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

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Capital Reporting Company

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

Introductory Remarks

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a neonatologist.

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

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

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

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

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

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

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

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

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

The Landscape of Neonatal Anti-Infective Drug Development

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

(Laughter.)

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

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

PARTICIPANT: No.

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

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

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

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

(Laughter.)

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

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

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

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

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

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

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

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

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

pediatric studies.

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

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

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

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

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

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

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

Two important points to keep in mind, which

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

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

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

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

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

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

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

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

easy to find.

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

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

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

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

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

(Laughter.)

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

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

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

You can come up and help me if you want. Can you make this be full screen?

(Pause.)

DR. FARLEY: It's back. We're good. Okay. I'm just going to do it with the arrow. Thanks.

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

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

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

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

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

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

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

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

I highlighted those that are used in extremely low birth weight infants. One of the --

(Slides malfunction.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

So thanks very much.

(Applause.)

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

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

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

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

on the central nervous system.

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

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

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

I want to emphasize here where the course of

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

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

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

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

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

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

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

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

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

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

For hospital-acquired bacterial --

(Technical difficulties.)

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

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

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

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

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

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

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

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

Now, each of these infections, we do think

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

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

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

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

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

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

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

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

timing of samples.

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

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

Thank you.

(Applause.)

CNS Dissemination in Neonatal Infections

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

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

Pediatric Trials Network.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

clinical parameters or the presence of bacteremia is really perfect.

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

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

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

awarded it to us. Thank you, NICHD.

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

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

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

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

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

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

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

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

So with that, I'll close. Thanks.

(Applause.)

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

(Break.)

Pharmacokinetic and Pharmacodynamic Considerations in Neonates

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

So this is my disclaimer, that the opinions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

neonates, and we have seen this with ceftriaxone.

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

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

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

There is also limited P-gp expression in the

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

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

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

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

So for Phase 1 enzymes, there is delayed

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

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

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

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

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

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

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

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

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

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

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

reaches adult values by 2 years of age.

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

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

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

ototoxicity.

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

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

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

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

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

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

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

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

Thank you.

(Applause.)

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

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

DR. KOVANDA: We'll see.

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

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

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

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

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

In my 18-year tenure at Astellas, we have

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

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

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

Before proceeding into a pediatric

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

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

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

mean of around 100 mg h/L.

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

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

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

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

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

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

In addition, it was important to all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

And in one country, it was particularly

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Now for our lessons learned.

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

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

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

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

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

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

So what are our thoughts on the future

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

Thank you.

(Applause.)

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

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

(Attendees in agreement.)

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

clinical trial networks in neonatal studies.

Thanks, Brian.

The Role of Clinical Trial Networks in Neonatal Studies

DR. SMITH: Thanks, John.

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

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

So those are my disclosures.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

And the data come from babies that are 25 to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thanks.

(Applause.)

Clarifying Questions from Audience/Panelists

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

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

DR. ALEXANDER: Okay.

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

So thanks a lot.

Gary, do you want to go ahead?

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

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

DR. NOEL: Okay.

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

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

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

DR. ALEXANDER: Certainly. So the idea

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

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

DR. FARLEY: Other questions and thoughts?

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

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

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

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

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

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

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

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

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

to make sure that that baby survives and survives intact.

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

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

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

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

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

Thanks.

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

DR. BRADLEY: Please.

(Laughter.)

DR. BRADLEY: Hi, Mark.

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

DR. BRADLEY: Thank you.

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

DR. BRADLEY: Great.

DR. TURNER: Another is that although they

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

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

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

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

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

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

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

DR. TURNER: Yeah.

DR. FARLEY: Gary?

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

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

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

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

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

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

right time whenever you pick them up.

DR. FARLEY: Susie?

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

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

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

DR. TURNER: Maybe I can try and address

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

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

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

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

DR. FARLEY: Did you want to comment?

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

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

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

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

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

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

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

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

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

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

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

DR. NAMBIAR: That's all the questions for

Dr. Bradley's comment.

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

DR. NAMBIAR: Okay. No.

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

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

DR. FARLEY: You go first.

DR. NAMBIAR: Mine is more --

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

(Laughter.)

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

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

PARTICIPANT: Yes.

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

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

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

DR. FARLEY: Do you want to answer that?

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

I also have a view that probably more than

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

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

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

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

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

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

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

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

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

Thank you.

DR. FARLEY: Danny.

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

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

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

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

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

(Laughter.)

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

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

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

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

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

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

So, Gary?

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

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

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

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

designing a trial.

DR. FARLEY: Right.

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

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

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

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

and enrollment rates.

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

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

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

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

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

DR. FARLEY: Yeah.

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

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

DR. TURNER: Yeah, we often have a dialogue

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

DR. NAMBIAR: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

accessing networks.

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

(Laughter.)

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

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

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

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

first.

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

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

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

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

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

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

DR. FARLEY: Christmas eve?

DR. KOVANDA: 2003 I think?

DR. FARLEY: Christmas Eve 2002.

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

DR. FARLEY: Yeah.

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

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

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

DR. FARLEY: Yeah.

Laura, did you want to say anything?

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

DR. FARLEY: Danny?

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

go ahead and advise the company to stop the study. That's number one.

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

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

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

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

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

certainty based on almost no data.

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

PARTICIPANT: John's card is up.

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

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

But I do want to push back a little bit on

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

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

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

PARTICIPANT: The last time we checked.

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

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

DR. FARLEY: Okay. Great.

DR. FERNANDEZ CORTIZO: Are you hearing me now?

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

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

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

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

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

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

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

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

DR. NAMBIAR: (Off mike) question.

DR. FARLEY: Yeah.

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

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

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

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

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

DR. FARLEY: Absolutely. Good points.

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

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

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

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

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

And the curve of anxiety among those that do

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

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

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

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

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

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

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

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

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

So maybe a good question for us would be,

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

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

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

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

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

DR. FARLEY: Yeah.

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

DR. FARLEY: Mm-hmm. John?

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

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

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

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

DR. FARLEY: Sure, John.

DR. BRADLEY: Unless you want to --

DR. FARLEY: Absolutely. Nope.

DR. BRADLEY: Okay.

DR. FARLEY: That's good.

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

to shift directions as you're going?

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

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

DR. TURNER: Can I just comment on that?

DR. FARLEY: Sure.

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

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

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

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

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

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

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

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

DR. FARLEY: Great. Gerri?

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

uncertainty.

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

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

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

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

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

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

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

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

(Lunch.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

this isn't being recorded, but --

PARTICIPANT: Yes.

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

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

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

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

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

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

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

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

should be for neonates.

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

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

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

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

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

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

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

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

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

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

(Laughter.)

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

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

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

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

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

hollow fiber and the rabbit models.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

correction.

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

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

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

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

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

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

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

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

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

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

I think it's important that we study more

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

And with that I'll stop. Thanks.

(Applause.)

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

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

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

Danny.

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

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

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

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

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

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

DR. HOPE: Right. So --

DR. BENJAMIN: Which is not trivial.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. RUBINO: Yes, I'm fine.

DR. FARLEY: Good. Okay.

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

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

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

DR. RUBINO: Thanks, John.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

extrapolated model.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

studies with too few patients.

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

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

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

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

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

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

signal is daunting to say the least.

So the good thing is there's a signal here. And I'm talking specifically from a pharmacokinetic standpoint. I'm not talking about clinical data or even pharmacodynamics, but just from the basic PK standpoint, there's a strong signal. We know that there are differences there, and that helps us, we can pick these differences up.

The problem is all of the action, if you will -- and all of these are different graphs. So this one on the left is very similar to what Lily presented earlier, but the maturation of different CYP enzymes relative to adult levels, and this is just the same publication from a rodent that used for the maturation of renal function.

But what you see here, if you look at the scales, these are all in years, it's in that first year where all the action is, and that's why we need to cut up into little buckets, because a lot is happening there.

We had a call the other day, actually your colleagues from Duke and I, with one of the sponsors,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you.

(Applause.)

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

Obtaining Clinical Safety and Efficacy Data in Neonatal Infections

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

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

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

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

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

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

are archived in the world of non-reproducible results.

(Laughter.)

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

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

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

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

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

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

Now, with regard to safety, our goal is that we have some understanding of these potential risks, hopefully a good understanding of those risks, but also those risks as they relate to treating a specific patient population for which that therapy is going to be directed, and which is important to consider when we start thinking about studying newborn infants, is that that information certainly may be coming from

populations other than newborn infants. They're unlikely to be coming from newborns that aren't suspected of having an infectious disease, but in many instances, that information may not be coming from infants who actually have the bacterial infection that we're hoping to treat.

And for that reason, I think the state of the art, the current state of the art, is that we construct these profiles in newborn infants considering observations made in older children and adults. That's certainly short of saying that we extrapolate efficacy, but in many ways we are doing that, understanding that if we do see a safety signal in adults or in older children, that we are concerned about that occurring in newborn infants.

But it also has to be weighed against or consider the heterogeneity of the newborn population that we have that data in, and that this is -- and I think this point has been made repeatedly -- this is a very heterogeneous population with regard to their maturational age, the onset of their infectious disease, whether it be within the first days versus

the first weeks of life, and all these things need to be taken into consideration when we're looking at the safety profile.

Now, there's a tail end to that because I'm not seeing the whole slide here because there are two more points. That's being cut off. But in any case, so comorbid conditions are also I think important to consider, that there are a variety of different comorbid conditions that we need to consider when we're constructing this profile in this population and concomitant medications. I guess we're going to open up not only concomitant medications that we invariably use when we're treating serious infectious diseases in infants because it's seldom the case that these patients are on mono-drug therapy.

And then the last issue that I want to share with you visually is this issue of sample size. And, again, this slide is not projecting.

I learned this early in my pharmaceutical career. I had been exposed to it as a clinician, but it became very important for me to recognize this as I started out. When we generate these data in clinical

trials -- and this has been referred to as the rule of three -- when we are essentially doing a study or we're looking at an experience of 3,000 patients, our statisticians, our mathematicians, are very keen to point out to us that if we don't observe an adverse event in that population, specific event, that it's greater than 90 percent probability that that event, if it does occur, is occurring in less than 1 in 1,000 patients. And then this is a logarithmic function, so that if you were to include a study of 300 patients and you don't see that event, you, in effect, are ruling that out in 1 in 100 patients.

And the point I'm trying to make in showing this to a group that's thinking about newborn infants is that it's seldom the case that we're going to get an experience even of 300 homogeneous newborn infants to really have great certainty as to whether or not we really understand the frequency of an adverse event or if a unique adverse event is occurring in a newborn infant compared to an older child or adult.

So at least the way I have approached this and the way I would advocate, and I think that it's

the consensus of the group that I'm hearing discussing this today, is that we certainly need to recognize the strengths and the limitations, be comfortable with the uncertainty that we have based on the data that we will generate in these studies.

But I go further in saying that when we do that, we need to be committed to continue to explore, to study, to understand the safety and tolerability of these drugs as they get out and are used more frequently in the trials. And I think that if I were to propose something that we can do to address this issue of risk, is to start thinking about ways that we can sort of uniformly assess after labeling of the drug continued experience capturing that, especially in critically ill children where I think we really need to understand best the tolerability and safety of these new drugs.

So then let me quickly turn to efficacy and again underscore that this is -- as a pharmaceutical physician, what we're asking is, what is the benefit of using this drug, the potential benefit? And, again, we're focused on a specific infectious disease.

I think our conclusions of efficacy need to continue to be based and influenced by our observations made in adults. Again, that's a different way of saying extrapolation seems to be acceptable or the best we can do at this point. But it really does need to consider the uniqueness of infectious diseases.

And I think this goes beyond just host responses and the pathophysiology of the disease, but I think there are some uniquenesses to the microbiology of some of these infectious diseases. You know, when we talk about pneumonia in the neonatal intensive care unit, we're talking about things like Group B streptococcal pneumonia. We have no idea about Group B streptococcal pneumonia when we're completing a package in nosocomial pneumonia for a new antibiotic.

Now, there is good reason to believe that it will be effective, but there are some major differences between the microbiology, the importance of coagulase-negative staphylococci in a neonatal intensive care unit. Many of the pathogens that I've

been involved with in developing new antibiotics really don't have extensive experience in treating coagulase-negative staphylococci.

Now, again, that doesn't mean that we can't extrapolate from other diseases and response concentration relationships, but there are some major differences, and I think those need to be considered.

And I think the last point that should be on that slide is that I think we'll seldom have the luxury of having a sufficiently sized, randomized, double-blind controlled trial to really assess efficacy in newborn trials.

So conclusion, I think our current understanding, we need to come to terms and to deal with the uncertainty behind building our conclusions about efficacy based on observations made outside the NICU.

I did want to point out that there are some diseases where there may be great similarity between what happens in the newborn infant and older infants and children. I point out vascular catheter-associated infection. I'm quite comfortable as an

infectious disease subspecialist in extrapolating efficacy in adults when we're dealing with treating a vascular catheter-associated infectious disease. But that might be the only disease that I know of where I'm comfortable in it, and that's not something that I think, Sumathi, you're seeing a lot of labeled indications for.

And certainly I think efficacy does need to be based on our understanding of pharmacokinetics and dynamics, that we can study in newborn infants, and we can get good information on, and then move from that to extrapolating efficacy based on drug exposure.

So let me turn to what I think is more interesting to talk about in this forum today, given that other people have more expertise than I do with regard to pharmacokinetics and pharmacodynamics and even extrapolation. But I think the challenges that we face clearly go beyond just the science here. And there are some things that I don't think have been mentioned in great detail at the meeting, but that maybe future workshops certainly do need to consider.

I think designing these trials with

objectives that we can clearly communicate to parents, and for that matter, all stakeholders, clearly be able to communicate that, is critical to the success of these programs.

I'm raising that because I do review a lot of protocols internally, not in infectious disease these days, but in other therapeutic areas, and I think one of the great challenges that drug developers have in bringing trials forward in children is lack of real clear ideas about what this trial is actually going to show. What are its limitations? That needs to be communicated to parents. It needs to be communicated to the physicians who are enrolling children.

I couldn't help but think when I made the comment earlier today about assumptions being made that are going to drive -- are going to be needed in order to test the hypotheses that are posed in the trial.

You know, if we think that these trials have the risk of not completing, I think risks like that should be communicated to our clinicians and should be

communicated to our parents. I think parents deserve the right to know when they're exposing their trial to an investigational study that there is a chance that the scientific question that's being asked is not going to be sufficiently answered. And we don't do that routinely.

But if we are going to sit here as a group and accept the risk that these trials aren't feasible, that's the kind of risks that I think do need to be shared.

And I think too often we don't, as sponsors, really lay out very clearly for our investigators what the objectives are of the trial and how they can best communicate that to their ethics committees and to their practitioners.

The other point that has been touched on, but I've got to underscore it because of my experience as an investigator as well as experience in trying to develop drugs in children, is the challenge that we have in providing true informed consent, especially in the critically ill infant.

And we do need to think about ways that we

can prepare our investigators, prepare neonatal intensive care units, such that they can and they are able to provide true informed consent in this very chaotic environment, a critically ill child, I think that we need to continue to further define what the great challenges are in getting parents to consent to being included in clinical trials.

I just came back from an EMA meeting where I was surrounded by a group of neonatologists, and we did have some informal discussions about the sociologic geographic challenges that sometimes exist in enrolling patients in clinical trials.

And I think keep in mind that many of these patients -- many of these parents of newborn infants are single parents, they can have very poor social connections and support systems. They're going through the chaotic experience of having a newborn that's now in a critical care unit.

In many instances, the experience is that these patients, these newborns, have been transported tens of miles from their home, so parents are challenged in actually visiting the child.

So these are things that not are necessarily unique to the newborn infant, but I think developing a culture of understanding the importance of doing clinical trials and engaging parents, which I think the point Mark has made, not only in the process of developing these trials, but even in the process of their experience in the neonatal intensive care unit of understanding how critical it is to have clinical trials ongoing in order to understand best how to use these new medicines.

And so I thought in my last slide here I would go into some additional sort of bullet points that highlight what I think might be particularly fruitful to pursue if we're really going to make a meaningful change to deal with some of the uncertainty that exists in this area.

Again, I said I had this bias about host response, specifically about mononuclear phagocyte function in newborn infants, but I think it's incorrect to assume that we know -- have a real good understanding of the pathophysiology of these infectious diseases in newborn infants, and I think

that there is an enormous amount of work that can be done to better define that.

And I would be surprised if that information doesn't have great import in understanding differences. I assume that it will establish some similarities, but that it will establish some differences, and that those differences may be important to consider when choosing the right antibiotic and even the right dose to treat these patients.

I think being able to define the comparability in pathogenesis of the disease is central to this concept of using extrapolation. And I think that one thing that can be done as we're learning more about host responses is to engage a group of informed neonatal immunologists, some neonatal infectious disease people, and ask them to give us the best information about the understanding of the pathogenesis of the disease so we really do have some data-driven understanding of what the differences are between a complicated skin infection in a healthy 35-year-old and one in a 2-week-old 28-

week preemie.

And these would be things that would be entirely amenable, in my opinion, to a white paper that could be constructed in the matter of several months by an informed group provided they were given the resources and the incentives. And I'm not volunteering Johnson and Johnson resources to do that, but I think --

(Laughter and applause.)

DR. NOEL: But I would point out that now Merck and Pfizer basically own every antibiotic that's currently been licensed in the United States and that maybe they have some interest and a more vested, albeit conflicted, interest in defining the similarities and differences.

There's more on that slide. The next thing I think was diagnostics. Yes.

Now, there is a considerable amount of energy that's being put into advancing the concept of bacteriologic diagnosis and fungal diagnoses in the acutely ill adult, and so there are platforms now that are commercially available. But I think it's critical

to start to work with these manufacturers to start thinking about how, if these platforms are first amenable, to diagnosing the specific bacterial infections in newborn infants. In some instances, the material that would be necessary to do the testing is just not compatible with testing newborn infants.

And it may be that we would need to have a better understanding of the pathogenesis of the disease to understand whether or not it makes sense to use some of these diagnostics.

But I think in order to construct more efficient trials, we do need to be able to have some confidence that first and foremost we're dealing with a bacterial infectious disease in these newborn infants.

Otherwise, we are stuck with another risk that we would face as a sponsor of a clinical trial, and that is doing an enormous amount of work and having an evaluation of an intent-to-treat population for which only maybe 5 percent of those patients actually have a bacteriologic diagnosis, and that's not a very informative study with regard to really

making me more confident that I have a drug that's going to be effective in the neonatal intensive care in the newborn infant.

Oh, and the last issue, which I do want to raise, and I hope that the group at least expresses some interest in discussing this further, there are now probably a dozen, maybe two dozen, papers that are appearing in the literature supporting the concept that the use of broad-spectrum antibiotics in newborn infants is capable of influencing the microbiome in such a way that it could have long-term effects on newborn infants, effects on obesity, effects on intelligence, and these are hypotheses now that are being generated that invariably are going to need to be tested.

I learned, again, at the EMA meeting from some of my neonatology colleagues, that there is an ongoing trial where there is a placebo randomized trial of infants born to mothers with chorio-amnionitis. And when I asked the question, well, what was the rationale behind that? and the rationale was that there was a hope that those placebo-treated

children would not be exposed to broad-spectrum antibiotics that could make them less intelligent and more obese.

So I think invariably these questions are going to be raised, and I think that it's critical before we start generating these hypotheses to really understand whether these do occur, these shifts or these changes in the microbiome does occur in the newborn.

But first and foremost, I think we really need to define the natural development of the microbiome in the newborn infant, and I think that might contribute to our understanding of whether or not we even need to do these studies.

But I think to ignore that at this point would be shortsighted because I think that's getting a considerable amount of attention and one that I think is going to -- maybe not within the next year, but maybe within the next 10 years, be something that we're going to need to understand in order to assess the potential benefits of new antibiotics.

So in summary, it's clearly important to

understand the safety and efficacy in order to provide the best intensive care. We do all appreciate the limitations of obtaining the best data in order to support conclusions.

The point I would want to leave you with is that we don't have a complete understanding of these infectious diseases. We need to include, as our partners in this development, those people who are studying host defense in newborn infants, who are on the front lines understanding the concepts of developmental biology when it comes to host defense in these diseases, and that they should have a seat at the table voicing their concerns and making their recommendations.

(Applause.)

DR. FARLEY: Thanks, Gary.

And last we'll hear from Mark Turner, who will be talking about neonatal master protocols in infections. And he is also from the University of Liverpool.

Neonatal Master Protocols in Neonatal Infections: Pharmacokinetic, Safety, and Outcome Assessment

DR. TURNER: Thank you very much for the opportunity to learn so much and benefit from so many wise opinions. The problem with going last is that all the clever people before me have said all the important things, and even worse, they have said all the most interesting things.

But going last also gives me the advantage of being able to selectively reinforce the messages that I think are important based on clinical experience or bias. So you'll have to put up with both of those.

Just to mention that all the problems that Brian and other people mentioned about diversity in trials happen all across Europe and I'm sure everywhere in the world as well, so it's not just a U.S. problem, and it's not just an antimicrobial neonatal problem.

Australians come upside-down, so that's the way you come when you're sideways. But I've got some interests which will eventually appear.

(Laughter.)

DR. TURNER: So I'm sort of conflicted in

some ways.

I would like to reinforce that my bias is towards networks because they are going to overcome many of these problems.

And we had a meeting just yesterday in London with many of the same attendees that showed that regulatory science has engaged neonatologists, and people can be energized, and I think is something that we can work with very much in antimicrobials as well.

Thank you.

Now, I normally have trouble moving from Macs to PCs, but today I'm having trouble moving from one Mac to the other, so if you'll forgive the rather view of it. The logo is going to contaminate all these slides.

So INC, International Neonatal Consortium, can take this sort of thing on and be that independent, pre-competitive space. I know that CTTI is working in this area in pediatrics. And also the European Network of Pediatric Research EMA has a pediatric antimicrobial working group. But maybe we

need to find a special space for the babies.

Okay. Maybe you'll need to refer to your handy handout.

So I'll talk about the state of the art very briefly. Then the components of the master protocol and potential designs of a master protocol. I think a master protocol in this area is quite challenging, but at least it gives us a chance to review some of the issues.

So here's a paper just summarizing some aspects of pediatric antimicrobial trials, including some very distinguished authors in the room, which shows that basically anything goes in studies of neonatal sepsis.

There are some recommendations from EMA which have had adults, and they are very liberally interpreted when it comes to newborn babies.

And the time of clinical endpoints and days of treatment varies widely between trials, which isn't very helpful when it comes to designing master protocols.

Okay. I'm just going to have to trust you

got the slides. Yeah.

So the components of the master protocol will include the alignment of the inclusion criteria, the target groups, the outcomes, and the methodology.

The inclusion criteria in Europe might be the consensus statement from the EMA group of experts about inclusion criteria, and these are being validated as we speak in clinical trials, so hopefully in the next few months there will be some data about how relevant they are and whether they can be trimmed to meet reality.

The target groups need to be agreed, and I'll build on what Gary said about this.

Outcomes and methodology needs to be aligned as well.

So this slide was an attempt to say what Gary said much more eloquently, which is the big blue bar on the far left represents all the babies, and then a proportion of all babies get exposed to empiric antibiotics. And in the U.K., this is about 10 percent of all newborn babies because of risk factors and symptoms, none of which are very specific.

And then about 10 percent of them go on to have a confirmed infection, which can either be culture-positive, which would be this red bar, which might be about half of the babies with confirmed infection, and the other half obviously have an infection, they have many inflammatory markers, they look just the same as the babies with the culture-positive, but they are culture-negative.

And an even smaller group goes on to need rescuing because of antimicrobial resistance or because we can't find the right dose or because the neonatologists get bored and just change antibiotics every 12, 24, or 48 hours depending on their degree of tolerance of ambiguity.

So it's very difficult to pin down which group you're going to study because the -- and just to reinforce this point about proven late-onset -- culture proven late-onset infection. This is data from the NeoMero study, which was another European program, Framework Programme 7 study. Each of these countries -- there's Estonia, Greece, Italy, Turkey, Spain, and Lithuania -- and the culture-positive rate

is in blue, which means that the culture-negative clinical infections are in red. And in Estonia, nearly 80 percent of the late-onset sepsis were culture-positive, and in Italy, 30 percent were culture-positive. So when it comes to doing a multinational study, let alone a master protocol, there's an intrinsic variability in the ascertainment of culture positivity, which makes it very difficult even when you've worked out which group you want to aim for.

So the advantages with treating the empiric group was that you get everybody. The trouble is that there is post-randomization imbalance and all sorts of things, and then whether the empiric antibiotic is continued or not is subject to bias, you lose about 90 percent of the babies, and large numbers of them don't have any bacteria or any other infection. So they're pretty good for PK-PD in short courses, but they may not be much more informative in other areas.

In terms of confirmed groups, and if you randomize or recruit at this stage, then you will know which bacteria you're dealing with often, and they are

enriched to a large extent, but by the time they get into this confirmed group, they have been on antibiotics for 36, 48, 72 hours, which means that your efficacy signal may be contaminated if you're studying the antibiotics they're on already. Or if you're studying another antibiotic introduced when the baby becomes confirmed with infection, then there may be some cross -- well, you hope there is some cross-reaction between the existing antibiotics and the new one.

So starting off when the babies become confirmed with infection is prone with difficulty, and even more so if you're trying to test antimicrobial resistance possibilities. If you randomize or recruit babies when they move into the rescue phase, then they've also been treated effectively hopefully, and then there will also be considerable variation between clinicians as to when they think a baby needs rescue treatment.

People who change antibiotics after 12 hours will get onto rescue therapy pretty quickly, whereas people who change every 48 hours because they're

waiting for the antimicrobial to come to steady state before making a judgment may be further down the process. So all of this is subject to bias depending on your belief about the antibiotic.

So there are a number of reasons why it's difficult to recruit a consistent group within a single study, but within a master protocol, this would be exaggerated. And, of course, there are a number of clinical groups that we've heard about, early onset, late onset, specific infections, confounded by the gestational age at birth.

So what this slide is supposed to say is there is some marked variation between settings in terms of microbiology. The standards applied in settings vary considerably. Getting people to comply with Eucast or other standards is very difficult. And most clinical laboratories don't go that far and have all sorts of variations in like culture conditions and in their estimates of susceptibility and resistance let alone any quantitative MIC. And you can try and centralize things, but that does lead to a degree of variability, and then you have all the problems in

multiple sources of information.

As we've heard, the standard of care varies enormously both in terms of choice of antimicrobial, but then thresholds for starting antibiotics and so forth. And the threshold for moving between confirmed and rescue infection inevitably leads to a number of protocol deviations, which make it difficult to assess the data.

And the other thing that varies considerably is clinical culture, and we've heard many aspects of this. It takes a long time to change clinical culture, but basically we're used to dealing with bucket chemistry as clinicians, and you find a baby, you find the antibiotic, you put the two together, and either the baby gets better or you change the antibiotic until the baby gets better or moves on to working in other parts of the cosmos.

Neonatologists have a habit of ignoring recommendations. We wrote a national guideline about early-onset infection 5 years ago in the U.K., and people are still getting to grips with what pre-labor rupture of membranes means let alone which antibiotic

to give. So there were challenges there in implementation science let alone in implementation of clinical protocols.

So a master protocol could have numerous goals. It could be used to develop PK models. It could be used to attain the percentage of probability attainment of a PK-PD target. It could be used to assess efficacy. Or it could be used to assess safety.

And as Gary said, you need to be crystal clear about which is your primary purpose and which of these goals is going to fill the information gaps most efficiently. And particularly for a master protocol, that needs to be set up in advance. And again in a master protocol, each antimicrobial may have a different goal that it needs to meet during its stage of development, so that might be a challenge.

With respect to PK and PD data, I think it is possible to collect this data, these PK data, in a reliable way. PTN have shown that, and we've shown that in the U.K. with our NAPA (ph) study, which has looked at four or five different beta-lactams across

10, 15 units in the U.K. And it's possible to ship samples and do the assay centrally in a reliable way. So all these methodological issues can be resolved.

But that doesn't resolve a critical issue that again our colleagues with NeoMero found. These panels show time concentration drafts for a number of countries in Europe that were following the same protocol. So again we've got Estonia, Spain, the U.K., Greece, Italy, Lithuania, the Netherlands, and Turkey.

And maybe I can just draw your attention to the contrast between the Greek panel, which is second down on the left, and next to it, the Italian panel. And we can see that the initial concentrations are broadly similar, but then the concentrations between 4 and 8 hours appear to be different. And the Greeks were more likely to have higher concentrations into those intervals than the Italians.

And so even following the same protocol with the same medicine, centers and countries can vary between their concentrations, which might make implementation in a master protocol difficult, let

alone even a standard protocol.

So safety raises some issues which are generic to all neonatal problems, they are the background events of prematurity or sick babies who are born at term, and there are drug-specific issues that may be predictable or unpredictable. And then there may be some infection-specific effects as well. And we need definitions, shared assessments of severity, and shared methodologies of assigning causality.

And I think it's safe to say that we're at ground zero on -- ground floor on all of these issues when it comes to defining a master protocol, although we are beginning to come together to work on these.

Now, people have talked about efficacy outcomes. So what we've been thinking about this for a number of clinical trials, what elements are there in an efficacy outcome, be it clinical or microbiological?

And it's going to have to have several components because you want to know whether the person is alive or dead, and generally speaking, death is not

a marker of efficacy in neonates, although there may be some excuses occasionally.

Then you want some resolution of the clinical features, whatever it was that started off the infection, or at least led to the screen. And if the baby is having apneas and bradycardias before the infection and they get worse and then they get better again, but they're still having some afterwards, which is what you would expect, then how do you classify the deterioration in the apneas and bradycardias? And how do you recognize when it's got better enough to stop the antibiotics? Now, that's a challenge in clinical practice, but it's even more of a challenge in a standardized way in clinical trials.

And then the resolution of the microbiological features, given that half the babies don't have any microbiological features of infection, repeat cultures don't always help.

Then you want to make sure that there has been no change in therapy ideally because people will stick with a treatment that's working.

And then no new microbiological concerns,

there has not been any breakthrough infection.

And all of these are extremely difficult to operationalize, and they're very difficult to get people to stick to consistent protocols. So this is maybe a particular challenge in a master protocol, but I'm sure our friends from Duke have overcome all these and can share successful experience.

So how do we choose which outcome to use? Well, we need feasibility, we need timing in the study, the guidance. In EMA, it's you want to wait for five half-lifes after the antibiotic has been stopped so that you can be sure that the infection has settled down. So you need to know what the half-life is, and you need to assume that all babies have the same half-life.

Now, that is a challenge. We did a study of ciprofloxacin in newborn babies, and we found even accounting for specific gestational ages or postmenstrual ages, the clearance can vary ninefold within the same postmenstrual age.

So if the clearance is varying ninefold, then the half-life is going to vary to something

similar as well, which means that each baby is going to have a different half-life, come to steady state at different times, and when you're going to judge the antimicrobial as having been eliminated is going to be quite difficult. And if you do it for a very long time, then you're going to misjudge the situation because of the random infections that crop up, and this is common to all neonatal studies.

So I personally have a lot of difficulties with using efficacy as the primary outcome. I think that there are some difficulties with ascertainment, and how do you handle culture-negative cases which are clearly infected but may have a Gram-negative infection or may have a Gram-positive infection? You may have one that your antimicrobial is going to be useful for or it may not, depending on what's going on. So you can't always design feasible studies around culture-positive cases.

I've mentioned issues that arise with other treatments, particularly before randomization, although you can pre-consent and you can get telephone consents and so on. You can get deferred consent.

We've used all three in antimicrobial studies. That still leaves you with a need to treat the baby before you can do something about the study. So most babies will get some kind of antimicrobial unless you're recruiting at empiric treatment.

And then particularly in the world of antimicrobial resistance, when you're looking for people with MDR or XDR, actual proven cases of that are quite rare, and you need to have quite a large birth cohort and population sampling frame before you can reliably pick up numbers in the tens, twenties, and thirties of these.

So for all of these reasons, I personally favor the sort of approach that we heard from Laura, which is a parameter-based approach backed up with registry data for safety. And for me, the main reason for this is the babies vary, so you're going to have to come up with a parameter space to capture the babies. But the bacteria vary as well.

And the MIC distributions vary considerably even within a group that's labeled as susceptible. And this is exemplified by coagulase-negative staph,

and despite John's ethical resistance to use vancomycin and other glycopeptides, I can assure you that many, many units in Europe do that, which it's just an example of what Danny and Brian were saying, one man's ethical impossibility is another man's ethical imperative.

And we did come across this when trying to introduce therapeutic drug monitoring in our vancomycin study. For me, therapeutic drug monitoring of vancomycin is an ethical imperative, but there are many parts of Europe where it's ethically impossible to do for other reasons. So there are many ways around this problem. But most isolates of coagulase-negative staph have quite high MICs, but it's still declared as susceptible.

And the commonly used doses of vancomycin or teicoplanin will not treat many susceptible labeled coagulase-negative staph. So we need to take into account the MIC distribution as well as all the variability that we've heard in the babies.

And so if we're going to do an efficacy study that covers the whole range of MIC variability

within susceptible cohorts as well as all the variation within the babies, then that's going to be an enormous efficacy study for every type of bacterium.

So for me, it's much more comfortable coming up with a parameter space that reflects the variation in the babies, which we can capture, and the variation in the bacteria, which we can capture, and then put that together in a form which allows us to use DDM or controls or some other way of synthesizing that data in a way that's relevant to that baby based upon his or her PK parameters and his or her infecting bacteria's parameters, plus a bit of guesswork for culture-negative cases.

So an efficacy study based upon, "Do you meet targets in an acceptable proportion of babies?" makes a lot more sense feasibility-wise and is generalizable in a way that an efficacy study may not be because you may just have a random selection of babies and a random of selection of bacteria that may not be generalizable. (Inaudible) PK-PD study and good epidemiology about the microbiology will allow

you to come with a generalizable set of models with safety being included in various ways.

So coming on to the topic of master protocols, now, this was the first slide I drafted, which was a complete blank about master protocols, but I did manage to come up with some thoughts, mainly inspired by SCAMP and other things.

Of course, we have a SCAMP study, which is about nutrition, which did cause us some confusion, and there is also a SCAMP study in the U.K. about attention-deficit/hyperactivity disorder, which did confuse some of our families who looked up our SCAMP on the Internet.

So master protocols. The first design would be to look for sites that are using the antibiotic of interest and capture them, and that's where a network would come in handy. And then you just hit those babies with a well-designed PK study, optimal sampling, combining some purposeful sampling with a lot of scavenge sampling, which works nicely for some antimicrobials.

And then in your master protocol, that is

done in a similar way with similar inclusion criteria, similar outcome criteria, and you come up with some PK data which you've warehoused, and you can pool and take account of this.

And in Europe, at least, this would lead to a natural experiment of different dosage regimens because each center would use different dosage regimens. In the U.K., we did a survey of vancomycin doses -- sorry, John -- we got 48 units to supply us with 24 different dosing regimens.

So if you did an opportunistic PK study, then you would end up with some of the dosage variation that is necessary to build up good variation. You could, of course, try again to get the same thing, but that might be difficult.

And then this could be combined with PD targets. And then you could expand this to include a safety surveillance study with registries and so forth in the same sites, which might even allow you to use anonymized data in the U.K. without getting consent, but again ethics.

Another design, which I'm sure has been done

by people more effective than me would be to select sites according to which antibiotics they are prepared to use rather than the ones that they are using, and this then allows you to do some kind of comparison, and the people could be randomized to a single target group, be it empiric, confirmed, or rescue, depending on what that antimicrobial is looking at.

And then you could vary this between centers depending on what they wanted to use. And you might have to have more than one comparator. But that is actually quite useful because it gives you more variation to play with in your PK-PD models. And this then gives you some prospective comparative data for both efficacy or whatever you want to use, and safety.

So in any master protocol, the key assumptions would be that data can be pooled across sites and PK warehousing, so you need to be able to stratify by site, GA band, and target group.

And, finally, a common comparison may be difficult, so you might like to borrow a concept that the Systematic Review has used, sort of a network analysis, where if A is better than B, and B is better

than C, then A is probably better than C. And I think building that into your models, structuring that into your models, might be helpful so that you can take account of the maximum number of studies and sites.

So my final slide would be to conclude that master protocols can be developed, that PK data can be pooled, the safety issues are generic to neonates but do need to be improved on. Outcomes may be problematic. Comparisons may be problematic. But trying to come up with a master PK-PD model that allows you to look at the variability without subjecting millions of babies to the clinical trial I would say is the best way forward.

And I came with a message from colleagues at the EMA to say please work with your jurisdictions. It's proven quite difficult to do that face-to-face and quite challenging to do it remotely. So someone told me that the best way to cross the Atlantic is go Business Air with Iceland Air because that's the cheapest way. So maybe we can all meet in Iceland and then all travel cost effectively in business class.

Thank you very much.

(Applause.)

DR. FARLEY: Thanks very much, Mark.

And you all will be relieved to know that we'll be done projecting for the day.

(Laughter.)

DR. FARLEY: We're going to take a 15-minute break. Then we'll take on panel discussion questions. The audience will be welcome to participate in the panel discussion via the microphones. If a member of the general public wishes to give a formal presentation to the workshop, please see me at the break.

Thanks very much. We'll see you back at 3:15.

(Break.)

Panel Discussion (Covering All Topics)

DR. FARLEY: Welcome back, everybody. Those were great presentations.

What we're going to do is work through some questions for a panel discussion, and you'll find those on the very last page of the agenda packet that you should have been able to pick up the door. Does

anybody need an agenda that doesn't have one?

(No audible response.)

DR. FARLEY: And how about the panel? Everybody is good?

(No audible response.)

DR. FARLEY: Great. And, Chris and Anne, I can't see you very well, so wave.

So John and I are going to be co-moderating this discussion with Sumathi jumping in on occasion just to see if there's clarification.

So I guess the first topic is the issue of extrapolation and the issue of clinical conditions in which extrapolating efficacy from adults and older pediatric populations are acceptable for neonates.

So, Tom, you've named some of those. And then the second is for indications or extrapolations not feasible, how certain ways forward on getting to demonstration of efficacy.

So anyone volunteering to kick off the discussion?

John Bradley is the other narrator. This is the nice John, not "the" John.

(Laughter.)

DR. FARLEY: Danny?

DR. BENJAMIN: So let me just make sure I understand. Extrapolation meaning if I have a similar disease in a different patient population, given similar exposure, the impact of the therapeutic is going to be similar across patient populations. Right? So --

DR. ALEXANDER: Close. I mean, the distinction would be the idea that you need actually both. The idea of extrapolation is one that requires both of those items, that you have a disease or condition that's similar enough in the group that you're extrapolating from to the neonates. But the other part of that is that the response to treatment is also then expected to be similar in those two groups and that those two things together is what allows you to extrapolate.

For our purposes for infection, we don't necessarily worry all that much about response to treatment because we are still looking at what we're talking about with regards to efficacy for

antibacterial drugs. So a lot of what we're relying on there seems to be with regards to antibacterial efficacy. But there certainly are occasions where you might be worried about the response to treatment with a particular antibacterial being different, that you can't just rely on sort of the fact that the drug is just expected to kill the bacteria or kill the fungus that you're dealing with.

DR. BENJAMIN: And the second clarification on this is we're talking about both antibiotics and antifungals, but not antivirals, or are we just talking antibiotics?

DR. FARLEY: I think we had in mind primarily antibacterials and antifungals at this point.

DR. BENJAMIN: Okay.

DR. FARLEY: Antivirals have the advantage of generally having viral tests, which we all wish we had.

DR. BENJAMIN: So I would say that there are three areas that I would be uncomfortable. There are a whole lot of areas that I would be comfortable, but

there are three areas that I would be uncomfortable. The area of least comfort would be invasive mold infections, for example, aspergillosis. We see aspergillosis so infrequently in the neonatal intensive care unit, I'm not always sure what we're doing when we deal with it. And I get calls from all over the world about that, and I don't know what to do.

The second area where I have some discomfort is invasive candidiasis primarily because the real difference for the neonate is that it goes to the brain with much higher frequency than older humans.

And then the third is probably around kind of the community-acquired pneumonia for babies less than 1 month of age. I have -- you know, of those three, I'm the most comfortable with that, but I have discomfort with that group.

As far as urinary tract, complicated urinary tract, infections, it's bad for you if you don't respond to the therapeutic.

Complicated intra-abdominal infections, you've got like we may want to bicker about that

medically some other time. I think if you spend enough time with babies with medical NEC and you see how often they can go to surgical NEC, you might feel a little more comfortable there.

But for the most part, other than those three top ones, I'm pretty comfortable extrapolating.

DR. NOEL: I just want to make a point actually. Chris talked about with new antibiotics coming through, the need to accept and better and better to look at these smaller packages. And I just wonder whether or not we're asking for less and less data to support efficacy in adults that we will come to a point where we're sort of extrapolating upon extrapolation, and I think we need to keep that in mind when we're looking at some of these newer agents maybe and seeing experience in 500 patients. How well have we really established safety and efficacy that we're willing to take that?

The other point also would be that as we're extrapolating, we also need to underscore the importance of established response -- exposure response relationships, and how rigorous has that

response exposure relationship been established in the adult experience that we can be confident that we can extrapolate on that as well?

So those would be two points that I sort of point to as being generic considerations.

DR. NAMBIAR: Danny, just another question. So if it's a neonate with (off mike) sepsis (off mike) neonate, and you really (off mike) the drug does anything to the central nervous system, would you be comfortable in extrapolating (off mike)?

DR. BENJAMIN: Yeah, (off mike) central nervous system. I'm sorry, I just thought that was so -- I'm sorry. You've got to know if that drug gets into the central nervous system. I figured everybody in the room was on board with that. But the highway is just -- you know, the 1970s highway is littered not only with Star Wars movies, but also with aminoglycoside failures where you essentially selected for ventriculitis of the central nervous system and knowing what to do after that.

DR. NAMBIAR: So I think that certainly leads me to the second question. How do we know that

the drug penetrates or does anything to the central nervous system? Is it all based on CSF PK penetration data (off mike) potentially looking at the -- rather than (off mike) infection. If you just (off mike) that you see in the CSF space. I think (off mike).

DR. BENJAMIN: So I think that the number of humans that you have access to and the amount of human data is so small for the therapeutics and the lift to get them is so big that a few things need to happen and a couple of things ideally would happen. Okay?

Number one that needs to happen, you need to maximize multiple different models. The fundamental premise of epidemiology, we want to know, why does smoking cause lung cancer? There has actually never been a randomized trial to show that, but we believe that to be true because different investigators using different methods at different time and space have replicated each other's work. Right? Whereas we don't necessarily believe that coffee causes pancreatic cancer based on one paper. Right? So different investigators, different methods, different models, across time. So that's number one.

Number two, I think that some human, older human, data is also required.

And number three, some neonatal data is required. And a good, albeit imperfect, way to look at things is older human shunt data and neonatal shunt data and see if you get any surprises there. Because if you're not getting surprises there, I think you're -- it's not perfect, but you're less likely to have surprises. And shunt studies and shunt PK is a lot easier to do than getting a lumbar puncture from the big one-off meningitis patient.

Then the things that I think ideally would happen that the agency itself has less influence over is for companies to be encouraged to collaborate postmarketing in a rigorous assessment like the -- similar to the POPS study. We've given the POPS study to the agency before when they've wanted to use it in an area outside of infectious disease. It's a publicly funded study, it's available. We're happy to do whatever can be helpful there.

And I think that this is an area that public-private partnership actually as it relates to

the National Institutes of Health and FDA and companies is worthwhile because this is a heavy enough lift. And it's not a crisis for us today. It's pretty rarely that we have babies who get infected where there's absolutely no therapeutic today, it's pretty uncommon. But it's --

DR. FARLEY: John?

DR. BRADLEY: So if I can be the loyal opposition, and I wish William were here, I think there is virtually no infections in neonates that can be extrapolated from older children and adults for many of the reasons we've discussed. And I know this is all on the record, and everything we've said is taped, so I won't go through the immune-compromised issues that I had earlier today.

Complicated intra-abdominal infections we study in children, and I think they're different than NEC. And I know Danny recognizes this, so I'm not disagreeing with him, I'm sort of fleshing out the overall problem.

But we, since '79, have been trying to study NEC during my fellowship, and we thought it was the

toxin-producing Klebsiella, and, of course, we still don't know exactly what causes it, but what is NEC? The baby stops eating and the intestines get a little bit distended, that's pre-NEC or NEC scare. Neonatologists have like five different names for it, and they all get antibiotics, the feeds get stopped. I don't know how many of them truly have an infection. Perforation, of course, can be picked up radiographically. And some surgeons go in, some will wait for a while because they want fewer manipulations.

We had a baby with medical NEC for a week and was doing well, the CRP actually was down to 3 to 4, just above normal, and then they tried to feed him, and he ended up having four perforations and (off mike).

So it's in part inflammatory bowel disease, so looking at endpoints from the infection are different than the endpoints perhaps from whatever vascular event caused the NEC in the first place. And, again, we've talked about the confusion of the outcomes being complicated by the natural history of

the disease process.

The vascular lines, I don't even know if the coag-negative staph infection can be extrapolated from adults. I know adults, I've heard, just pull the line and stop the antibiotics. In children, we pull the line and keep the antibiotics going for a while, 3 to 5 days.

And in babies, especially PICC lines that have been in for a while, there is a clot along that vessel where the PICC line is, and I agree that there is endovascular infection, and we'll probably treat it for a couple of weeks, but if you send the baby home and they get recurrent coag-negative staph, it's a very non-severe disease with very vague symptoms that would be very difficult perhaps for the parents to pick up.

So I don't even know if catheter coag-negative staph infection could be extrapolated.

But the problem, of course, is, how do we study it? So I don't want to tell you everything is bad about --

DR. FARLEY: Just stop all studies.

DR. BRADLEY: Yeah, stop all studies. We can't do that.

There is minimal safety data that I think are required to let us feel comfortable using the drug.

And then efficacy, the first pass, and this is where modeling and then adding to your model, the first pass could be extrapolation, so despite what I've said, you could extrapolate the exposure for complicated appendicitis down to a baby.

And then right after the drug is approved on some limited basis, for babies, this is all just for babies, then some post-approval setting where you could continue to collect data so that you're not requiring a huge amount up front before the drug gets approved, because that will never happen, and you're also not just getting a little safety data and then just letting everyone use the drug willy-nilly because then there may be safety signals and non-efficacy signals which may pop up later, which none of us also want. So extrapolation, limited release, and then post-release review as the drug gets more used.

Now, especially for these new Gram-negative drugs, in the EU, the EU is not homogeneous, as Mark really beautifully showed, and most of the papers on multidrug-resistant Gram-negatives in neonates that are even colistin -- several of them colistin resistant, are from Greece, which the last time I checked was still in the EU. England, that's just -- you're in Europe, not necessarily. Anyway.

(Laughter.)

DR. BRADLEY: Studies can be done, efficacy studies, in these babies, because they've got culture techniques. I don't know why they have so many infections, but on Mark's slide, he said infections with drug resistant organisms are rare. Well, that's in the U.K., but maybe not in Greece, perhaps Italy.

So there is opportunity to study these, and not only in the EU. Latin America. I'm sure Danny gets calls from sites in Latin America where they have babies in NICUs that are infected with multidrug-resistant organisms, and they were actually trying to steer one group in Buenos Aires to AstraZeneca to get ceftazidime/avibactam used in one of their nurseries.

So there are other parts of the world where the disease is there, the babies are dying, and there's a critical need for studies, and perhaps that might be a place where you can get efficacy data that you just can't get in the U.S. because we don't see it, and that involves politics I'm sure as well as science, and I won't even go there.

And for the CSF, just one last comment. In our hospital, we have an idea of who all gets lumbar punctures, and we don't do too many. We're not like one of those sites, but we do probably average at least.

But you know when a baby is going to get an LP, and the decision is made. It's usually not, "Oh, my god, this baby needs an LP right now." You decide the baby is not doing well, irritability, questionable -- there's something that wants you to do an LP, and you've got a few hours before that LP is done, and if you've got the neonatologist or the emergency medicine doctor and ID team primed so that as soon as someone says, "I think we need an LP," it's possible to give a single dose of an investigational agent prior to the

LP.

That will make your culture not as good, so it's impacting care in that way, so you don't get something for nothing, but the balance of getting information on CSF penetration of the drug and knowing that most of these babies will have normal LPs anyway, that the juice might be worth the squeeze. We have to run that by IRBs I imagine.

DR. FARLEY: Yeah. I'm sure that other folks may have comments. Just sort of on the -- so that was a lot.

(Laughter.)

DR. FARLEY: Let me focus on one thing because I think one of the -- you know, for me, medicine is all about trying to reduce the uncertainty as best you can, and one answer, as we've talked about, is CSF penetration of drugs.

So when you all do opportunistic sampling, maybe I'm misunderstanding how it works because the scenario John is laying out sounds like the exact scenario we run into in nosocomial pneumonia where the patient is critically ill, you're trying to find the

family to enroll them into a study. Do you guys -- you don't give them dose in your -- or some medicine, you just -- it's just whatever medicine they happen to receiving at the time. Is that right?

DR. BENJAMIN: So it's worked out a couple of different ways. For the meropenem study, they were enrolled in the meropenem study, and then if they were getting cerebrospinal fluid per standard of care, then we got cerebrospinal fluid. So we were not tapping them just to tap them.

DR. FARLEY: Right. Right. Or hanging meropenem just because.

DR. BENJAMIN: To tap them. Right.

DR. FARLEY: Right. So does that -- so I'm a little -- I'm wondering sort of, trying to understand your idea a little bit more.

DR. BRADLEY: Right. So most of the protocols for the past 5 years have had this if you get CSF, please (off mike), and hopefully there is a serum sample that you compare with it within a few hours. But getting CSF is difficult, and one can look at when kids are tapped.

I mean, we can say what are the circumstances surrounding the last 100 children who got LPs who were under 2 months of age? And many of them will be rule out sepsis from the community who are irritable, and then there will be the babies in the nursery who start having apnea and bradycardia, and it's an aggressive neonatologist.

So the LP is the big event. That's -- to talk to parents, "Your baby needs a spinal tap," is like, "Oh, my god, that's horrible." But once that decision has been made, then extra risks from giving ceftazidime/avibactam, or meropenem is a small added risk, and there will be many parents who will refuse, but what I'm doing is trying to take the opportunity of a baby who is destined to get an LP and see if we can't leverage that into a single-dose PK CSF study. That's all. It's just a thought. I'm not -- it's just a thought.

DR. FARLEY: Mark.

DR. TURNER: So we've heard from the (off mike), I guess I would like to take (off mike) sit between the two (off mike) extrapolate all bacteria

except for brains, and John said no extrapolation at all.

I confess I'm more on Danny's end of the clinical spectrum. But I guess I would reframe it a little bit in terms of, do we need to demonstrate (off mike) I just want (off mike) information (off mike) that this is safe is my first guess because I'm going to have to change the antibiotic (off mike).

So is it (off mike)? And is that what we mean by efficacy or is it demonstrating efficacy a little bit more than the (off mike) of the (off mike)?

DR. BRADLEY: Just getting safety and using extrapolation and then --

DR. TURNER: Use -- use --

DR. BENJAMIN: The kind of rudimentary pre-thinking, and then that might be housed in (off mike). If we don't get efficacy, then there is no dosing that goes into the American label and there is no safety information that goes into the American label unless it's a (off mike). And so you then don't need to get the drug studied, so then (off mike). Okay?

So if we don't have a pathway to efficacy,

we're not going to be studying these drugs in the NICU. So that's why we're talking about efficacy, because you've ultimately got to end up there.

Now, the number of agents that one needs to study is much less if you extrapolate than if you do one or two pivotal, blinded, low-power trials.

DR. FARLEY: And we heard about that in kind of excruciating detail this morning challenging that.

DR. KOVANDA: And who is going to sign up for two?

(Laughter.)

DR. FARLEY: So maybe moving us along a little bit, I'm sure this is sort of -- we're hearing about kind of using multiple different models. And my understanding of what that allows you to do is kind of this iterative process between the neonate and the hollow fiber model and bunnies. And I think what that allows you to do is to get to a reasonable neonatal exposure with using less neonates. Am I understanding that correctly? That's kind of the major purpose of that.

And then once you're there, where do you see

that going next? In other words, do you have to then do a trial with that dose? Or do you think you're done?

DR. BENJAMIN: Chris is (off mike) because I'm not saying it precisely, but ultimately when you do the bunny and the other animal models and the hollow fiber, you get two key pieces of information. One is it helps you some with PK, which reduces sample size within a dosing stratum, and the other is that it potentially helps you considerably with PD, which is very important to say, so the so-called bridge. All right?

So kind of as I see it, you need multiple different models, and use that to go into the neonate so that the information from the adults and the information from the children, the information from the shunt studies, the information from the animal and hollow fiber models all then confers at the point of at least get some neonatal samples so that you avoid what I would call the tenfold dosing surprise.

DR. FARLEY: Right. Right. And I would imagine the precision about the dose, there is less

variability because right now what we've heard is that sometimes multiple different doses are being used, and then you're getting a CSF sample, and I would assume that would be harder to interpret. So anyway.

DR. BENJAMIN: The hardest thing for me for interpreting the CSF stuff is that you're typically only getting one sample, and so really it's very hard to do anything but estimate area under the curve or time above MIC, but you at least have some human data in the target population when you get that percentage.

DR. RUBINO: So I'll speak for William, since he had to leave. Hopefully I'll get the gist of what he was going for there. But I think one of the points he brought up that really struck me was the concept of validating these models using drugs that we already use. Right?

I assume, John, that amp/gent for early-onset sepsis, you say, well, that's what we use them to do. Right?

So we have a model that uses those drugs that were already accepted as being useful, show that, yes, these in vitro models or the animal models are

replicating reality with those drugs, that gives us some comfort that we're not going to be having a false bridge. Okay?

And I think -- I obviously am going to come down on the side of thinking that extrapolation is always going to be useful, and in most cases, it's possible. And I think a lot of the stuff that John is bringing up, all valid points, are not necessarily a problem of extrapolation, but it's a problem of the underlying models and it's a problem of what we don't know about where the drug is going to go. Right?

If the drug kills bacteria in a model, we can't ask it to do anything else in the body but kill bacteria. The problem is it's not getting where it needs to be, the drug that is, or if our model isn't replicating the human condition well, then we're off and we can't extrapolate. But otherwise, we should be able to extrapolate in any situation, there is just -- we have a long way to go with some of those models.

And there's just one other point on CSF I wanted to make, is those PD-PK systems, acknowledging what William said about the diversity of the central

nervous system and the fact that we're only sampling CSF, that's the next step. Right? Let's try to get the first step. But the PD-PK models, one of the great advantages is there have been studies that show the properties of the drug that allow it to get into the CSF, and we know we can test those -- we know we need to test those properties in humans, we know that it's based on physicochemical properties.

So we can make some predictions about what's going to happen and then use whatever data we can get to try to support those predictions. And I think the thing that I think is difficult is in adults in bacterial development -- and you guys can correct me if I'm wrong -- but we don't see many studies where they're getting CSF in adults.

So that's a bigger jump, and I'm nervous about, yeah, we can get a few kids, but there is this big hole where we don't know that PD-PK system for neonates yet, so we know it better in adults, but we don't have that qualification of adult CSF data.

So I think that's a step we're going to have to talk a little bit about, is what kind of studies

would sponsors have to run for a new drug to show that it's getting into the CSF in adults?

DR. FARLEY: One thing I just want to make sure that we talked about was people have mentioned VP shunt patients as potential subjects where we might get CSF data. We haven't seen that in a regulatory submission, so I'm wondering if it's actually -- how feasible folks really think that is.

DR. NAMBIAR: So I think, John, a few years ago we had one sponsor who I think -- not a lot of data that we're getting submitted. Do you remember that one, John? I don't. There were a handful of samples. But I think -- I mean, we obviously are open to the idea of at least trying to collect CSF from VP shunts or external devices. But the question really is, how different or similar is it to (off mike) that the U.K. has (off mike) infected?

But I think Danny's point is valid. If you get that in adults and you get that in children, at least -- I think at the end of the day it's putting all the pieces together. No one piece is going to be perfect, every one of them is going to be imperfect.

So at some point, will we ever be comfortable with all these little pieces that head in the same direction that's going to appear?

And I think the other point Danny made currently was that even if we do all of this and we get to a label, I think it's still based on very limited information with a lot of deep faith. And so then we have to continue to try to collect the data postmarketing where you're using networks or some other tool so that you continue to collect the information where then the opportunistic sampling will be a lot easier because that drug is then being used in the rest of the population.

DR. ALEXANDER: I would say that the situation that we did see the attempt to use VP shunt infections or VP shunt patients in order to get PK data was something where we were initially pushing to try and get a drug that was a Gram-positive agent study for VP shunt infections.

And the one thing that you can do in the PK study for children is say that these kids who will be getting a VP shunt placed will usually be receiving

some sort of antimicrobial prophylaxis, so if you have something that's being used as a -- that you're wanting to study that's a Gram-positive agent or has some activity in Staph and Strep, then that study design may be reasonable to say, okay, instead of getting your usual prophylaxis, we're going to give you this novel agent instead, and then obtain the CSF data afterwards from the patient who is getting the VP shunt placed. It may be problematic if what you're dealing with is something that's a Gram-negative agent and something that we see are infections or some of these other things where you're worried about more the activity in Gram-negative infection.

DR. NOEL: I would just like to point something out to you in regards from the sponsor's position. So you can see that there can be a dramatic difference in opinion on what's needed, and if the goal is to truly label the drug, I would point out to you that sponsors typically bringing people like John and Danny together, it may very well be that the sponsor is not going to be comfortable with extrapolating data from adults.

And in the past, that was reconciled, the distant past, George McCracken (ph) would go out and study the PK and make a recommendation in literature.

I think our goal is to get these things labeled. Okay? So I think it's important for you when you're having this discussion with the sponsor to get the level of their comfortableness in that extrapolation and to be clear that if we're doing this PREA-required program, that they're going to be comfortable about the label of the drug. Because I think we still have an option as a sponsor to meet our requirements, even to get exclusivity, without being compelling to put that information in the label.

And I can point to my Levaquin experience and say that's exactly what happened. Levaquin had to -- you know, randomized controlled trials that jot out this design to show the efficacy in kids with pneumonia and otitis media, but the company pursued not to put that in the label. So my intent is to have that option.

DR. BENJAMIN: The laws changed. If you do the studies, the pediatric data become -- information

from that trial becomes publicly available, whether it's the medical summary or the pharmacology summary or whatever. Now --

DR. FARLEY: Let's ask John to go over the current policy.

DR. ALEXANDER: So I think that the idea that Danny has expounded on is the idea that there is a requirement to have some description, even negative studies, so if there are results that are important to put in to describe about either negative effects of the drug, then those things would still be expected to be put in, but more limited in terms of what we would then add.

We wouldn't be adding information about dosing, information about what the outcomes were for the trial, if the idea is that there was some safety concern or overall risk-benefit consideration that led you not to label the drug for a particular indication.

But I don't think that it's necessarily that the law has changed, I think that the issue for Levaquin may be one where in the consideration with regards to otitis media about what the overall risks

of using a quinolone is versus the benefit for otitis media.

DR. NOEL: That is not an FDA decision, that was the sponsor's decision to go that route, and as a result, that information is not on that label. And I don't see how it couldn't -- I'm not saying that it would, but I'm saying that it could happen if we get a group of John Bradleys there telling us that this is not sufficient enough data to be comfortable with the efficacy, a sponsor very well may opt not to put that kind of information in (off mike).

DR. NAMBIAR: Okay. Just so that I understand. So how would you meet the PREA requirements (off mike) go down to (off mike)?

DR. NOEL: Do the studies.

DR. NAMBIAR: Oh, you mean you would do a separate --

DR. NOEL: You would do the studies, but they would choose not to put it in the label.

DR. NAMBIAR: I don't think that option is there. So you're saying you would do a neonatal study separate and choose not to put that in the --

DR. NOEL: I wouldn't put labeling in there to say that the drug is indicated for use in newborn infants.

DR. NAMBIAR: I think that will be my next (off mike).

DR. NOEL: I'm just pointing it out because we're seeing a very -- if everybody was (off mike), this is not an issue, but if a sponsor is going to hear those opinions, and I think they are, they hear a lot of those opinions that John is voicing, I think there's enough concern there.

DR. FARLEY: So I'm mindful of the time. Are there burning topics for the next 2 minutes? One thing I can tell you is that you should look forward to more data on the in vitro/in vivo human approach that William described. There are some projects underway, and that's going to be exciting, and I think we're really just learning about this model. So we've got that launched.

Other topics that we want to make sure we get to today?

PARTICIPANT: Lisa had one.

DR. FARLEY: Lisa, sorry.

DR. MULUGETA: Lily. I just have a question. It was really targeted to Danny. He left. It was really around the question of interpretation of CSF concentration. The limited data we have on many drugs is that it's extremely variable in this population to the point where we can't make any conclusion out of it.

So even if we were to get some data, what are we looking for? Is it the ratio of the CSF concentration to the serum concentration? Or that there is just any penetration? Like what do we do with the data?

And anyone can answer those questions.

DR. NAMBIAR: That's the exact same question we have. At the end of the day, we struggle, and then we get 60 or such samples, one of which may be (off mike). And I think the meropenem study that Danny's group did, I think it was five or six babies had CSF data collected and it was (off mike). So when we updated the (off mike), we only approved it for CIAI in babies less than 3 months because we were not

comfortable with the data we had.

So it's like a lot of body fluids. I've learned PK (off mike), but I don't know (off mike).

DR. RUBINO: Well, I don't know if I can educate, but what I can say is in those situations, it's absolutely critical to know the exact time that it is drawn --

PARTICIPANT: Right.

DR. RUBINO: -- and the exact time that the dose was given because those bits of -- when I see that data and it looks like it's all over the place, and it happens -- we see a lot of (off mike) studies, but it happens in places where folks aren't doing a good job of it, and most of the time I don't really -- you know, the protocol says when the sample should be drawn relative to the dose, but that's secondary, just knowing exactly when it was drawn, because there is so much variability on this, you can't always get that out of the equation, and then we can't do (off mike).

DR. FARLEY: Mark?

DR. TURNER: (Off mike) response to that question. I guess (off mike) clinics towards the (off

mike) because, as a clinician, I want to know whether this has good or bad penetration, and that's good enough for me. I don't need to know precision, I don't need to know that cefotaxime is better than (off mike), but if you talk about that, (off mike) suspicion of meningitis. So I think it's important (off mike) labels, it's important to have that (off mike) met, but (off mike) want to know, which drug should I use? And sometimes causes of inflammation is useful even though it's not as extremely quantitative as it might be.

So (off mike) answer that. Any information is better than none, particularly (off mike).

DR. MULUGETA: But in this setting, I guess where we're using that as the basis for extrapolation, how much data do we need and how much certainty? And just to sort of answer the question around timing of the sample despite having that data because there is huge variability, I'm not sure if some of it is due to the way that LPs are conducted and the variability of technique, but the data is highly variable, and it's really very difficult to say that it penetrates the

CNS (off mike) because it's just so variable.

DR. RUBINO: Can I just make one quick one, John?

So one thing I would say is with the way that the modeling is going in terms of incorporating physiology, I could see a situation where we could take the little bit of information we have from each drug, put it into the same system, which says that these physicochemical properties of the drug predict where it should go in neonates, and then increase the power of the entire -- because we'll say, okay, we've got this many meropenems, this many on this other drug, and you combine five drugs together, our model system, you can be relatively agnostic and just say I don't care what drug it is, I'm going to predict for that drug and leverage it all together and learn something about neonates that way. It's just a thought.

DR. FARLEY: John, I think we'll take maybe two or three more comments and then we'll need to wrap up.

DR. BRADLEY: We did a meningitis study 20

years ago, I forget how long, but just in regular children there was incredible variation, and probably 10 percent of the samples there was no meropenem activity at all, which made me really -- and all the kids got better. So I don't -- there's a disconnect between what we measure and outcomes, and I don't know how to answer that question.

In terms of animal models, I believe it was gatifoxacin was used in a rabbit model where there was an indwelling ventricular catheter, and there were beautiful curves that showed histories of serum levels followed by CSF levels to attain an AUC.

So the models can be created from the animal model, and then as you get neonatal samples, you can plot those time after dose to try and see if they fit the model, and I think that's the best.

DR. FARLEY: So John has made an optimistic comment. I would like for the record to reflect that.

(Laughter.)

DR. FARLEY: Anne?

DR. ZAJICEK: I have a question. So, John, we've been talking about hanging the whatever it is,

investigational antibiotic for a kid that didn't need an LP emergently but needed it at some point.

DR. BRADLEY: Yeah.

DR. ZAJICEK: Was that the first dose of a regimen or was that just one dose?

DR. BRADLEY: No, one dose PK.

DR. ZAJICEK: One dose.

DR. BRADLEY: Yes.

DR. ZAJICEK: Okay. All right.

DR. BRADLEY: It's a study. We need to get informed consent, the whole -- yes.

DR. KOVANDA: So the one thing I guess I -- and maybe it's too late to say this, but the one thing about the study that we conducted, that we recognize that we've worked really hard to keep it as close to standard of care as possible, which meant that you had to put windows around everything.

And so if you notice from the CSF samples that we were able to -- or CSF cultures and LPs that we were able to get, they were largely at baseline, only three patients during therapy. So those three are doing cultures. So three samples during -- you

know, could have been used for PK sampling.

So it's all -- I think having -- being able to get concentrations may not be in the setting of an efficacy study. I guess that's where I'm --

DR. FARLEY: Yeah. Okay. So any other burning comments?

(No audible response.)

Concluding Remarks

DR. FARLEY: We're very grateful for everyone coming to the table, and I think we'll look forward to having an opportunity to do that again.

We're pretty optimistic in terms of small incremental steps that could happen. And the two things we're thinking of are further work with the modeling that has been described, perhaps moving toward the vision that Chris just articulated a few minutes ago. So that would be one thing maybe we could look forward to happening over the next year or two, and learning more about just what that -- where that can take us.

The second piece I think in terms of feasibility that we've heard about with the CTTI

project is the importance of engaging parents and engaging investigators. CTTI is continuing to do more work in that area, and I think that will be important as well.

So we're not going to strike a rock and have water come out, but maybe a little manna will fall and we'll continue to make progress.

I look forward to talking with you all again soon about this. So thanks very much for coming.

(Applause.)

(Whereupon, at 4:05 p.m., the meeting was adjourned.)

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September 27, 2016 Deborah J. Arbogast

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