we've seen, but as we do NONMEM models,
17 you just add more covariates for the different tissue
18 compartments and the different age of maturation of
19 the enzyme systems.

20 But the concept of, "What PD target do we
21 need in a baby?" I think is one that we hardly scratch
22 the surface, and should we shoot for 90 percent or

1 should we shoot for higher? And these aren't topics
2 that are usually discussed on the ground level, but in
3 the back of my mind, that's what makes me anxious when
4 I'm trying to care for a baby.

5 So I would love everyone's input, and I know
6 the FDA is responsible for safety and efficacy of
7 drugs used in babies, and we all are working together
8 to try and help them come up with something that's
9 reasonable.

10 Thanks.

11 DR. FARLEY: So do folks want to make John
12 less anxious?

13 DR. BRADLEY: Please.

14 (Laughter.)

15 DR. BRADLEY: Hi, Mark.

16 DR. TURNER: Hi, John. I'll do my best.

17 DR. BRADLEY: Thank you.

18 DR. TURNER: I think one factor is that
19 babies may have a smaller inoculum because they are
20 more sensitive to it, so that may be helpful.

21 DR. BRADLEY: Great.

22 DR. TURNER: Another is that although they

1 miss some of these protections or neutrophils, they
2 still mount a pretty aggressive inflammatory response,
3 and sometimes it's that inflammatory response which is
4 causing the trouble. The bug can go away. In many
5 other infections, the bug goes away, then the
6 inflammatory response is causing the damage.
7 Meningococcal sepsis might be one example. And I
8 suspect it's the same in babies as well.

9 So giving babies E. coli damages their
10 brain, but giving them LPS damages the brain as well.
11 And sometimes it's that kind of storm that may be
12 making things worse. They may have an unbalanced
13 immune response rather than a completely deficient
14 one.

15 So I think our job is to get the inoculum
16 down as quickly as possibly by keeping them clean, by
17 having our hands washed, and by giving antibiotics so
18 babies have a chance of mopping things up. Because in
19 a good proportion of babies, the inflammatory response
20 does settle down very quickly.

21 William and our group have looked at the CRP
22 response in animals and in humans, and if you get the

1 dose right, then a CRP response will half every day in
2 a predictable sort of way. And if you don't get the
3 dose right, then the CRP response doesn't come down
4 and babies will have other stimuli to inflammatory
5 response.

6 So I think there is room for optimism.
7 Getting the dose right is one thing we can control.
8 And many babies will benefit from that push-up.

9 DR. BRADLEY: Thank you. And the dose to do
10 that is a little higher than one would have expected,
11 so --

12 DR. TURNER: Yeah.

13 DR. FARLEY: Gary?

14 DR. NOEL: The appropriate comment, Mark,
15 and I understand that position, but as I'm hearing you
16 talk about it, absolutely there is evidence that
17 newborns don't mount the inflammatory response that
18 adults and older children might. But I think the
19 other side of that is that often by not being able to
20 mount that response, we don't detect that infection
21 and the disease until it's at a different stage in its
22 progression.

1 So that adds yet another complexity and some
2 pessimism in my thinking, that intervening at that
3 point is not the same intervention in the disease
4 process that we intervene in when we're talking about
5 older children and adults.

6 DR. TURNER: Yeah. I guess that means we
7 need better biomarkers, so in our unit, we start
8 antibiotics half the time because the baby has a high
9 CRP response, and half the time because of symptoms.
10 And so the CRP is often our backstop because the
11 symptoms don't show up.

12 On the other hand, if you deploy something
13 like the HeRO system, where you're looking at heart
14 rate variability, then you can pick up some babies
15 sooner than they would manifest otherwise. So there
16 is a range of options.

17 Also better diagnostics, if we can ever get
18 them to work, would be helpful, too.

19 So I guess that's a call for co-development
20 of diagnostics and biomarkers as well as
21 antimicrobials. But I think the problem still
22 remains, is a valuable place for the right dose at the

1 right time whenever you pick them up.

2 DR. FARLEY: Susie?

3 DR. MCCUNE: Yeah. I just wanted to add to
4 what Mark was talking about in terms of some of those
5 changes from an inflammatory perspective adds to some
6 of the confusion of our being able to look at long-
7 term safety or look at -- identify safety issues that
8 may be associated with the drugs that we're giving
9 because you've got safety issues associated with the
10 infection itself, you've got safety issues associated
11 with inflammation, especially in a preterm brain, and
12 what that means from a neurodevelopmental perspective,
13 and then you're adding whatever drug that you are
14 looking at on top of a number of other potential drugs
15 and other comorbidities in this population.

16 So I think teasing out some of the safety
17 issues that we're going to have to talk about are
18 really going to be pretty complex, but it's something
19 that needs to kind of be talked about.

20 So sorry to be not quite so positive, Mark,
21 but --

22 DR. TURNER: Maybe I can try and address

1 that. In clinical practice, neonatology is all about
2 accepting uncertainty, and a lot of the time if you're
3 surfing a wave of ambiguity, and sometimes we get
4 better and better at what we do, and sometimes we get
5 worse in what we do.

6 I mean, this is a radical thought, but is
7 there space in the regulatory domain for a slightly
8 different approach to neonates compared to other
9 populations where we're never going to get to the
10 bottom of the safety? There are so many factors
11 contributing to poor long-term outcomes.

12 We were talking about this in another
13 setting. We see it as the home setting as much as
14 anything else. I'm looking at 1-year, 2-year, 5-year
15 outcomes. It's going to be confounded by so many
16 other things, and giving definitive answers in the way
17 that you can for skin infections or other things is
18 going to be more difficult.

19 And is there space for tolerance of some
20 types of uncertainty in the regulatory domain? That
21 may be too radical.

22 DR. FARLEY: Did you want to comment?

1 DR. NAMBIAR: Sure. I mean, I think we're
2 more than willing to accept uncertainty, and I think
3 that's a given when you are looking at neonates given
4 that you are going to have such a small number of
5 babies that you can study. So I think that is a
6 given, that there is going to be a fair degree of
7 uncertainty.

8 But in terms of safety, I think it's -- you
9 know, long-term safety outcomes in the kinds of
10 studies we do to validate antibacterial drugs would be
11 rather challenging because most of these drugs are
12 fairly short-term. But unless, of course, there is a
13 particular safety concern that one has in mind and one
14 then requires long-term or maybe it will have to be
15 done in the context of a registry or some other
16 mechanism other than the study that you do to really
17 evaluate the efficacy and safety of the drug.

18 DR. FARLEY: Yeah. I can sort of relate
19 some of our experiences in working with unmet need in
20 the adult arena.

21 I think with respect to safety, even if you
22 do not need a randomized trial for efficacy, it's very

1 helpful to have some comparison group for safety
2 because otherwise you do have a lot of those
3 questions. And you'll still have those questions
4 because of the sheer number.

5 You're not likely to get to the 300 in the
6 subgroup that you're really interested in where you
7 have sort of some degree of being able to detect a 1
8 percent event. But I think we found that to be very
9 helpful.

10 I think, you know, you had brought up --
11 other folks had brought up external controls -- I
12 think actually Laura had mentioned that -- for
13 efficacy, and I think that's sort of another set of
14 issues with how comparable the external control group
15 is in terms of risk and comorbidities and those sorts
16 of things, and this is kind of a highly variable group
17 of infants to begin with in terms of birth weight and
18 other factors.

19 But I do think a comparator group in a study
20 actually helps you a lot with safety because things
21 can look very disturbing, and it usually is
22 reassuring.

1 DR. NAMBIAR: Yeah, I think certainly in a
2 sicker patient population, not having a comparative
3 group, it's very hard to make any sense of the data.
4 I mean, the data is limited to start with, but then
5 you might have an adverse event or two, which really
6 is a manifestation or reflection of the underlying
7 illness of the patient population, nothing to do with
8 the drug. But you have nothing to compare it with,
9 then it's hard to say that the drug is absolutely not
10 responsible.

11 So, again, as John said, even the adult
12 studies that are now underway which are targeting
13 patients with unmet need, the sample sizes are really
14 small, but we do encourage sponsors, should they
15 embark on such trials, even if it's an imbalanced
16 randomization, have some comparative data so at the
17 end of the day, you can make some assessment.
18 Otherwise, should one or two patients have a bad
19 outcome, it's very difficult to interpret that study.

20 DR. FARLEY: Oh, did you want to say
21 something?

22 DR. NAMBIAR: That's all the questions for

1 Dr. Bradley's comment.

2 DR. FARLEY: Sure. And then we'll get to
3 Danny.

4 DR. NAMBIAR: Okay. No.

5 DR. FARLEY: No, go ahead. No, go ahead.

6 DR. BENJAMIN: Because then maybe I can get
7 to double-dip and talk about --

8 DR. FARLEY: You go first.

9 DR. NAMBIAR: Mine is more --

10 DR. FARLEY: You're the division head. You
11 get to go first.

12 (Laughter.)

13 DR. NAMBIAR: I am just from the Division
14 here, nothing else. Mine is more a clarifying
15 question because I do want to make sure I understood
16 you correctly.

17 So I think what you are proposing is that
18 potentially neonates, these sick babies, the PD
19 parameters that we look at might be different.

20 PARTICIPANT: Yes.

21 DR. NAMBIAR: And so I was just going to
22 seek input from our PK experts here, how might we

1 evaluate that? Because the number 90, 95, 93 percent
2 probability of target attainment, a lot of that is --
3 I mean, it's not set in stone. I mean, that's our
4 best guess, and while the PD parameters are derived
5 from animal models of infection.

6 So how do we do that for neonates? How do
7 we factor in that the neonates are different? Do we
8 consider different animal models of infection? Or
9 will our other in vitro models, like the hollow fiber,
10 where you can make changes -- I just wanted your input
11 because I don't have the answer, but I thought if
12 that's what we need to do, then a discussion of how we
13 might get there and what is the expectation would be
14 helpful.

15 DR. FARLEY: Do you want to answer that?

16 DR. HOPE: Sure. I'm going to talk after
17 lunch on that. So I think that while I have an
18 opinion that trying to recapitulate disease is really
19 important, and neonates, therefore, are different from
20 adults (inaudible) models, adult skin and soft tissue
21 infection don't apply.

22 I also have a view that probably more than

1 one lab animal model or more than one model system is
2 required because they teach you different things about
3 that they provide different perspectives then on the
4 truth.

5 John's problem and anxiety is a complete
6 failure of current paradigms of drug development,
7 really I think, and Mark mentioned that CRP, as a
8 biomarker where individual babies are allowed to tell
9 you with better and better biomarkers how much drug
10 they actually need themselves.

11 So the problem is that we spend a lot of
12 time and get very obsessed and anxious about
13 quantifying PK variability and then take all of that
14 for a single PD measurement where we assume that --
15 you know, that's a population, if you like, derived
16 value, and then we put it in simulators because then
17 we have to have 90 or 95 percent, and then we just
18 take ourselves out of the game because you can't solve
19 the problem because in simulators, you just trade up
20 and down efficacy and toxicity and safety.

21 So it's a failure of a one-size-fits-all
22 approach to life as we know it, and until we solve

1 that problem, I don't think we can make John less
2 anxious.

3 DR. FARLEY: John, did you have any comments
4 you wanted to make? And then we'll do Danny and Gary.

5 DR. BRADLEY: Yeah, no, I think William hit
6 the nail on the head, and he will be addressing this
7 more later on today. But neonates are different and
8 their responses are different, and we all know that,
9 everyone in this room knows that. And yet we all
10 treat them, they need to be treated, they're sick, and
11 we just need to be able to study. It will take longer
12 to study them because they are more difficult, and we
13 need to just acknowledge that.

14 And on the model that you talked about with
15 multidrug-resistant antibiotics, fewer patients
16 studied and released earlier, perhaps we can build on
17 that and have some data available for all these NICUs
18 that are already using the drugs and have some sort of
19 postmarketing collection of data that's more
20 stringent. And I know that puts a burden on industry
21 and academics, but if you have only 300 babies that
22 you study mostly for safety, the efficacy signal may

1 not be apparent until you have 3,000. And I know the
2 comparator population would be nice to have, but some
3 way to move forward.

4 Thank you.

5 DR. FARLEY: Danny.

6 DR. BENJAMIN: So just a couple items just
7 to make sure we're all on the same page as far as
8 therapeutic use. Really 99 percent of the
9 therapeutics that were given, 99.5 in already practice
10 are for given empirically, the infant never has a
11 documented infection, let alone a documented infection
12 that you think you might be treating when you're
13 dumping a bunch of antibiotics into them.

14 So to me, dose event safety remains in this
15 -- in relevant tissues really is the big get, if we
16 can get those two things right. And then the central
17 nervous system specifically because it's another --
18 just the highway is fraught with failures there, bad
19 outcomes.

20 And just two things to consider that relates
21 to safety. One is in the exclusivity program, when we
22 last looked at this, 30, 40 percent of the time there

1 was a surprise, if you will, when you did the study.
2 It was either big dosing change, safety problem, or
3 efficacy problem, and a lot of the efficacy problems
4 were around, "Hey, do we really understand the
5 endpoints?" For example, migraine. Sometimes the
6 efficacy, though, was related to dosing; for example,
7 the antihypertensives.

8 When you look across peds in drug
9 development, if you've gotten exposure correct, the
10 number of safety problems when you go down is really
11 pretty uncommon. And even within that pretty uncommon
12 group, most of the safety problems are either going to
13 be not relevant in the nursery, like sibling
14 aggression. Okay?

15 (Laughter.)

16 DR. BENJAMIN: I know it starts early, but
17 it ain't starting at 3 days of age. You know?
18 Sibling aggression, maybe some suicide ideation with
19 some of the -- again, I mean, you know, a serious
20 problem for adolescents, maybe not something
21 measurable in a 5-day-old.

22 And so, yes, so when I think about how the

1 Division has been approaching this over the last 10
2 years, I think the numbers and the expectations that
3 you guys have had has -- I think you're doing a pretty
4 good job there, that you're taking a pretty reasonable
5 approach there of we've got risk and benefits, we've
6 got to balance these competing interests, we need some
7 safety data, it's got to pass the red face test, but
8 it's going to be imperfect.

9 And then, finally -- I've said this before
10 in other settings -- but I love the slide that Laura
11 -- I guess it was Don Beulah (ph) initially came up
12 with, but that Laura put up there about here are the
13 probabilities using this particular dosage of getting
14 above these levels, because it's really a tradeoff.

15 DR. FARLEY: Yeah, and I think it's trying
16 -- Sumathi has done a huge and great job as the
17 Division leader, particularly in advocating for
18 pediatric development, and I think it's thinking
19 smart, it's kind of the "quality by design" principle.
20 In other words, do you really need to monitor the site
21 with 100 percent source stock verification? And does
22 that really make sense in the modern world? And I

1 think the Division has tried to think about that in
2 terms of safety as well. So it's a smartening of the
3 standards, not a lowering of the standards.

4 So, Gary?

5 DR. NOEL: Yeah, I wanted to bring up
6 something completely different. But I also wanted to
7 point out that my experience in coming to these
8 workshops is that they often raise more questions than
9 provide answers to, so that's our goal.

10 So in the interest of raising a question,
11 Laura mentioned it in her presentation, Brian touched
12 on it a little bit, about the assumed enrollment rate
13 versus the actual enrollment rate.

14 And I think one of the challenges as we get
15 more experience in this space is that at some point --
16 and maybe we're already there -- people who are
17 viewing these protocols are going to be looking at the
18 sample sizes and characterize them as magical thinking
19 rather than reality.

20 And the issue there isn't simply one of
21 saying, "Are we just wasting our time doing that?" I
22 think it's a real issue in terms of the ethics of

1 designing a trial.

2 DR. FARLEY: Right.

3 DR. NOEL: We should not be engaged in
4 enrolling a trial of newborn infants if we can't be
5 real certain that we're going to complete it as
6 designed.

7 And so I think we need to spend time as we
8 move forward trying to look at tools where we can
9 really hone these feasibility studies and know
10 beforehand, before we start enrolling kids in trial,
11 increased confidence that we really can complete the
12 studies.

13 DR. FARLEY: Good point. I think it's
14 interesting that sort of in the internal dialogue
15 within the FDA, feasibility comes up frequently, and
16 often less experienced companies, that's kind of one
17 of the things where we're kind of hammering home. And
18 we've learned a lot over the last decade.

19 DR. NOEL: And just to add, I think one of
20 the potential solutions to this is to sort of task our
21 newly forming networks to recognize that as a high
22 priority, to be data-driven in assessing feasibility

1 and enrollment rates.

2 DR. TURNER: So just to comment on behalf of
3 European networks, I guess the question here and in
4 EMA is, how much rigor would the agencies accept in
5 feasibility assessments? We've heard from the hard
6 learned experience of one company, we've heard from
7 the hard learned experience on PTA.

8 Is that enough for you to accept companies
9 who make suggestions about feasibility based upon that
10 level of experience, or is there some deep rigor
11 broader experience?

12 I mean, I think what we've heard so far is
13 it's about as good as it's going to get. And is that
14 enough now to accept that, yes, 1 in 10, 1 in 20, 1 in
15 30 babies will contribute to a CSF sample? Or the
16 recruitment is that difficult?

17 Because what I hear from companies in Europe
18 is that they get pushback when they present that kind
19 of data, that, well, sure, you can try harder, or,
20 sure, you can find more sites. And I don't know how
21 common that kind of response is in the U.S., but is
22 there going to come a time when the agencies do

1 recognize that even with resources, even with
2 experience, the investigators and networks, and these
3 problems are often insurmountable, and the actual
4 number of patients who can be recruited is in the
5 order of thirties and fifties rather than two to three
6 hundreds?

7 DR. FARLEY: Yeah.

8 DR. NAMBIAR: So I think the answer is it
9 really depends. There are some people who will come
10 and tell us we've tried, and when you ask for
11 evidence, "What have you done to show that such a
12 trial is not feasible?" The data they provide is
13 very, very limited.

14 So certainly we do look for some evidence.
15 We need some information that you have really gone out
16 and tried to either enroll or you've reached out to
17 sites, you've reached out to IRBs, but the example
18 that Laura went over, I think it would be hard to say
19 that they have not put in a good-faith effort. So I
20 certainly wouldn't look at that and say they didn't
21 try.

22 DR. TURNER: Yeah, we often have a dialogue

1 in Europe about how to enrich that statement. It
2 depends because that doesn't help us move forward
3 verified. It depends on what.

4 DR. NAMBIAR: Yes.

5 DR. TURNER: And is the next company that
6 comes along with an antifungal going to be able to
7 comment on Laura's experience, or do they have to go
8 through the same process again?

9 DR. NAMBIAR: So I think in a program like
10 this, it's very important that there are important
11 lessons learned. We certainly don't want to make the
12 same mistakes. And I think there are a lot of lessons
13 we learn from trials as they are completed.

14 So I think there is a lot we have learned
15 and they have learned, as a company, and we have
16 learned, as regulators, that we certainly would not
17 want to make the same mistake again.

18 And part of the reason we are having this
19 discussion is because it is so challenging to do these
20 studies, and I think to send another company off to go
21 do a 300- or 225-patient neonatal candidiasis study, I
22 think we shouldn't be doing if we are not in the right

1 mind. So I think that's the reason for this
2 discussion.

3 But, again, you know, we see the spectrum.
4 We do see people who come and tell us this drug is not
5 feasible, and they have done nothing. I mean, they
6 have done nothing. They haven't even gone out to a
7 site. They've tried nothing. So it's very hard for
8 us to tell them, "Yeah, you've put in your best
9 faith," best -- what's the word? But anyway, that,
10 "You're putting the right effort, so we'll either
11 defer your studies," or, "We'll waive the studies,"
12 that just cannot happen.

13 So I think if you've really gone and you've
14 tried, and there are practical limitations, I think
15 common sense dictates that we reassess the situation
16 and then decide what's the best path forward.

17 DR. TURNER: A point to press, that
18 investigators and companies would value some kind of
19 points to consider document in doing that, because at
20 the moment, it all depends, and that doesn't help
21 people plan their strategies. So again, we're going
22 to have these conversations in Europe next month and

1 afterwards about what -- how far can we take this?
2 Because I appreciate that it all depends on the
3 circumstances you face with each drug and each
4 condition, but at the same time, somehow programmatic
5 thinking would help people structure their efforts so
6 that they make the most use of your time and advice.

7 DR. NAMBIAR: I think a very valid point,
8 it's just hard to put it all on paper and say if
9 you've done X, Y, and Z, you're okay. But I think
10 it's a valid point.

11 DR. FARLEY: I think -- I had sort of two
12 thoughts about sort of ways forward, and some of this
13 is already happening.

14 So I think network data about what's going
15 on in the real world is very important as both the
16 agency and the companies talk about kind of what's
17 feasible.

18 I mean, I have a habit of kicking over
19 hornets' nests, so I'm sure I'm doing this here, but
20 not using AmBisome as a comparator when everybody was
21 using AmBisome in clinical practice, it's sort of
22 something that we could have easily learned from

1 accessing networks.

2 And the one thing about pediatrics is that
3 we really are better at collaborating than the adults.
4 I mean, I think we should give ourselves credit for
5 that.

6 (Laughter.)

7 DR. FARLEY: But I think using some of that
8 data, you know, that's available, and the Europeans
9 are ahead of us on networking, but I think that we can
10 do some of that in the United States.

11 The other thing is some of the regulatory
12 science considerations are, what can you do
13 recognizing that you are going to have fewer CSF
14 samples? Could you use animal and in vitro work to
15 sort of guide your dosing better, et cetera?

16 I'm not smart enough to be able to make a
17 really intelligent comment about this, that's why we
18 invited you guys, but clearly we need to recognize
19 that we're not going to have much CSF data, and how
20 can we maximize it?

21 So those are sort of two thoughts as to ways
22 forward. And I think I saw Susie's tent card up

1 first.

2 DR. MCCUNE: So I'm going to go, sorry, back
3 to Danny's comment because I really agree. You know,
4 I think we're doing better from a safety perspective,
5 and I would really like to put a plug in for Lily's
6 talk because I think that's really the underpinnings
7 of where we're going to be able to have more
8 confidence, at least using some of these drugs,
9 understanding some of the metabolic pathways.

10 We still have a large amount of work to do
11 to understand the ontogeny of all of those pathways,
12 but I think if we think back to chloramphenicol and
13 the gray baby syndrome and the things, the problems,
14 we had associated with that, and some of the
15 kernicterus that we saw, I think that we could now do
16 a better job of predicting where we might have more
17 problems in the neonatal population with some of the
18 medications.

19 So I think we're doing a better job. I
20 think that's really thanks to a lot of the work that
21 Lily presented for us. We still have a long way to
22 go, but I think we're making some headway there, so at

1 least we can utilize, as John was talking about, all
2 of those modalities to try to understand how to move
3 forward.

4 DR. FARLEY: Chris, I think I saw your card
5 go up first.

6 DR. RUBINO: Thanks. So back to the issue
7 of your comparator -- okay? -- and making that
8 decision. So you had that nice graph that showed how
9 the paradigm was shifting over time and when your
10 study started enrollment. But my question would be,
11 when did you guys start like first draft that protocol
12 relative to that 2011 timeframe?

13 DR. FARLEY: Christmas eve?

14 DR. KOVANDA: 2003 I think?

15 DR. FARLEY: Christmas Eve 2002.

16 DR. RUBINO: So that's actually the point I
17 wanted to make, is the timeframe on these things is
18 huge. And Laura can speak to this, but once those
19 protocols get written, my experience in consulting
20 with a lot of different companies is this is a yacht
21 that is not easy to change course with once those
22 things start.

1 DR. FARLEY: Yeah.

2 DR. RUBINO: And I'm kind of just throwing
3 this out there, and I don't have the answer to it, but
4 it's something we have to address in some way, shape,
5 or form.

6 A lot of times we were doing some of the
7 things that was done for micafungin where we're giving
8 people advice about which dose to use using modeling
9 and simulation. And if we get some new data, and I
10 say, "Well, we want to change that slightly," it's a
11 huge uproar at the clients because all those different
12 steps that you mentioned about going to the different
13 health authorities has to happen.

14 And that huge timeframe we have I often
15 struggle with when people ask me to help them write
16 PIPs or pediatric study plans that are 6 years in the
17 future. I'm like, "I don't know what's going to
18 happen 6 years from now. I can give you advice on
19 what if you can start your study tomorrow." And that
20 flexibility I think needs to be built into the system
21 somehow.

22 DR. FARLEY: Yeah.

1 Laura, did you want to say anything?

2 DR. KOVANDA: Well, I was just going to add
3 just that I think if you look at that same graph, you
4 know, when we started talking about the study in 2003,
5 2004, and 2005 with the FDA, there was still quite a
6 lot of invasive candidiasis out there, and the uptake
7 of prophylaxis really happened during our designing
8 and getting to that study start. So I think that's
9 where -- you know, just understanding the epidemiology
10 and continuing -- someone continuing to monitor it
11 like the Duke group has I think really makes a
12 difference, but being aware of it.

13 DR. FARLEY: Danny?

14 DR. BENJAMIN: Yeah, a couple items. One,
15 Gary's question about ethics. So Gary asked about
16 some of these trials, was the scientific advisory
17 board aligned with the decision? And in point of
18 fact, the scientific advisory board had been watching
19 the rate of invasive candidiasis go down every year,
20 and they kept saying, oh -- you know, and as we got
21 it, we started enrollment, we had a lot of discussions
22 about that, and ultimately that vote was unanimous to

1 go ahead and advise the company to stop the study.

2 That's number one.

3 Because we had real-time monitoring of epi,
4 that's unique to our group that other groups don't
5 have and are not so fortunate in neonatal
6 therapeutics.

7 The other thing, John, not to be too
8 corrective, but you may not have been involved
9 intimately with the protocol at this time, but at the
10 agency's request, we actually rank-ordered for
11 everybody involved the various amphotericin products
12 and their use and did a safety analysis before
13 finalizing on amphotericin B deoxycholate, and it
14 turns out that not only was it more commonly used in
15 the U.S. than the lipid formulations, but there are
16 some concerns about how it penetrates, the lipid
17 formulations, how it penetrates the kidneys, if there
18 was real rationale for that, and we were seeing a
19 safety signal for that in the U.S. And I think
20 Laura's point is that reasonable people can disagree
21 about whether or not you use deoxycholate or lipid
22 complex.

1 And I think Brian's point -- and I just want
2 to loop all these together -- is that as investigators
3 and the agency and as sponsors, we can say reasonable
4 people can disagree, and we can give the data for
5 that, and we can make a rational, ethical decision,
6 but if we're going to do a global trial with over 50
7 or 100 sites, which is the nature of peds drugs
8 development right now, reasonable people do disagree.

9 But they are so steadfast in their
10 disagreement and so certain that they are correct,
11 that there is no way that they would use lipid complex
12 amphotericin in Nebraska, that would be unethical, and
13 there is no way that in the country of Italy they
14 would use deoxycholate, because that would be
15 unethical, and I can't tell you the number of times I
16 heard that, and Laura must have heard it more than me.

17 And, you know, the same thing is true with
18 Lasix. We've got sites that will not participate
19 because babies might get enrolled to a low dose or to
20 no dose, and we've got sites that won't participate in
21 Lasix because babies might get enrolled to a low dose
22 or to a high dose. We've got a whole lot of ethical

1 certainty based on almost no data.

2 DR. RUBINO: The comment about pip-tazo
3 struck me the same way. You're coming to them with
4 the best amount of data about pip/tazo and what the
5 right dose is, and yet they are completely certain
6 that you're wrong, and we have this gut feeling, we've
7 always used this dose. It's very frustrating, I'm
8 sure.

9 PARTICIPANT: John's card is up.

10 DR. FARLEY: John, sorry. Sorry, John.

11 DR. ALEXANDER: Not a problem. But I was
12 going to comment, first of all, on the conversation
13 that went back and forth a little bit between Mark and
14 Sumathi. I think that part of hopefully what we're
15 doing here is sort of trying to define what we think
16 is the best path forward for trying to think of
17 studies that are feasible because we could all come
18 away with saying, well, none of these studies are
19 feasible, we can just stop right there. But that's
20 not really an answer. So the issue becomes one of,
21 what can be collected and what can we do?

22 But I do want to push back a little bit on

1 what Mark had said because it sounds like the idea is
2 that we're going to accept a screening and eligibility
3 process that only obtains .1 percent of the infants
4 that are screened coming in to enrollment or providing
5 valuable samples.

6 And I think that part of this program also
7 needs to look at, what can we do to improve that? And
8 that may not be what FDA can do, but that that is
9 something that we have to think about as a group as a
10 whole.

11 DR. FARLEY: So I'm just going to interrupt
12 for a second because we actually do have the EMA -- or
13 EME colleagues on the phone.

14 PARTICIPANT: The last time we checked.

15 DR. FARLEY: The last time we checked. So
16 we wanted to see if they had any comments that they
17 wanted to make. So I'm wondering, those of you who
18 are in Europe on the phone, if you can hear me, this
19 is John Farley, we're welcoming any comments you might
20 make, and I think we can actually hear you in the
21 room. We're about to find out. Anyone there? We're
22 not sure.

1 DR. FERNANDEZ CORTIZO: Yeah, yeah. I was
2 mute, sorry.

3 DR. FARLEY: Okay. Great.

4 DR. FERNANDEZ CORTIZO: Are you hearing me
5 now?

6 DR. FARLEY: Yes, we're hearing you very
7 well.

8 DR. FERNANDEZ CORTIZO: Okay. Because I was
9 mute. I'm sorry. This is Maria Fernandez Cortizo. I
10 am (off mike) member. I'm also infectious disease
11 (off mike). Thank you very much for allowing us to
12 participate in the meeting.

13 My comments, I mean, (off mike) somehow.
14 (Off mike) perhaps neonates are the age group where
15 their circulation is really (off mike) somehow, but on
16 the other hand, there are some PK and safety data.
17 And PK, perhaps (off mike) dose, not (off mike) dose.

18 We have in our minds (off mike) and our --
19 all our -- most of our investigations that we have
20 planned, people that are (off mike) late-onset sepsis
21 (off mike) because we somehow feel that this was the
22 model. We see the (off mike) that we don't know a lot

1 (off mike) antibiotics or the particular antibiotics
2 (off mike) penetrate the CNS.

3 And I would like to ask (off mike), perhaps
4 I already did it. And it was (off mike) that in this
5 late-onset (off mike), it is possible to exclude
6 children with many (off mike). Because I think this
7 would be extremely difficult because of the several
8 findings that (off mike) showing that (off mike) are
9 really difficult.

10 So do you think that this would be possible?
11 We're still dealing with many (off mike) from late-
12 onset sepsis trials?

13 DR. FARLEY: Sumathi, do you want to --

14 DR. NAMBIAR: (Off mike) question.

15 DR. FARLEY: Yeah.

16 DR. NAMBIAR: Maria, this is Sumathi. I
17 think what you're asking is, is it okay to enroll
18 neonates in studies as long as one has excluded many
19 (off mike) especially babies with late-onset sepsis.
20 Is that the question?

21 DR. FERNANDEZ CORTIZO: Sumathi, I cannot
22 hear you. But perhaps if (off mike), overall, I think

1 that we should have the same consent, except that we
2 are finding -- we have no experience with the trials
3 in neonates (off mike). We haven't seen any, again,
4 (off mike). We know that they face, according to the
5 evidence, (off mike) issues (off mike) even for those
6 that (off mike) to PK.

7 So I would like now (off mike) to share with
8 FDA and with (off mike) how to deal with this and how
9 to arrive (off mike), how this is (off mike).

10 DR. NAMBIAR: So thank you, Maria. I think
11 we will bring that up for discussion during the panel
12 discussion this afternoon.

13 DR. FARLEY: Absolutely. Good points.

14 John, did you have a point you wanted to
15 make?

16 DR. BRADLEY: Yes. And it has to do with
17 clinical trial enrollment and all of the information
18 Mark has mentioned, and Brian and Danny. And I had
19 the anxiety factor of the neonatologists and
20 infectious disease doctors, so you can probably put
21 variance around anxiety. And when we take on a
22 protocol for neonates, I want to be almost certain

1 that it's going to work. I don't want to take on
2 risks that the drug won't work. And when the
3 micafungin protocols first came out and the fact that
4 the word was it didn't get into CSF, I basically
5 thought I can't take a risk of treating a baby who
6 will have disseminated Candida and have CNS infection
7 and I would be not treating them with a drug that
8 would work.

9 And I apologize for not citing, I probably
10 should have, but managing anxiety of neonatologists I
11 think is something that we need to recognize. And,
12 Mark, you were saying, "Is this as good as it's going
13 to get?"

14 I think, just like we have a consent that we
15 give to parents to say, "You're realizing that we're
16 using an experimental drug, and it may not work," and
17 we wouldn't give it to them if we didn't think it
18 would have a high probability of working, but they're
19 taking a risk that it won't work. Well, when you give
20 an investigator a protocol, the investigator has to
21 take on a risk that that won't work.

22 And the curve of anxiety among those that do

1 neonatal trials has shifted to the right. We're not
2 willing to take on as much risk of a failure, one baby
3 with Candida meningitis, that's my fault because I put
4 him on a study, is just too much to accept on a
5 personal.

6 I can step back and say from an academic
7 level, oh, we need these data, these are good for the
8 population, but for babies -- and it's not -- you
9 know, kids are valuable, too, but when you talk about
10 babies and the anxiety that surrounds the emotions of
11 the parents and the other family members and the
12 people who are taking care of the baby, it's a
13 different metric that we have to deal with. And,
14 Mark, I think if we realize that, somehow we can
15 package the trials.

16 The neonatologists that wouldn't do Q12
17 dosing of gentamicin because they're worried it won't
18 work, they're uncomfortable, yet we use Q8 and it
19 works for us, and it's the same anxiety, that if they
20 do something different, they'll fail.

21 And I think we all, as the drug
22 investigating community, can do a better job of

1 communicating risk with these people and allow them to
2 take on some risk and share that.

3 So that was my attempt to try to pull in
4 some of these observations.

5 DR. FARLEY: Okay. I think Lily and I'm
6 going to -- we'll take a few more comments, and then
7 we do need to move toward lunch.

8 DR. MULUGETA: I think another important
9 topic we probably need to discuss is timing of
10 initiation of pediatric studies. So the anti-
11 infectives data typically submitted -- adult data has
12 been submitted and reviewed before we initiate studies
13 in pediatrics. And there are multiple age strata
14 within the pediatric age groups, so studies are
15 initiated in adolescence, and then in 6 to 12, and
16 then it goes down.

17 So by the time we initiate studies in
18 neonates, it's several years after approval in adults.
19 And we have multiple studies. We have a single-dose
20 PK study followed by multiple-dose PK studies, and
21 some are efficacy-safety studies.

22 So maybe a good question for us would be,

1 how much data do we need in terms of safety and
2 efficacy in adults? And how much data do we need in
3 terms of PK and safety in older pediatric age groups
4 before we're comfortable with initiating studies in
5 this age group?

6 The average time for approval for products
7 in children after approval in adults is 9 years, and
8 for some antivirals and anti-infectives, it's 15
9 years. And we've learned from many investigators that
10 after a couple of years have elapsed after approval in
11 adults, the equipoise is really not there.

12 So I think initiation, even when we know the
13 study design that we want, the timing is going to be a
14 major factor.

15 DR. FARLEY: Good point. Other things folks
16 want to bring up?

17 DR. RUBINO: I just want to add to what Lily
18 was saying, that maybe the acceptance of risk in the
19 neonatal population is not going to be -- we're going
20 to want to see the older kids' data before we move on
21 to the neonates.

22 DR. FARLEY: Yeah.

1 DR. RUBINO: But at least in the programs
2 I've been working on, we're pushing that the oldest
3 age group of kids is not that different than adults.
4 So can we push these studies to, you know, once Phase
5 2 studies or something like that? That just kind of
6 moves the timeline forward. I could see it happening.

7 DR. FARLEY: Mm-hmm. John?

8 DR. ALEXANDER: So I just wanted to comment
9 on that because I think that is one of the advantages
10 that we have with the new pediatric legislation and
11 the idea of having pediatric study plans in place.

12 One of the things that we are pushing
13 towards is saying, okay, you are at the end of Phase 2
14 or soon afterwards you are starting your studies in
15 adults, bringing us a pediatric study plan allows us
16 the chance to sort of comment on a couple of ideas.
17 Why aren't you including adolescents in a study that
18 you are ready to conduct in adults, especially for a
19 drug, let's say, that we know we cleared, so you're
20 not really worried that the pharmacokinetics of the
21 drug is going to be markedly different in that
22 population than it is in the adults that you're

1 studying? The whole idea of sort of considering and
2 getting those adolescent studies initiated sooner so
3 that you are not waiting for the approval in the
4 adults.

5 There is still the consideration, though, if
6 you have to have some evidence of the efficacy of the
7 drug before sort of moving into that population. So
8 hopefully you would have addressed that at least
9 through some Phase 2 or some preliminary events to
10 give you the idea that this probably is likely to
11 work. That's why you're going into Phase 3.

12 DR. FARLEY: Sure, John.

13 DR. BRADLEY: Unless you want to --

14 DR. FARLEY: Absolutely. Nope.

15 DR. BRADLEY: Okay.

16 DR. FARLEY: That's good.

17 DR. BRADLEY: Okay. Perfect. And even with
18 all that information, when you go into babies, they'll
19 be down. One of the things that Danny has been able
20 to accomplish beautifully with NIH and FDA is this
21 sort of rapid review of the data, and how are the data
22 being collected and again interpreted, and the ability

1 to shift directions as you're going?

2 And industry has not quite had that same --
3 even though they can't -- don't -- I see the look of
4 surprise. There is clear open door from the FDA for
5 industry, but the critical path which is now
6 sponsoring pediatric clinical trials, I know that
7 there is a neonatal one that they started out, one of
8 the networks, but in pediatrics, they're creating an
9 FDA industry academics group that would review
10 protocols as they're ongoing.

11 And for neonates, I think that's the key,
12 and it may be going on right now with critical path,
13 that I'm sure you know far more about that than I do.
14 But that rapid cycle of review of data where, "No one
15 is getting enrolled? How can we change this? Why are
16 they not enrolling?" I think for babies is critical.

17 DR. TURNER: Can I just comment on that?

18 DR. FARLEY: Sure.

19 DR. TURNER: So John is alluding to the
20 pediatric trials (off mike) which is now a nonprofit
21 entity (off mike) children. As I understand it, (off
22 mike) standing advisory groups in a range of (off

1 mike) areas, including neonates. And the idea is that
2 will provide (off mike), and that builds upon the
3 experience of having the U.K. where (off mike) groups
4 have been able to give real-time feedback to sponsors
5 of those sorts.

6 The International Neonatal Consortium, which
7 is (off mike) institute initiative, is more of an
8 advisory group, and that is looking at a range of
9 various (off mike). (Off mike) is not stuck, many of
10 our colleagues because we've actually had a lot of
11 (off mike) with --

12 DR. FARLEY: Yeah. We think it's glamorous,
13 too, but --

14 DR. TURNER: We did have a meeting and
15 discuss a lot of (off mike) and did consider neonatal
16 topics. But I think there was not quite enough
17 consensus as to where the low-lying fruit lies.

18 So I think one useful output of this meeting
19 would be a direction, a steer, for INC as to what
20 topic about neonatal infection to talk about at the
21 (off mike) between stakeholders in various parts of
22 the world from industry, regulators, and

1 investigators, and most importantly from parents, who
2 are a particular voice that is missing from this
3 conversation.

4 But if this group could give us the steer,
5 then that would help resolve some ambiguity (off
6 mike). There are so many things to discuss. But that
7 is the mechanism on a global scale for coming up with
8 elements of a common protocol, a standard protocol, or
9 even (off mike), but either (off mike) or (off mike)
10 INC is open to that, I think, but it does need some
11 parameters to what the most important topics would be.
12 I think Gerri might want to comment on that.

13 DR. FARLEY: Great. Gerri?

14 DR. BAER: This is not really a scientific
15 comment per se, but in really looking at some of the
16 presenters and the difficulties with enrollment and
17 also some of the comments about clinicians and not
18 being able to enroll for ethical reasons, I think one
19 of the things -- and again this is probably outside
20 the scope of this workshop -- but one of the things
21 that we really need to look at is how to build the
22 culture of uncertainty, that there really is

1 uncertainty.

2 So amongst clinicians, amongst nurses,
3 amongst pharmacists to really get out there and say,
4 "You know, we really don't know, and here's why. Here
5 are examples in neonatology where we thought we knew,
6 but we really don't know."

7 And then the flipside of that also is
8 helping advocates, helping parents, and then utilizing
9 parents to help other parents understand the
10 importance of the research, the different layers of
11 protection that exist for children, all the different
12 ways that you can contribute, which don't necessarily
13 mean being part of a randomized trial.

14 But really it pains me to see these huge
15 programs that people have put so much work and years
16 and years of effort, money, sweat, and the yield is so
17 small.

18 And I think there needs to be some sort of a
19 root cause analysis. Why can't we enroll babies?
20 It's not that there aren't babies. Now, in the case
21 of neonatal candidiasis, there aren't babies,
22 thankfully, but in other realms, there are babies,

1 it's just that we need to figure out how we get to
2 that level and capture that.

3 DR. FARLEY: Thanks. I'm just going to make
4 just one comment that we hadn't mentioned because
5 parents aren't in the room today, and they're a very
6 important constituency group and stakeholder.

7 The Clinical Trials Transformation
8 Initiative has a project going on to look at
9 challenges in pediatric drug development writ large,
10 so all age groups. And one of the most interesting
11 things I think for me to come out of that was
12 interviews with parents primarily in the NICU. So
13 that report will be out hopefully by December-ish of
14 this year, and I think there are some interesting data
15 from the parent interview piece of that to consider.

16 So at this point, I think I'm going to
17 invite us all to eat. And we're going to take a lunch
18 break, and I think we'll come back right at 1:00. And
19 there is a restaurant downstairs, but there are also
20 restaurants and plenty of eating establishments
21 walking south on Georgia Avenue. So thanks very much
22 for a great morning.

1 (Lunch.)

2 Session 2: Resources and Path Forward in
3 Neonatal Infections/Studies

4 Use of In Vivo and In Vitro Models in Guide Dose
5 Selection for Neonatal Infections

6 DR. HOPE: So thank you very much. The
7 microphone is on.

8 So I am going to try and tell a few stories,
9 tell you about some of the advances in the field of
10 pharmacodynamics and PK-PD bridging, and some of my
11 recent thinking about this area.

12 We've been interested in neonatal PK-PD
13 bridging studies for quite some years now in
14 collaboration with many of you in the room. I just
15 want to pick up some of the important points that I
16 heard in the morning. So, John, the talk is not
17 entirely for you, but in part. You can interrupt me,
18 that might not be customary, but if you want to do
19 that, then that's also fine.

20 Here are my disclosures. We do a lot of
21 drug development work.

22 So first of all, so I'm on the Microbe

1 Planning Committee, and it was sort of astounding to
2 me to learn a week ago that there are people in the
3 scientific community that do not know what PK-PD is.
4 We were explaining it to all the marine micro-
5 biologists and so forth, and at the end of the day, it
6 was PD-PK, but they thought that it was an interesting
7 thing. But I just thought that I would give you my
8 version of what PK-PD is, or pharmacodynamics or
9 exposure response relationships.

10 So first -- and we've heard about some of
11 this, this morning -- the dose of a drug is given, and
12 it equilibrates with somewhere in the body that you
13 think is important. And for neonates, we've heard
14 this morning that the brain may be an important site
15 of infection.

16 And then that drives some. It docks at that
17 site with its target, which is a microorganism in the
18 case of infectious diseases. And biomarkers can be
19 useful in determining or measuring that response. And
20 then that links out to something that ultimately is of
21 importance, so that's survival or clinical response.

22 And, of course, if I did this -- this is

1 what most of us do in our clinical practice, we just
2 link dose with some clinical outcome. And all
3 pharmacodynamics is for me is understanding,
4 quantifying, and therefore controlling those
5 relationships between dose and ultimate clinical
6 outcome.

7 And the reason that I think that we should
8 all be interested in pharmacodynamics is this curve,
9 where -- and this is what this workshop is largely
10 about, I think, is about accelerating and derisking
11 drug development. You want to go faster, you want to
12 go more safer, you want to cut drugs that are not
13 going to work because that costs money and it costs
14 lives as well.

15 And dynamics is a derisking process. And
16 given the problems that John was sort of elucidating
17 before, it's actually pretty much all we have as tools
18 to derisk, sitting on the derisking, and giving us the
19 evidence that we need that the drugs that we use are
20 real, they're not sham, they're not snake oil, and
21 furthermore, we understand how to use them optimally.

22 And so my old boss, Mike Whippy (ph), I hope

1 this isn't being recorded, but --

2 PARTICIPANT: Yes.

3 DR. HOPE: It is, yeah. He used to say,
4 well, this dynamics is all well and good, but it
5 doesn't explain why -- this was a little tongue-in-
6 cheek -- why I can give drugs to my patients and they
7 work.

8 And he's sort of right, because I go to work
9 every day and do the top part of this. I do normal
10 therapeutics. I give a dose of a drug and I expect an
11 outcome. And the clinical trials we do is drug A
12 versus drug B, but the point of dynamics that's
13 sitting underneath this is pharmacodynamics is the
14 bedrock of all therapeutics. So it's invisible, it's
15 there all the time, but you can operate as a physician
16 without knowing any pharmacodynamics.

17 Okay. And so now I'm just going to pick up
18 some points as we move forward now because there were
19 some questions about extrapolation. Well, John got
20 there before me in his comments. Right?

21 So scaling doesn't work really. It's not
22 the PK that gets in the way of scaling, it's the PD

1 that gets in the way of scaling. And Lily started
2 bringing up some of these points.

3 And this is an important thing. So the
4 conditions that govern exposure response relationships
5 in neonates need to be carefully considered. And if
6 you're going to make predictions from model systems,
7 you better be sure that you're setting up the right
8 model conditions. That means that you get an answer
9 that is helpful to you. You always get an answer,
10 it's whether it's helpful. And so you ignore this at
11 your peril.

12 So, now, in collaboration with many in this
13 room, we actually have three examples now where we
14 have tried to use experimental models to predict
15 dosages or regimens for neonates. The first actually
16 was when I was with Tom Walsh, and that was where I
17 first met Laura, and Laura has presented that story,
18 being described nicely this morning.

19 The second was with anidulafungin with
20 Pfizer. They also had the primary question of HCME,
21 hematogenous Candida meningoencephalitis, and trying
22 to work out what the right dose of anidulafungin

1 should be for neonates.

2 And then on the back of that work, when I
3 moved to Liverpool in collaboration with Mark
4 primarily, NeoVanc, which is a European project, to
5 work out or provide some dose justification and get
6 registration or licensure for vancomycin in neonates.
7 This was NeoVanc.

8 And then this is where Mark and I first met
9 one another. And this is the first time where I had
10 to think, well, what model systems are we going to
11 make to get to the bottom of this question? Certainly
12 not a thigh model. And then I saw Danny's data with
13 all your list of Stenotroph is up on the left side,
14 and then coag-negative staph always down on the right
15 where you don't get CNS involvement.

16 And so I actually had to ask Mark about what
17 sort of things he saw in the clinic to -- I'm an adult
18 physician -- right? -- so I needed to understand
19 exactly what sort of model systems there were, and
20 that was part of some of the questions that you asked
21 us about what sort of model systems we should use.

22 And I'm going to show you -- these next few

1 slides are a little difficult, and you may have to go
2 away and consume them slower. We'll come back to
3 these, so let's not get too hung up.

4 But the first question that came up in the
5 clinical trial was there's a large part of the
6 European community that thought vancomycin should be
7 infused. And so we were able to use a hollow fiber.
8 I'm going to come back and describe what a hollow
9 fiber model is.

10 But we were able to show that for coag-
11 negative staph, using a hollow fiber model and dose
12 fractionation studies, that the AUC -- this was a
13 concentration-dependent agent, so the AUC or the Cmax,
14 the AUC is at the top and Cmax in the middle there,
15 both accounted for both the effect and the emergence
16 of drug resistance -- but really didn't do a good job
17 in terms of -- time above MIC didn't do a good job in
18 accounting for drug effect, suggesting that infusing
19 vancomycin would not be a useful strategy.

20 So just the next thing that I'm going to
21 point out to you, if you look up on the right, the top
22 right, which is the resistance curve, so you have a

1 free AUC/MIC there of somewhere between 300 and 400 is
2 required to shut resistance down, which that's free
3 drug, so with 50 percent binding, that jumps up to
4 600, which is more than the 400 that we all sort of
5 cite.

6 So the good Professor Bradley says, "Well, I
7 don't think that that's right because --," well, you
8 may, you may reasonably say that.

9 (Laughter.)

10 DR. HOPE: So I was also worried. Well, I
11 was worried about this. So we also designed a bunny
12 model, and the bunny model I now can't use, use as a
13 primary model readout, because coag-negative staph is
14 not very virulent, so you can't count it. It doesn't
15 get into organs. It doesn't get into the brain.

16 And so really in collaboration and
17 conversation with Mark, we decided to use CRP as a
18 primary readout because Mark likes CRP, and we think
19 that it derives or gives -- it's biologically valid,
20 it's clinically valid. And so we designed a rabbit
21 model, and the rabbit model had a line in. So we
22 intentionally infected the line with coag-negative

1 staph, just like happens in babies, so the
2 pathogenesis being infection of the line, an
3 inflammatory state, not direct involvement of the CNS,
4 but the inflammatory state per se or primarily driving
5 potential neurotoxicity and late neurodevelopmental
6 problems or outcomes. So that was actually -- I
7 learned that from Mark. It's a difference between
8 direct involvement of the brain versus just having a
9 sick baby that's infected and having actually to do
10 both things, control systemic inflammation and the
11 effect site, which is the brain.

12 And here are the data. So it's a little
13 messy, but we could show that controls on the upper
14 left, 10 mg/kg given daily to bunnies on the bottom
15 left, and then 15 mg/kg given twice daily was required
16 to control CRP in bunnies.

17 We were able to construct this relationship,
18 which is a sort of more classical inhibitory sigmoid
19 Emax curve. And you see now this number of 500 to 600
20 really being required to be sure that you've quieted
21 the whole inflammatory state down. So it was nice for
22 us that there was some degree of concordance between

1 hollow fiber and the rabbit models.

2 This, we struggled, I struggled, for a long
3 time about what to do about this because it was
4 discordant from clinical practice, and I was very
5 afraid of being accused of arbitrarily cutting this
6 continuous relationship, you know, because it would be
7 arbitrary.

8 So I showed the variability in PK when we
9 bridged it this way by these are projected CRP
10 concentrations in babies receiving different regimens.
11 So we decided to use these data to bridge by showing
12 the spread of CRPs that could be expected. So it's a
13 bit like a PTA, a probability of target attainment,
14 but we're showing the expected outcomes in terms of
15 the pharmacodynamics as a result of PK variability.
16 It's got nothing to do with PD variability here at
17 all.

18 And so we were able to advise that we
19 thought that the current European regimen of
20 vancomycin for at least beneath 29-weekers was too low
21 and that a higher dose of giving that dose every 12
22 hours should be used. It's quite difficult, actually

1 -- we can come back to this -- but to show this in a
2 way that you show the -- to show how variable these
3 systems are. You can sanitize them very easily, but I
4 think that that's a little disingenuous actually. So
5 you get this problem of having an answer like 42
6 versus actually showing what the real world looks
7 like. So anyway.

8 So now, so after reflection, I'm just going
9 to wind back now and just tell you what I think what
10 my vision of reality is at the moment.

11 So the first thing, and the questions came,
12 experimental models for neonates. So choose your
13 weapon. On the left are these hollow fiber models.
14 So hollow fiber models are now actually accepted by
15 both agencies as being a valid model for drug
16 development.

17 And these are like dialysis catheters.
18 Organisms are put into these capillaries, and you can
19 see that the capillaries are shown in these yellow
20 hollow structures, which are drugs being moved
21 through, and the organism and the infection sitting on
22 the outside of this.

1 And it's plugged into a circuit, and the
2 circuitry means that you can replicate or simulate any
3 sort of PK profile that you want. So that could be an
4 adult profile, it can be a pediatric profile, it can
5 be a neonatal profile, and it can be at any bodily
6 site that you want to do. And then, of course, you
7 have mice, which are just but one laboratory animal
8 model.

9 And so I just thought that I might go
10 through what I think are the strengths and weaknesses
11 of these.

12 So hollow fiber models. So here are their
13 strengths. So they enable significant perturbations
14 in dosing to define the relevant biology and
15 pharmacology. So you can use them to do really whacko
16 silly things that would kill any lab animal. So you
17 can use it to define the extremes of what happens. So
18 it may be that current neonatal regimens just result
19 in maximal effect every time. And so you can use
20 hollow fiber models to, inverted commas, to examine
21 unethical strategies. So you can figure out what
22 might be happening with the biology.

1 They are very good for resistance studies.
2 They are very data rich. You get rich data from PK
3 and PD from each model system. And there is
4 increasing comfort that they're useful models, they
5 can be used for drug development.

6 But the limitations are that they don't have
7 protein. They're very, very expensive to run; they're
8 much more expensive than running lab animal models.
9 They don't have immune effectors. You need to
10 understand which compartment you're simulating,
11 whether it might be the CSF concentration time profile
12 or the plasma.

13 And here is the chicken-and-egg problem:
14 you actually need to have some human PK to understand
15 which PK profile you want to replicate. So if you
16 have a brand-new drug, you have to use something like
17 allometric scaling to get the first foot in so you can
18 start doing some experiments.

19 But, of course, if you don't have that,
20 there is no way to be able to predict what's happening
21 in CSF. So you've got to get some clinical data, and
22 then you can't get the clinical data because you don't

1 have any justification. So it's that sort of absurd
2 circle that you've got to get around somehow.

3 So unvalidated in many contexts. We have
4 more work to do. And here, it's become to clear to me
5 when you are writing packages for drug -- for
6 regulatory purpose, you actually have quite a few
7 audiences to please. You have regulators to please.
8 You have the company to please. You have the
9 company's investors to please. You have to tell a
10 very clean story to all of those different people.

11 Clinicians, John, I think, don't like -- you
12 know, "I treat babies, I don't treat mice." Right?
13 I've had that. "Well, I treat mice, and I don't think
14 I like treating hollow fiber models." I mean, they're
15 very, very emotionally removed from what we do every
16 day.

17 And then the other big problem you can have
18 is binding of drug to the circuit. That can be a
19 real, real problem.

20 So lab animal models. The strengths. They
21 can and should provide a faithful mimic of human
22 disease. And I think I would argue that we did that

1 nicely with the rabbit model, Mark, that we developed.
2 They do have anatomical barriers that are humanlike,
3 so that's good for the central nervous system.

4 They enable site-specific idiosyncrasies to
5 be captured. So everyone knows about the daptomycin
6 example in lung, which you might not have predicted
7 from a thigh model, for example. They do have protein
8 and they do have immune effectors, coming back to a
9 point that John again raised this morning, that
10 neonates have immature immune effectors. So we can
11 talk about that a little bit more maybe.

12 So the limitations. Really the primary
13 limitation is that the PK can be significantly
14 different in neonates. And so the dogma is that you
15 can correct with that by transforming to AUC/MIC,
16 Cmax/MIC, time above MIC, but I think we'll ask Chris
17 what he thinks, but there can be times where you can
18 get badly fooled by that. And so if you have very
19 discordant PK, I think there are times where you can
20 make bad, bad mistakes from lab animals.

21 So lab animals, too, are expensive. They're
22 certainly resource-intensive. And really in this

1 current era, it can be very difficult to use them to
2 examine the emergence of drug resistance. The
3 inoculum is just too low. If you go about 10(6),
4 10(7), you start killing everything. And so it
5 depends on what the mutational frequency is. And the
6 duration of these models is too short often to allow
7 the emergence of drug resistance.

8 So what do I do then? What do I think? So
9 I think that we should consider both. And maybe a
10 good package actually has both. And maybe it is that
11 you do a lot of heavy lifting in one model system and
12 then you can confirm key ideas in the other model
13 system or the second system.

14 And the information, I would argue, is
15 complementary. So you learn about resistance from the
16 hollow fiber model, but you learn more about the
17 regimen that may be clinically valid from the lab
18 animals.

19 So it can be very difficult if you are
20 considering resistance as a primary endpoint and you
21 have to shut resistance down and you don't have any
22 immune effectors and you have a very high inoculum,

1 you were saying at lunchtime that it just may be that
2 that takes you into areas where you don't have any
3 toxicological coverage and you have to shut the drug
4 down, and that's not what any of us want.

5 And, of course, if you have two model
6 systems, you have to be prepared to manage discordant
7 results. And, of course, if you have two model
8 systems, that's going to be very expensive and it's
9 going to take longer.

10 But I do think that replicating human
11 pathogenesis and disease is extraordinarily valuable,
12 especially for neonates where, because they do have
13 these pharmacodynamic differences where a thigh model
14 may not be predictive of what happens in the brain.

15 Right. So now let me just hang my dirty
16 washing out on a few other things.

17 So protein binding, that came up this
18 morning, and I really just have to admit I have no
19 idea what to do about this. So it's helpful when
20 binding is similar in lab animals and humans, that's
21 easy, you can just use total. It's pretty easy when
22 drugs are not highly bound because you can make a

1 correction.

2 But I really don't know what to do about
3 this problem of changes in binding in early life. I
4 just don't know what to do about that. But I'm pretty
5 sure no one else does either, other than people say
6 that free drug explains all of the world's problems.
7 I just don't think that that's true.

8 Juvenile animals, this doesn't bother me at
9 all, but it bothers other people, because I think that
10 this comes up actually repeatedly. And I know it has
11 to do with penetration of drug into the CSF and trying
12 to -- Lily made this point about the brain may -- so
13 maybe it's right, but for the hassle of having to get
14 juvenile animals, I'm just not entirely sure. And I
15 think it's more important to replicate the conditions
16 under which the drug may engage with the
17 microbiological target.

18 So to have a faithful mimic of human disease
19 is much more important to me. And maybe you have to
20 speak with people like Mark and Danny and Brian to
21 convince them that what you're making is clinically
22 relevant. You know, you have histopathology, you have

1 other laboratory markers like white counts, you have
2 CRP, and that you're sort of -- you can believe that
3 the data that's coming out of those models is
4 believable is important. That's more important to me,
5 I think, than the other stuff. That's a relevance
6 question.

7 And tissue penetration. Right. So arguably
8 much of this workshop is convened on this point. And
9 I do agree that CSF and ELF, epithelial lining fluid,
10 can and should be measured if possible. But I am sort
11 of, of the view that brain infections involve multiple
12 subcompartments. The cerebrum behaves much
13 differently from the CSF space from the vitreous of
14 the eye, from the spinal cord, from the aqueous, from
15 -- you know, they're all different compartments, and
16 they're behaving differently.

17 The problem for me when you measure drug in
18 any of these compartments is it's nice to see it's
19 there, but it's very hard to interpret an absolute
20 value. And so I'm broadly of the view that I don't
21 really -- so I do them, but I think that the
22 interpretation -- let the pharmacodynamics tell you

1 about the relevance. So if you do a model and you can
2 document infection in that space, and you give a drug,
3 and it clears out, you could argue that you had
4 effective concentrations to do that. The problem with
5 that argument -- it's a good argument, but there are
6 times when it falls to pieces.

7 The best example where it's falling to
8 pieces is in the ceftobiprole story where there was
9 discordance in the penetration of drug in patients
10 versus mice.

11 So that an assumption is made for all of
12 these models that tracking of trafficking of drug from
13 the blood into these effect sites is the same in mice
14 and rabbits and even hollow fiber as well. Most of
15 the time that assumption is okay, especially if you
16 have a valid model, but if there really are
17 differences, then there can be problems in that
18 regard.

19 All right. So I learned this in other
20 dimensions of my life. So what else do I think is
21 important?

22 I think it's important that we study more

1 than one strain. I don't know how many because this
2 is expensive work. It's more rather than less. You
3 can't sort of study everything because that defeats
4 the purpose of developing the drug. You would be
5 there for 10 years sort of chasing down every
6 resistance mechanism and every organism, but you have
7 to do more than one.

8 I think it's good to have more than one
9 study endpoint, you know, to ensure an unrelated --
10 you drive the biomarker down, but the biomarker is
11 completely outside the whole pathogenesis, and it's
12 completely meaningless therefore.

13 And you may need to have more than one lab,
14 I think. I think that that's important. And the
15 importance comes from you're putting so much emphasis
16 now on these preclinical studies that being sure is --
17 these are taking the place of Phase 2 studies
18 basically, and being sure is really important.

19 So here's the next problem, the endpoint
20 problem. So I hate cutting continuous data. I said
21 that to you before. And so if this is a new drug and
22 you generate this sort of exposure response

1 relationship and you're wondering which part of it you
2 think is important to take over to neonates when
3 you're designing the dose, you say, "Well, I'll have
4 everything that I can take and I'll put it right down
5 there." And the problem with doing that is that you
6 can shut down the window between efficacy and toxicity
7 once you start building into the variability that
8 you're going to see, and quickly you can lose the
9 upper toxicity bound from GLP studies.

10 And in our world, this -- Chris has often
11 described as one log skill and two log kills and three
12 log kills and stasis. And where do they come from?
13 They're sort of made up really in many regards.

14 So I've come to thinking the better way to
15 handle this is to benchmark, and that means using an
16 established agent to see how that established agent
17 works in this model, and it provides a decline in
18 infectious burden that's the minimum that you should
19 take.

20 So it's a bit like a port buoy, you know,
21 you do not go to the left of that when you see that,
22 and you're designing the regimen of the new drug, you

1 mustn't choose a dose that results in less activity
2 than that standard benchmarked agent.

3 And that sort of is just a nice way of
4 getting away from this continuous data problem where
5 people can use their bias to -- you know what I mean.
6 So I think that's what I'm trying to do now.

7 So that means that you have to have positive
8 controls in experiments. And one thing that a forum
9 like this could do is think about what those positive
10 controls could be so that these are agents that have a
11 clinical indication. We understand pretty well what
12 the regimen is that's effective, and we have enough
13 information to enable bridging from preclinical models
14 to the clinic, and so that there's a virtual circle
15 that enables some validation of these models and
16 reality. The models are embedded in reality, as it
17 were.

18 And with that repertoire of models, there
19 are positive controls. They could be used, therefore,
20 to assess the performance of a new agent so that the
21 new agent must at least compete with that positive
22 control in these model systems.

1 Setting up experimental models that produce
2 on-scale readouts. So we heard some of this, this
3 morning, too. The behavior of all experimental models
4 is arbitrary and the things that are arbitrary and in
5 the investigator's control are the strain that's used,
6 the inoculum that's used, the background
7 immunosuppression that's used, the delay in the
8 initiation of treatment that's used, the duration of
9 the experiment, have all profound influences on the
10 exposure response relationships.

11 And so the key idea is not really any of
12 those, it's that the model should be set up to deliver
13 useful information so that a standard agent should
14 induce a response that's right in the middle of the
15 exposure response relationship so you can see stuff to
16 the left, you can see stuff to the right. So not too
17 much and not too little.

18 And then sort of coming to the end now.
19 What do I think then a PK-PD package should contain
20 for neonates? Well, it will be generic information,
21 mechanism of action studies, chemistry, solubility,
22 formulation. Some information about the relevant

1 pharmacodynamic index I think is important, that links
2 both effect and the emergence of resistance. The
3 spectrum of activity, so vast amounts of MIC data, of
4 course, which that's pretty standard.

5 But neonate-specific PK-PD studies. So
6 using neonatal PK, or the best -- either real or the
7 best guess, with the ability to recheck once you've
8 done the early clinical studies, maybe only 5 or 10
9 patients, and you can come back in and check that that
10 PK is adequate or appropriate.

11 And you do have to have due consideration
12 for protein binding, site-specific PK, and explicit
13 demonstration of activity at that site. So if you
14 think the brain is important, I do think you have to
15 have a model in there that at least enables you to
16 replicate that and study and demonstrate efficacy at
17 that site.

18 And in terms of early-phase neonatal PK,
19 like PK in plasma for sure, and CSF, we have been
20 discussing. And these can be used not only to move
21 forwards, but also to move backwards to inform
22 experimental models and to enable for a bridge.

1 And with that, I think we're there, just to
2 say thank you. It's an exciting and rapidly moving
3 field, I think. And there are many people to thank
4 and acknowledge, many of whom are in this room, that
5 have helped develop these ideas. And, well, they are
6 listed there. There are more. I'm sorry to offend
7 any that are left off.

8 And with that I'll stop. Thanks.

9 (Applause.)

10 DR. FARLEY: Thanks. Thanks, William. And
11 lots of information to further discuss this afternoon.

12 So we're going to try and switch our
13 computer that has the rest of the talks on it. Keep
14 your fingers crossed, and hopefully that will work.

15 Actually, while we're doing that, William,
16 do you mind entertaining any questions from folks with
17 that? That would be great. Thanks. Any questions
18 for William following his talk?

19 Danny.

20 DR. BENJAMIN: I do. We talked about this
21 before and it's just been a little bit since I've seen
22 you.

1 So what are your thoughts on -- you know,
2 one of the things we talk about in modeling is
3 modeling (off mike) modeling is often wrong (off mike)
4 model is less wrong than (off mike).

5 And my question for you is when I think
6 about PK and PK modeling, and I think about
7 physiologic-based PK modeling, I've grappled with it
8 enough that I kind of hang my head, I still need to do
9 the trial, but because I did it, I get X amount (off
10 mike) where X varies, maybe instead of having to do 20
11 (off mike) do 10 or -- you know, where X kind of
12 varies, it depends on whether it's metabolized (off
13 mike) or just eliminated by the kidneys. I would be
14 interested in your thoughts on we do the hollow fiber,
15 we do the animal model study, we look at doing
16 bridging, and we want to think about central nervous
17 system penetration, we get through all of that, what's
18 the gain in not having -- in enrolling fewer patients?

19 DR. HOPE: I'm not sure that PD models help
20 with that question. I think that's separate. I mean,
21 the only way that you get fewer patients maybe is you
22 have an innovative endpoint like -- a powerful

1 endpoint like a biomarker. I think all of the PD
2 studies do derisk and enable you to have the best
3 chance of studying the first dose at the right time.

4 DR. BENJAMIN: So essentially being able to
5 eliminate a dosage problem.

6 DR. HOPE: Right. So --

7 DR. BENJAMIN: Which is not trivial.

8 DR. HOPE: Which is not trivial. So in that
9 sense, it replicates Phase 2, exactly, because you
10 probably (off mike) the clinical data is so noisy (off
11 mike) that, yes, it might be that. That way you could
12 have some confidence about the regimen that you're
13 going to study.

14 It would be great to have a neonatal
15 biomarker that was better than CRP, that could mean
16 you could get much earlier (off mike) in Phase 2 that
17 would help you sort of sort out exposure response
18 relationship (off mike) dose, but I'm not sure that
19 that's going to happen anytime soon.

20 DR. BENJAMIN: Yeah, because the (off mike)
21 CRP is also directly related to one ZIP Code or (off
22 mike).

1 DR. TURNER: (Off mike) in the same (off
2 mike) from reality. I think we found (off mike) 10 or
3 12 potential doses that people are using (off mike).
4 I mean, there are up to (off mike) that could then
5 (off mike) put head to head in a clinical trial (off
6 mike) excluded when (off mike) people used them. So
7 in that sense, it may (off mike) a two-arm trial (off
8 mike).

9 DR. BRADLEY: Beautiful presentation. I
10 agree with 99.9 percent (off mike). The emotional
11 endpoint -- and I get all of the logic for getting it
12 in the middle, but in the middle, of course, you've
13 got toxicity on one side and clinical failure on
14 another. And you've got adult training, but you have
15 a demeanor (off mike) pediatric (off mike). I really
16 strongly about that.

17 In the United States, when we get consent
18 from parents, it's not just the physician, but the
19 investigators on the team can get consent from the
20 parents.

21 And just to add a dimension to your
22 knowledge of the whole area, and acknowledging that

1 this is a neonatal workshop, and neonates are so
2 difficult to study, and that's why we're all here,
3 that if he can get you on the protocol to get consent
4 for, say, ceftazidime, avibactam, or ceftolozane, one
5 of those drugs, single dose PK, and have you actually
6 pitch the study to the parent, the emotional
7 breakpoint will have more personal relevance perhaps.

8 And I get it, and I don't want to take your
9 scientific focus, laser focus, away from what you're
10 doing, but in reality, babies are treated differently,
11 and the headlines on the newspaper if the baby dies in
12 a research study has way more impact than if an adult
13 dies, not that that would ever happen, it's just --

14 DR. HOPE: The problem, John, the reality is
15 that from GLP studies, you have a (off mike), and it
16 will be 200. If your question (off mike) if that's
17 what you're objecting to, but I think that the more
18 important thing (off mike) is to be able to have a
19 story that's believable.

20 DR. BRADLEY: So I don't think vancomycin
21 should be used (off mike). I think it's too toxic.
22 But that -- or combination therapy, which is something

1 we haven't even touched. I'm not opening -- I am
2 opening a can of worms (off mike).

3 DR. FARLEY: How about we open that during
4 the panel? We'll open that during the panel
5 discussion. Are you doing okay over there, Chris?

6 DR. RUBINO: Yes, I'm fine.

7 DR. FARLEY: Good. Okay.

8 DR. RUBINO: I think we got it straightened
9 out.

10 DR. FARLEY: Great. So Chris Rubino from
11 the Institute for Clinical Pharmacodynamics in
12 Schenectady, New York, to talk about pharmacometrics
13 to facilitate design and analysis of drug studies in
14 neonates.

15 Using Pharmacometrics to Facilitate the Design and
16 Analysis of Anti-Infective Drugs Studies in Neonates

17 DR. RUBINO: Thanks, John.

18 Here are my conflicts. I think the first
19 one is probably the most important one in that I am a
20 partner in ICPD, and we do pharmacometric services for
21 the industry, so there is certainly a self-serving
22 interest here in me talking to you about this. But I

1 think, as we've all talked about today, everyone sees
2 how pharmacometrics fits in here.

3 And then there are several companies on
4 there. I will you that I counted them up earlier this
5 morning, and we're working on pediatric programs in
6 some way, shape, or form, usually just in helping them
7 design the program with 10 of these sponsors. So
8 there's a lot of this work going on right now.

9 So I'm going to touch on two topics mainly
10 today, and it's funny because the second one has got
11 more of the slides, and a lot of what we talked about
12 I could almost skip to the end of that and just give
13 the last slide, and everyone would be, "Yeah, well,
14 that's what we've been saying," but that's okay. I'm
15 going to give you a little bit of detail at least.

16 But I want to talk about pharmacometrics in
17 general, where it fits in here. I'm going to give you
18 a couple examples. And I'm going to focus more on the
19 pharmacokinetics. William touched on the
20 pharmacodynamics.

21 And then the second half, just some study
22 design issues and how we use those models. So Laura

1 presented some great information, and it's right along
2 those same lines that I'm going to talk about.

3 So I use this slide all the time just to
4 show how -- this is from Chuck Bonapace back in 2004,
5 but what I really put it up there for is so you can
6 see the different facets of drug development, where
7 pharmacometrics fits in.

8 And it's funny because when I started doing
9 this 20 years ago or so, we were really pushing hard
10 to try to get companies to pay any attention to
11 pharmacometrics, and now I spend a lot of time trying
12 to get companies to pump the brakes a little bit on
13 how they think that metrics is going to solve all of
14 their problems, and it won't, but it's an important
15 tool, and we're glad we have it, but just the
16 dichotomy is pretty striking to me.

17 So this is just a cartoon that we like to
18 show folks of what kind of information we need to
19 adequately apply pharmacometrics to drug development
20 programs. And we've talked about a lot of this today,
21 the pharmacodynamics, as William just mentioned. We
22 talked about the difficulties in collecting clinical

1 data. The microbiology actually of all of these
2 things is one of the easiest ones to hit. Right? We
3 can do surveillance studies of MIC distributions
4 pretty easily, so we'll always have that one down.

5 Modeling and simulation is just a tool that
6 we can always apply, but we have to evaluate what
7 comes out of that tool based on the information that
8 we put into it. So at the end of this, I hope you get
9 a good feel for what I see as the issue. Obviously, I
10 believe in the modeling in what we do, but I'm more
11 focused when I'm dealing with clients and sponsors of
12 let's make sure we have the best data. Okay? And
13 then pharmacokinetics, obviously that's what I'll
14 spend the most time talking about in terms of the
15 approaches.

16 So I'm not going to get into real down in
17 specifics, you won't see any equations on my slides,
18 but I want to give you an overview of the two main
19 approaches that we take to pharmacokinetics and how
20 they can apply to neonates.

21 And there is really -- for those of you who
22 don't read this literature, there are two general

1 philosophies that I guess a couple years ago you could
2 say we're battling and now we're all kind of coming
3 together, and I'll talk about that later.

4 But there's the top-down approach and the
5 bottom-up approach. And the top-down approach is
6 where you have the data that you observe is really
7 driving the model that you generate. This is the
8 standard, what you all probably think of as population
9 pharmacokinetic studies, where we have some data, we
10 do an empirical model that describes that data well,
11 and then we try to use that to do simulations.

12 The bottom-up approach is taking it, as you
13 might expect, from the opposite. It says, okay, we
14 understand the physiology of all of this, and can we
15 develop a model that explains the physiology and then
16 use the observations to confirm what we think?

17 And mathematically they're very different.
18 If you think of vanilla top-down and vanilla bottom-
19 up, they're the opposite extremes. You're doing a lot
20 of estimating with the box on the left, and you're
21 doing simulating and what we call tweaking with the
22 bottom-up approach.

1 But as you'll see, we're all kind of the two
2 sides, because traditionally I came from top-down, I
3 learned NONMEM first, and I've always developed these
4 empirical models, and you can think of like the folks
5 at Simcyp and some of the other folks, they're the
6 bottom-up. So those are the two groups. We're all
7 kind of coming to the middle now and using bottom-up
8 theory to start and top-down to get some estimations.
9 And I'll explain why.

10 So I'm going to give you just two examples,
11 one example for each of these two methods.

12 So what we have here is an approach, a top-
13 down approach, we took with the drug cefazolin. So
14 John mentioned off-patent medication, we talked a lot
15 about that. This was actually sponsored by Broughton,
16 a generics company, to run a study. They had only two
17 sizes of their infusion bag cefazolin, and they came
18 to us and said, "We need to decide when to use 2 grams
19 and when to use 1 gram."

20 So we had some adult data. We created the
21 model that's up on the left. So we created this model
22 here. We used that model, we scaled it down to kids,

1 did some simulations to see what weight cutoffs --
2 this was all about, where do we cut off the weight to
3 go from 2 grams to 1 gram in postsurgical kids?

4 The important thing here is we were only
5 going down to 10 years of age, and because the
6 smallest they had was 1 gram. So cefazolin is an
7 extremely easy drug from a pharmacokinetics
8 standpoint. If you saw the fit of our model to the
9 adult data, it's amazingly easy to fit data to
10 cefazolin, it's just very clean, as we say.

11 So we were able to come up with these
12 projections. They ran a PK study where they used this
13 weight cutoff, and they got information in a group of
14 kids age 10 to 13 years of age.

15 What I'm showing in the bottom right here is
16 the gray zones are the -- on this panel here, well, in
17 both, but on this panel here, we've got the gray zone
18 is the model projections, and the black dots are the
19 observed concentrations, and what you can see here is
20 that we enrolled this study, it was in postsurgical
21 kids, and our model was underpredicting the
22 concentrations pretty much universally, so the

1 extrapolated model.

2 And what we found was that these
3 postsurgical kids weren't normal healthy adults, and
4 essentially their entire curve was shifted up for
5 whatever reason, so we had to tweak that model. And
6 we then go from there and we say, well, our age cutoff
7 wasn't right, we're going to go back and simulate from
8 that model this new system and look at different
9 weight cutoffs and see how we can standardize it. So
10 that's kind of how we would use a top-down approach.

11 So there are two things I wanted to point
12 out here. So it was a very simple process overall to
13 apply this, but ironically in a situation where I
14 would have thought we would do an excellent job of
15 extrapolating down -- and we use maturation factors,
16 and we made sure we were doing everything kind of
17 state of the art at the time, and we still missed
18 because these kids were postsurgical and just had
19 slightly different PK.

20 Now, we changed the cutoff, I believe, from
21 40 kilos to 50 kilos, so is that such a big deal? I'm
22 not sure, but I think we got it right now.

1 Okay, the second one I want to show you is a
2 bottom-up approach. And there are a couple things I
3 wanted to kind of get across here, so the complexity
4 of what we're dealing with, but also the timeline.

5 So this is a very sort of general review of
6 the timelines we're looking at, but what we're doing
7 here, this is not an anti-infective, this is a drug
8 that I can't say the name of, we're going to be
9 presenting it next month at the pharmacometrics
10 meeting, but a drug that is for an orphan disease in
11 kids, does not have an approval in adults, so there is
12 no extrapolation that's going on. That's why you can
13 see the Phase 3 studies here are necessary to show
14 that it works in this disease.

15 It's a drug that was on the market at one
16 time, so we do have a little bit of information.
17 Unfortunately, that was a long time ago, and the data
18 that we have isn't so great, but we were able to
19 leverage that information to develop a PBPK model for
20 the drug under investigation.

21 The other part of the complexity is we've
22 got combination therapy here, and this is a disease

1 that requires combination therapy. The drug is a CYP
2 substrate, so we have to add in two other drugs into
3 our system. So we're using this entire system to get
4 to which doses we're going to use in these kids.

5 So because the adult data was old, they ran
6 an adult study, which has finished. So we developed a
7 model system. We're using the adult data to qualify
8 that system. And then they're running a small run-in
9 -- now, this is the mono therapy arm where we think we
10 have a good idea of what's going on there, so we were
11 able to start that ahead of time just based on
12 projections from the older data.

13 But we don't know anything about these DDI.
14 So we're using this model system to project what the
15 starting doses should be in the kids that will be on
16 combination therapy.

17 Our plan was just to go right into phase --
18 well, my suggestion was to just go right into Phase 3
19 after we get the adult data, much like what we're
20 talking about here, where the neonatologists are
21 nervous about moving right into a situation where you
22 might not know exactly what dose to use. The

1 investigators in this program were the same. They
2 said, "We want to see some data in kids on combination
3 therapy before we move forward."

4 So we designed this little run-in phase
5 where we are going to get this data, look at our
6 model, see how they're projecting everything, run the
7 simulations, and get to the dose for the Phase 3
8 combination therapy.

9 And then once we get all of this data,
10 because we're getting sparse sampling in all the
11 Phase 3, we'll then update the entire system once
12 again.

13 So that's it for the examples. Now, I want
14 to go into the second half. I'm going to talk a
15 little bit about study design considerations.

16 Now, I put up the title of this publication
17 from 2012 from the FDA where they put out this
18 clarification on precision criteria for getting sample
19 size estimations in kids. And I think this was a
20 publication that was the result of what they were
21 seeing at the time, which was pediatric studies that
22 were inadequate, and they were getting a lot of

1 studies with too few patients.

2 And the industry was probably doing
3 something like we're doing today, where we say, "Well,
4 we need a little more feedback on what you're looking
5 for," and that's what this publication came out about.
6 And I think it was an excellent way to set the stage
7 and start a discussion.

8 And back in 2012, I think just before or
9 just after this was published, there was a meeting of
10 the -- it was the Pharmacology Advisory Committee down
11 in Arlington there, or south of Washington, D.C.,
12 where we talked through all of this, these issues, and
13 had folks from the modeling side and pediatric
14 pharmacologists talking through all these issues, and
15 they set criteria, which I thought, and I still do
16 think, is very reasonable, where if you know the
17 bioequivalence window, it's 80 percent to 125 percent
18 of precision, they made it wider, they said 60 to 140
19 percent, so they were able to accept maybe a little
20 higher degree of uncertainty here.

21 But the problem I think, and kind of where
22 I'm going with all of this, is that's fine in the

1 larger age buckets, but here with neonates we're
2 talking about very small buckets, even within
3 neonates, we're talking about preemies that are less
4 than so many days old and preemies that are more, and
5 then we have very, very low, and just there are a lot
6 of little buckets that you deal with. When you have
7 to meet those criteria for every little bucket, that's
8 when it becomes difficult. Okay?

9 So designing these studies and coming up
10 with sample size estimations or optimal sampling, as
11 Laura mentioned, the optimal sampling that was done
12 for micafungin, it's all about signal noise, signal-
13 to-noise ratio, and the bigger the signal and the
14 lower the noise, the fewer patients you need.

15 So this is just a generic picture from the
16 Web showing signal-to-noise ratio, but if this is what
17 we were dealing with in kids, a huge signal and a tiny
18 amount of noise, this would be very easy, we wouldn't
19 need very many patients. But unfortunately, in many
20 cases, it's more like this, where you can barely see
21 the signal within the noise, and just the amount of
22 data that's in that picture, to try to pick up that

1 signal is daunting to say the least.

2 So the good thing is there's a signal here.

3 And I'm talking specifically from a pharmacokinetic

4 standpoint. I'm not talking about clinical data or

5 even pharmacodynamics, but just from the basic PK

6 standpoint, there's a strong signal. We know that

7 there are differences there, and that helps us, we can

8 pick these differences up.

9 The problem is all of the action, if you

10 will -- and all of these are different graphs. So

11 this one on the left is very similar to what Lily

12 presented earlier, but the maturation of different CYP

13 enzymes relative to adult levels, and this is just the

14 same publication from a rodent that used for the

15 maturation of renal function.

16 But what you see here, if you look at the

17 scales, these are all in years, it's in that first

18 year where all the action is, and that's why we need

19 to cut up into little buckets, because a lot is

20 happening there.

21 We had a call the other day, actually your

22 colleagues from Duke and I, with one of the sponsors,

1 and there was a recommendation to have very small
2 buckets of different doses for this clinical trial,
3 and essentially where you would change a kid from one
4 dose to the other if they were on the study at the
5 beginning and if they were on the study 2 weeks later,
6 and the sponsor kind of was very concerned about this,
7 "How are we going to put this into our protocol?" And
8 the recommendations came from Duke.

9 So they asked me, "What do you think of
10 this?" I said, "Well, that's what happens." If
11 you're in a NICU and you're giving someone gentamicin
12 on their first day of life, they might need dosing
13 once every 48 hours, but if you're giving it to them
14 3, 4, 5 weeks later, they're probably going to need it
15 once a day, maybe every 12 hours, and that's just the
16 way it works. But trying to design a study around
17 that is very difficult.

18 Okay. So there's a signal there, though.
19 The problem is kids are noisy. This is from a survey
20 of neonatal PK-PD studies in pediatric development by
21 some folks at the FDA, and it's general pediatrics, so
22 you'll see -- I'm sorry that this doesn't show up that

1 well, but we've got linezolid on there. So there is
2 one anti-infective. It was good to see that was the
3 one that was on your table that goes all the way down
4 to zero, to birth, because Brenda Sorencioni (ph) and
5 I were involved with that program many, many years
6 ago, so I'm kind of proud that that was on there.

7 But what you can see here, this is the mean
8 and the standard deviation around the weight-
9 normalized clearance values, and although there are
10 differences, and the youngest kids are always at the
11 low end, it's quite predictable. These bars are
12 overlapping, so that's just an indication of the
13 amount of noise that's in the system. Part of that is
14 experimental, it's not necessarily physiologic, but
15 it's there and it's something we need to keep in mind
16 as we design these studies.

17 So we can handle this. We have the tools to
18 deal with these unknowns, and we can come up with
19 sample size estimates for these studies using top-down
20 approaches because we can just run clinical trial
21 simulation. Top-down approaches have models. They
22 have their issues certainly, but they have models

1 where we can quantify inter-individual variability and
2 we can quantify the uncertainty in our parameter
3 estimates so we can run these clinical trial
4 simulations and generate power on sample size and
5 optimal sampling schemes for these studies.

6 With vanilla -- and I use the term "vanilla"
7 because these are the older standard PBPK models. For
8 the folks that know about PBPK, I don't want to sound
9 like I'm underselling it, but for older PBPK models,
10 those really were just based on mean patients and
11 they're designed to take uncertainty or inter-
12 individual variability at their heart into account.

13 So we can inject inter-individual
14 variability, and the way we do this is we take certain
15 parameters and we put variability around them to
16 create these sorts of ranges of concentrations, and we
17 can then compare that to the observations.

18 So this is the model system I was just
19 talking about where we're taking the drug's
20 physiologic parameters, generating a concentration
21 time curve from a PBPK model, injecting inter-
22 individual variability into it. The red circles are

1 the observed data we've had from adults. So we had to
2 make a little tweak to the model, but we're getting
3 great fit out of our system for the adult values.

4 Once we start getting -- now, the stars are
5 hypothetical pediatric data, because we don't have any
6 yet, but what we're going to get is a little sporadic
7 data here and there, and what we have to say at this
8 point, if we only had five points, we would have to
9 say, well, is our model wrong or is the data just
10 showing us some of the outliers? This is the tricky
11 part of dealing with, again, what I will term vanilla
12 PBPK models.

13 What's been proposed? And this is a cartoon
14 I stole from an excellent publication from the folks
15 at Manchester and Simcyp, is a process, a hybrid of
16 the two, where we're using PBPK concepts to develop
17 these models, collecting clinical data, figuring out
18 which parameters within these -- because these models
19 are huge, right? They have hundreds of parameters in
20 them.

21 We cannot fit -- as good as the computers
22 are, we can't fit all those parameters, we don't have

1 enough data, so we have to go and collect this
2 clinical data, but at the same time, evaluate those
3 models to find what parameters we can put some
4 variability around, and then have a nice hybrid of the
5 benefits of both approaches, because I really do think
6 that PBPK is the way to go in terms of quantifying
7 physiology, especially in terms of neonates, where
8 we're learning this information and we can do a better
9 job of extrapolating down than we can with empirical
10 models.

11 So this slide, I didn't have a great place
12 to put it, but we have these great tools, and we can
13 help folks design studies very well, but reality gets
14 in the way. And we've talked about this already, but
15 this is data from a review of I think 73 PIP
16 applications. So it's EMA data, and they looked at
17 the PK studies in those 73 PIP applications, and what
18 they found was in any of the studies that had to do
19 with PK, the median number of subjects across all age
20 categories was 30, and there was a clear difference, a
21 clear drop, in the number of subjects for neonates.
22 So this yellow-light greenish bar is the neonates.

1 And then in terms of number in samples, same issue.

2 So I don't want to belabor this because
3 we've talked about that already, but clearly the
4 problem isn't just here in the United States, it's in
5 Europe as well.

6 So I threw this in, and I showed this to
7 Mark after he made a statement earlier because he used
8 the term "greater degree of uncertainty," and I swear
9 I put this slide in before he said that. But this is
10 from the Tripartite meeting between EMA, FDA, and
11 PMDA, and it has nothing to do with neonates on its
12 surface, it's more related to getting new antibiotics
13 to address antimicrobial resistance, but I would
14 submit that this is -- we should be taking the same
15 sort of tactic for neonates where we accept a greater
16 degree of uncertainty, weighing safety and efficacy,
17 of course, but not necessarily holding ourselves to
18 the same bar of precision as we might in the larger
19 age buckets in pediatrics.

20 And then I put this quote, because I use
21 this with my folks at ICPD all the time when they
22 start to go off and develop crazy models, but I think

1 it applies here as well. And I put the Italian one in
2 there because folks attribute this to George Drusano a
3 lot, and he's my favorite Italian scientist, but it
4 does not come from George, he did not start this, but
5 it did actually -- Voltaire kind of popularized it,
6 but he got it from an Italian philosopher before that.
7 But I really think it applies. "The better," in this
8 case, "perfect," "can be the enemy of the good," and
9 we need to keep that in mind.

10 Thank you.

11 (Applause.)

12 DR. FARLEY: Thanks, Chris. That was great.
13 And let me get Gary's slides loaded.

14 Obtaining Clinical Safety and Efficacy Data in
15 Neonatal Infections

16 DR. NOEL: Thank you. So my name is Gary
17 Noel. I am a full-time employee of Johnson and
18 Johnson.

19 And Sumathi asked me to give this talk to
20 give, I guess, a pharmaceutical physician's
21 perspective of studying new antibiotics or antibiotics
22 in newborns.

1 I have a disclosure here that I'm a full-
2 time employee and that these opinions and positions
3 don't reflect my employer or my J&J colleagues.

4 But in hearing the discussion through this
5 morning, I also wanted to share with you a bias that I
6 have, and the bias that I have goes back to the start
7 of my career. After finishing in my ID fellowship, I
8 joined Paul Edelson's laboratory at Cornell. Paul was
9 a graduate of Zan Cohn's laboratory at Rockefeller,
10 who was focused on macrophage biology. That's where
11 Ralph Steinman came from and did a lot of his
12 dendritic work.

13 And when I joined that lab, Paul sat me down
14 and said something very similar to what Danny said,
15 and that was that infants don't localize infection
16 very well. And then he went on to say and it must be
17 because their mononuclear phagocytes don't work very
18 well.

19 And so I spent the next decade and a half of
20 my life in the laboratory trying to figure that out,
21 and I've observed some very amazing things, some of
22 which were shared through publications, other which

1 are archived in the world of non-reproducible results.

2 (Laughter.)

3 DR. NOEL: But, nonetheless, I think one of
4 the biases I have when I think about studying newborn
5 infants aligns very much with what John shared with
6 the group, and that was a concern that the
7 pathophysiology of the disease, of infectious diseases
8 and bacterial infectious diseases, in newborns are
9 very different in newborns than they are even in older
10 infants and children, and we have to deal with that
11 uncertainty as we move forward and try to develop
12 these drugs.

13 So I'm going to spend some time, the first
14 part, really basically just reiterating some of the
15 things that are already said, and basically what I'm
16 going to say is that this is the best we can do given
17 our understanding of these diseases now and the state
18 of the art of antibiotic development in newborns.

19 But then I wanted to spend probably most of
20 my talk, only one of my slides, but sharing some
21 thoughts and hopefully generating some discussion
22 among the group about what we might be able to do

1 going forward to really improve what we can do in this
2 area.

3 So to start with safety and efficacy, let me
4 speak for my pharmaceutical physician colleagues and
5 say that we are completely aligned with the regulatory
6 authorities and our academicians and our clinicians in
7 wanting to be certain that we understand what the
8 risks and the benefits of these drugs are.

9 And I can say categorically that every
10 physician that I've worked with in industry is guided
11 by wanting to be certain that they have the best
12 information they can about a drug's safety and its
13 efficacy before they can stand behind labeling that
14 drug and getting that drug out to their clinicians.

15 Now, with regard to safety, our goal is that
16 we have some understanding of these potential risks,
17 hopefully a good understanding of those risks, but
18 also those risks as they relate to treating a specific
19 patient population for which that therapy is going to
20 be directed, and which is important to consider when
21 we start thinking about studying newborn infants, is
22 that that information certainly may be coming from

1 populations other than newborn infants. They're
2 unlikely to be coming from newborns that aren't
3 suspected of having an infectious disease, but in many
4 instances, that information may not be coming from
5 infants who actually have the bacterial infection that
6 we're hoping to treat.

7 And for that reason, I think the state of
8 the art, the current state of the art, is that we
9 construct these profiles in newborn infants
10 considering observations made in older children and
11 adults. That's certainly short of saying that we
12 extrapolate efficacy, but in many ways we are doing
13 that, understanding that if we do see a safety signal
14 in adults or in older children, that we are concerned
15 about that occurring in newborn infants.

16 But it also has to be weighed against or
17 consider the heterogeneity of the newborn population
18 that we have that data in, and that this is -- and I
19 think this point has been made repeatedly -- this is a
20 very heterogeneous population with regard to their
21 maturational age, the onset of their infectious
22 disease, whether it be within the first days versus

1 the first weeks of life, and all these things need to
2 be taken into consideration when we're looking at the
3 safety profile.

4 Now, there's a tail end to that because I'm
5 not seeing the whole slide here because there are two
6 more points. That's being cut off. But in any case,
7 so comorbid conditions are also I think important to
8 consider, that there are a variety of different
9 comorbid conditions that we need to consider when
10 we're constructing this profile in this population and
11 concomitant medications. I guess we're going to open
12 up not only concomitant medications that we invariably
13 use when we're treating serious infectious diseases in
14 infants because it's seldom the case that these
15 patients are on mono-drug therapy.

16 And then the last issue that I want to share
17 with you visually is this issue of sample size. And,
18 again, this slide is not projecting.

19 I learned this early in my pharmaceutical
20 career. I had been exposed to it as a clinician, but
21 it became very important for me to recognize this as I
22 started out. When we generate these data in clinical

1 trials -- and this has been referred to as the rule of
2 three -- when we are essentially doing a study or
3 we're looking at an experience of 3,000 patients, our
4 statisticians, our mathematicians, are very keen to
5 point out to us that if we don't observe an adverse
6 event in that population, specific event, that it's
7 greater than 90 percent probability that that event,
8 if it does occur, is occurring in less than 1 in 1,000
9 patients. And then this is a logarithmic function, so
10 that if you were to include a study of 300 patients
11 and you don't see that event, you, in effect, are
12 ruling that out in 1 in 100 patients.

13 And the point I'm trying to make in showing
14 this to a group that's thinking about newborn infants
15 is that it's seldom the case that we're going to get
16 an experience even of 300 homogeneous newborn infants
17 to really have great certainty as to whether or not we
18 really understand the frequency of an adverse event or
19 if a unique adverse event is occurring in a newborn
20 infant compared to an older child or adult.

21 So at least the way I have approached this
22 and the way I would advocate, and I think that it's

1 the consensus of the group that I'm hearing discussing
2 this today, is that we certainly need to recognize the
3 strengths and the limitations, be comfortable with the
4 uncertainty that we have based on the data that we
5 will generate in these studies.

6 But I go further in saying that when we do
7 that, we need to be committed to continue to explore,
8 to study, to understand the safety and tolerability of
9 these drugs as they get out and are used more
10 frequently in the trials. And I think that if I were
11 to propose something that we can do to address this
12 issue of risk, is to start thinking about ways that we
13 can sort of uniformly assess after labeling of the
14 drug continued experience capturing that, especially
15 in critically ill children where I think we really
16 need to understand best the tolerability and safety of
17 these new drugs.

18 So then let me quickly turn to efficacy and
19 again underscore that this is -- as a pharmaceutical
20 physician, what we're asking is, what is the benefit
21 of using this drug, the potential benefit? And,
22 again, we're focused on a specific infectious disease.

1 I think our conclusions of efficacy need to
2 continue to be based and influenced by our
3 observations made in adults. Again, that's a
4 different way of saying extrapolation seems to be
5 acceptable or the best we can do at this point. But
6 it really does need to consider the uniqueness of
7 infectious diseases.

8 And I think this goes beyond just host
9 responses and the pathophysiology of the disease, but
10 I think there are some uniquenesses to the
11 microbiology of some of these infectious diseases.
12 You know, when we talk about pneumonia in the neonatal
13 intensive care unit, we're talking about things like
14 Group B streptococcal pneumonia. We have no idea
15 about Group B streptococcal pneumonia when we're
16 completing a package in nosocomial pneumonia for a new
17 antibiotic.

18 Now, there is good reason to believe that it
19 will be effective, but there are some major
20 differences between the microbiology, the importance
21 of coagulase-negative staphylococci in a neonatal
22 intensive care unit. Many of the pathogens that I've

1 been involved with in developing new antibiotics
2 really don't have extensive experience in treating
3 coagulase-negative staphylococci.

4 Now, again, that doesn't mean that we can't
5 extrapolate from other diseases and response
6 concentration relationships, but there are some major
7 differences, and I think those need to be considered.

8 And I think the last point that should be on
9 that slide is that I think we'll seldom have the
10 luxury of having a sufficiently sized, randomized,
11 double-blind controlled trial to really assess
12 efficacy in newborn trials.

13 So conclusion, I think our current
14 understanding, we need to come to terms and to deal
15 with the uncertainty behind building our conclusions
16 about efficacy based on observations made outside the
17 NICU.

18 I did want to point out that there are some
19 diseases where there may be great similarity between
20 what happens in the newborn infant and older infants
21 and children. I point out vascular catheter-
22 associated infection. I'm quite comfortable as an

1 infectious disease subspecialist in extrapolating
2 efficacy in adults when we're dealing with treating a
3 vascular catheter-associated infectious disease. But
4 that might be the only disease that I know of where
5 I'm comfortable in it, and that's not something that I
6 think, Sumathi, you're seeing a lot of labeled
7 indications for.

8 And certainly I think efficacy does need to
9 be based on our understanding of pharmacokinetics and
10 dynamics, that we can study in newborn infants, and we
11 can get good information on, and then move from that
12 to extrapolating efficacy based on drug exposure.

13 So let me turn to what I think is more
14 interesting to talk about in this forum today, given
15 that other people have more expertise than I do with
16 regard to pharmacokinetics and pharmacodynamics and
17 even extrapolation. But I think the challenges that
18 we face clearly go beyond just the science here. And
19 there are some things that I don't think have been
20 mentioned in great detail at the meeting, but that
21 maybe future workshops certainly do need to consider.

22 I think designing these trials with

1 objectives that we can clearly communicate to parents,
2 and for that matter, all stakeholders, clearly be able
3 to communicate that, is critical to the success of
4 these programs.

5 I'm raising that because I do review a lot
6 of protocols internally, not in infectious disease
7 these days, but in other therapeutic areas, and I
8 think one of the great challenges that drug developers
9 have in bringing trials forward in children is lack of
10 real clear ideas about what this trial is actually
11 going to show. What are its limitations? That needs
12 to be communicated to parents. It needs to be
13 communicated to the physicians who are enrolling
14 children.

15 I couldn't help but think when I made the
16 comment earlier today about assumptions being made
17 that are going to drive -- are going to be needed in
18 order to test the hypotheses that are posed in the
19 trial.

20 You know, if we think that these trials have
21 the risk of not completing, I think risks like that
22 should be communicated to our clinicians and should be

1 communicated to our parents. I think parents deserve
2 the right to know when they're exposing their trial to
3 an investigational study that there is a chance that
4 the scientific question that's being asked is not
5 going to be sufficiently answered. And we don't do
6 that routinely.

7 But if we are going to sit here as a group
8 and accept the risk that these trials aren't feasible,
9 that's the kind of risks that I think do need to be
10 shared.

11 And I think too often we don't, as sponsors,
12 really lay out very clearly for our investigators what
13 the objectives are of the trial and how they can best
14 communicate that to their ethics committees and to
15 their practitioners.

16 The other point that has been touched on,
17 but I've got to underscore it because of my experience
18 as an investigator as well as experience in trying to
19 develop drugs in children, is the challenge that we
20 have in providing true informed consent, especially in
21 the critically ill infant.

22 And we do need to think about ways that we

1 can prepare our investigators, prepare neonatal
2 intensive care units, such that they can and they are
3 able to provide true informed consent in this very
4 chaotic environment, a critically ill child, I think
5 that we need to continue to further define what the
6 great challenges are in getting parents to consent to
7 being included in clinical trials.

8 I just came back from an EMA meeting where I
9 was surrounded by a group of neonatologists, and we
10 did have some informal discussions about the
11 sociologic geographic challenges that sometimes exist
12 in enrolling patients in clinical trials.

13 And I think keep in mind that many of these
14 patients -- many of these parents of newborn infants
15 are single parents, they can have very poor social
16 connections and support systems. They're going
17 through the chaotic experience of having a newborn
18 that's now in a critical care unit.

19 In many instances, the experience is that
20 these patients, these newborns, have been transported
21 tens of miles from their home, so parents are
22 challenged in actually visiting the child.

1 So these are things that not are necessarily
2 unique to the newborn infant, but I think developing a
3 culture of understanding the importance of doing
4 clinical trials and engaging parents, which I think
5 the point Mark has made, not only in the process of
6 developing these trials, but even in the process of
7 their experience in the neonatal intensive care unit
8 of understanding how critical it is to have clinical
9 trials ongoing in order to understand best how to use
10 these new medicines.

11 And so I thought in my last slide here I
12 would go into some additional sort of bullet points
13 that highlight what I think might be particularly
14 fruitful to pursue if we're really going to make a
15 meaningful change to deal with some of the uncertainty
16 that exists in this area.

17 Again, I said I had this bias about host
18 response, specifically about mononuclear phagocyte
19 function in newborn infants, but I think it's
20 incorrect to assume that we know -- have a real good
21 understanding of the pathophysiology of these
22 infectious diseases in newborn infants, and I think

1 that there is an enormous amount of work that can be
2 done to better define that.

3 And I would be surprised if that information
4 doesn't have great import in understanding
5 differences. I assume that it will establish some
6 similarities, but that it will establish some
7 differences, and that those differences may be
8 important to consider when choosing the right
9 antibiotic and even the right dose to treat these
10 patients.

11 I think being able to define the
12 comparability in pathogenesis of the disease is
13 central to this concept of using extrapolation. And I
14 think that one thing that can be done as we're
15 learning more about host responses is to engage a
16 group of informed neonatal immunologists, some
17 neonatal infectious disease people, and ask them to
18 give us the best information about the understanding
19 of the pathogenesis of the disease so we really do
20 have some data-driven understanding of what the
21 differences are between a complicated skin infection
22 in a healthy 35-year-old and one in a 2-week-old 28-

1 week preemie.

2 And these would be things that would be
3 entirely amenable, in my opinion, to a white paper
4 that could be constructed in the matter of several
5 months by an informed group provided they were given
6 the resources and the incentives. And I'm not
7 volunteering Johnson and Johnson resources to do that,
8 but I think --

9 (Laughter and applause.)

10 DR. NOEL: But I would point out that now
11 Merck and Pfizer basically own every antibiotic that's
12 currently been licensed in the United States and that
13 maybe they have some interest and a more vested,
14 albeit conflicted, interest in defining the
15 similarities and differences.

16 There's more on that slide. The next thing
17 I think was diagnostics. Yes.

18 Now, there is a considerable amount of
19 energy that's being put into advancing the concept of
20 bacteriologic diagnosis and fungal diagnoses in the
21 acutely ill adult, and so there are platforms now that
22 are commercially available. But I think it's critical

1 to start to work with these manufacturers to start
2 thinking about how, if these platforms are first
3 amenable, to diagnosing the specific bacterial
4 infections in newborn infants. In some instances, the
5 material that would be necessary to do the testing is
6 just not compatible with testing newborn infants.

7 And it may be that we would need to have a
8 better understanding of the pathogenesis of the
9 disease to understand whether or not it makes sense to
10 use some of these diagnostics.

11 But I think in order to construct more
12 efficient trials, we do need to be able to have some
13 confidence that first and foremost we're dealing with
14 a bacterial infectious disease in these newborn
15 infants.

16 Otherwise, we are stuck with another risk
17 that we would face as a sponsor of a clinical trial,
18 and that is doing an enormous amount of work and
19 having an evaluation of an intent-to-treat population
20 for which only maybe 5 percent of those patients
21 actually have a bacteriologic diagnosis, and that's
22 not a very informative study with regard to really

1 making me more confident that I have a drug that's
2 going to be effective in the neonatal intensive care
3 in the newborn infant.

4 Oh, and the last issue, which I do want to
5 raise, and I hope that the group at least expresses
6 some interest in discussing this further, there are
7 now probably a dozen, maybe two dozen, papers that are
8 appearing in the literature supporting the concept
9 that the use of broad-spectrum antibiotics in newborn
10 infants is capable of influencing the microbiome in
11 such a way that it could have long-term effects on
12 newborn infants, effects on obesity, effects on
13 intelligence, and these are hypotheses now that are
14 being generated that invariably are going to need to
15 be tested.

16 I learned, again, at the EMA meeting from
17 some of my neonatology colleagues, that there is an
18 ongoing trial where there is a placebo randomized
19 trial of infants born to mothers with chorio-
20 amnionitis. And when I asked the question, well, what
21 was the rationale behind that? and the rationale was
22 that there was a hope that those placebo-treated

1 children would not be exposed to broad-spectrum
2 antibiotics that could make them less intelligent and
3 more obese.

4 So I think invariably these questions are
5 going to be raised, and I think that it's critical
6 before we start generating these hypotheses to really
7 understand whether these do occur, these shifts or
8 these changes in the microbiome does occur in the
9 newborn.

10 But first and foremost, I think we really
11 need to define the natural development of the
12 microbiome in the newborn infant, and I think that
13 might contribute to our understanding of whether or
14 not we even need to do these studies.

15 But I think to ignore that at this point
16 would be shortsighted because I think that's getting a
17 considerable amount of attention and one that I think
18 is going to -- maybe not within the next year, but
19 maybe within the next 10 years, be something that
20 we're going to need to understand in order to assess
21 the potential benefits of new antibiotics.

22 So in summary, it's clearly important to

1 understand the safety and efficacy in order to provide
2 the best intensive care. We do all appreciate the
3 limitations of obtaining the best data in order to
4 support conclusions.

5 The point I would want to leave you with is
6 that we don't have a complete understanding of these
7 infectious diseases. We need to include, as our
8 partners in this development, those people who are
9 studying host defense in newborn infants, who are on
10 the front lines understanding the concepts of
11 developmental biology when it comes to host defense in
12 these diseases, and that they should have a seat at
13 the table voicing their concerns and making their
14 recommendations.

15 (Applause.)

16 DR. FARLEY: Thanks, Gary.

17 And last we'll hear from Mark Turner, who
18 will be talking about neonatal master protocols in
19 infections. And he is also from the University of
20 Liverpool.

21 Neonatal Master Protocols in Neonatal Infections:
22 Pharmacokinetic, Safety, and Outcome Assessment

1 DR. TURNER: Thank you very much for the
2 opportunity to learn so much and benefit from so many
3 wise opinions. The problem with going last is that
4 all the clever people before me have said all the
5 important things, and even worse, they have said all
6 the most interesting things.

7 But going last also gives me the advantage
8 of being able to selectively reinforce the messages
9 that I think are important based on clinical
10 experience or bias. So you'll have to put up with
11 both of those.

12 Just to mention that all the problems that
13 Brian and other people mentioned about diversity in
14 trials happen all across Europe and I'm sure
15 everywhere in the world as well, so it's not just a
16 U.S. problem, and it's not just an antimicrobial
17 neonatal problem.

18 Australians come upside-down, so that's the
19 way you come when you're sideways. But I've got some
20 interests which will eventually appear.

21 (Laughter.)

22 DR. TURNER: So I'm sort of conflicted in

1 some ways.

2 I would like to reinforce that my bias is
3 towards networks because they are going to overcome
4 many of these problems.

5 And we had a meeting just yesterday in
6 London with many of the same attendees that showed
7 that regulatory science has engaged neonatologists,
8 and people can be energized, and I think is something
9 that we can work with very much in antimicrobials as
10 well.

11 Thank you.

12 Now, I normally have trouble moving from
13 Macs to PCs, but today I'm having trouble moving from
14 one Mac to the other, so if you'll forgive the rather
15 view of it. The logo is going to contaminate all
16 these slides.

17 So INC, International Neonatal Consortium,
18 can take this sort of thing on and be that
19 independent, pre-competitive space. I know that CTTI
20 is working in this area in pediatrics. And also the
21 European Network of Pediatric Research EMA has a
22 pediatric antimicrobial working group. But maybe we

1 need to find a special space for the babies.

2 Okay. Maybe you'll need to refer to your
3 handy handout.

4 So I'll talk about the state of the art very
5 briefly. Then the components of the master protocol
6 and potential designs of a master protocol. I think a
7 master protocol in this area is quite challenging, but
8 at least it gives us a chance to review some of the
9 issues.

10 So here's a paper just summarizing some
11 aspects of pediatric antimicrobial trials, including
12 some very distinguished authors in the room, which
13 shows that basically anything goes in studies of
14 neonatal sepsis.

15 There are some recommendations from EMA
16 which have had adults, and they are very liberally
17 interpreted when it comes to newborn babies.

18 And the time of clinical endpoints and days
19 of treatment varies widely between trials, which isn't
20 very helpful when it comes to designing master
21 protocols.

22 Okay. I'm just going to have to trust you

1 got the slides. Yeah.

2 So the components of the master protocol
3 will include the alignment of the inclusion criteria,
4 the target groups, the outcomes, and the methodology.

5 The inclusion criteria in Europe might be
6 the consensus statement from the EMA group of experts
7 about inclusion criteria, and these are being
8 validated as we speak in clinical trials, so hopefully
9 in the next few months there will be some data about
10 how relevant they are and whether they can be trimmed
11 to meet reality.

12 The target groups need to be agreed, and
13 I'll build on what Gary said about this.

14 Outcomes and methodology needs to be aligned
15 as well.

16 So this slide was an attempt to say what
17 Gary said much more eloquently, which is the big blue
18 bar on the far left represents all the babies, and
19 then a proportion of all babies get exposed to empiric
20 antibiotics. And in the U.K., this is about 10
21 percent of all newborn babies because of risk factors
22 and symptoms, none of which are very specific.

1 And then about 10 percent of them go on to
2 have a confirmed infection, which can either be
3 culture-positive, which would be this red bar, which
4 might be about half of the babies with confirmed
5 infection, and the other half obviously have an
6 infection, they have many inflammatory markers, they
7 look just the same as the babies with the culture-
8 positive, but they are culture-negative.

9 And an even smaller group goes on to need
10 rescuing because of antimicrobial resistance or
11 because we can't find the right dose or because the
12 neonatologists get bored and just change antibiotics
13 every 12, 24, or 48 hours depending on their degree of
14 tolerance of ambiguity.

15 So it's very difficult to pin down which
16 group you're going to study because the -- and just to
17 reinforce this point about proven late-onset --
18 culture proven late-onset infection. This is data
19 from the NeoMero study, which was another European
20 program, Framework Programme 7 study. Each of these
21 countries -- there's Estonia, Greece, Italy, Turkey,
22 Spain, and Lithuania -- and the culture-positive rate

1 is in blue, which means that the culture-negative
2 clinical infections are in red. And in Estonia,
3 nearly 80 percent of the late-onset sepsis were
4 culture-positive, and in Italy, 30 percent were
5 culture-positive. So when it comes to doing a
6 multinational study, let alone a master protocol,
7 there's an intrinsic variability in the ascertainment
8 of culture positivity, which makes it very difficult
9 even when you've worked out which group you want to
10 aim for.

11 So the advantages with treating the empiric
12 group was that you get everybody. The trouble is that
13 there is post-randomization imbalance and all sorts of
14 things, and then whether the empiric antibiotic is
15 continued or not is subject to bias, you lose about 90
16 percent of the babies, and large numbers of them don't
17 have any bacteria or any other infection. So they're
18 pretty good for PK-PD in short courses, but they may
19 not be much more informative in other areas.

20 In terms of confirmed groups, and if you
21 randomize or recruit at this stage, then you will know
22 which bacteria you're dealing with often, and they are

1 enriched to a large extent, but by the time they get
2 into this confirmed group, they have been on
3 antibiotics for 36, 48, 72 hours, which means that
4 your efficacy signal may be contaminated if you're
5 studying the antibiotics they're on already. Or if
6 you're studying another antibiotic introduced when the
7 baby becomes confirmed with infection, then there may
8 be some cross -- well, you hope there is some cross-
9 reaction between the existing antibiotics and the new
10 one.

11 So starting off when the babies become
12 confirmed with infection is prone with difficulty, and
13 even more so if you're trying to test antimicrobial
14 resistance possibilities. If you randomize or recruit
15 babies when they move into the rescue phase, then
16 they've also been treated effectively hopefully, and
17 then there will also be considerable variation between
18 clinicians as to when they think a baby needs rescue
19 treatment.

20 People who change antibiotics after 12 hours
21 will get onto rescue therapy pretty quickly, whereas
22 people who change every 48 hours because they're

1 waiting for the antimicrobial to come to steady state
2 before making a judgment may be further down the
3 process. So all of this is subject to bias depending
4 on your belief about the antibiotic.

5 So there are a number of reasons why it's
6 difficult to recruit a consistent group within a
7 single study, but within a master protocol, this would
8 be exaggerated. And, of course, there are a number of
9 clinical groups that we've heard about, early onset,
10 late onset, specific infections, confounded by the
11 gestational age at birth.

12 So what this slide is supposed to say is
13 there is some marked variation between settings in
14 terms of microbiology. The standards applied in
15 settings vary considerably. Getting people to comply
16 with Eucast or other standards is very difficult. And
17 most clinical laboratories don't go that far and have
18 all sorts of variations in like culture conditions and
19 in their estimates of susceptibility and resistance
20 let alone any quantitative MIC. And you can try and
21 centralize things, but that does lead to a degree of
22 variability, and then you have all the problems in

1 multiple sources of information.

2 As we've heard, the standard of care varies
3 enormously both in terms of choice of antimicrobial,
4 but then thresholds for starting antibiotics and so
5 forth. And the threshold for moving between confirmed
6 and rescue infection inevitably leads to a number of
7 protocol deviations, which make it difficult to assess
8 the data.

9 And the other thing that varies considerably
10 is clinical culture, and we've heard many aspects of
11 this. It takes a long time to change clinical
12 culture, but basically we're used to dealing with
13 bucket chemistry as clinicians, and you find a baby,
14 you find the antibiotic, you put the two together, and
15 either the baby gets better or you change the
16 antibiotic until the baby gets better or moves on to
17 working in other parts of the cosmos.

18 Neonatologists have a habit of ignoring
19 recommendations. We wrote a national guideline about
20 early-onset infection 5 years ago in the U.K., and
21 people are still getting to grips with what pre-labor
22 rupture of membranes means let alone which antibiotic

1 to give. So there were challenges there in
2 implementation science let alone in implementation of
3 clinical protocols.

4 So a master protocol could have numerous
5 goals. It could be used to develop PK models. It
6 could be used to attain the percentage of probability
7 attainment of a PK-PD target. It could be used to
8 assess efficacy. Or it could be used to assess
9 safety.

10 And as Gary said, you need to be crystal
11 clear about which is your primary purpose and which of
12 these goals is going to fill the information gaps most
13 efficiently. And particularly for a master protocol,
14 that needs to be set up in advance. And again in a
15 master protocol, each antimicrobial may have a
16 different goal that it needs to meet during its stage
17 of development, so that might be a challenge.

18 With respect to PK and PD data, I think it
19 is possible to collect this data, these PK data, in a
20 reliable way. PTN have shown that, and we've shown
21 that in the U.K. with our NAPA (ph) study, which has
22 looked at four or five different beta-lactams across

1 10, 15 units in the U.K. And it's possible to ship
2 samples and do the assay centrally in a reliable way.
3 So all these methodological issues can be resolved.

4 But that doesn't resolve a critical issue
5 that again our colleagues with NeoMero found. These
6 panels show time concentration drafts for a number of
7 countries in Europe that were following the same
8 protocol. So again we've got Estonia, Spain, the
9 U.K., Greece, Italy, Lithuania, the Netherlands, and
10 Turkey.

11 And maybe I can just draw your attention to
12 the contrast between the Greek panel, which is second
13 down on the left, and next to it, the Italian panel.
14 And we can see that the initial concentrations are
15 broadly similar, but then the concentrations between 4
16 and 8 hours appear to be different. And the Greeks
17 were more likely to have higher concentrations into
18 those intervals than the Italians.

19 And so even following the same protocol with
20 the same medicine, centers and countries can vary
21 between their concentrations, which might make
22 implementation in a master protocol difficult, let

1 alone even a standard protocol.

2 So safety raises some issues which are
3 generic to all neonatal problems, they are the
4 background events of prematurity or sick babies who
5 are born at term, and there are drug-specific issues
6 that may be predictable or unpredictable. And then
7 there may be some infection-specific effects as well.
8 And we need definitions, shared assessments of
9 severity, and shared methodologies of assigning
10 causality.

11 And I think it's safe to say that we're at
12 ground zero on -- ground floor on all of these issues
13 when it comes to defining a master protocol, although
14 we are beginning to come together to work on these.

15 Now, people have talked about efficacy
16 outcomes. So what we've been thinking about this for
17 a number of clinical trials, what elements are there
18 in an efficacy outcome, be it clinical or
19 microbiological?

20 And it's going to have to have several
21 components because you want to know whether the person
22 is alive or dead, and generally speaking, death is not

1 a marker of efficacy in neonates, although there may
2 be some excuses occasionally.

3 Then you want some resolution of the
4 clinical features, whatever it was that started off
5 the infection, or at least led to the screen. And if
6 the baby is having apneas and bradycardias before the
7 infection and they get worse and then they get better
8 again, but they're still having some afterwards, which
9 is what you would expect, then how do you classify the
10 deterioration in the apneas and bradycardias? And how
11 do you recognize when it's got better enough to stop
12 the antibiotics? Now, that's a challenge in clinical
13 practice, but it's even more of a challenge in a
14 standardized way in clinical trials.

15 And then the resolution of the
16 microbiological features, given that half the babies
17 don't have any microbiological features of infection,
18 repeat cultures don't always help.

19 Then you want to make sure that there has
20 been no change in therapy ideally because people will
21 stick with a treatment that's working.

22 And then no new microbiological concerns,

1 there has not been any breakthrough infection.

2 And all of these are extremely difficult to
3 operationalize, and they're very difficult to get
4 people to stick to consistent protocols. So this is
5 maybe a particular challenge in a master protocol, but
6 I'm sure our friends from Duke have overcome all these
7 and can share successful experience.

8 So how do we choose which outcome to use?
9 Well, we need feasibility, we need timing in the
10 study, the guidance. In EMA, it's you want to wait
11 for five half-lives after the antibiotic has been
12 stopped so that you can be sure that the infection has
13 settled down. So you need to know what the half-life
14 is, and you need to assume that all babies have the
15 same half-life.

16 Now, that is a challenge. We did a study of
17 ciprofloxacin in newborn babies, and we found even
18 accounting for specific gestational ages or
19 postmenstrual ages, the clearance can vary ninefold
20 within the same postmenstrual age.

21 So if the clearance is varying ninefold,
22 then the half-life is going to vary to something

1 similar as well, which means that each baby is going
2 to have a different half-life, come to steady state at
3 different times, and when you're going to judge the
4 antimicrobial as having been eliminated is going to be
5 quite difficult. And if you do it for a very long
6 time, then you're going to misjudge the situation
7 because of the random infections that crop up, and
8 this is common to all neonatal studies.

9 So I personally have a lot of difficulties
10 with using efficacy as the primary outcome. I think
11 that there are some difficulties with ascertainment,
12 and how do you handle culture-negative cases which are
13 clearly infected but may have a Gram-negative
14 infection or may have a Gram-positive infection? You
15 may have one that your antimicrobial is going to be
16 useful for or it may not, depending on what's going
17 on. So you can't always design feasible studies
18 around culture-positive cases.

19 I've mentioned issues that arise with other
20 treatments, particularly before randomization,
21 although you can pre-consent and you can get telephone
22 consents and so on. You can get deferred consent.

1 We've used all three in antimicrobial studies. That
2 still leaves you with a need to treat the baby before
3 you can do something about the study. So most babies
4 will get some kind of antimicrobial unless you're
5 recruiting at empiric treatment.

6 And then particularly in the world of
7 antimicrobial resistance, when you're looking for
8 people with MDR or XDR, actual proven cases of that
9 are quite rare, and you need to have quite a large
10 birth cohort and population sampling frame before you
11 can reliably pick up numbers in the tens, twenties,
12 and thirties of these.

13 So for all of these reasons, I personally
14 favor the sort of approach that we heard from Laura,
15 which is a parameter-based approach backed up with
16 registry data for safety. And for me, the main reason
17 for this is the babies vary, so you're going to have
18 to come up with a parameter space to capture the
19 babies. But the bacteria vary as well.

20 And the MIC distributions vary considerably
21 even within a group that's labeled as susceptible.
22 And this is exemplified by coagulase-negative staph,

1 and despite John's ethical resistance to use
2 vancomycin and other glycopeptides, I can assure you
3 that many, many units in Europe do that, which it's
4 just an example of what Danny and Brian were saying,
5 one man's ethical impossibility is another man's
6 ethical imperative.

7 And we did come across this when trying to
8 introduce therapeutic drug monitoring in our
9 vancomycin study. For me, therapeutic drug monitoring
10 of vancomycin is an ethical imperative, but there are
11 many parts of Europe where it's ethically impossible
12 to do for other reasons. So there are many ways
13 around this problem. But most isolates of coagulase-
14 negative staph have quite high MICs, but it's still
15 declared as susceptible.

16 And the commonly used doses of vancomycin or
17 teicoplanin will not treat many susceptible labeled
18 coagulase-negative staph. So we need to take into
19 account the MIC distribution as well as all the
20 variability that we've heard in the babies.

21 And so if we're going to do an efficacy
22 study that covers the whole range of MIC variability

1 within susceptible cohorts as well as all the
2 variation within the babies, then that's going to be
3 an enormous efficacy study for every type of
4 bacterium.

5 So for me, it's much more comfortable coming
6 up with a parameter space that reflects the variation
7 in the babies, which we can capture, and the variation
8 in the bacteria, which we can capture, and then put
9 that together in a form which allows us to use DDM or
10 controls or some other way of synthesizing that data
11 in a way that's relevant to that baby based upon his
12 or her PK parameters and his or her infecting
13 bacteria's parameters, plus a bit of guesswork for
14 culture-negative cases.

15 So an efficacy study based upon, "Do you
16 meet targets in an acceptable proportion of babies?"
17 makes a lot more sense feasibility-wise and is
18 generalizable in a way that an efficacy study may not
19 be because you may just have a random selection of
20 babies and a random of selection of bacteria that may
21 not be generalizable. (Inaudible) PK-PD study and
22 good epidemiology about the microbiology will allow

1 you to come with a generalizable set of models with
2 safety being included in various ways.

3 So coming on to the topic of master
4 protocols, now, this was the first slide I drafted,
5 which was a complete blank about master protocols, but
6 I did manage to come up with some thoughts, mainly
7 inspired by SCAMP and other things.

8 Of course, we have a SCAMP study, which is
9 about nutrition, which did cause us some confusion,
10 and there is also a SCAMP study in the U.K. about
11 attention-deficit/hyperactivity disorder, which did
12 confuse some of our families who looked up our SCAMP
13 on the Internet.

14 So master protocols. The first design would
15 be to look for sites that are using the antibiotic of
16 interest and capture them, and that's where a network
17 would come in handy. And then you just hit those
18 babies with a well-designed PK study, optimal
19 sampling, combining some purposeful sampling with a
20 lot of scavenge sampling, which works nicely for some
21 antimicrobials.

22 And then in your master protocol, that is

1 done in a similar way with similar inclusion criteria,
2 similar outcome criteria, and you come up with some PK
3 data which you've warehoused, and you can pool and
4 take account of this.

5 And in Europe, at least, this would lead to
6 a natural experiment of different dosage regimens
7 because each center would use different dosage
8 regimens. In the U.K., we did a survey of vancomycin
9 doses -- sorry, John -- we got 48 units to supply us
10 with 24 different dosing regimens.

11 So if you did an opportunistic PK study,
12 then you would end up with some of the dosage
13 variation that is necessary to build up good
14 variation. You could, of course, try again to get the
15 same thing, but that might be difficult.

16 And then this could be combined with PD
17 targets. And then you could expand this to include a
18 safety surveillance study with registries and so forth
19 in the same sites, which might even allow you to use
20 anonymized data in the U.K. without getting consent,
21 but again ethics.

22 Another design, which I'm sure has been done

1 by people more effective than me would be to select
2 sites according to which antibiotics they are prepared
3 to use rather than the ones that they are using, and
4 this then allows you to do some kind of comparison,
5 and the people could be randomized to a single target
6 group, be it empiric, confirmed, or rescue, depending
7 on what that antimicrobial is looking at.

8 And then you could vary this between centers
9 depending on what they wanted to use. And you might
10 have to have more than one comparator. But that is
11 actually quite useful because it gives you more
12 variation to play with in your PK-PD models. And this
13 then gives you some prospective comparative data for
14 both efficacy or whatever you want to use, and safety.

15 So in any master protocol, the key
16 assumptions would be that data can be pooled across
17 sites and PK warehousing, so you need to be able to
18 stratify by site, GA band, and target group.

19 And, finally, a common comparison may be
20 difficult, so you might like to borrow a concept that
21 the Systematic Review has used, sort of a network
22 analysis, where if A is better than B, and B is better

1 than C, then A is probably better than C. And I think
2 building that into your models, structuring that into
3 your models, might be helpful so that you can take
4 account of the maximum number of studies and sites.

5 So my final slide would be to conclude that
6 master protocols can be developed, that PK data can be
7 pooled, the safety issues are generic to neonates but
8 do need to be improved on. Outcomes may be
9 problematic. Comparisons may be problematic. But
10 trying to come up with a master PK-PD model that
11 allows you to look at the variability without
12 subjecting millions of babies to the clinical trial I
13 would say is the best way forward.

14 And I came with a message from colleagues at
15 the EMA to say please work with your jurisdictions.
16 It's proven quite difficult to do that face-to-face
17 and quite challenging to do it remotely. So someone
18 told me that the best way to cross the Atlantic is go
19 Business Air with Iceland Air because that's the
20 cheapest way. So maybe we can all meet in Iceland and
21 then all travel cost effectively in business class.

22 Thank you very much.

1 (Applause.)

2 DR. FARLEY: Thanks very much, Mark.

3 And you all will be relieved to know that
4 we'll be done projecting for the day.

5 (Laughter.)

6 DR. FARLEY: We're going to take a 15-minute
7 break. Then we'll take on panel discussion questions.
8 The audience will be welcome to participate in the
9 panel discussion via the microphones. If a member of
10 the general public wishes to give a formal
11 presentation to the workshop, please see me at the
12 break.

13 Thanks very much. We'll see you back at
14 3:15.

15 (Break.)

16 Panel Discussion (Covering All Topics)

17 DR. FARLEY: Welcome back, everybody. Those
18 were great presentations.

19 What we're going to do is work through some
20 questions for a panel discussion, and you'll find
21 those on the very last page of the agenda packet that
22 you should have been able to pick up the door. Does

1 anybody need an agenda that doesn't have one?

2 (No audible response.)

3 DR. FARLEY: And how about the panel?

4 Everybody is good?

5 (No audible response.)

6 DR. FARLEY: Great. And, Chris and Anne, I
7 can't see you very well, so wave.

8 So John and I are going to be co-moderating
9 this discussion with Sumathi jumping in on occasion
10 just to see if there's clarification.

11 So I guess the first topic is the issue of
12 extrapolation and the issue of clinical conditions in
13 which extrapolating efficacy from adults and older
14 pediatric populations are acceptable for neonates.

15 So, Tom, you've named some of those. And
16 then the second is for indications or extrapolations
17 not feasible, how certain ways forward on getting to
18 demonstration of efficacy.

19 So anyone volunteering to kick off the
20 discussion?

21 John Bradley is the other narrator. This is
22 the nice John, not "the" John.

1 (Laughter.)

2 DR. FARLEY: Danny?

3 DR. BENJAMIN: So let me just make sure I
4 understand. Extrapolation meaning if I have a similar
5 disease in a different patient population, given
6 similar exposure, the impact of the therapeutic is
7 going to be similar across patient populations.
8 Right? So --

9 DR. ALEXANDER: Close. I mean, the
10 distinction would be the idea that you need actually
11 both. The idea of extrapolation is one that requires
12 both of those items, that you have a disease or
13 condition that's similar enough in the group that
14 you're extrapolating from to the neonates. But the
15 other part of that is that the response to treatment
16 is also then expected to be similar in those two
17 groups and that those two things together is what
18 allows you to extrapolate.

19 For our purposes for infection, we don't
20 necessarily worry all that much about response to
21 treatment because we are still looking at what we're
22 talking about with regards to efficacy for

1 antibacterial drugs. So a lot of what we're relying
2 on there seems to be with regards to antibacterial
3 efficacy. But there certainly are occasions where you
4 might be worried about the response to treatment with
5 a particular antibacterial being different, that you
6 can't just rely on sort of the fact that the drug is
7 just expected to kill the bacteria or kill the fungus
8 that you're dealing with.

9 DR. BENJAMIN: And the second clarification
10 on this is we're talking about both antibiotics and
11 antifungals, but not antivirals, or are we just
12 talking antibiotics?

13 DR. FARLEY: I think we had in mind
14 primarily antibacterials and antifungals at this
15 point.

16 DR. BENJAMIN: Okay.

17 DR. FARLEY: Antivirals have the advantage
18 of generally having viral tests, which we all wish we
19 had.

20 DR. BENJAMIN: So I would say that there are
21 three areas that I would be uncomfortable. There are
22 a whole lot of areas that I would be comfortable, but

1 there are three areas that I would be uncomfortable.
2 The area of least comfort would be invasive mold
3 infections, for example, aspergillosis. We see
4 aspergillosis so infrequently in the neonatal
5 intensive care unit, I'm not always sure what we're
6 doing when we deal with it. And I get calls from all
7 over the world about that, and I don't know what to
8 do.

9 The second area where I have some discomfort
10 is invasive candidiasis primarily because the real
11 difference for the neonate is that it goes to the
12 brain with much higher frequency than older humans.

13 And then the third is probably around kind
14 of the community-acquired pneumonia for babies less
15 than 1 month of age. I have -- you know, of those
16 three, I'm the most comfortable with that, but I have
17 discomfort with that group.

18 As far as urinary tract, complicated urinary
19 tract, infections, it's bad for you if you don't
20 respond to the therapeutic.

21 Complicated intra-abdominal infections,
22 you've got like we may want to bicker about that

1 medically some other time. I think if you spend
2 enough time with babies with medical NEC and you see
3 how often they can go to surgical NEC, you might feel
4 a little more comfortable there.

5 But for the most part, other than those
6 three top ones, I'm pretty comfortable extrapolating.

7 DR. NOEL: I just want to make a point
8 actually. Chris talked about with new antibiotics
9 coming through, the need to accept and better and
10 better to look at these smaller packages. And I just
11 wonder whether or not we're asking for less and less
12 data to support efficacy in adults that we will come
13 to a point where we're sort of extrapolating upon
14 extrapolation, and I think we need to keep that in
15 mind when we're looking at some of these newer agents
16 maybe and seeing experience in 500 patients. How well
17 have we really established safety and efficacy that
18 we're willing to take that?

19 The other point also would be that as we're
20 extrapolating, we also need to underscore the
21 importance of established response -- exposure
22 response relationships, and how rigorous has that

1 response exposure relationship been established in the
2 adult experience that we can be confident that we can
3 extrapolate on that as well?

4 So those would be two points that I sort of
5 point to as being generic considerations.

6 DR. NAMBIAR: Danny, just another question.
7 So if it's a neonate with (off mike) sepsis (off mike)
8 neonate, and you really (off mike) the drug does
9 anything to the central nervous system, would you be
10 comfortable in extrapolating (off mike)?

11 DR. BENJAMIN: Yeah, (off mike) central
12 nervous system. I'm sorry, I just thought that was so
13 -- I'm sorry. You've got to know if that drug gets
14 into the central nervous system. I figured everybody
15 in the room was on board with that. But the highway
16 is just -- you know, the 1970s highway is littered not
17 only with Star Wars movies, but also with
18 aminoglycoside failures where you essentially selected
19 for ventriculitis of the central nervous system and
20 knowing what to do after that.

21 DR. NAMBIAR: So I think that certainly
22 leads me to the second question. How do we know that

1 the drug penetrates or does anything to the central
2 nervous system? Is it all based on CSF PK penetration
3 data (off mike) potentially looking at the -- rather
4 than (off mike) infection. If you just (off mike)
5 that you see in the CSF space. I think (off mike).

6 DR. BENJAMIN: So I think that the number of
7 humans that you have access to and the amount of human
8 data is so small for the therapeutics and the lift to
9 get them is so big that a few things need to happen
10 and a couple of things ideally would happen. Okay?

11 Number one that needs to happen, you need to
12 maximize multiple different models. The fundamental
13 premise of epidemiology, we want to know, why does
14 smoking cause lung cancer? There has actually never
15 been a randomized trial to show that, but we believe
16 that to be true because different investigators using
17 different methods at different time and space have
18 replicated each other's work. Right? Whereas we
19 don't necessarily believe that coffee causes
20 pancreatic cancer based on one paper. Right? So
21 different investigators, different methods, different
22 models, across time. So that's number one.

1 Number two, I think that some human, older
2 human, data is also required.

3 And number three, some neonatal data is
4 required. And a good, albeit imperfect, way to look
5 at things is older human shunt data and neonatal shunt
6 data and see if you get any surprises there. Because
7 if you're not getting surprises there, I think you're
8 -- it's not perfect, but you're less likely to have
9 surprises. And shunt studies and shunt PK is a lot
10 easier to do than getting a lumbar puncture from the
11 big one-off meningitis patient.

12 Then the things that I think ideally would
13 happen that the agency itself has less influence over
14 is for companies to be encouraged to collaborate
15 postmarketing in a rigorous assessment like the --
16 similar to the POPS study. We've given the POPS study
17 to the agency before when they've wanted to use it in
18 an area outside of infectious disease. It's a
19 publicly funded study, it's available. We're happy to
20 do whatever can be helpful there.

21 And I think that this is an area that
22 public-private partnership actually as it relates to

1 the National Institutes of Health and FDA and
2 companies is worthwhile because this is a heavy enough
3 lift. And it's not a crisis for us today. It's
4 pretty rarely that we have babies who get infected
5 where there's absolutely no therapeutic today, it's
6 pretty uncommon. But it's --

7 DR. FARLEY: John?

8 DR. BRADLEY: So if I can be the loyal
9 opposition, and I wish William were here, I think
10 there is virtually no infections in neonates that can
11 be extrapolated from older children and adults for
12 many of the reasons we've discussed. And I know this
13 is all on the record, and everything we've said is
14 taped, so I won't go through the immune-compromised
15 issues that I had earlier today.

16 Complicated intra-abdominal infections we
17 study in children, and I think they're different than
18 NEC. And I know Danny recognizes this, so I'm not
19 disagreeing with him, I'm sort of fleshing out the
20 overall problem.

21 But we, since '79, have been trying to study
22 NEC during my fellowship, and we thought it was the

1 toxin-producing Klebsiella, and, of course, we still
2 don't know exactly what causes it, but what is NEC?
3 The baby stops eating and the intestines get a little
4 bit distended, that's pre-NEC or NEC scare.
5 Neonatologists have like five different names for it,
6 and they all get antibiotics, the feeds get stopped.
7 I don't know how many of them truly have an infection.
8 Perforation, of course, can be picked up
9 radiographically. And some surgeons go in, some will
10 wait for a while because they want fewer
11 manipulations.

12 We had a baby with medical NEC for a week
13 and was doing well, the CRP actually was down to 3 to
14 4, just above normal, and then they tried to feed him,
15 and he ended up having four perforations and (off
16 mike).

17 So it's in part inflammatory bowel disease,
18 so looking at endpoints from the infection are
19 different than the endpoints perhaps from whatever
20 vascular event caused the NEC in the first place.
21 And, again, we've talked about the confusion of the
22 outcomes being complicated by the natural history of

1 the disease process.

2 The vascular lines, I don't even know if the
3 coag-negative staph infection can be extrapolated from
4 adults. I know adults, I've heard, just pull the line
5 and stop the antibiotics. In children, we pull the
6 line and keep the antibiotics going for a while, 3 to
7 5 days.

8 And in babies, especially PICC lines that
9 have been in for a while, there is a clot along that
10 vessel where the PICC line is, and I agree that there
11 is endovascular infection, and we'll probably treat it
12 for a couple of weeks, but if you send the baby home
13 and they get recurrent coag-negative staph, it's a
14 very non-severe disease with very vague symptoms that
15 would be very difficult perhaps for the parents to
16 pick up.

17 So I don't even know if catheter coag-
18 negative staph infection could be extrapolated.

19 But the problem, of course, is, how do we
20 study it? So I don't want to tell you everything is
21 bad about --

22 DR. FARLEY: Just stop all studies.

1 DR. BRADLEY: Yeah, stop all studies. We
2 can't do that.

3 There is minimal safety data that I think
4 are required to let us feel comfortable using the
5 drug.

6 And then efficacy, the first pass, and this
7 is where modeling and then adding to your model, the
8 first pass could be extrapolation, so despite what
9 I've said, you could extrapolate the exposure for
10 complicated appendicitis down to a baby.

11 And then right after the drug is approved on
12 some limited basis, for babies, this is all just for
13 babies, then some post-approval setting where you
14 could continue to collect data so that you're not
15 requiring a huge amount up front before the drug gets
16 approved, because that will never happen, and you're
17 also not just getting a little safety data and then
18 just letting everyone use the drug willy-nilly because
19 then there may be safety signals and non-efficacy
20 signals which may pop up later, which none of us also
21 want. So extrapolation, limited release, and then
22 post-release review as the drug gets more used.

1 Now, especially for these new Gram-negative
2 drugs, in the EU, the EU is not homogeneous, as Mark
3 really beautifully showed, and most of the papers on
4 multidrug-resistant Gram-negatives in neonates that
5 are even colistin -- several of them colistin
6 resistant, are from Greece, which the last time I
7 checked was still in the EU. England, that's just --
8 you're in Europe, not necessarily. Anyway.

9 (Laughter.)

10 DR. BRADLEY: Studies can be done, efficacy
11 studies, in these babies, because they've got culture
12 techniques. I don't know why they have so many
13 infections, but on Mark's slide, he said infections
14 with drug resistant organisms are rare. Well, that's
15 in the U.K., but maybe not in Greece, perhaps Italy.

16 So there is opportunity to study these, and
17 not only in the EU. Latin America. I'm sure Danny
18 gets calls from sites in Latin America where they have
19 babies in NICUs that are infected with multidrug-
20 resistant organisms, and they were actually trying to
21 steer one group in Buenos Aires to AstraZeneca to get
22 ceftazidime/avibactam used in one of their nurseries.

1 So there are other parts of the world where
2 the disease is there, the babies are dying, and
3 there's a critical need for studies, and perhaps that
4 might be a place where you can get efficacy data that
5 you just can't get in the U.S. because we don't see
6 it, and that involves politics I'm sure as well as
7 science, and I won't even go there.

8 And for the CSF, just one last comment. In
9 our hospital, we have an idea of who all gets lumbar
10 punctures, and we don't do too many. We're not like
11 one of those sites, but we do probably average at
12 least.

13 But you know when a baby is going to get an
14 LP, and the decision is made. It's usually not, "Oh,
15 my god, this baby needs an LP right now." You decide
16 the baby is not doing well, irritability, questionable
17 -- there's something that wants you to do an LP, and
18 you've got a few hours before that LP is done, and if
19 you've got the neonatologist or the emergency medicine
20 doctor and ID team primed so that as soon as someone
21 says, "I think we need an LP," it's possible to give a
22 single dose of an investigational agent prior to the

1 LP.

2 That will make your culture not as good, so
3 it's impacting care in that way, so you don't get
4 something for nothing, but the balance of getting
5 information on CSF penetration of the drug and knowing
6 that most of these babies will have normal LPs anyway,
7 that the juice might be worth the squeeze. We have to
8 run that by IRBs I imagine.

9 DR. FARLEY: Yeah. I'm sure that other
10 folks may have comments. Just sort of on the -- so
11 that was a lot.

12 (Laughter.)

13 DR. FARLEY: Let me focus on one thing
14 because I think one of the -- you know, for me,
15 medicine is all about trying to reduce the uncertainty
16 as best you can, and one answer, as we've talked
17 about, is CSF penetration of drugs.

18 So when you all do opportunistic sampling,
19 maybe I'm misunderstanding how it works because the
20 scenario John is laying out sounds like the exact
21 scenario we run into in nosocomial pneumonia where the
22 patient is critically ill, you're trying to find the

1 family to enroll them into a study. Do you guys --
2 you don't give them dose in your -- or some medicine,
3 you just -- it's just whatever medicine they happen to
4 receiving at the time. Is that right?

5 DR. BENJAMIN: So it's worked out a couple
6 of different ways. For the meropenem study, they were
7 enrolled in the meropenem study, and then if they were
8 getting cerebrospinal fluid per standard of care, then
9 we got cerebrospinal fluid. So we were not tapping
10 them just to tap them.

11 DR. FARLEY: Right. Right. Or hanging
12 meropenem just because.

13 DR. BENJAMIN: To tap them. Right.

14 DR. FARLEY: Right. So does that -- so I'm
15 a little -- I'm wondering sort of, trying to
16 understand your idea a little bit more.

17 DR. BRADLEY: Right. So most of the
18 protocols for the past 5 years have had this if you
19 get CSF, please (off mike), and hopefully there is a
20 serum sample that you compare with it within a few
21 hours. But getting CSF is difficult, and one can look
22 at when kids are tapped.

1 I mean, we can say what are the
2 circumstances surrounding the last 100 children who
3 got LPs who were under 2 months of age? And many of
4 them will be rule out sepsis from the community who
5 are irritable, and then there will be the babies in
6 the nursery who start having apnea and bradycardia,
7 and it's an aggressive neonatologist.

8 So the LP is the big event. That's -- to
9 talk to parents, "Your baby needs a spinal tap," is
10 like, "Oh, my god, that's horrible." But once that
11 decision has been made, then extra risks from giving
12 ceftazidime/avibactam, or meropenem is a small added
13 risk, and there will be many parents who will refuse,
14 but what I'm doing is trying to take the opportunity
15 of a baby who is destined to get an LP and see if we
16 can't leverage that into a single-dose PK CSF study.
17 That's all. It's just a thought. I'm not -- it's
18 just a thought.

19 DR. FARLEY: Mark.

20 DR. TURNER: So we've heard from the (off
21 mike), I guess I would like to take (off mike) sit
22 between the two (off mike) extrapolate all bacteria

1 except for brains, and John said no extrapolation at
2 all.

3 I confess I'm more on Danny's end of the
4 clinical spectrum. But I guess I would reframe it a
5 little bit in terms of, do we need to demonstrate (off
6 mike) I just want (off mike) information (off mike)
7 that this is safe is my first guess because I'm going
8 to have to change the antibiotic (off mike).

9 So is it (off mike)? And is that what we
10 mean by efficacy or is it demonstrating efficacy a
11 little bit more than the (off mike) of the (off mike)?

12 DR. BRADLEY: Just getting safety and using
13 extrapolation and then --

14 DR. TURNER: Use -- use --

15 DR. BENJAMIN: The kind of rudimentary pre-
16 thinking, and then that might be housed in (off mike).
17 If we don't get efficacy, then there is no dosing that
18 goes into the American label and there is no safety
19 information that goes into the American label unless
20 it's a (off mike). And so you then don't need to get
21 the drug studied, so then (off mike). Okay?

22 So if we don't have a pathway to efficacy,

1 we're not going to be studying these drugs in the
2 NICU. So that's why we're talking about efficacy,
3 because you've ultimately got to end up there.

4 Now, the number of agents that one needs to
5 study is much less if you extrapolate than if you do
6 one or two pivotal, blinded, low-power trials.

7 DR. FARLEY: And we heard about that in kind
8 of excruciating detail this morning challenging that.

9 DR. KOVANDA: And who is going to sign up
10 for two?

11 (Laughter.)

12 DR. FARLEY: So maybe moving us along a
13 little bit, I'm sure this is sort of -- we're hearing
14 about kind of using multiple different models. And my
15 understanding of what that allows you to do is kind of
16 this iterative process between the neonate and the
17 hollow fiber model and bunnies. And I think what that
18 allows you to do is to get to a reasonable neonatal
19 exposure with using less neonates. Am I understanding
20 that correctly? That's kind of the major purpose of
21 that.

22 And then once you're there, where do you see

1 that going next? In other words, do you have to then
2 do a trial with that dose? Or do you think you're
3 done?

4 DR. BENJAMIN: Chris is (off mike) because
5 I'm not saying it precisely, but ultimately when you
6 do the bunny and the other animal models and the
7 hollow fiber, you get two key pieces of information.
8 One is it helps you some with PK, which reduces sample
9 size within a dosing stratum, and the other is that it
10 potentially helps you considerably with PD, which is
11 very important to say, so the so-called bridge. All
12 right?

13 So kind of as I see it, you need multiple
14 different models, and use that to go into the neonate
15 so that the information from the adults and the
16 information from the children, the information from
17 the shunt studies, the information from the animal and
18 hollow fiber models all then confers at the point of
19 at least get some neonatal samples so that you avoid
20 what I would call the tenfold dosing surprise.

21 DR. FARLEY: Right. Right. And I would
22 imagine the precision about the dose, there is less

1 variability because right now what we've heard is that
2 sometimes multiple different doses are being used, and
3 then you're getting a CSF sample, and I would assume
4 that would be harder to interpret. So anyway.

5 DR. BENJAMIN: The hardest thing for me for
6 interpreting the CSF stuff is that you're typically
7 only getting one sample, and so really it's very hard
8 to do anything but estimate area under the curve or
9 time above MIC, but you at least have some human data
10 in the target population when you get that percentage.

11 DR. RUBINO: So I'll speak for William,
12 since he had to leave. Hopefully I'll get the gist of
13 what he was going for there. But I think one of the
14 points he brought up that really struck me was the
15 concept of validating these models using drugs that we
16 already use. Right?

17 I assume, John, that amp/gent for early-
18 onset sepsis, you say, well, that's what we use them
19 to do. Right?

20 So we have a model that uses those drugs
21 that were already accepted as being useful, show that,
22 yes, these in vitro models or the animal models are

1 replicating reality with those drugs, that gives us
2 some comfort that we're not going to be having a false
3 bridge. Okay?

4 And I think -- I obviously am going to come
5 down on the side of thinking that extrapolation is
6 always going to be useful, and in most cases, it's
7 possible. And I think a lot of the stuff that John is
8 bringing up, all valid points, are not necessarily a
9 problem of extrapolation, but it's a problem of the
10 underlying models and it's a problem of what we don't
11 know about where the drug is going to go. Right?

12 If the drug kills bacteria in a model, we
13 can't ask it to do anything else in the body but kill
14 bacteria. The problem is it's not getting where it
15 needs to be, the drug that is, or if our model isn't
16 replicating the human condition well, then we're off
17 and we can't extrapolate. But otherwise, we should be
18 able to extrapolate in any situation, there is just --
19 we have a long way to go with some of those models.

20 And there's just one other point on CSF I
21 wanted to make, is those PD-PK systems, acknowledging
22 what William said about the diversity of the central

1 nervous system and the fact that we're only sampling
2 CSF, that's the next step. Right? Let's try to get
3 the first step. But the PD-PK models, one of the
4 great advantages is there have been studies that show
5 the properties of the drug that allow it to get into
6 the CSF, and we know we can test those -- we know we
7 need to test those properties in humans, we know that
8 it's based on physicochemical properties.

9 So we can make some predictions about what's
10 going to happen and then use whatever data we can get
11 to try to support those predictions. And I think the
12 thing that I think is difficult is in adults in
13 bacterial development -- and you guys can correct me
14 if I'm wrong -- but we don't see many studies where
15 they're getting CSF in adults.

16 So that's a bigger jump, and I'm nervous
17 about, yeah, we can get a few kids, but there is this
18 big hole where we don't know that PD-PK system for
19 neonates yet, so we know it better in adults, but we
20 don't have that qualification of adult CSF data.

21 So I think that's a step we're going to have
22 to talk a little bit about, is what kind of studies

1 would sponsors have to run for a new drug to show that
2 it's getting into the CSF in adults?

3 DR. FARLEY: One thing I just want to make
4 sure that we talked about was people have mentioned VP
5 shunt patients as potential subjects where we might
6 get CSF data. We haven't seen that in a regulatory
7 submission, so I'm wondering if it's actually -- how
8 feasible folks really think that is.

9 DR. NAMBIAR: So I think, John, a few years
10 ago we had one sponsor who I think -- not a lot of
11 data that we're getting submitted. Do you remember
12 that one, John? I don't. There were a handful of
13 samples. But I think -- I mean, we obviously are open
14 to the idea of at least trying to collect CSF from VP
15 shunts or external devices. But the question really
16 is, how different or similar is it to (off mike) that
17 the U.K. has (off mike) infected?

18 But I think Danny's point is valid. If you
19 get that in adults and you get that in children, at
20 least -- I think at the end of the day it's putting
21 all the pieces together. No one piece is going to be
22 perfect, every one of them is going to be imperfect.

1 So at some point, will we ever be comfortable with all
2 these little pieces that head in the same direction
3 that's going to appear?

4 And I think the other point Danny made
5 currently was that even if we do all of this and we
6 get to a label, I think it's still based on very
7 limited information with a lot of deep faith. And so
8 then we have to continue to try to collect the data
9 postmarketing where you're using networks or some
10 other tool so that you continue to collect the
11 information where then the opportunistic sampling will
12 be a lot easier because that drug is then being used
13 in the rest of the population.

14 DR. ALEXANDER: I would say that the
15 situation that we did see the attempt to use VP shunt
16 infections or VP shunt patients in order to get PK
17 data was something where we were initially pushing to
18 try and get a drug that was a Gram-positive agent
19 study for VP shunt infections.

20 And the one thing that you can do in the PK
21 study for children is say that these kids who will be
22 getting a VP shunt placed will usually be receiving

1 some sort of antimicrobial prophylaxis, so if you have
2 something that's being used as a -- that you're
3 wanting to study that's a Gram-positive agent or has
4 some activity in Staph and Strep, then that study
5 design may be reasonable to say, okay, instead of
6 getting your usual prophylaxis, we're going to give
7 you this novel agent instead, and then obtain the CSF
8 data afterwards from the patient who is getting the VP
9 shunt placed. It may be problematic if what you're
10 dealing with is something that's a Gram-negative agent
11 and something that we see are infections or some of
12 these other things where you're worried about more the
13 activity in Gram-negative infection.

14 DR. NOEL: I would just like to point
15 something out to you in regards from the sponsor's
16 position. So you can see that there can be a dramatic
17 difference in opinion on what's needed, and if the
18 goal is to truly label the drug, I would point out to
19 you that sponsors typically bringing people like John
20 and Danny together, it may very well be that the
21 sponsor is not going to be comfortable with
22 extrapolating data from adults.

1 And in the past, that was reconciled, the
2 distant past, George McCracken (ph) would go out and
3 study the PK and make a recommendation in literature.

4 I think our goal is to get these things
5 labeled. Okay? So I think it's important for you
6 when you're having this discussion with the sponsor to
7 get the level of their comfortableness in that
8 extrapolation and to be clear that if we're doing this
9 PREA-required program, that they're going to be
10 comfortable about the label of the drug. Because I
11 think we still have an option as a sponsor to meet our
12 requirements, even to get exclusivity, without being
13 compelling to put that information in the label.

14 And I can point to my Levaquin experience
15 and say that's exactly what happened. Levaquin had to
16 -- you know, randomized controlled trials that jot out
17 this design to show the efficacy in kids with
18 pneumonia and otitis media, but the company pursued
19 not to put that in the label. So my intent is to have
20 that option.

21 DR. BENJAMIN: The laws changed. If you do
22 the studies, the pediatric data become -- information

1 from that trial becomes publicly available, whether
2 it's the medical summary or the pharmacology summary
3 or whatever. Now --

4 DR. FARLEY: Let's ask John to go over the
5 current policy.

6 DR. ALEXANDER: So I think that the idea
7 that Danny has expounded on is the idea that there is
8 a requirement to have some description, even negative
9 studies, so if there are results that are important to
10 put in to describe about either negative effects of
11 the drug, then those things would still be expected to
12 be put in, but more limited in terms of what we would
13 then add.

14 We wouldn't be adding information about
15 dosing, information about what the outcomes were for
16 the trial, if the idea is that there was some safety
17 concern or overall risk-benefit consideration that led
18 you not to label the drug for a particular indication.

19 But I don't think that it's necessarily that
20 the law has changed, I think that the issue for
21 Levaquin may be one where in the consideration with
22 regards to otitis media about what the overall risks

1 of using a quinolone is versus the benefit for otitis
2 media.

3 DR. NOEL: That is not an FDA decision, that
4 was the sponsor's decision to go that route, and as a
5 result, that information is not on that label. And I
6 don't see how it couldn't -- I'm not saying that it
7 would, but I'm saying that it could happen if we get a
8 group of John Bradleys there telling us that this is
9 not sufficient enough data to be comfortable with the
10 efficacy, a sponsor very well may opt not to put that
11 kind of information in (off mike).

12 DR. NAMBIAR: Okay. Just so that I
13 understand. So how would you meet the PREA
14 requirements (off mike) go down to (off mike)?

15 DR. NOEL: Do the studies.

16 DR. NAMBIAR: Oh, you mean you would do a
17 separate --

18 DR. NOEL: You would do the studies, but
19 they would choose not to put it in the label.

20 DR. NAMBIAR: I don't think that option is
21 there. So you're saying you would do a neonatal study
22 separate and choose not to put that in the --

1 DR. NOEL: I wouldn't put labeling in there
2 to say that the drug is indicated for use in newborn
3 infants.

4 DR. NAMBIAR: I think that will be my next
5 (off mike).

6 DR. NOEL: I'm just pointing it out because
7 we're seeing a very -- if everybody was (off mike),
8 this is not an issue, but if a sponsor is going to
9 hear those opinions, and I think they are, they hear a
10 lot of those opinions that John is voicing, I think
11 there's enough concern there.

12 DR. FARLEY: So I'm mindful of the time.
13 Are there burning topics for the next 2 minutes? One
14 thing I can tell you is that you should look forward
15 to more data on the in vitro/in vivo human approach
16 that William described. There are some projects
17 underway, and that's going to be exciting, and I think
18 we're really just learning about this model. So we've
19 got that launched.

20 Other topics that we want to make sure we
21 get to today?

22 PARTICIPANT: Lisa had one.

1 DR. FARLEY: Lisa, sorry.

2 DR. MULUGETA: Lily. I just have a
3 question. It was really targeted to Danny. He left.
4 It was really around the question of interpretation of
5 CSF concentration. The limited data we have on many
6 drugs is that it's extremely variable in this
7 population to the point where we can't make any
8 conclusion out of it.

9 So even if we were to get some data, what
10 are we looking for? Is it the ratio of the CSF
11 concentration to the serum concentration? Or that
12 there is just any penetration? Like what do we do
13 with the data?

14 And anyone can answer those questions.

15 DR. NAMBIAR: That's the exact same question
16 we have. At the end of the day, we struggle, and then
17 we get 60 or such samples, one of which may be (off
18 mike). And I think the meropenem study that Danny's
19 group did, I think it was five or six babies had CSF
20 data collected and it was (off mike). So when we
21 updated the (off mike), we only approved it for CIAI
22 in babies less than 3 months because we were not

1 comfortable with the data we had.

2 So it's like a lot of body fluids. I've
3 learned PK (off mike), but I don't know (off mike).

4 DR. RUBINO: Well, I don't know if I can
5 educate, but what I can say is in those situations,
6 it's absolutely critical to know the exact time that
7 it is drawn --

8 PARTICIPANT: Right.

9 DR. RUBINO: -- and the exact time that the
10 dose was given because those bits of -- when I see
11 that data and it looks like it's all over the place,
12 and it happens -- we see a lot of (off mike) studies,
13 but it happens in places where folks aren't doing a
14 good job of it, and most of the time I don't really --
15 you know, the protocol says when the sample should be
16 drawn relative to the dose, but that's secondary, just
17 knowing exactly when it was drawn, because there is so
18 much variability on this, you can't always get that
19 out of the equation, and then we can't do (off mike).

20 DR. FARLEY: Mark?

21 DR. TURNER: (Off mike) response to that
22 question. I guess (off mike) clinics towards the (off

1 mike) because, as a clinician, I want to know whether
2 this has good or bad penetration, and that's good
3 enough for me. I don't need to know precision, I
4 don't need to know that cefotaxime is better than (off
5 mike), but if you talk about that, (off mike)
6 suspicion of meningitis. So I think it's important
7 (off mike) labels, it's important to have that (off
8 mike) met, but (off mike) want to know, which drug
9 should I use? And sometimes causes of inflammation is
10 useful even though it's not as extremely quantitative
11 as it might be.

12 So (off mike) answer that. Any information
13 is better than none, particularly (off mike).

14 DR. MULUGETA: But in this setting, I guess
15 where we're using that as the basis for extrapolation,
16 how much data do we need and how much certainty? And
17 just to sort of answer the question around timing of
18 the sample despite having that data because there is
19 huge variability, I'm not sure if some of it is due to
20 the way that LPs are conducted and the variability of
21 technique, but the data is highly variable, and it's
22 really very difficult to say that it penetrates the

1 CNS (off mike) because it's just so variable.

2 DR. RUBINO: Can I just make one quick one,
3 John?

4 So one thing I would say is with the way
5 that the modeling is going in terms of incorporating
6 physiology, I could see a situation where we could
7 take the little bit of information we have from each
8 drug, put it into the same system, which says that
9 these physicochemical properties of the drug predict
10 where it should go in neonates, and then increase the
11 power of the entire -- because we'll say, okay, we've
12 got this many meropenems, this many on this other
13 drug, and you combine five drugs together, our model
14 system, you can be relatively agnostic and just say I
15 don't care what drug it is, I'm going to predict for
16 that drug and leverage it all together and learn
17 something about neonates that way. It's just a
18 thought.

19 DR. FARLEY: John, I think we'll take maybe
20 two or three more comments and then we'll need to wrap
21 up.

22 DR. BRADLEY: We did a meningitis study 20

1 years ago, I forget how long, but just in regular
2 children there was incredible variation, and probably
3 10 percent of the samples there was no meropenem
4 activity at all, which made me really -- and all the
5 kids got better. So I don't -- there's a disconnect
6 between what we measure and outcomes, and I don't know
7 how to answer that question.

8 In terms of animal models, I believe it was
9 gatifaxacin was used in a rabbit model where there was
10 an indwelling ventricular catheter, and there were
11 beautiful curves that showed histories of serum levels
12 followed by CSF levels to attain an AUC.

13 So the models can be created from the animal
14 model, and then as you get neonatal samples, you can
15 plot those time after dose to try and see if they fit
16 the model, and I think that's the best.

17 DR. FARLEY: So John has made an optimistic
18 comment. I would like for the record to reflect that.

19 (Laughter.)

20 DR. FARLEY: Anne?

21 DR. ZAJICEK: I have a question. So, John,
22 we've been talking about hanging the whatever it is,

1 investigational antibiotic for a kid that didn't need
2 an LP emergently but needed it at some point.

3 DR. BRADLEY: Yeah.

4 DR. ZAJICEK: Was that the first dose of a
5 regimen or was that just one dose?

6 DR. BRADLEY: No, one dose PK.

7 DR. ZAJICEK: One dose.

8 DR. BRADLEY: Yes.

9 DR. ZAJICEK: Okay. All right.

10 DR. BRADLEY: It's a study. We need to get
11 informed consent, the whole -- yes.

12 DR. KOVANDA: So the one thing I guess I --
13 and maybe it's too late to say this, but the one thing
14 about the study that we conducted, that we recognize
15 that we've worked really hard to keep it as close to
16 standard of care as possible, which meant that you had
17 to put windows around everything.

18 And so if you notice from the CSF samples
19 that we were able to -- or CSF cultures and LPs that
20 we were able to get, they were largely at baseline,
21 only three patients during therapy. So those three
22 are doing cultures. So three samples during -- you

1 know, could have been used for PK sampling.

2 So it's all -- I think having -- being able
3 to get concentrations may not be in the setting of an
4 efficacy study. I guess that's where I'm --

5 DR. FARLEY: Yeah. Okay. So any other
6 burning comments?

7 (No audible response.)

8 Concluding Remarks

9 DR. FARLEY: We're very grateful for
10 everyone coming to the table, and I think we'll look
11 forward to having an opportunity to do that again.

12 We're pretty optimistic in terms of small
13 incremental steps that could happen. And the two
14 things we're thinking of are further work with the
15 modeling that has been described, perhaps moving
16 toward the vision that Chris just articulated a few
17 minutes ago. So that would be one thing maybe we
18 could look forward to happening over the next year or
19 two, and learning more about just what that -- where
20 that can take us.

21 The second piece I think in terms of
22 feasibility that we've heard about with the CTTI

1 project is the importance of engaging parents and
2 engaging investigators. CTTI is continuing to do more
3 work in that area, and I think that will be important
4 as well.

5 So we're not going to strike a rock and have
6 water come out, but maybe a little manna will fall and
7 we'll continue to make progress.

8 I look forward to talking with you all again
9 soon about this. So thanks very much for coming.

10 (Applause.)

11 (Whereupon, at 4:05 p.m., the meeting was
12 adjourned.)

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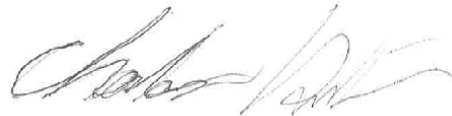
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September 27, 2016

Deborah J. Arbogast

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