FOOD AND DRUG ADMINISTRATION (FDA)

DEVELOPMENT OF NEW TUBERCULOSIS DRUG REGIMENS-SCIENTIFIC AND CLINICAL DESIGN CONSIDERATIONS PUBLIC WORKSHOP

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TABLE OF CONTENTS

P R O C E E D I N G S

DR. COX: I wanted to welcome everybody today to our TB drug development workshop. We will be talking a lot about a regimen development and having some discussions around all that. I really do appreciate everybody making the time to join us here today.

And, first, let me just start off with some logistics, just so we can plan ahead a little bit. You may have noticed as you walked in, there is a window just beyond these large rooms and it is where lunch is served. And so, if you can order ahead of time, so if we can get your orders in, say, by about 10:30 in the morning, that can help a little bit with the lunchtime crunch, because then they're all prepared for serving the individuals. So, it's always important to make sure that everybody gets fed during lunchtime, so just check with that window, if you can. Hopefully, we'll be able to do that during the break. The folks over there should be expecting people to come out.

Now, moving on to the topic for today. I mean, as folks know here, probably better than I, the

TB issue with global burden of disease really is phenomenal, a tremendous cause of morbidity and mortality with 10.4 million new cases of TB reported worldwide by the WHO. With 2.2 million cases in patients living with HIV, and estimates of 480,000 cases of MDR-TB in 2015. So, the burden of disease is tremendous.

We also know, too, folks working this area know how particularly challenging it is to develop new therapies for TB, and the treatments are long, require multiple drug therapy. And it's really not an area that is economically attractive for drug development. While we know the burden of disease is large, the areas of the world where the burden of disease is largest are not ones that have resources. And typically, it's low and middle-income countries where there is limited resources to be able to afford treatment and access to care can oftentimes be challenging.

But, really, despite these challenges, as I look around the room and think about the accomplishments of this group, the folks that have been involved in TB work, I mean, it really is remarkable.

And lots of credit goes to the TB community, including the drug developers, the philanthropists, scientists from all sectors, patient advocacy groups, folks in government, both here in the US and abroad, and nongovernmental organizations that remain dedicated to the work of developing new therapies for TB and caring for patients with TB.

And, at least in my view, as I reflect on the area, I think one of the things that has made things so successful in this area is really the attention to sound scientific principles and the dedication to work in this field. We all recognize that this is an area where there are unmet needs and that we can exercise flexibility and balance benefits and risks. But I think what allows us to do that is that underlying this foundation of flexibility is the sound science that is going on in the field, and that's great.

If we can think back to TB therapies, the last new TB drug approval here in the US was bedaquiline for MDR-TB that was approved in late 2012. But for those that follow the field, there has also been a lot of other important activity that has been going on out

there reported in journal articles and press releases, and such. And so, we thought it would be a good opportunity to get the field together to discuss some of the important progress that has been made in the field and share that more broadly. That's one of the reasons, too, why we'll talk some about regimen development.

And we're grateful, too, for the field's general willingness to describe ongoing development programs and have the chance to hear from the groups that are involved in this work. We'll hear some preliminary results from clinical trials to date, and I think we'll all benefit by hearing and learning from their experiences.

And then if you'll look at the agenda, too, today, you'll see that we're going to span a range of topics over a really fairly packed agenda. We'll start out with hearing some about the current TB landscape patient needs, and then move on to preclinical and clinical development with a focus on TB regimen development. And then to guide our discussion over the course of the day, following the talks in the morning

and the talks in the afternoon, we have a series of questions that we'll try and cover during panel discussions, both in the morning and the afternoon. I look forward to hearing those discussions, and I hope everybody has a chance to engage in the panel discussions.

Today is a workshop, which is different than an advisory committee. It's an informal chance for discussion; it's not a chance for formal advice to the FDA. So, that lets you know that it's a little more freefalling, a little more flexible, and we think that's a good opportunity, a good way to talk about where things are in TB drug development.

So, thank you all again for your interest, your dedication, your commitment to the field of TB therapeutics and with the shared goal of focusing on developing and improving treatments for patients with tuberculosis.

So, now at this point I'd like to ask the panelists to introduce themselves. And if you can just tell people who you are and also your affiliation. And so, that folks know, too, in the meeting materials we

also have disclosures of conflicts of interest that are available so that folks may, if you're interested in peoples' affiliations and the works that they're involved in, that will be in the printed materials. So, maybe at this point I'll ask Dakshina Chilukuri to start out with the introductions, and then we'll go around the table this way. Dakshina?

DR. CHILUKURI: Good morning. My name is Dakshina Chilukuri. I'm a clinical pharmacology reviewer at FDA.

DR. PELOQUIN: I'm Chuck Peloquin. I'm the director of the pharmacokinetics lab at the College of Pharmacy at the University of Florida.

DR. PATEL: Good morning. My name is Sheral Patel. I'm a medical officer at FDA.

DR. STARKE: Hi. I'm Jeff Starke. I'm a pediatrician from Baylor College of medicine and run a kids TB clinic.

DR. GEITER: Larry Geiter, vice president, global clinical development for TB for Otsuka Pharmaceuticals.

DR. TOERNER: Good morning. I'm Joe Toerner.

I'm the deputy director for safety in the Division of Anti-Infective Products at CDER, FDA.

DR. NAHID: Good morning. My name is Payam Nahid. I'm at the University of California-San Francisco. I am a TB clinical trialist working with the CDC TB trials consortium.

DR. GITTERMAN: Steve Gitterman. I'm with the Division of Microbiology Devices in the Center for Devices at FDA.

DR. SCHITO: Marco Schito, scientific director at Critical Path TB Drug regimens, Critical Path Institute in Tucson, Arizona.

DR. VERNON: Good morning. I'm Andy Vernon. I'm chief of the clinical research branch in the Division of TB Elimination at CDC, and my group oversees the TB trials consortium.

DR. HANNA: Debra Hanna. I'm the executive director of the Critical Path, the TB drug regimens initiative at the Critical Path Institute, Tucson, AZ.

DR. BANSBACH: Good morning. I'm Cathy Bansbach from the Bill & Melinda Gates Foundation. I play a role of the portfolio and platform lead, which

basically means I work on product development with our grantees and partners to try to have the greatest impact we can. So, pleased to be here. Thank you.

DR. SPIGELMAN: Morning. My name is Mel Spigelman and I'm from the Global Alliance for TB Drug Development.

DR. NAMBIAR: Good morning. I'm Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. LOBUE: Good morning. I'm Phil LoBue. I'm director of the Division of TB Elimination at CDC.

DR. FARLEY: Good morning. John Farley, deputy director of the Office of Antimicrobial Products at CDER, FDA.

DR. LIENHARDT: Good morning. I'm Christian Lienhardt. I'm working at the World Health Organization in Geneva, where I'm leading a team on the research for TB elimination, and that, among other things, is doing guidelines for introduction of new drugs and regimens for tuberculosis for countries, member states of the World Health Organization.

DR. WELLS: Good morning. I'm Charles Wells.

I'm the head of development for the infectious disease therapeutic area at Sanofi.

DR. HUGHES: Good morning. David Hughes. I'm the senior global program head responsible for anti-infective development at Novartis.

MS. HIGGINS: Hi. I'm Karen Higgins. I'm the statistical team leader supporting the Division of Anti-Infective Products at FDA.

DR. PHILLIPS: Good morning. I'm Patrick Phillips. I'm a statistician now at the University of California-San Francisco.

MS. LESSEM: Hi. I'm Erica Lessem. I'm the director of the TB project at Treatment Action Group, a science-based activist organization.

DR. NUERMBERGER: Good morning. Eric Nuermberger, Johns Hopkins University with research interest in preclinical and translational TB drug development.

DR. YASINSKAYA: Good morning. My name is Yuliya Yasinskaya, clinical team leader at the Division of Anti-Infective Products, FDA.

DR. IARIKOV: Good morning. Dmitri Iarikov.

I'm acting deputy division director of the Division of Anti-Infective Products, FDA.

DR. COX: Thank you all. And I guess I didn't introduce myself. I'm Ed Cox, director of the Office of Antimicrobial Products. And just so folks know, too, the meeting is being webcast and it's also -- there will be a transcript that will be available on the meeting webpage after they produce the transcript. So, it will probably be a few weeks after, same place where the materials are already posted.

So, at this point, thank you again for joining, and now I will turn the chairship over to John Farley and Phil LoBue, who will guide us through the morning session. John?

DR. FARLEY: Thanks, Ed. So, Phil and I will be taking us through the morning session, and the focus of the morning session is Landscape and Preclinical Approaches to Inform Clinical Candidates for TB Combination Regimens. And Phil is our first speaker. As he mentioned, he's director of the Division of TB Elimination at CDC. He's been at CDC since 1999, and has served as chief of the medical consultation team,

as well as the associate director for science before being appointed TB division director. So, Phil, thanks very much for being here with us today.

DR. LOBUE: Thank you very much for inviting me. So, the outline of my talk, I'm going to briefly talk about the TB burden in the United States and globally, and current treatment regimens. And doing this pretty quickly at a high level, as I expect the vast majority of people in the room are familiar with a lot of this information, but just for completeness, for those who may not be as familiar. And then spend the rest of the presentation talking about some of the challenges, at least from the CDC perspective.

So, for those of you who are not familiar with kind of the standard abbreviations for drugs and some of the other terms, I just wanted to lay those out here. So, the international single letter abbreviations for various drugs. H is isoniazid, R is rifampin, P is rifapentine, E is ethambutol, Z is pyrazinamide. I use FQN for fluoroquinolones, MDR for multi-drug resistant TB, which is TB where the isolate is resistant to isoniazid and rifampin. It could be

other drugs in addition to that. A subcategory of MDR is extensively drug-resistant TB, or XDR, which is MDR plus resistance to at least fluoroquinolones and injectables. And then LTBI is latent tuberculosis infection, which is a condition where a person tests positive by a skin test or interferon-gamma release assay but don't have any clinical evidence of disease by x-ray or symptoms. But those people are at risk for progressing to TB disease and getting sick.

So, a brief overview of the burden of TB, both in the United States and globally. United States is a low incidence country and as you'll see on this slide, we're talking about orders of magnitude difference in terms of the US problem versus globally. So, starting out with the number of new cases of disease, in the United States we have a little over 9,000 cases, where globally there are over 10 million each year. Those translate into case rates for the US of 2.9 per 100,000 as opposed to 142 per 100,000 globally. In the US our prevalence of MDR is fairly low at about 1%, so in 2015 it was 89 cases of MDR-TB as opposed to globally, where, as Ed already mentioned, we're talking about

almost 500,000 cases each year.

XDR in the US, usually we have between 0 and 6 cases per year. We had one in 2015, the last year that we have our surveillance data for, and globally estimates of about 45,000. Also, obviously, the prevalence of HIV among persons with TB varies quite a bit from country-to-country. In the US, it's less than 10%. We had 539 cases in 2016; globally there were 1.2 million, but there are obviously parts of the world, such as Sub-Sahara in Africa, where the prevalence can be 50%, 60% or more of HIV among persons with TB. We have relatively few deaths at 493 as opposed to 1.8 million worldwide.

And then, finally, latent tuberculosis, which although it is an asymptomatic condition and doesn't cause any immediate issues and persons are not infectious, the problem is that these are people who are at risk for ultimately getting TB disease. In fact, in the US, that's where about 85% of our cases ultimately come from, and both in the US and globally recognize that if we're going to eliminate disease, we actually have to deal with this problem more

effectively. There have been multiple models that have shown that ultimately you cannot eliminate TB under current circumstances without effectively addressing LTBI.

But disease burden is not kind of uniformly distributed. It tends to be concentrated globally. Sixty percent of TB cases occurred in just six countries, and I show them here. Not surprisingly, these are the most populous countries in the world, such as China or India, but other countries which are low income, such as Nigeria, Pakistan, have quite high TB rates and contribute substantially to the global TB burden.

Analogously in the US, almost 60% of our TB cases occur in just six states. Not surprisingly, again, these are some of the more populous states, including California and Texas, New York, Florida, Illinois and Georgia.

So, moving on to current TB regimens. So, for drug-susceptible TB disease we divide the regimen into an intensive phase, which is the first two months, then a continuation phase, which is the next four months.

And the standard regimen both in the US and globally starts with the four drugs of isoniazid, rifampin, pyrazinamide and ethambutol for the intensive phase, and then isoniazid and rifampin for four months in the continuation phase. The dosing is daily recommended globally, and daily is the preferred dosing regime in the US. For directly observed therapy, which I'll talk a little bit about later, it actually is generally the recommended way of treating TB in the US, and the World Health Organization guidance says it may be offered.

Moving on to multidrug-resistant TB. So, in the US, basically, we use regimens of four to six effective TB medicines, and those are based on the results of drug susceptibility testing. The conventional duration is 18 to 24 months. There is now a shorter duration of regimen recommended globally, and that's for people who are not previously treated with second-line drugs, and who -- resistance to fluoroquinolone and second-line injectable agents is excluded or considered highly unlikely. That regimen is not currently recommended in the US. However, globally, as you can see, that 9- to 12-month regimen

may be used instead of the conventional regimen for patients who fit those categories. For those who don't, the recommendation globally is that there are at least five effective TB medicines during the intensive phase, which is the first eight months, and then 20-month total duration for conventional treatment is generally what is recommended for most patients.

Moving on to latent tuberculosis, there are a number of regimens that are available. The oldest one is isoniazid alone, and both the US and WHO recommend that for 6 to 9 months daily. More recent regimens are isoniazid and rifapentine for 12 weekly doses; rifampin, which in the US is recommended for 4 months daily, globally 3 to 4 months daily, and then the combination of isoniazid and rifampin, which is not currently recommended in the US but is recommended globally for 3 to 4 months daily.

So, I'm going to move on now to the challenges that we face with these current treatment regimens from the CDC's perspective.

So, number one is duration, and Ed already mentioned that and I've already covered that basically

by going through each regimen duration, but you can see that generally for TB disease we're dealing with at least six months of treatment. For drug-resistant TB, it can be two years or longer, so long regimens with multiple drugs. That can engender substantial cost, as I will talk about in subsequent slides. There is substantial toxicity associated with a lot of these drugs and regimens. There are issues with drug-drug interactions with these long regimens, which are multidrug and potential toxicity. We have issues with adherence. And then, finally, obviously, outcomes, what we're all about. We would like to cure pretty much everyone, and with drug-resistant TB, that really becomes a significant issue.

So, while I went through that list, I don't think you can really talk about these challenges in isolation because there are inter-relationships and there is interplay between them. So, if you have an increased duration of a regimen, that's going to increase the cost, it's going to tend to decrease adherence and increases the risk of toxicity, because the longer, just by probability, longer a person's on a

drug the more chance there is for toxicity. Toxicity will increase costs and decrease adherence. Increased costs will decrease adherence if people have to pay for part, even part of their regimen, which is fairly typical in many parts of the world and in the United States. And then obviously if you don't have good adherence you're going to get worse outcomes, and also with worsening toxicity you're going to get worse outcomes. I don't need to cover every permutation of this, but just to make the point that these things are highly interrelated and all of them pose a problem.

So, let's start talking with costs. So, if we just look at the direct costs of treatment, globally for drug-susceptible TB the estimates are that the direct costs are between $100 and $1,000 for a course of treatment. That goes up substantially with MDR-TB, where the estimates are $2,000 to $20,000. In the US, the costs are even more. For latent TB, the cost is about $500 to treat, for example, with 3HP. For treating TB disease, the estimated average cost is about $18,000. Now, a lot of that is not related to drugs. I'll show those specific drug costs in the next

slide, but in US, where other medical costs are high, particularly when you factor in hospitalization costs for average cost, the costs are substantial, so about $18,000 to treat TB disease in the US. But when you start moving into the drug-resistant forms of TB, which is shown in the panel on the right, we start off with drug-susceptible, as I said, $18,000 direct cost. If you start factoring productivity and other indirect costs, so societal costs, that can go up to $45,000. However, once you move to MDR-TB, where the treatment is much longer and more toxic with more difficult to manage drugs, the direct costs, where hospitalization is also more, it can go up to $154,000 with the productivity costs almost $300,000. And then moving to XDR, the most resistant form of TB, the direct costs are just under $0.5 million, $494,000, and then when you add in the productivity losses and other societal costs, we're coming close to $700,000 per case.

As I said, those costs are not just the drugs; there are many other costs that go into it. So, when we look at just the cost of drugs in the US, for drug-susceptible TB, it's about $400 for just the drugs for

drug-susceptible. The global, as you get drugs to the global drug facility, it's about $40 internationally. When you start moving to MDR, the conventional regimen, the drug costs in the US are about $58,000. Global drug facility internationally is $2,000 to $5,000. We don't use the short course treatment in the US, but you can decrease costs internationally to about $1,000 if you use the MDR short course. And then we have estimated drug costs for the US for XDR at $164,000. So, you can see that with drug-resistant TB these costs jump quite substantially and become really a burden on patients and public health programs.

And then toxicity. I did not go through every possible form of toxicity, but there are many, but just wanted to illustrate a few points. When we deal with drug-susceptible TB, there are obviously a number of other toxicities associated with each of the individual drugs. But primarily the ones that programs have the most problem with is hepatotoxicity, especially since you have multiple hepatotoxic drugs in that regimen particularly isoniazid and pyrazinamide.

With drug-resistant TB, you really start

seeing multiple toxicities and severe ones from hepatotoxicity -- kidney disease, ototoxicity, psychosis, this whole list of individual toxicities associated with the various drugs and many of which can be very serious and often result in that individual drug having to be stopped, and which obviously impacts the ability to complete the regimen.

And then for LTBI, again, the two main ones that we tend to see are hepatotoxicity, particularly with isoniazid-containing regimens, and then hypersensitivity reactions with rifamycin-containing regimens. Again, those are not exhaustive lists, but I think the major ones for these different forms of disease.

And I mentioned drug-drug interactions, and here I just used two examples, isoniazid and rifampin, which obviously are very commonly used in the regimens. And, as you can see, for both isoniazid and rifampin, I'm not going to go through these whole lists, but you can see there lots of drugs with interactions that occur that really people have to be aware of. And they have to at least alter dosing of either the TB drug or

the drug which it interacts with. And so, this is another issue that has to be considered when you're treating people with TB.

And adherence. So, if you're going to get a cure, the person needs to be adherent to the regimen. And this is where directly observed therapy comes in, which is the practice of having patients swallow the antituberculosis medicines. The point is, you don't want people, one, not completing, but also taking individual drugs at different times, which is one of the ways that drug resistance develops. And so, to prevent that from happening, having someone make sure that the patient takes all their drugs all the time through completion of therapy is a standard practice in the US and in many places globally. But it is resource-intensive and costly because the standard practice has been actually to have some kind of trained worker from the health program do this. Various areas in the US and globally now looking at ways of using different technology, video, electronics, smartphones, to try to cut down some of those costs. And so, that may help, but this still resource-intensive.

And then there are other things that we try to do to get patients through, what we call patient-centered care. And so, incentives, which are innovations that try to motivate the patient that are tailored to individual patient desires and needs. And they should be meaningful, things like gift cards and food vouchers. And then the other thing that is used are enablers, which are other interventions to assist the patient in completing therapy. Really, it's more about removing barriers, so making sure they can get to clinic. They want to get clinic but they can't because they don't have transportation or that clinic hours are just inconvenient for their work schedule. So, things that enable them and help them get through their treatment. Again, these things cost money.

So, finally, outcomes. So, if we do everything right, where do we went up? Well, I think in general, other than drug-resistant TB, these are fairly good. But obviously 100% would be -- or as close as possible, 100% would be better. But we start with latent TB, treatment efficacy for the regimen is around 90%. The issue there is completion. Especially

with a longer course regimen of nine months of isoniazid, at best you might see 50%. There are many studies which show completion much, much less than that. We have found with the shorter regimens, such as three months of isoniazid or rifapentine, now we can do substantially better, somewhere around 80%.

With drug-susceptible TB, most of the clinical trials show you reach about a 95% cure. When you translate it in the programmatic setting it's not quite as good, and that very much depends on how good the program is. But generally, you're looking at 85% to 95% success measured by cure or completion.

With MDR, not as good. We were surprised to find that actually in the US programmatic setting that recent publication showed that we could get about 80%, 90% success. Overall, globally it's been closer to 50%, although there are definitely places that do substantially better, and especially with the newer short-course MDR therapy seeing higher success rates than that 50%.

So, finally, again, from our perspective at CDC and mainly focused domestically, what are the

things that we're looking at and trying to improve, and what has been our focus? Really, our focus has mainly been on duration and shortening duration, because as I showed earlier, duration affects so many other things -- cost, toxicity, adherence. We know with current treatment we can do pretty well and get pretty good results, but it would really be better in terms of resources if we could get this shorter and actually potentially use some of the saved resources to expand more into the LTBI realm.

So, Andy Vernon is going to talk in more detail about TBTC, but just to give you an idea, overview of our focus, looking at trying to decrease the duration of drug-susceptible TB to four months, for example, or decrease the duration of treatment for LTBI for four to six weeks. And globally there are many, many other things that are being addressed, and so I certainly -- this is not an exhaustive list, but just for completion of talking about MDR-TB, again, in terms of duration, people are aiming to get to more of the six- to nine-month range, which is being addressed in trials. And also with that shorter course, want to get

to the 85% to 90% success as opposed to the overall average of kind of 50% currently. So, I will conclude there and thank you, and turn it back to my colleague, John. So, I don't know about timing, whether we'll have time for questions or whether we're going to hold based on where we are?

DR. FARLEY: Sure. Why don't we see how we do after Cathy's talk?

DR. LOBUE: Okay. Thank you.

DR. FARLEY: Shall I introduce Cathy?

DR. LOBUE: Yes.

DR. FARLEY: So, Cathy Bansbach is portfolio and platform lead for the Bill & Melinda Gates Foundation, global health program strategy team for TB. Their goal was to reduce the incidence of infection and disease, and she has worked in this field for over 20 years. We look forward to hearing form her this morning.

DR. BANSBACH: Thank you. I'm relatively new to the field of TB, only having joined the foundation two years ago, but I do have quite a bit of experience in drug development.

Being new to the field, I went to my first union meeting in Liverpool last year, and I learned a very sobering statistic, which is that someone dies of TB every 18 seconds. That was a reminder of why we do what we do.

At the Gates Foundation, our goal is to try to accelerate the decline in incidents by breaking transmission. And in order to identify where we could best place our investments to have the maximum impact, we commissioned a Patient Pathway Analysis from 11 of the highest prevalence countries and learned that in the world overall, approximately 25% of people are never even diagnosed with disease. Of those who are diagnosed, approximately 12% never initiate treatment, and of those who do start treatment, almost 20% don't complete. This is an abysmal picture and something that gives us a lot of opportunity for investment, but there was no specific one place that we felt we should place all of our bets. And so, the foundation's approach has been to develop a portfolio of interventions to try to close some of these gaps in the care cascade. And the one we'll be focusing on today

is the work that we're doing to support a shorter universal drug regimen. But before going there, I just wanted to review what's been on drug development in TB over the past decade.

There are five basic approaches. The first is actually one that's borrowed somewhat from oncology, where you take standard of care and you add on an additional compound in the hopes of improving efficacy. Although since it's an add-on, you really don't do anything for the underlying safety issues with the background therapy or the duration or the cost. In fact, adding on will probably add cost. What you do gain is faster development time. So, we consider this a fast-to-market but unfortunately slow to impact, because you're only affecting the MDR population.

A slight variation on that model would be to switch out one of the molecules in the optimized background regimen and substitute it with a better compound, again with the goal of increasing efficacy. And you may, if you switch out a toxic element, actually increase safety, but the question mark as to whether you can affect duration, chances are the new

agent won't be in lower cost than the one you're switching out but, again, you have a faster development time. Both of these approaches, however, have a liability that by adding into what could be a failing regimen, you do carry the risk of resistance to the new drug.

Again, borrowing from our friends in oncology, the TB Alliance has taken a very brave approach to developing a brand-new regimen in the XDR and pre-MDR -- pre-XDR population, where they combine bedaquiline, pretomanid and linezolid. And here they saw, as Mel, I think, will tell you a little bit later, dramatic efficacy, and improvement in safety compared to what XDR patients are generally treated with, and a much, much shorter duration -- six months as opposed to the up to 20 months that we heard about just now. Cost will not be lower. Development time was rather quick considering, and the risk of resistance, because all of the compounds in that regimen are new, should be extremely low.

Then if you move from the MDR-XDR patient populations that can tolerate some risk given the

benefit and look at the rifampin-sensitive population, there are two models. One was used in the REMox studies, where you swap out one element, in this case either the isoniazid or the ethambutol and replace it with moxifloxacin. Here the goal was to shorten treatment. As we all know, that didn't work. The regimen was effective, but no more effective than HRZE itself.

And then, finally, the pathway that the foundation is currently supporting, which is our unified development regimen, which enrolls patients both rifampin-sensitive and rifampin-resistant. And the idea here is, at least in the rifampin-resistant, to improve efficacy. I don't know that we can actually demonstrate improved efficacy over 90%, 95%, which we see in clinical trials for the rifampin-sensitive population, but we should see better safety, better convenience and duration. Cost will probably not be lower, but it will take more time. Development time is the cost you pay for having a greater impact by being able to address all of the patients in the TB population and not specific subsets.

So, to expand a little bit on what the unified development path looks like, it's pretty vanilla up until you get through Phase 1. Then you would move into a 14-day study in TB patients for the first time to look at antibacterial activity, that's your monotherapy EBA. Then you would open up a new study or potentially amend -- carry on in your initial EBA with combinations of various regimens that either preclinical data or clinical information have given you a sense would be good regimens, test a variety of them in the rifampin-sensitive patients only, because if there is a problem you have a salvage therapy in HRZE. Then take that information and then study, rather than for 14 days, look at the regimen for two months to get additional safety. Now we move into both the rifampin-resistant and rifampin-sensitive populations and we use HRZE as a control for the drug-sensitive, the rifampin-sensitive population, but we also have the rifampin-resistant arm as an experimental.

And then, finally, if we find a regimen that meets all of our criteria, you would move into Phase 3. You would be looking to demonstrate shortened

treatment. Four month is the current model, but we hope at some point we'll be able to make that even shorter. And here we're looking for noninferiority in the rifampin-sensitive population and hopefully increased efficacy in rifampin-resistant.

So, what can we do with this drug development pathway to accelerate? When I first looked at the pathway, I said to myself, 14 days in healthy volunteers, then 14 days in patients; can't we do both of those studies in patients? And the reason I asked that question was, my background in hepatitis C research, where we have a very good, real-time biomarker in viral load, and we were able to enroll patients in Phase 1, the multiple ascending dose study, which was probably more important in hep-C than in most therapeutic areas because we don't have an animal model that we can trust in hepatitis C. So, getting the answers about activity in the patients as soon as possible was very important.

And during that program we went through three lead compounds, very rapid succession. The third compound had the potency that we were looking for, but

we noticed that after four days we could see resistance emerging in the population. So, we amended the protocol and did a combination study in the MAD study, where we added interferon, which is part of the standard of care. And now, to our surprise, not only did we see greater antiviral activity right from day one, but we were able to overcome the resistance problem. So, here very quickly we were able to get a lot of information about how our drugs were performing in the population of interest, not the least of which is we get to understand the safety in what can be a more sensitive patient population. So, that's one thing. Let's combine the MAD and EBA.

There is no reason not to link the combination and monotherapy parts of the EBA study, provided you have the underlying preclinical toxicology to support that. And one of the things that you could gain from that is if you have a compound like bedaquiline that doesn't have particularly strong activity in a 14-day EBA, by then very quickly getting information of what happens when you put it into a potential regimen can really accelerate development.

And while we're on the topic, why stop there? Why not combine option 1 and option 2, so that you use patients in your MAD study and you go right into a combination study.

And then, finally, once we have our hands on a real-time biomarker, it would be fantastic if we could do adaptive Phase 2/3 designs, where you take a number of promising regimens into your Phase 2 part of the study, very quickly identify which ones are potentially better, and then carry out the full Phase 3 six-month cure with those regimens.

So, that's where we're thinking of going. I'm hoping that we can have a nice panel discussion around what sorts of nonclinical and other information you would want to have in order to try some of these options in the field.

So, we mentioned the universal regimen. What I've done here is basically summarized a lot of work that was done with Chris John and the members of the WHO task force to talk about what would be the regimen profile. And here we're looking for shorter regimens. I have six months there, but I think we'd all like to

see four months or less.

Simpler. One of the great notions behind the universal, or pan-TB regimen, is that when a patient walks into the clinic and receives a diagnosis of tuberculosis, you could initiate therapy right then and there. You don't need to know if they're rifampin-sensitive or resistant to isoniazid, sensitive or resistant, because the regimen won't contain any of the compounds for which there is pre-existing resistance in the population. We're hoping that the regimen will be all-oral, so it's easier to take. Of course, we will be considering, as they are developed, whether long-acting injectables can play a role here. And, of course, in order to help prevent cross-resistance of compounds, it would be great to have fixed dose combinations, where that is possible.

As far as safety, I know it's aspirational, but we would like to have no laboratory or clinical monitoring, because the reality in the field is that even if the drugs are labeled for monitoring, it's not getting done. And so, if you can build inherent safety into the regimen by choosing the right individual

compounds, you should be able to address this. Again, if we're going to be using FDCs, we can't have a lot of dose adjustments, so we need to have compounds that don't need to be weight-banded or don't have other liabilities like that. And obviously, because of the co-epidemics of HIV and diabetes, we have to be very thoughtful about the potential DDI liabilities. And all, of course, at affordable cost.

So, where is the chemical matter coming from to build these fabulous new regimens? This is a page from the Working Group for New Drugs that shows what is currently in late-stage preclinical and through Phase 3. I've squared in red the compounds in which the foundation is currently investing either through grants to the TB Alliance or our work with Lausanne on PBTZ, and we are in discussions currently with Otsuka about supporting their work in this area.

So, in summary, what are the challenges of this brave new world that we're about to enter into? We finally have a pipeline, which is very exciting but is also very challenging. How do you choose the best combinations of drugs out of this rich diversity? And

so, Debra Hanna will be telling us a little bit about the work that is going on at CPTR to try to develop a holistic view, bringing together the data from in vitro, in vivo and clinical information to try to give us some better sense of how to find the best combinations. By looking at two-month data and extrapolating to what might happen after six months of treatment or even six months' follow-up, we do wind up carrying a lot of risk into our Phase 3 studies, and I think that that's something that the field needs to think about. How can we better utilize data from 14-day or two-month studies to help increase our probability of success of cure?

I've said before, if we finally had a treatment response biomarker what I couldn't do, and so the field is looking at a variety of opportunities, sputum and non-sputum assays, between Otsuka and CPTR, we're in the midst of trying to qualify a lamb sputum assay. Cliff Barry and his group are doing a lot of work with PET-CT imaging to see if that can be used as an early indicator of activity, and there is a lot of work going on in immune response markers, be they

genetic or otherwise.

Two questions I'd like to leave you with, for the panel to discuss later, and that is, we all know we have to do regimen development. Resistance is real. What kind of preclinical safety information do we really need in order to study combinations in the clinic? Do we need to do nonclinical combination safety studies? Are they really helpful or is understanding the liabilities of each of the individual components and knowing what to monitor for, when we get to the clinic, sufficient? And, again, the continuing question of how do we find the best regimens, and what is best? Thank you. Ten million people waiting for us.

DR. LOBUE: Thank you. Our next speaker will be Erica Lessem. Erica is director of TB-HIV at the Treatment Action Group; an independent research and policy think tank. Erica oversees TAG's activism for research and access to improve tools and services to prevent, diagnose and treat TB and TB-HIV. Thank you, Erica.

MS. LESSEM: Thank you. I'd like to start by

thanking the FDA for hosting this important workshop, and for allowing a member of civil society such an early slot on the agenda today. It's very appreciated. It's not that common, and just one of the many examples of how FDA's Office of Antimicrobial Products under Dr. Cox's leadership really tries to meaningfully engage with the community. So, I just wanted to acknowledge that. And I wanted to thank all of you for being here, because I think it's clear that even though we might have some differences of opinions about the best way to proceed, all of us really are trying to do better for people who are affected by TB. And I think what we've seen from the earlier presentations is that what's really most important for patients is how we can get safer, easier, and in the case of drug-resistant TB, more effective treatment.

So, why do we need new treatments? I think Dr. LoBue and Dr. Bansbach presented it very nicely, but here's another way of looking at it. This is from an activist poster at the Union Conference in 2014. It's just not good enough. We wouldn't accept these kind of side effects in almost any other disease area,

and we certainly shouldn't in TB, since we've been treating it for so many decades.

We have made a lot of progress in recent years, but TB has been operating from a position of scarcity, and that doesn't poise us well to do better. And I think we need to really think about taking a more bold approach and asking for more for patients, and building that, really, into the research and regulatory pathways. We all here are very well aware of the critical funding gaps, and given the short time frame for the talk today, I'll leave the questions of investments for another day and just kind of focus on the research and regulatory considerations that those of us in the room can influence, and how we can best employ the resources that we have.

So, I think there are several overarching questions that I and some of the other community groups that we work with have been thinking about. I hope you can see the text. I might have had some Mac-to-PC conversion issues here. So, there are a lot of questions. When is it -- when do we have enough information to go into Phase 3? How can we balance the

need for really wanting to accelerate research with making sure we have all of our ducks in a row; to make sure that we're being ethical in terms of moving forward when we really know enough about safety and efficacy to open up a trial and to start going for regulatory approval? When, if ever, is it appropriate to forego a control or to forego randomization? This is a real problem in drug-resistant TB, as all of you know, since we don't have a great, validated standard of care.

How can trials generally be conducted ethically in a way that we get information about a drug or regimen while standards of care are changing? And how can adopting new treatments that we have some evidence, especially from kind of routine programmatic use, and we want to do the best things for patients, how can we balance that with being able to make sure we can still collect enough data and not inhibiting data collection?

How can we avoid perpetuating the current state that we're in, where we're using drugs and regimens because it's the best thing that we have, but

we still don't have the complete evidence that we would want to to support their safety and efficacy and optimal use? And how can we balance the urgency of the immediate access needs that we see for patients around the world with the importance of really knowing the full profiles of the drugs or regimens that we're using?

And another thing that I want to ask, since we're here at FDA is, how can FDA be empowered to hold sponsors accountable for delivering on conditions of approval? How can we better position FDA to really ask for what's needed in this field? And I think it's important to point out the broader regulatory climate here.

There is a misconception, I think, among some policymakers that patient groups only want faster access to treatment, and that's not true. Patients want access to safe and effective treatment that has been studied. And TAG, where I work, was founded by people with HIV, who really wanted more research and more data to know whether the treatments that were being given actually worked and were safe. And I think

because TB has been the victim of decades of underinvestment and we still don't have an optimal standard of care for MDR-TB, that puts us in a difficult position to say what the ideal trial design should be.

And so, we have a lot of TB-specific issues, but more broadly there is a climate of pushing for increasing regulatory laxity from the 21st Century Cures bill that was approved in the end of last year to the Right to Try Movement, which is really pushing for much earlier preapproval access. And some parties are vilifying the important role that regulatory authorities play and they are over-simplifying the complex challenges of bringing a [product to market]. It's much easier to say, oh, it's the government that is being too slow. Well, we know that that's not true. And I think if these pushes are successful, we're really in danger of being in a pre-FDA era, and that's not going to be good for any of us, either for patients, for the broader community, or even for the sponsors, who would then really be on the hook for this.

In our experience, FDA has been highly transparent and timely in its reviews. Already has a lot of useful pathways for guaranteeing preapproval access and for accelerated approval, and has several incentives for drug development. So, that's why we sent FDA a valentine last February. But since a lot of us are really focused on TB, I just want to kind of frame this in the bigger picture that TAG is really concerned about, about jeopardizing the very strong and transparent regulatory authority that we have here in the US.

So, going back kind of more specifically to TB, some of the things that we've been thinking about as a community are approaches to finding this balance between getting the answers and moving trials efficiently and having access in the meantime. So, a lot of these things need to be considered on a case-by-case basis. But I think we're already learning a lot from the experience that we've had in the past decade or so of some revitalization of clinical research for TB treatment.

So, just to point out a few of these kind of

options and things that we want you to think about and I hope will solve all of this today. Seamless designs would be -- are really useful, I think, for maximizing efficiency. They allow the most advantageous arms to move forward, but also really cut down on the delays that might happen for having to go through regulatory approval in multiple countries for multiple sites. We're also very supportive of Phase 2c designs, to gather more evidence about our regimen before moving to Phase 3, as well as to validate endpoints. As we heard from Cathy's talk, we really need some better endpoints and biomarkers in TB.

And speaking of endpoints, I'd like to encourage the group here to consider endpoints that might be an alternative to kind of standard relapse-free care, especially if we're thinking about pre-XDR, XDR. It might be useful to think about adverse event-free, relapse-free care as an outcome. That could help reduce sample size as well as give a lot of information that is very relevant to patients and providers, and we could kind of build some of the safety considerations into the outcome itself and allow for superiority

studies to happen in that way even when a regimen is not expected to increase efficacy. So, I'm just thinking, if the regimen that is being studied in the NIX trial, the BPaL regimen winds up continuing to look as good as we're all hoping it does, then what's next? That would potentially set a higher bar for efficacy. We might not want to be focusing on increasing the efficacy in terms of superiority, but certainly we would want to reduce the linezolid toxicity. And so, can we think of other endpoints that really capture what's important to patients and to programs and to providers in that?

And thinking also about this, we have some concerns that noninferiority studies may be setting the bar too low in some cases, especially when margins allow for potentially even worse performance than the comparators. So, I think if we can think of innovative endpoints, we might be able to think more about doing superiority studies rather than noninferiority studies for some conditions which really don't help us kind of move the forward bar forward or raise the bar for patients.

And then there's the question of a control, and I didn't put bullets under this because it's really hard to summarize. But I think the main point here is we really want to move the field out of the dark that we're in right now of not knowing how regimens perform in clinical trial settings or compared to each other. And we acknowledge the limitations of the existing feasible controls for M/XDR TB particularly. But we hope that if the regimens that are in development now continue to perform well, we can have a new standard of care that would set a higher bar for a control and can obviate some of these questions.

And I just wanted to flag, too, with the question of controls, because we've heard this as we reviewed some protocols that a regulator might have approved a study design. But I wanted to flag to you that for studies proceeding without a comparator, normative guidance can still be very challenging to formulate, as can garnering community practitioner and programmatic support.

So, one question is the regulatory piece, but that's not really the only approval that would need to

be in place to actually get regimens to patients. And so, I would encourage everybody in the room to be thinking about what does it really take to get a drug or a regimen into bodies, and how can we set up for research in a way that would have the most efficient pathway to get there?

Something else to flag, and I see that we'll discuss some of it later in the panel discussions, but inclusion of vulnerable populations. There is systematic exclusion of pregnant women and of adolescents and children from research, and this is not ethical and it's not scientifically sound.

There was a recent paper from community representatives including my colleague, Lindsay McKenna in CID, and I think this is a really powerful quote. "In the absence of research, each pregnant woman treated for TB becomes an individual experiment." Pregnant women will get TB, people with TB will get pregnant, and we need to know how drugs and regimens will work in them. A lot of drugs could potentially be safe in pregnant women, but there's a lot of fear around including pregnant women in trials due to

concerns about liability, getting insurance, getting through ethics boards. Same for adolescents.

There is real consensus now that adolescents metabolize drugs similarly to adults. There was a consensus statement coming out of an NIH workshop several years ago, that adolescents should be included in later stage trials along with adults. And we also need pediatrics-focused research, to make sure that in children who do metabolize drugs differently or might present disease differently that we know what the best regimens and drugs to use are in them and the best dosing for doing so.

Unfortunately, there is what's intended to be an incentive for developing orphan drugs actually perversely disincentivizes research in children. There is a regulation here in the US that drugs must be studied in children, there must be a pediatric plan, but the Orphan Drug Act actually allows an exemption for that. So, in children with TB, who are probably one of the populations in most need of research, we're actually trying to incentivize drug development by saying that you don't have to study TB in this

population. And so, I think we really need to think of regulatory solutions and legislative solutions to get us out of that hole. And from TAG's perspective, the default really should be to include pregnant women and adolescents in research unless there is a rationale for opting out. So, the current approach is opt-in, and almost nobody is doing that. But I will give credit to some of the studies, including from TBTC and ACTT, that are trying to go down to age 12 or 15, in some cases. But I think we need to reframe our thinking in that the default must be to include these populations in research unless there is a specific reason to take them out, as well as to have a really robust pediatric research plan in parallel to whatever is happening with adults.

Another thing that would be really useful in TB is a registry for pregnant women and seeing what drugs they're on and note some of the outcomes. That has been really helpful in the HIV field and it has been expanded to hepatitis B as well. It would be really useful to have this kind of registry in pregnant women since it's unlikely that there would be enough

people to kind of have a separate clinical trial of a certain product in pregnant women.

And then just to flag, there are other special populations that are often excluded from studies because we don't want to have the "noise" that might detract from finding the efficacy and safety that we're hoping to see in the broader population. But we see it reflected a lot in the guidelines because people haven't been included in the research. So, we need some additional research in a lot of special populations, including people of advanced age. In a lot of countries, the majority of TB is happening in people who are over 65. We need people with very low CD4 counts. They're at the highest risk of dying, but for a lot of reasons they're excluded from clinical trials, so we don't know really what the best options for them are.

And then also people who use drugs or alcohol or opioid substitution therapy, where there might be extra concerns about toxicity and about drug interaction.

So, there are a lot of issues to consider, and

just to note that we're here to help. TAG and the community groups that we work with, in particular, the Global TB Community Advisory Board and the Community Research Advisors Group have a lot of experience reviewing protocols and study concepts and are available to do this for any sponsor that wants to share with us, and we encourage everybody to do so. And we've been able to review almost all of the late-stage MDR-TB trials in the last six years. We haven't been able to review the Otsuka protcols, but other than that, I think it's been pretty much everything late in the pipeline and most of the late-stage prevention and drug-susceptible TB trials, pivotal ones that are happening.

And there is a nice publication about -- or presentation about what we've kind of found across this, and it's just something to think about as you're developing your research plans. But what can be included upfront, more information about results dissemination, plans for post-trial access. Again, this issue of the control arm, what the composition of it is, or whether it even exists. Using

nonstigmatizing language in study documents, so we facilitate participation, and appropriate inclusion of key affected populations, like I mentioned on the last slide. So, feel free to email me if you want us to take a look at anything you're working on. We'd be very happy to.

One more thing on kind of the R&D side is thinking about what we need to do with some of these older drugs that are being repurposed for TB, or maybe have been used for a long time for TB but don't have an official TB indication. And two that I think are on our minds and probably a lot of yours are clofazimine and linezolid. And we need to think about how to balance, again, the urgent access needs for these drugs that we have a lot of evidence from routine use work quite well, but we don't have a lot of great evidence from clinical trials in the case of clofazimine.

So, how can we ethically gather the data that are still missing for optimal use of the drug when it's now part of a standard of care? What would a control look like if there was going to be one, and how can we kind of ethically do that? And then how can we also

balance the urgent access needs? In the US, there has to be an individual IND submitted for each patient who wants to get clofazimine, and it's really unsustainable and not feasible from a patient or provider perspective. So, we know that the FDA is thinking about these issues and we really encourage finding ways to balance the immediate access needs with also still finding ways forward for requiring some more data to inform the optimal use.

In kind of a different situation we have linezolid, which is -- we do have some clinical trial information about efficacy of the drug. We know it's not optimal in terms of safety, but side effects can be manageable and are certainly, in some cases, preferable to going deaf or to dying from TB. But there is not a clear regulatory pathway for the pediatric formulation, and this is something that we really need to think about is how we're disincentivizing future product development, especially for populations, and can we think of some kinds of flexibilities that might allow a path forward to get new products, especially for the populations in most need.

Just looking into the access front, preapproval access plans, as mentioned before, really should be built into the research plan. There is a movement in the US to try and push for what's called the Right to Try, which is preapproval access as early as Phase 1. We think that this could do a lot of harm without addressing some of the barriers. In our experience and I think data go to show that preapproval access options under expanded access in the US are really functional, they're working well. This is just an excerpt from the paper that shows that nearly all applications are accepted and very few wind up affecting clinical holds or the product development pathway. So, we're very happy with the expanded pathway in the US and don't want to jeopardize the stringency that FDA has right now.

But we do think that preapproval access is really important and globally that there needs to be a lot more of it. It's important for patients who are in urgent need and it also allows for more experience and familiarity with the product. This isn't why it exists, but it really helps programs gain more

familiarity with a drug and gain some real-world use with it, to then be able to roll out if the regimen does wind up kind of being successful in trials and approved.

So, one thing that we're thinking about is there are several barriers to compassionate use or to preapproval access, and can we find -- can we build some kind of more unified platform and approach to this where we manage some of the risk on the developer side? Do we set more clear criteria for when it's appropriate to start compassionate use, and also provide some more support for getting through some of the importation and regulatory hurdles. And helping countries harmonize their approach to preapproval access to make it easier on the sponsors, and also easier on providers and patients so they don't have to individually apply to each sponsor for potential access.

So, that is something to look out for. We'll be putting out a concept note about that soon, and just wanted to flag that. I think this is a really important area where we want to maintain the current levels of stringency in the US, but try to enable

access in other countries and also support sponsors to provide access earlier and in a more efficient way.

On the access side, here in the US we also have a lot of problems that are very related, price hikes and drug shortages. And this is an example. The top is a table. It's probably hard to read, but just to show you that between 2011 and 2013, several TB drugs were in shortage here in the US. At the same time, a few years ago there was a huge price hike for cycloserine that wound up being resolved, but it jumped from $480 for a month's supply to $10,000. And these are really two sides of the same coin, because we have this low incidence paradox here. I think this is a term coined by the CDC. But we're very vulnerable here in the US because we have actually a relatively few number of cases.

So, it's not a particularly attractive market when we're thinking about the active TB market. And the underlying causes for both the drug shortages and the price hikes are unaddressed, so we haven't seen one of these in the past year or so. But we're always in danger of this, and it's because it's very hard to

attract and keep manufacturers invested in the US TB market. It would be great if we could harmonize the domestic drug supply with the global drug supply and think of ways to do that. And I think it would address what Dr. LoBue raised earlier, which is the wide disparity in prices in the US and the global market. But also, it could be really helpful to have a lot more of the products in the global market kind of go through the FDA review, especially now that WHO prequalification fees are getting implemented. We might want to have some of those products be registered here with FDA, and they could also access the global market through that stringent regulatory authority approval.

So, I think one thing I'd like to flag here is that it would be great to have more support for the FDA to be able to facilitate importation of global quality-assured medicines to help harmonize the market and create a more stable supply here so the US market can kind of benefit from the bigger demand globally. Also, it would be great if FDA could be more empowered to enforce reporting of drug shortages and even to create

something like a list of essential medicines or a formulary so that if there were a shortage or a supply issue, there might be some recourse for either trying to import a drug that was quality-assured from elsewhere or really signaling to manufacturers that these are priorities to invest in. And certainly, TB as a communicable disease, I think products would feature heavily on whatever list or formulary could be developed.

We have a lot more information about this. I have the links at the bottom of the slide. But I wanted to just end by trying to summarize as much as possible the various issues here.

I'll close with remarks from Mark Harrington, my boss, which was made up hearing about the bedaquiline for its approval several years ago, and he encouraged us to be bold and to make history, but to do it stringently. And I think that this still holds true today and really underpins the balance that we want to see in access promoting innovation and providing accountability for evidence.

So, just to close, our regulatory and research

environments I think are really in jeopardy, and I encourage all of you to take action as you are able to. And TAG is creating a kind of list of how we can better engage various partners, from researchers to clinicians to policymakers. So, you can sign up on our website to get kind of alerts about actions that you can take either in your individual or organizational capacity. And I've also included my email address, so anybody can feel free to reach out with questions or comments, or to have us review a protocol. Thank you.

DR. FARLEY: Thanks very much, Erica. Our next speaker is Eric Nuermberger from Johns Hopkins, where he is a professor of medicine, and he's been primarily engaged through his career in preclinical TB drug development, research using both animal and in vitro models. He has been a big part of the TB work at the ACTG as well as a core science group of the CDC TB Trials Consortium. So, thanks for being here.

DR. NUERMBERGER: Thank you. So, thanks very much for the invitation to come and speak. It's always a pleasure, and I think this is a very important reason to be getting together and talking. So, at the risk of

beginning with a clichéd quote, I thought that in the limited time that we have it would be reasonable, a reasonable way to frame the comments and perspectives that I'd like to add today. And this is, I think, too often, in thinking about preclinical drug development, we get caught up in how well a given model, whether in vitro or in vivo, mimics a particular disease state in tuberculosis patients, or mimics a particular subpopulation of persisters, and think less about whether the data that are being provided by the model are useful in some way, and whether they have to be useful in a comprehensive way or useful in a complementary way. And so, I'd like to provide the perspective that I think we are better served by thinking about how models can be used in a complementary to provide useful data.

But that then introduces the idea that we also need to know how to use these data effectively. And so there is whether the model provides useful data and whether we have useful ways of using the data that are provided that really go into this question. And so, these are a few things that I'd like to hit on some

today.

So, I've been asked to talk about both in vitro and in vivo models. And again I'm going to focus on some of the models that are a bit further along the path, if you will, in drug discovery and in development, and talk really from an in vitro perspective only about a model such as the in vitro hollow fiber system model, which provides an opportunity to expose the bacteria to dynamic or fluctuating concentrations of drug over time, as I think that that has a greatest degree of applicability to the kinds of questions that we're talking about today.

But these in vitro models, like the hollow fiber system model, have a number of real advantages. Most importantly you can expose the organism to drug under very well controlled conditions. Manipulating media conditions, manipulating the various populations of bacteria susceptible in drug resistance, if you would like, and a variety of other conditions.

One can also obviously expose the organisms to a wide range of drug doses and exposures that are

untenable in in vitro systems and certainly untenable in patients, altered dosing schedules for long monotherapy, etc., etc. And there is the opportunity to precisely measure the concentrations that the organisms are being exposed to at the effective site of infection, something that is challenging to do in in vitro tuberculosis models.

And, lastly, one of the cardinal advantages is the opportunity to serially sample the organisms from a single cartridge, in the case of the hollow fiber system, which lends a great deal of advantage in terms of statistical analysis. So, of course, the downside is that you don't have the opportunity to introduce the influence of the host into this system, and so one can manipulate the environment to try and create nonreplicating organisms, or organisms that may be, you think, are mimicking certain niches within the infected host. But one can certainly not get the kind of spatial alignment or arrangement of organisms inside of lesions that are seen in the host, effects of the host immune response on the organisms in the system, and other aspects. So, one really has to go into in vitro

models to be able to incorporate that in a comprehensive way and really look at that in a dynamic system.

The other value, I think, of looking in in vitro models is, of course, you have a mixture of various subpopulations, if you will. Depending on how the model is set up, those subpopulations may be present in different proportions, and at least in some of those cases you would hope that some of these proportions are actively multiplying and nonmultiplying and slowly multiplying and persisting and dormant are present in some sort of clinically-relevant proportion. So, that potential is there.

The cons, of course, are many of the things that are advantages to the in vitro systems. There are limitations to the schedule. It's often difficult to mimic the human PK very precisely, and any given in vitro model may not represent all of the various disease presentations or lesions types that are found in patients.

So, I want to, rather than pitting these two types of models against each other, of course, we want

to get to -- you know, emphasize that I think these are models that should be used in a complementary fashion that really amplifies their -- each unique advantages.

And so, we, in collaboration with Debra and the team at the CPTR, embarked on a landscape analysis of preclinical models. This is now maybe five years ago, maybe more, and really tried to survey what was out there in terms of preclinical models and what evidence there was to support their utility in the drug development process. And we quickly identified the hollow fiber system as a system for which there had been enough data and the right kinds of data, meaning quantitative data that had been used to try and address key PK/PD-related questions related to the development of TB drugs that would make that model suitable for an evidence-based analysis of its utility to inform key drug development decisions. And, again, most of these related to PK/PD-based decisions. And so, this work was largely done with Tawanda Gumbo and his team and facilitated by the folks at CPTR. Pulled together data both sort of retrospective and prospective for this hollow fiber system and eventually wound up presenting

the data package here at FDA, also at EMA. And at EMA this presentation ultimately ended in this qualification opinion for the hollow fiber system. And I present this only to say that, one, this is evidence of one approach that can be done to take an evidence-based approach to demonstrating the utility of a tool that is not meant to be a be-all, end-all tool to tell you what to do with a drug or a regimen, but to complement decisions. To show that this has value in informing regulatory submissions, there was, again, the statement included a statement that this was qualified for use in regulatory submissions. And provided some core areas in which -- in core questions in which this model could be used in this capacity, where it was qualified for this purpose. Now, most of these relate to, again, PK/PD decision points looking at individual drugs, identifying PK/PD drivers and targets and susceptibility breakpoints that then ought to be verified in further studies.

And also, stated here is the ability to provide proof of -- preliminary proof of concept for developing a specific drug or combinations. Suffice it

to say there is not a great deal of combination data on a variety of common issues. (Sounding of alarm.) Is that an offensive statement?

DR. COX: Okay. So, we'll exit and we'll reconvene, we hope, after this.

Welcome back, everybody.

DR. NUERMBERGER: All right. Well, evidently a hot topic, as someone said. So, I think we were in the midst of talking about this hollow fiber model of tuberculosis. And I think really the point that I wanted to leave you with there is that this does appear to be a promising model for sorting out PK/PD-related questions. I think when it comes to regimen development that obviously can inform dose optimization, that can inform regimen selection to some extent, then you may be able to down-select regimens in which drugs don't appear to have a complementary or additive effects, although that remains somewhat preliminary. And so, it has real potential there. It also has potential to limit the numbers of animal study arms and doses and things that have to be tested and then validated in in vivo situations. So, that's

another aspect, I think, of the potential complementarity of this model.

There remain some important questions that have to be addressed, and I think this is still a model that has been used largely at two research laboratories. There are important questions about reproducibility, about transferability or transportability of the model to other sites. It is important to note that this model has been in use for other infectious organisms and used very effectively in the pharmaceutical industry. And so, it's not that there's not a wide range of experience in use of systems like this, but with respect to TB and some of the unique challenges with TB, the experience is relatively limited. Now, that is being addressed in some ongoing programs that I think Debra will probably want to talk about further.

I think another key question, especially as we think about bedaquilines and the clofazimines of the world, drugs that have very high protein binding, are very lipophilic, distribute very differently through different tissues. One really important question is

how do you begin to estimate the drug exposures at the site of infection that you should be simulating in systems like this. And I think the experience for those types of drugs is very limited to date, and these are important questions.

Predictive accuracy as well. Getting into the regimen questions, there are novel regimens now being studied in these systems to try and address, again, questions about their ability to rank order, the efficacy of novel regimens in comparison to standard of care. And even to begin to think about estimates of treatment duration that may come from such studies, but to date I think this process is early.

And, lastly, the way to different actively growing and persister subpopulations are modeled and these systems are indistinct, experiments in distinct cartridges, and so how do you begin to merge the data coming from those different populations into a synthetic whole that is predictive of overall drug efficacy in a patient?

And this model, in addition to being qualified by EMA, also was endorsed by FDA in a nice editorial

that accompanied the papers describing the qualification approach. But despite the promise of the model, of course, there is, again, this emphasis that this model could not be expected to be used in isolation certainly at this point in its development. And there will probably always be reasons that the hypotheses generated in this model need to be validated in in vivo systems.

And so, the in vivo systems that have been used most extensively and thoroughly in these preclinical studies, especially in recent decades, have been murine models of tuberculosis. I'm presenting here sort of a general schematic to make sure we're all on the same page about some of the readouts that are generally look at here. So, this describes an experimental setup that we tend to use in our combination development program that we collaborate on with the TB Alliance.

So, mice are infected by an aerosol route and at day zero they start with a very large bacterial population bordering on 10 to the 8th, or sometimes exceeding 10 to the 8th organisms in the lung. And the

primary endpoints that are looked at are lung CFU counts over time at different time points. Resistant subpopulations can be quantified as well during that time by plating on drug-containing agar. And then because we often with many regimens, we'll get to a point in time where we're not able to cultivate any organisms from the lung at the time the treatment ends, but yet holding mice for additional periods of three or six months will eventually result in resumed culture-positive status. We put a lot of stock in this assessment of relapse-free cure. So, holding mice after different durations of treatment for an additional three to six months without treatment to assess whether they remain culture-negative when we grind up the entire lung and plate it in its entirety on the organ. So, this obviously has some similarities to the kind of Phase 3 relapse assessments that are done for novel regimens that lend some extra interest in this endpoint. But it also accommodates some of the issues pertaining to drug persistence in the lungs at the time the treatment ends. And as we've observed with clofazimine and bedaquiline, drug activity can

continue beyond the end of treatment and could lead to additional cure that happens despite the fact that the mice are not still being treated on a daily basis.

Now, this also, being able to stop the treatment at various time points and look at cure allows for an opportunity to ask what is the effect size of a novel regimen? What is the treatment shortening potential if you compare it to the standard of care, which is typically a five- or six-month cure in these? How much shorter can you go with a novel regimen without resulting in excessive numbers of relapses, or higher numbers of relapses?

So, the way that this model is often used in the context of drug development -- again, this is drawn largely from our experience with the TB Alliance, is to derive or confirm PK/PD relationships that help to select the optimal dose of component drugs, to rank order, drug -- novel drug combinations in terms of efficacy. And this is often initially done on the basis of serial CFU counts from the lungs, but eventually for selected regimens on the basis of treatment-shortening potential relative to standard of

care; to estimate the treatment-shortening potential in the way that I just mentioned.

And then more recently now, efforts to incorporate this so-called Kramnik mouse strain that I'll talk about in a moment, to try and assess the impact of caseous pathology on the efficacy of drugs and regimens. And the implication here, the BALB/c mice and other mice that have been traditionally used in this capacity, don't develop caseating necrotic lesions that better resemble caseating lesions in TB patients. And so there has always been some concern that the intracellular bacterial populations in these mouse lesions and these lesions themselves likely don't fully represent the bacterial phenotypes present in caseating lesions, likely don't represent the need for drugs to distribute through the caseous portions of lesions to reach extracellular bacilli in that space. And so, we'll speak some more to this in a moment.

And then, again, something that has not had as much prominence as I think it perhaps should is the use of experimental systems like this, if we're really seeking to develop novel regimens, I don't think we

should be complacent that simply putting three or four drugs together is -- of uncertain efficacy is going to automatically result in restriction of drug-resistant mutant selection. And I think there are key questions for novel regimens related to how stringently they will suppress the emergence of resistance. That really ought to be explored in preclinical models.

So, I don't want to spend a lot of time, but I think, again, to get back to this idea of what is the evidence base and how can we demonstrate utility of the models? And certainly, the best case for the mouse model was made by the fact that there were -- it was studies in the mouse model that really first demonstrated the treatment-shortening potential of rifampin and pyrazinamide, the only two drugs that we recognize at this point to be clinically validated treatment-shortening drugs. And on the flip side, every other drug that has been in existence up until the last decade or so does not have that treatment-shortening potential in mouse models or in clinical trials, as far as we know.

Now, in addition, there have been a number of

more novel regimens that have progressed to the clinic with some basis, evidence base in these high-dose aerosol BALB/c mouse models. I think the one that has obviously attracted most attention is the substitution of moxifloxacin into the standard of care, because that's a regimen for which there are now Phase 3 data. And certainly, a lot has been said about whether the mouse or early clinical endpoints predicted the outcomes of this Phase 3 trial or not. But an exercise that we've gone through for this regimen and are now going through for other regimens that are either in or moving through clinical trials is to go back and aggregate the mouse data, to really look as carefully as we can at the treatment shortening effect that was demonstrated in mouse studies, and to try and relate that to clinical observations. And I think as we'll hear again more later, this is an ongoing project that is supported by the CPTR program, the PCS working group of that.

And so, I'm just showing you here in this table an example where there are novel regimens that are either in or planning to progress to Phase 3.

We'll have relapse endpoints and have been subjected to this analysis where there have been at least two relapse studies that have been examined. And so, one looks, and when you really aggregate these data for the REMox regimens, there is not a compelling case for a two-month, an absolute two-month shortening effect of the moxifloxacin in the mice. And in that sense these data are not inconsistent with what was observed clinically in these trials.

And, indeed, there are, as has been alluded to, some emerging data with a BPaL regimen, which do support this thus far. Very preliminarily, of course, as a six-month regimen that is effective within a six-month time frame. And so, relative to RHC, that's been an effect comparable to what was seen in these mouse studies.

So, the real game-changer in the mouse studies has been the combinations that include bedaquiline and pyrazinamide. And those comprise a component of regimens that we don't really have -- won't have relapse data for soon, but will, again, provide an important test for the mouse model as we expand the

number of regimens for which we can reflect on, on the relationship between treatment-shortening effects in mice and treatment-shortening effects in patients.

One aspect, obviously, again, in these preclinical models is the opportunity to deconstruct regimens and to look at the contribution of component drugs. I'm showing here as an example from the, again, work we've done with the TB Alliance, looking at bedaquiline, pretomanid, moxi and PZA as a four-drug regimen here in blue. And then looking at each of the three drug components and asking does every drug contribute to the activity of this regimen? And so, one can see here the four-month -- I'm sorry, the four-drug regimen is here and it's actually overlapping in CFU counts with the same combination but minus moxifloxacin. So, in this particular experiment, moxifloxacin really didn't contribute much in the way of bactericidal effect. But when one looks at the relapse rates, there was a significantly lower relapse rate after 1.5 months of treatment with this regimen if moxifloxacin was in the regimen. And in subsequent experiments we've seen a small effect on CFU counts as

well as reproduced this sterilizing effect.

And so, one can do these kinds of experiments and ask not only does each drug contribute, so there is evidence presented here that each drug does contribute to that combination, although the contribution of pretomanid is not shown here. That's been shown in a different study. One can also gauge the level or the extent to which that drug contributes and see which drugs tend to anchor the activity of the regimen based on the effect of removing that drug from the regimen.

Obviously, one can also look at the impact of drugs on prevention or killing of spontaneously resistant -- drug-resistant mutants that are present at the beginning of treatment, and also look at different durations of treatment for different components of the drugs. And just allows a lot of flexibility that really can't be done for very long periods in patients.

So, I've already alluded to one, I think, of the key challenges in trying to translate data from these traditional so-called sterilizing mouse models to human trials, and that is the issue of the caseous lesion. And here, as opposed to what is seen in BALB/c

mice as the predominant lesion, it's a non-necrotizing lesion in which the pink acid-fast bacilli are found here inside of cells virtually uniformly. Inside of cells where they are still pretty well linked to a blood supply is only part of the story in the Kramnik mice, in humans, and lots of other larger mammalian species.

So, in these caseating granulomas, which are really the hallmark of adult tuberculosis, one finds not only these cellular populations around the rim of these caseating lesions, but also extracellular populations inside the caseum, whether it's a closed lesion or an open lesion or cavitary lesion where the caseum has largely been expectorated and there is just a thin rim of caseum surrounding. And it's in these environments where there is less impact of the host immune response, the organisms are felt to be more likely to be actively replicating. Organisms are also extracellular as opposed to intracellular, and so this may have a variety of effects on drug effect. And that may pertain to differences in Mtb growth rate; that may pertain to intracellular or extracellular residence and

drug distribution either into cells or into the caseum, where the extracellular organisms are, as well as different aspects of the lesion microenvironment. So, the areas of these caseating lesions tend to be more hypoxic. In the case of the Kramnik mouse are relatively neutral in pH as opposed to the acidic compartments inside the cells of activated macrophages. And these may all have important effects on the readout of drug efficacy in animal models.

And so, we've been -- we and others have been pursuing studies to try and better understand how well these Kramnik mice may contribute information to drug and regimen development. And what stands out already are several examples where drug activity is represented differently in these Kramnik mice as opposed to BALB/c mice.

And one case in point is pyrazinamide, a drug that appears to have limited bactericidal effect within mice, Kramnik mice that have large caseating lesions, where again the caseum has been shown to have a relatively neutral pH and is thought to be, then, conducive to PZA activity, which requires more acidic

pH. And this is not to invalidate the model, because we do know that PZA works on some subset of organisms within these mice. Because PZA is capable of shortening the treatment duration when it's added to a first-line drug combination in this strain of mice. And so, looking at monotherapy over four weeks in mice with large caseous lesions is not the only way to look at the contribution of a drug to a regimen. And so, longer studies of drugs in combination may be necessary to better reveal the drug's effect against the important subpopulations within a heterogeneously-involved lung.

So, clofazimine is another example of a drug that as the monotherapy over four to eight weeks doesn't show very pronounced bactericidal effect in Kramnik mice, and very much in contrast to its efficacy over the same time frame in BALB/c mice. And there may be a number of issues here. The drug does not distribute well into caseous lesions. It accumulates to a great extent inside cells but doesn't distribute well through caseum, and so that may be one reason that it's being overly represented in terms of activity in

BALB/c mice and perhaps underrepresented in Kramnik mice. But there are also issues with respect to a neutral pH, which may affect clofazimine activity adversely, and hypoxia, which may also to some extent compromise the activity if clofazimine.

And bedaquiline may be in a similar can to the extent that it also does not appear to, again, because of physical chemical characteristics, to diffuse quite as well through caseous lesions as some of the other drugs that we use. Although the diminishment of its activity seems to be less pronounced than that of pyrazinamide or clofazimine.

So, this also, this argument about using caseous disease models for drug development has been certainly part of the rationale for looking at larger animal models in the context of drug development. Guinea pigs, rabbits, nonhuman primates all develop these caseating lesions. And so, what I have here is not meant to in any way disparage these models. I think these models certainly could have substantial utility. You know, one of the most prominent issues, of course, is the cost and the amount of resources that

have to go into studying these. But if we want to ask, is there an evidence base on which to support the use of these models for regimen development, then that evidence base at this point is modest. And this is an admittedly somewhat cursory look at the literature, but the amount of evidence that would support their use is extremely limited.

Now, again, thinking about complementarity of models, how well could we use PK/PD-based approaches to understand the impact of caseous disease and think about how to integrate that with BALB/c mouse models, for example? There certainly are some very important tools, I think, being generated by Veronique Dartois and her group at Rutgers. I think many of you are familiar with these techniques. This MALDI-MSI technique, which provides semi-quantitative assessment of drug concentrations that yield these heat maps. So, these are maps rendered over TB lesions, caseating lesions here, and the heat map, the red is a higher drug concentration, the blue is a lower drug concentration. And what's encircled here are the caseous parts of the lesions. These studies are always

done with the neck section going for histopathology. And so, one can really try to orient now drug exposure with the lesion. And they are also paired with in vitro macrophage uptake studies. And so, one sees with this panel of drugs that were assessed here, very pronounced differences in how they distribute through lesions. Some that distribute -- the smaller hydrophilic compounds tend to distribute very well through the caseum, and as they do in the cells lining the caseum, whereas, as you go down the list and molecules become more lipophilic, they tend to accumulate in the cellular regions around the lesions but not to diffuse as well into the caseum. And so, one could certainly imagine that these may have important effects on drug exposure and efficacy in these caseous lesions.

But these are semi-quantitative assessments, and what would be much more valuable is to have real quantitative assessments. And her group has now published on an even more exciting tool, I think, that couple's laser capture or microdissection and dissecting out small portions in various places on this

lesion section and quantifying drug concentrations by LC-MS. And so, one is now getting absolute quantification from various sections of the TB lesions that would allow a more precise and geographically relevant estimation of drug exposures at the site of infection.

Now, there are a number of other issues that come up in terms of translating preclinical data to clinical data, not the least of which is interspecies differences in drug PK. But, of course, many of these studies are done in inbred mice with a single laboratory TB strain, a single aerosol dose, and very limited, if not single range of drug doses. And so, when you think about the vast heterogeneity in human populations and TB patients, how could we really expect that any one of these experiments would map directly onto patient treatment? So, how do we begin to account for PK variability in patients over population? So, very different levels of severity of disease, different degrees of immune status, different degrees of adherence to treatment, and then various distributions of drug susceptibility among TB populations that are

bound out in the world.

And so, for a number of these I really think to really try and make the most confident or predictive translation from preclinical to clinical systems, we really need a quantitative PK/PD-based translational mathematical model to help translate results. And we've, in collaboration with Rada Savic and her team at UCSF have started down this path to try and build a model that relies on mouse PK and efficacy data perhaps informed by early PK data from humans to try and make predictions, develop models that can then simulate clinical trials to better inform a regimen's potential for treatment shortening. And so, this early iteration of the model includes PK data and PD data in terms of CFU counts from the mice. So, again dispensing with relapse in this particular setup. Human PK data that includes things like food effect that is known in the case of rifapentine and rifamycin, moxifloxacin drug-drug interaction. We derived an immune effect parameter that was based on comparisons of immunocompromised nude mice and BALB/c mice. And we took some information that had been learned in this

case from a clinical trial study, 2929X, about the impact of cavitary disease on the dose or exposure response relationship defining rifapentine's efficacy and incorporated that into the model. As well as study data from Veronique's study showing that rifampin can be retained and concentrated in caseum with repeated dosing.

And so, then we performed some clinical trial simulations to look at sputum culture status to estimate or predict sputum culture status at eight weeks and relapse status after one year of treatment for regimens that had gone on and been studied in the clinic. And so, again, it's a very preliminary, sort of first iteration of this type of model that is really just based on the rifamycins and moxifloxacin, but shown with -- you know, in the bars here are the simulated 95% confidence intervals for the predicted relapse-free, proportion of relapse-free patients. And then in green are the point estimates from the clinical trials.

And so, this was the four-month regimen replacing ethambutol with moxifloxacin, where we

somewhat underpredicted the activity of the regimen but was still pretty close. And then again from the RIFAQUIN study, the four-month arm that had a twice-weekly rifapentine continuation phase regimen and a six-month once weekly rifapentine/moxi-containing regimen. And, again, some underestimation of the activity of the regimens, but in both cases identified the four-month regimens as potentially less effective than the standard of care. Have also looked at the PanACEA trial data with increasing rifamycin exposures.

So, in our view, for first go, this model performed quite well. This is now in press. We're really trying to improve on this by incorporating individual PK/PD relationships for all the drugs in the regimen, as well as interrelationships. We have also simulated Study 31 and some other upcoming studies, but we are now I think in collaboration with the Alliance, hoping to move into some of the more novel regimens containing bedaquiline and pretomanid and to use a similar approach. And our ultimate goal is to try and merge this with some more mechanistic models that Rada has been working on to try and develop a really more

unified modeling platform in which, again, mouse and maybe early human PK data, as well as some patient clinical characteristics could be built in to try and better predict regimen efficacy.

I'm just going to skip over this in the interest of time. So, I think with respect to these -- the take-home points, the emphasis is that models that we have available today, I think, have complementary roles to play. The in vitro hollow fiber system, although there is still work to be done, especially with respect to evaluating drug regimens, I think has real potential in the PK/PD space, in dose optimization, and even potentially minimizing the number of animals that need to be studied in preclinical studies.

The mouse models do have an established track record, admittedly, though, with a very limited number of drugs and regimens, and there is really an important opportunity here with the newer drugs that are being studied in newer regimens. There are, I think, important variables that may impact the way that models like the BALB/c mouse model predict human trials. And

I think this is, again, especially important for drugs that may partition very differently into caseous lesions, the clofazimines, bedaquilines of the world, in particular.

And then just to emphasize this role, I think, for a more integrated platform in which we can further enhance our predictions using quantitative mathematical models. So, with that I'll stop. I've got a lot of people to thank, lots of collaborators and funders over the years, and appreciate the opportunity.

DR. FARLEY: Thanks very much. We apologize for the interruption earlier. We're going to take a 15-minute break at this point and remind you that this could be an opportunity for you to order lunch at the window. We are going to keep to time, meaning that we're planning on having lunch at about 12:35, and we're going to take the talks in the order of the program. So, we'll start with Chuck right after the break. So, if we could ask everybody to come back right at 11:05. Thanks.

[Break]

DR. LOBUE: I'd like to introduce Chuck

Peloquin, who is the professor of pharmacy and medicine at the University of Florida in Gainesville, where the University of Florida Infectious Disease Pharmacokinetics Laboratory is located. Dr. Peloquin and his lab are part of the University of Florida Emerging Pathogens Institute. His laboratory serves as a national reference center for the determination of serum concentrations for antimicrobial, antifungal, anti-HIV drugs, as well as beta-lactams and linezolid. Dr. Peloquin?

DR. PELOQUIN: Thank you for this opportunity to speak, and if Dr. Nuermberger can cause a fire alarm, who knows what I can cause. Is there a fault line near the building? Just asking. Now, I don't have any industry conflicts of interest to disclose. My laboratory, as mentioned, does do some therapeutic drug monitoring. The laboratory is not-for-profit and the clinical laboratory does not pay my salary.

So, I'm going to spend a minute on this slide, because I think it's essential and it speaks to everything that will follow. And I'm rapidly approaching 30 years as a tuberculosis clinician and a

tuberculosis researcher, and I'm impressed in the meetings that I've gone to and presented at that clinicians generally do not think in these terms. They generally don't think about what's happening to the drug after it's swallowed. They're interested in making a diagnosis and in giving the dose, right? But if we stop and think about it, the drug has to be absorbed from -- it dissolves in the stomach, it goes through the intestines, into the liver, from there to the right side of the heart, to the lungs, back to the left side of the heart, and then throughout the entire body. And then you have a gradient of distributions of drug. Some of the drug reaches where the TB lesions are, some of the drug from that portion gets to the bugs. Some of that portion gets into the bugs, and in a small fraction still actually binds to the target, typically a protein inside of the organism, and causes its effect. So, from the pharmacological standpoint, giving the dose is really just the kickoff of the football game and then things happen. All of what I just described are the pharmacokinetics of the drug, so if you don't have good PK, you don't get good

pharmacodynamics, or PD.

So, where are we now? I'll spend a few minutes talking about the RIPE -- rifampin, isoniazid, pyrazinamide and ethambutol regimen. So, a lot of clinicians think in terms of, well, I thought we just gave the dose. And the dose implies that every patient is the patient, in other words, they're clonal. And while in a mouse model they're inbred, typically humans are outbred, and therefore there is no average Joe. There is a wide variety that you're going to have to deal with, and all of the clinical trials clearly show a lot of inter-individual variability in the PK. So, why do we keep giving the dose? Well, it's tradition, right? Some of you are old enough to remember the Talking Heads and "same as it ever was."

So, here's June's issue of Pharmacotherapy, and there is an article on Personalized Medicine in the Management of Diabetes. There is another article on Driving Towards Precision Medicine -- the other term for that -- in Leukemias: Are we there yet? As there is an expectation that we're somehow late and we should be further along. Meanwhile, we have standardized

doses of the TB drugs. So, always remember that you are unique, just like everybody else.

So, here's the regimen developed in the 1970s by the British Medical Research Council, and we have a fixed dose of rifampin at 600 mg, which Denny Mitchison called the minimally effective dose of rifampin. We have a fixed dose if isoniazid at 300, and they looked at these milligram-per-kilogram doses for pyrazinamide at 35 and ethambutol at 25 mg/kg. So, this is the regimen they gave us the idea that we have a six-month regimen that is 95% effective. But the way we actually do it today, if you have someone who is my size -- yes, I weigh 80 kilograms, but I don't consider myself a giant person. I'm fairly typical for an American male. So, we're actually giving me 60% of the drug exposure that was given in the clinical trial. And likewise, we're giving me 60% of the drug exposure for isoniazid in those clinical trials. And arbitrarily in the US we've dropped the dose of PZA down to 20 to 25 mg/kg, and ethambutol to 15 mg/kg. So, all of these drugs show concentration-dependent killing. More drug, more killing. If you cut their doses by 40%, you're going

to get approximately 40% less killing.

So, if your patient happens to be this size compared to what was originally studied, you've given the full dose. But if your patients are my size, you're really giving a lot less drug than that. Or, if you like other pictures, if your patient looks like a Mini Cooper, you've probably filled them up; but if your patient looks like a Chevy Avalanche, you have not filled them up with enough drug to get the kinds of effects that were shown in those studies.

But here is the number one reason why people don't like to change. They say TB treatment is only six months long and it's 95% effective. Now, this is TB dogma. If you look at a review article or a chapter in a book, you're going to see this, and it is true that the British Medical Research Council showed using per protocol analyses that you could get those kind of responses. However, if you look at those papers, the numbers vary from paper-to-paper, but on average about 10% of the patients evaluated were not included into the study, and another 10%, approximately, dropped out during the study. So, they really analyzed about 80%

of the original people that they were looking at, which is still really good. Most clinical trials today have lower capture rates. But you might expect 76% efficacy in your clinic at six months, if this map is correct, right? That's wrong.

So, every year the CDC compiles the data from across the United States and they analyze it, and of course it takes a little while to do that. And then they publish a slide set every year, and I strongly recommend that you go their webpage and look at all the information that they have. And on approximately slide 30, and this is from the 2015 slide set, it shows completion of treatment. Now, we don't have cure as an endpoint in the public domain; we have completion of the scheduled doses. And so, we have completion of treatment, and this is ending in year 2013, at one year. Now, back in '93, at one year it was only about 64%, so there has been steady progress and it has kind of plateaued over here in the last five years. So, the natural question is, well, if this is at one year, what happened between six months and 12 months? And this is what happened.

At six months, 18% of the patients in the United States in 2013 had completed treatment. At seven months, which you might say is a more fair measure, because patients might be diagnosed in the hospital and have to transfer to public healthcare, so it's 45%, 46% at seven months. And here is the 89.6 shown on the prior slide. And it does get to 95, but it gets so at 19 months. Now, remember, the CDC is compiling the data, all right? So, they're your friends, they're making this data available. If you don't like the results, send your cards and letters to the individuals who treating TB. But, actually, nobody is doing anything wrong, all right? This is the reality of treating tuberculosis with the regimen that we've reduced the area under the curve, if you will, by 40% across a population giving standardized doses. This is what you're going to get. So, that's the TB dogma. This is what Phil Hopewell had to say about dogma: "There is a fine line between dogma and dog manure."

So, for the current regimen, and this is my point. It's not to criticize the current regimen or

what anybody is really doing with it, but what we should do is just tell it like it is. And the current regimen in the United States, RIPE, is about 90% effective at 12 months, and it's only about 20% effective at six months, and 46% effective at seven months. That's what we can compare any new regimen to.

So, where are we going? And I've been asked a similar number of questions as Eric was addressing, and I'll bring those back and look at them from a slightly different perspective, I hope. So, how do we bridge preclinical data to clinical data? And what you really want to do, as Eric was pointing out, is find the pharmacodynamic index, or the pharmacodynamically linked parameter. Typically, it's going to be the free drug, that's what the "f" stands for -- free drug AUC, or area under the curve, divided by the minimal inhibitory concentration, or MIC. For most TB drugs, this is the most closely linked parameter to efficacy. Sometimes it's the peak concentration, sometimes it's the trough concentration. An alternative is time above MIC, but percent time above MIC caps at 100%. So, if you have continuing improvement in efficacy and you're

at 100%-time above MIC, you can't really capture that, and the trough concentration, or C minimum, does a better job because it's a continuous variable. So, once you know what it is you're trying to optimize, then you can go about finding a dose and a frequency that actually allows you to optimize it.

Now, the PD linked, or pharmacodynamically-linked parameter, is conserved for each drug in organism pair. So, what you discover in the hollow fiber model is going to be true in the mouse model, in the mechanic model, and in the human model of the disease, because these are one-trick ponies, basically, or maybe they have two tricks. But the drugs only have so many things that they can do to a mycobacterium, and once you determine how to optimize what they do to a mycobacterium, that's what you focus on.

Now, I'll point up that the PD driver, because TB has different phases of growth, at least as we understand it, the driver for cell kill does not have to be identical to the driver for suppression of resistance.

So, what does this look like when you try to

look at it? So, these are data that we acquired in a study with the CDC in an MDR-TB outbreak in Micronesia and the Marshall Islands. And just sort of cutting to the chase for this study, and you'll have the reference for each of these so you can look them up later if you wish. This was the parameter we chose to optimize, and we chose to optimize this ratio at four possible values based on the fact that there were no clear data for TB and, depending on Gram-positive or Gram-negative infections, different target values were proposed for this ratio. We have the target attainment on the y-axis and minimal inhibitory concentration on the x-axis. And with the smallest dose, you have very poor target attainment regardless of which of the targets you're trying to hit. And as we go from 5 to 10 to 15 to 20 mg/kg, you see that if you're shooting for a low target, the 40 target, and your MIC is low, with the highest dose you have a very high probability of hitting that target. But if your MIC is high and you're not giving -- and you're aiming for this highest target, you're probably not going to get it.

So, if it turns out that 125 is what you need

for TB, even 20 mg/kg for levofloxacin, if the MID is 1, levofloxacin is not going to be really good in that situation.

So, how to fine-tune in patients. Well, no matter how good your stethoscope is, you can put it on the antecubital fossa but you cannot hear the drug going by, and you certainly can't quantitate it. So, if you want to know what's going on in your patient, you're going to have to draw a couple of blood samples. Now, for TB drugs it's basically the same as getting a chem panel, it's just the red top tube. And currently we can, and other labs, can measure all of the drugs with about 5 mL of blood, or 2.5 mL of serum, right? Do TB patients metabolize drugs differently? No, but they're much more variable than you would see in healthy volunteers.

Discuss PK variability and considerations across populations. Well, there is no single predictor of poor drug absorption, so, again, if you don't absorb the drug, it's never going to get to the lesion and it's not going to work. And there are different studies that have shown different populations with

malabsorption including the ones shown here, HIV/AIDS, diabetes, acutely ill or cachectic patients, but from study-to-study you see a lot of variability, and that's just unfortunately the fact of the matter. There is no one predictor for this.

Now, this is a study we did with David Perlman in an AIDS clinical trial group in Study 309, and I'll focus on rifampin, which is arguably the most important drug. So, in the light blue, those are healthy volunteers that were extensively sampled; in the dark blue, those are TB patients who were extensively sampled; in the purple, those are TB patients who only had two blood draws at two and six hours. So, it was pretty close to the pattern seen with the other two groups. And in the yellow, those are the AIDS patients. So, clearly, these patients have delayed absorption, they have malabsorption, and the 600-mg dose in this population, in this study, clearly was not the optimal dose.

This is a snapshot of quality control data from our clinical laboratory for 2016, and this is well over 800 rifampin samples, and just looking at the two-

hour sample. So, this is not a PK analysis; this is just a QA analysis, or quality assurance. But you can see that it ranged from 0, which is clearly not therapeutic, up to 45 mcg/mL with this pattern on the histogram. And if we look at the distribution of the doses, we had some pediatric patients, so that's why some of the doses are very small. We have the 450-mg dose that used to be recommended for people who were under 45 kg. I personally would not recommend that. The standard 600 mg dose, where most of the density of the data are. But you'll see there is a real distribution across the doses, and I'll point up the guys who got 1800 mg, they didn't have very high concentrations despite an 1800 mg dose. They were profound malabsorbers of rifampin, and you will see this in your population.

So, over time people have either been fans of or enemies of therapeutic drug monitoring in TB, and you can decide for yourself how you choose to look at it. But the decision to do TDM is really the same as the decision to get any other test, whether it's complete blood count, CAT scan or MRI. None of these

guarantees the outcome of treatment. If you want a guarantee, buy a fridge. For three years, anything goes wrong, you get a new fridge. But in the clinic, there is nothing like that, and you have to deal with the uncertainty, but all of these tests allow you to make an informed decision, and in this case an informed decision about dose for an individual patient. So, if you want the long-play version, this was published in Microbiology Spectrum in the end of 2016.

So, why use TDM? In the end, knowing is better than guessing. So, I would propose it's best, if possible, to get individual MIC data to know just how susceptible a patient's bug is, individual PK, and then you can optimize those parameters that I just showed you. So, you want to use smart bombs and not use dumb bombs, right?

How does PK change in TB patients over the course of the months? Well, clearly, the rifamycin have autoinduction, so their concentrations actually get lower from the first dose out to the seventh or fourteenth daily dose. Some patients take a full month to come to full autoinduction, but most of it happens

in the first seven days or so.

Isoniazid absorption can improve once the patient starts getting better. And so, we have patients who will have very, very low doses or rather concentrations of isoniazid, and we'll crank their dose from 300 to 600 mg daily. And then after about a month, if they're rechecked, they're in the normal range, and then after another month they might be at the upper end of the normal range and we can reduce the dose again. So, isoniazid is the one drug that clearly will show a rebound. For other drugs that depend on renal clearance, like ethambutol, levofloxacin and cycloserine, if you have a chance in your patient's renal function, you're going to have to change the dose.

What about the epithelial lining fluid, or ELF data? So, I asked the Keebler elf, but the Keebler elf had no data on this, nor do I. You could argue that the drug has to get into this fluid before it gets into the lesion, but that's not absolutely proven for TB. So, we await further study on this. There are data, including the data that Veronique Dartois has produced,

and Eric showed you that, about cavitary lesions. There is also another approach that we've taken. This is with Russell Kempker and the folks at Emory, and our colleagues in the Republic of Georgia, in Tbilisi, where we use microdialysis. So, this is a probe that actually measures the free drug concentration, and we put it in the center of a TB lesion that has just been removed from a patient who was going to surgery otherwise.

And one example, this is levofloxacin. You can get a series of serum concentrations, including a concurrent concentration in the serum; you can get cavitary concentrations. And then from that you can get a ratio. So, in this particular case the median ratio shows that there is more drug in the lesion for levo, a free drug in the center of the cavity, than was found simultaneously in the serum. So, that's kind of good news. You could argue that this number might vary depending on when you sample after the dose.

Are there PK-specific predictors of drug dosages from previous trials? Yes, including PK data that speaks to some of the issues that I just

mentioned. So, this is a study we participated in. This was the Tuberculosis Trials Consortium Study 22, which in in the continuation phase, after the first two months gave once-weekly INH and once-weekly rifapentine. And the patients who malabsorbed their isoniazid were essentially getting rifapentine monotherapy, and we selected for acquired drug resistance.

Continuing in this school of hard knocks, this was thrice weekly rifabutin and isoniazid in the continuation phase. There was concern that we would overdose people on rifabutin because of drug-drug interactions with protease inhibitors. The problem is, in some cases we underdosed them, and there was no mechanism in the trial to adjust doses based on the concentration. So, all of these data are post hoc data. But the patients with the low exposures to rifabutin had failure, relapse, and acquired rifamycin resistance, which is essentially MDR-TB. And the odds ratio for the rifabutin AUC being the driver for that was 23, which may be in the odds ratio hall of fame.

And why is that important? Well, Dr. LoBue

was pointing up some of the costs of treatment, and this is a nice study from Suzanne Marks and the TB Epidemiology Studies Consortium looking at how much it costs. So, these are slightly older data than what Phil presented. At the time, it was about $17,000, but if you, in the course of treatment, select for MDR-TB, not only have you eaten that $17,000, but now you have to pony up an additional $134,000, which is approximately 250 times the cost of therapeutic drug monitoring.

This is a prospective study on high-dose rifampin by Martin Boeree and company with the PanACEA Consortium, and in this publication, they went up to 35 mg/kg, but currently they are up to 50 mg/kg. So, in that study they are at 2,400 mg, but now they're up to basically 4,000 mg, a piperacillin-like dose of rifampin. And there are more than proportional concentrations. As you increase the dose of rifampin you get a larger than expected increase in Cmax and AUC. So, that's like a BOGO, you know, buy one, get one free. And what they showed is, like I've shown you in my clinical data, high interindividual variability.

So, even though the patient got the high dose, they don't necessarily get a high exposure of drug. And the patients who did get the greatest reduction in the sputum colony counts had the highest exposures.

Same thing was seen in the study by Susan Dorman and the TBTC with high-dose rifapentine. Knowing the dose, whether it was 600, 900 or 1,200, did not tell you how people were going to do. Knowing the exposures, which were highly variable, did tell you how people were going to do. So, again, it was the drug exposure that was the driver of efficacy in the studies that I just presented.

Now, TDM does allow you individualized therapy and it allows you to optimize the PD variables that I was talking about. The most popular argument against it is that it's expensive. So, we just round off the number of patients in the United States to 10,000, and if you did two and six-hour concentrations for RIP and E, that would set you back about $560 per patient, for a total of $5.6 million. So, that's a lot of money. But if you say it's a lot, you have to say compared to what? So, I'll compare it to the University of Florida

athletic budget, which this year is $128 million, and the increase, just the increase, is $6 million, right? Our football team is going to cost $25.5 million, but I would argue that's less than the cost of the Alabama team. I'm just saying, right?

So, there is nothing wrong with this; I enjoy athletics. But as a nation we spend billions of dollars on sports and entertainment. Wouldn't it be nice to spend comparable or even a fraction of that money on an airborne communicable disease?

So, I'd like to thank our top team of researchers in my lab. As I get older, everybody in my lab looks like this. So, do your assay and then clean your room, right? I'd like to thank TJ, Kyung Mee, Emily, Yas and Stacy, who are the employees of the lab, and my students, Wael, Mohammad, Yang, Toni, Carlos and Maggie. Thank you very much.

DR. FARLEY: Thanks, Chuck. I think we got the message. We're going to turn our attention to TB biomarkers and hear from Payam Nahid, who is a professor at the University of California-San Francisco School of Medicine, and focuses his TB research both in

the United States and in Vietnam.

DR. NAHID: That is a tough act to follow, Chuck. Let me start by echoing Erica's thanks to the FDA for organizing and hosting this workshop on tuberculosis. It's a disease that is often ignored, it's a disease of the poor, and that should not allow it to have such little attention given to it. So, I appreciate the FDA bringing this forward.

Several of the speakers this morning have alluded to somewhat strongly the need for biomarkers to move our decision-making forward around which regimens and drugs to move forward in the pipeline. And I must say I feel under a great deal of stress and pressure with my talk.

Here, I just have a couple of disclosures that I'm federally funded through the CDC contract, TB Trials Consortium and some NIH funding.

So, the overview of my talk will be, first, I just want to quickly review the current laboratory methods for TB drug testing. Second, I want to speak to you a bit about the challenge of culture-based systems. I think this is important to reflect on,

because there is virtually no other infectious disease entity that I'm aware of that has the complexities that we face with sputum and in a way, we do with the pathogen. I'm going to then talk to you a little bit about the microbacteriology we've undertaken in Study 31, and then close with some novel biomarkers on the horizon. I'll only be able to speak about a couple of them, but I've listed a handful here that seem to be emerging as interesting. So, let's just start first with current laboratory methods and the importance of microbacteriology in Phase 2 and Phase 3. Oops, this is the wrong slide set. The one I just sent this morning hasn't been replaced.

Well, while the correct slide set is found, I don't want to use this one because I would be -- yeah, that's the one; thank you. Perfect. Thanks very much.

So, these are the phases that you heard presented by Cathy earlier in the morning. On the bottom, you have the EBA studies, then Phase 2, and then on the top Phase 3. The endpoints vary according to these different phases, obviously. So, Phase 3 we're looking for disease-free survival at 12 months.

And, in fact, what we're really seeking for from our biomarkers is some high sensitivity and specificity in that follow-up period after treatment end to capture people who are relapsing.

In Phase 2, the classical endpoints that are used include the culture negative status at eight weeks on solid and liquid media separately, time to culture conversion, and some information on speed of decline of viable bacilli in liquid media is also being evaluated.

In EBA it gets even more complicated. It's logarithms of daily CFU counts per mL of sputum, usually over a 14-day period. And I don't think people quite appreciate the complexities of these assays. EBA endpoint studies required tenfold dilutions, quadruple cultures for each dilution. These are very burdensome assays. But the one thing that they all have in common is they all rely on culture. And in the Phase 3 setting we are really using it essentially as a diagnostic, if you will, liquid or solid culture. We're diagnosing patients as having relapsed during their follow-up, and that then leads -- provides isolates which we can use for gnomic sequencing and

determining whether or not a reinfection is occurring or a relapse.

The other Phase 2 endpoints, also liquid and solid culture at various time points, and in the EBA there is a very complex daily solid culture system that enumerates CFU. All rely on culture.

What can we say, then, about these culture-based systems? And there are some uncertainties around the prediction and surrogacy of these culture-based systems, and I'll go over them. And there is also technical and specimen-related issues.

Number one, EBA. It's well known, I think, and accepted that EBA is not predictive of the sterilizing activity or long-term outcomes. So, here is a cutout from a letter that Bob Wallace submitted to Lancet that shows you on the left here several groupings of drugs -- isoniazid alone, with a multi-drug regimen, and you can see at 14 days the essential EBA effect of a regimen that we know can treat TB for six months, and one we know that can't is about the same. So, there is no distinction there. And a similar point is illustrated here, that with a multi-

drug regimen, even if you extend it out to 28 days, you do see some difference there from a regimen that doesn't have rifamycins, but it's a modest difference, and while -- I guess you could ask whether that really does represent sterilizing or not.

The other part that bothers me about EBA is there are drugs that we know do have clinical efficacy. We use them in clinics. The linezolid that is used in the Nix-TB regimen that surely is contributing significantly at 600 mg twice daily here is showing modest to no EBA effect. So, EBA wouldn't have told us whether linezolid should be moved forward or not. The same is true for pyrazinamide in Amina Jindani's early work, showing that pyrazinamide that we know is critical for TB regimens, has poor EBA or minimal EBA.

So, then we move to two-month culture, and I think in the long view the two-month culture must be our best way of assessing sterilizing capability. And this is on an individual level prediction analysis. This is a meta-analysis forest plot showing to you that the sensitivity and specificity of culture status at two months is unacceptable for individual level

prediction. Sensitivity is in the 50%, specificity is modestly in the 80% range. So, on an individual level prediction, it doesn't seem to perform well and decisions based on it are hard to make.

On a surrogate level, which I think is something we really often have to remind ourselves as biomarker researchers, there is a distinction between prediction and surrogacy. This is work that Patrick Phillips conducted using 37 treatment comparisons from 49 British Medical Research Council trials. And using appropriate statistical techniques that involve trial surrogacy comparisons, the month 1 culture, the month 2 culture, and the month 3 culture. And the corresponding effect it has on log odds ratios of a poor outcome. You can see these squares are really dismal. So, R squares of the one-month culture of 0.36, 0.36 at two months, and modestly improved to 0.69 at three months. Yet we focused a lot of our intention on the month 2-time point. And I think this illustrates first the prediction versus surrogacy distinction, but also that there is uncertainty about what these time points are really telling us.

So, add to that the REMox trial, which you've heard about earlier this morning, were found that the two 4-month experimental regimens did not meet noninferiority, yet in their own data culture conversion was faster in the experimental regimens with moxifloxacin substituted. So, within this setting we also didn't -- whereas, we saw improved culture conversion, that didn't translate to treatment shortening at four months.

I think another interesting thing about this study in subsequent analyses that Patrick Phillips did is that not -- in a nonsignificant proportion of patients in REMox converted very quickly and yet still relapsed. So, that was also challenging. I think that leads to this issue of level of detection. So, we have our solid media that has a certain level of detection; we have our liquid media that maybe has slightly better level of detection; but after some point we no longer know what's going on. They are undetectable based on our culture systems.

Despite these significant, I think, issues, there are some newer ways of modeling this -- the data

that I've shown you and some more data that Bob Wallace has conducted and his colleagues. And he'll probably speak to this a bit more later today, wherein, you can essentially look at both the duration of the regimen and the culture conversion at two months and model some ability to predict the likelihood of that regimen succeeding. And I think what I would draw your attention to here is that really where a regimen is likely to reach an acceptable efficacy to meet noninferiority is on the range of having essentially 99% culture conversion at eight weeks. And this is where a four-month regimen in pink starts to get to recurrence of proportions that are, I guess, somewhat in the realm of acceptable. So, really, an almost near 100% conversion at eight weeks is what's needed.

So, going back to the surrogate endpoint issue, because this is obviously very important for regulatory agencies and well known to you. This is the classical definition to remind people that it has to -- changes induced by therapy on the surrogate endpoint are expected to reflect changes in the clinically meaningful endpoint. And Dr. Fleming and others, Dr.

Powers, have pointed out there's a lot of places this can go wrong. The intervention -- first of all, the surrogate endpoint might not even be in the causal pathway to the true clinical outcome. The intervention that you use may affect the surrogate endpoint, but there's other causal pathways where it doesn't have an effect, and so on. It gets more complicated.

But the point is that that classical intervention impacts the surrogate, which then leads in the causal pathway to the endpoint of interest isn't the case, in my opinion, for culture.

Let's move to the technical and specimen-related issues. It's plausible that we actually are working with the most informative surrogate marker available to us already. But could our technical methods be imperfect and need improving? There are technical challenges with sputum as a sample time that, as I would say, probably there is no other sample type that I can think of other than stool, that would be as complex. But we're dealing with Mtb in sputum, and in stool studies they are often looking at other markers. So, we really do face a big challenge technically here

with sample type, the need for culture, the requirement of training of laboratory staff and maintaining proficiency. This is not a minor issue, especially when one considers an international trials network that has variability in the way they collect specimens, transport specimens, process specimens. And there is frankly a lack of standardization in these methods across trial networks, trial sites internationally.

TB trials also occur where TB is, which is in resource-limited settings. And so, these are not state-of-the-art labs, as you might think of in other disease entities. Furthermore, drug TB trials are sponsored by not-for-profit networks with limited resources, and sometimes they are in settings in which there are a limited number of laboratories with expertise for culture. And in one case, in Kenya, currently there is only one laboratory in the entire country that is certified to do this kind of work for trials activities.

I'm going to give you a real-life example here. Here is a comparison of what -- hypothetically an identical specimen at baseline. Lab A has a one-

hour transport, 4 degrees' transport temperature. You see it's decontamination proportion used here. And it gives you a baseline TTP of seven days. Great, TB diagnosed.

Lab B, three days' transport time. It takes a long while to get to that Kenya lab. It's got 21 degrees' exposure during transport. It has a different decontamination for the sodium hydroxide used and slightly different methods. It gives you a TTP of 12 days. Great, TB diagnosed. That's fine for diagnosis. However, when you're looking at TB trials and you're looking at time to positivity as a marker or biomarker of interest, these details matter.

So, this is the same specimen now looked at eight weeks. At eight weeks, Lab A using these techniques and methodologies gives you a TTP of 21 days. And then you can use this for modeling work, PK/PD modeling work, and so on and so forth.

This identical sample will be negative culture because of these, if you will, aberrancies or differences in methodology. So, this sort of underscores why this is (a) it's a complex --

technically, it's complex specimen type. These details matter and they vary across sites worldwide.

So, is it challenging to standardize? Yes. However, and the however is in relation to what we're at least trying to do in Study 31, so please bear with me. But for one, the specimen is not sterile at collection. It has contaminants that will affect culture results. The specimen, unlike probably any other specimen, with the exception of stool, has to be manipulated, extensively processed, decontaminated, and these are tedious methods. It takes 1.5 hours to decontaminate a sputum specimen, and there are critical steps that I just showed you in terms of centrifugation, resuspension, and any lack of precision will affect your recovery and cause variability in the results. Further, we have to use harsh chemicals to reduce the likely of contaminants, and these will also destroy Mtb and reduce culture yield.

So, with those, I guess, playing cards, we've come up with some basic ways to come to a compromise. We expect a rate of contamination for cultures, 2.2% to 5% for solid media; 5% to 10% for liquid media is

standard. We try to get two culture media to prevent complete loss of a specimen due to contamination, wherein -- like if your culture has no results, that would be devastating. The whole patient contribution will be essentially lost to some degree.

We're using solid media -- the solid media types vary by labs and, to be frank, I was asked to address this. The solid media that is best for clinical trials remains uncertain, and it probably is still a scenario wherein a media type is best suited for a particular lab. And then it is also important that this contamination issue is worse during treatment as the sputum quality itself reduces weeks into therapy.

So, this is some of the activities we've done to address these issues, to try to mitigate them. Just to remind people, Study 31/A5349 is a large, 2,500-patient FDA registered trial comparison two 4-month daily high dose rifapentine-based regimens to a standard six-month regimen.

In this study, we have pursued what we're calling key elements. These are essentially attempts

to harmonize across trial networks, the TBTC and the AIDS Clinical Trials Group, 20 key steps in TB methods focusing on those that are most likely to impact endpoints and measures. This required a significant within-lab validation at some sites prior to the adoption of key elements. When you tell a lab, you've got change your concentration of your sodium hydroxide, their response is usually no, and we have to validate it. So, this took quite a lot of effort, but it has paid off, I believe.

In addition, thanks to systems that have been established with the data center at TBTC, we're doing real-time monitoring for deviations from standard methodology and reporting to assure quality data are collected real time. Why does that matter? The trial is 2,500 patients; it's going to take years to finish. We don't want to find out in 18 months that there's errors here or deviations from the methodologies recommended. And really what we want to do is maintain the QA continuously so that we can lock the database within a few weeks or a couple of months of the trial ending.

And we've also tried to collect the data in a CDISC-compliant manner so they can be pooled and transferability is possible with pooled analyses.

In terms of the cultures, we decided to use both liquid and solid media for Study 31. We used -- we are using MGIT 960, an automated system by all, except one site that currently uses manual MGIT. The use of MGIT and automated systems reduces variability, it uses a standard commercial media, it automates the time to detection. So, there's lots of advantages there, and Debra will likely speak to this.

We could not prescribe a particular solid type, as I told you. It's not clear that one media fits all labs, and so we'll be able to compare this, but so far, I was told that 75% of our specimens are being cultured on LJ, 74% on 7HllS, and 1% on 7H10.

One of the things that I want to call out and is essential for trials networks I think going forward is that I was impressed by the TBTC and ACTG leadership, for their strong support of this technical training for laboratorians, as well as lab focused site visits. And there is a lot you learn when you actually

go in the lab and process samples with these technicians. And the labs have been welcoming. That would be the other part of the story is that they have not felt it as a threat but as a partnership and collaborative approach that has been wonderful.

This is the 20 key elements, just a snapshot, to show you there is everything from the transport -- sputum collection and transport features in terms of the temperature, the processing of the sodium hydroxide concentrations, and so on and so forth. But this has been essentially presented; sites have been trained. Before a site can open they must prove they can do all 20 key elements and sign off on them, and that has caused delays for several of our sites from opening because their labs are still in the process of validation. So, this is an example of how we can try to harmonize and standardize and address those differences.

Lastly, I'm going to close with what I hope to be some positive and encouraging biomarker opportunities. One of the areas that I think is exciting is the potential to look at time to positivity

on liquid media as a way to replace classical EBA studies, which I told you have these very complex systems, 10 dilutions quadruple cultures for each dilution.

And this is work that is done by Andreas Diacon and colleagues. There has been other work done at other centers. But it essentially shows across 5,700 sputum samples from about 500 patients using sort of a formula here, there is the ability to convert the time to positivity to be at least highly correlated with the CFU, and this obviously has a spread to it. But this line would be a -- this solid line would be a perfect association or correlation, and it shows some promise there but needs further development.

I want to tell you about a new project that is embedded into Study 31 that is called Sputum Transcriptomic Expression Profiling. This is Study 31A of the clinical trial I just presented. And why I find this particular project exciting is that it's really, to my knowledge, for the first time really looking to alternatives to enumeration. Everything I've told you about has been about enumeration -- enumeration of

cycle thresholds, enumeration of CFU, the time to conversion. This is really looking at the Mtb physiologic state, because we know the physiologic state, as has been presented by Eric and others, is dynamic. We know that it is adapted to immunity and tissue microenvironments, and we know that this affects drug effectiveness. And we also know that it differs in vitro and in humans. We heard about various in vitro systems and whether or not these in vitro systems recapitulate what happens in humans has quite a lot of uncertainty to it.

So, this study is in humans, and what we're using is a nested qRT-PCR assay of 2,400 Mtb mRNA transcripts that covers about 60% of the genome. So, it was developed by Gary Schoolnik and Greg Dolganov at Stanford. And it essentially gives us the transcriptome of TB. This is not host transcriptomics; this is bacterial transcriptomics. Because mRNA half-life is minutes long, we think this gives us a biological snapshot of the Mtb population in sputum, the physiologic state. And what's been found is really fascinating.

First, there is the usual enumeration findings that I'm showing you here. DNA is slow to decline but it does decline over 60 days of treatment, but RNA has a very rapid drop. What was very exciting and interesting to see was that you can detect Mtb mRNA in 100% of patients at day 56, even those that are culture-negative. We achieved culture negativity in maybe 80% of patients. We can still detect mycobacterial mRNA, and that suggested there is viable mycobacteria present at that time point, even though we're not culturing it.

In regard to the actual physiology, this is also interesting. So, first of all, I acknowledge that there is massive alteration of the Mtb transcriptome within days of receiving anti-TB-type therapy, and at least 20% of the genes are differentially expressed each day. When you categorize these in sort of -- classify them into groupings, you can see that there are reductions in massive down-regulation. So, this is day 2, day 4 of treatment, day 7, day 14. In relation to baseline there is massive down-regulation of metabolism pathways, Mtb. So, it is adapting in

treatment, shutting systems down, and dealing with the physiologic stresses of the drugs in the immune system.

So, there is reduced energy metabolism; there is educed protein translation; there is reduced DNA synthesis; there is reduced lipid synthesis. These are all down-regulation pathways. Reduced expression of ESAT-6 genes. And then there's transcriptional regulation that seems to be increased oxidative stress response, increased translational regulators, increased transcriptional initiation factors, and increased stress signature. There's even findings that I think could potentially hold promise for finding new targets, drug targets. These are two efflux pumps that show up-regulation, significant up-regulation on treatment. And these are two efflux pumps that are involved with isoniazid and rifampin. So, if we could target which of these efflux pumps are being turned on in response to drug therapy, we would be able to potentially find new targets for action.

In closing, I wanted to tell you about a terrific resource. It is the Consortium for TB Biomarkers Biorepository CTB2. It's a collaborative

biobank accelerating development of new TB cures by validating biomarkers of response for TB drug treatments. The goal is to have about 1,000 patients with longitudinally collected samples. There are seven scheduled time points which samples are collected, a whole array of samples collected. This work, this bank would not be in existence were it not first for FDA to recognize its need and fund it as a first federal source of funding.

But you can see it's a partnership now with NIAID, Bill & Melinda Gates Foundation, and the patients are being enrolled at TB Alliance sites, ACTG sites and TBTC sites. And we've had several founds of application proposals and have had 11 submissions. And please distribute this information to as many people as possible, because it's a good resource for people exploring TB biomarkers of treatment effect.

So, in summary, all phases of TB drug development rely on culture. Sensitivity appears to be somewhat of a priority in Phase 3, but, really, accuracy and precision in enumeration are paramount for EBA in Phase 2. There are uncertainties still about

the prediction and surrogacy of these culture-based systems, because, frankly, mechanisms of relapse exist that are not fully captured by the culture-based intermediate markers because there are non-culturable bacilli present as the mRNA data showed you.

Standardization of methods is feasible

Standardization of methods is feasible and essential. I didn't write it in this slide, but I would say it's not done enough and requires more attention. These standards will assuredly reduce noise, increase precision, accuracy and sensitivity, classical things in research -- in the conduct of rigorous research. And I think more investment should be put into the standardization methods in the labs. And support for the labs, frankly. A lot of the labs are public labs that are contributing to trial network data. Harmonization across networks and sites is also essential. This will allow us to do multi-site, multi-trial pooled analyses.

And then biomarkers that move the field beyond the simple enumeration, at least in my mind -- and imaging is another one, by the way, that was mentioned

earlier -- holds some promise. I think the work that I showed you provide insights into the physiologic adaptations of TB in response to drugs, and they may vary by the drugs used, so this could be a potential EBA alternative in accessing new therapies. And then potentially we could identify the mechanisms of persistence that are indeed in the causal pathway to relapse, how TB is modifying its physiology to survive.

I just want to acknowledge the protocol team for Study 31. The data center at TBTC has been immensely helpful and supporting embedding biomarker studies in this trial. I want to call out Anne Purfield, who helped with feedback and input into this talk, as well as Andy Vernon. And this is the Express 31 transcriptional profiling collective. Thank you.

DR. LOBUE: Thank you, Payam. Next speaker, moving on to diagnostics, is Marco Schito, who is scientific director of the Critical Path to TB Drug Regimens. He leads several work groups to facilitate the development of novel TB drug diagnostics for wide collaboration between basic science approaches to better understand mechanisms of resistance, molecular

surveillance, drug resistance database efforts, and in vitro diagnostic assay developers. And prior to joining Critical Path Institute, he spent nine years in TB as HIV clinical research branch at Division of AIDS at NIH.

DR. SCHITO: Thank you very much. I would also like to echo some of the comments with regards to having the FDA produce this and have this type of meeting, especially for TB. And also for including TB diagnostics. Oftentimes that's left out. I'm going to provide a little bit of an overview, and it really is quite a big overview as opposed to going into a lot of details, especially for the culture and the molecular tools that are currently available. But I will be spending a little bit more time on sequencing-based assays, as well as those applications for clinical trials.

And just to begin, there have been a large number of classical ways in which diagnostics have been done not only in the US but, more importantly, outside in high burden countries, and those are represented on the left-hand side of the slide. And as you move to

the right, you can see over the past 10 years there have been a number of advances in those diagnostic tools that have been made. And even if you go further to the right, some additional ones, including the PET-CT scan that others have talked about as well.

But, really, TB, I'm not going to go into the background to it, but I would like to mention that it is a spectrum of diseases. It's not just you have TB or you don't have TB; it is a wide spectrum of disease. And the problem is that most of the diagnostic tests, at least the TST/IGRA, as you can see on the bottom of this, really span a wide variety and range of that spectrum. Whereas, the smear, microscopy, the culture and the molecular assays are really more towards the right-hand side, where it is looking more at active disease. So, to be able to identify what distinguishes individuals to move into these various different categories is really unknown, and we really don't understand why individuals progress to those various areas, whereas, those can remain latent for oftentimes decades.

And I'm not going to talk too much about the

gold standard, because other have already talked about this, and talking about the sample type primarily being sputum. But there are obviously some pathogens, specific challenges about TB growing slowly, contamination issues, laboratory delays. And that's just enabled to actually be able to identify TB, getting TB in culture.

But then there are phenotypic DST delays after that, which requires additional time for first-line, second-line, and obviously limited capacity in countries that have that capacity to do those.

And then there are some established challenges, obviously. There have been huge investments that have been made in the past decade. A lot of technical capacity has been gone on, infrastructure, a lot of the quality issues that Payam and others have talked about, contamination rates as well. But there are emerging challenges as well. The maintenance of equipment in labs; the infrastructure to get samples to those labs; the capacity of those labs; appropriate infection control measures; and programs for staff screening. And then there are additional new

costs more recently on legislation and international transfer. And all of this really culminates in the need for rapid and affordable point-of-care diagnostic tests. And over the past seven or eight years that's really been something that has been driven primarily as a result of the Xpert MTB/RIF assay that was WHO-endorsed back in 2010. And since then there really has been almost an explosion of different types of genomic tests that can be done at point-of-care. And this has gone throughout the different healthcare systems, going all the way up to the reference labs, where you have large companies, like Becton Dickinson, Abbott, as well as Roche, providing these types of diagnostic tests and reference labs, all the way down even to the microscopy center.

And then there are also other technologies other than molecular types of technologies that are in development including phage-based breath detection, which nobody has mentioned yet; biomarkers again come up as well. But even though you have commercially available diagnostics at the bottom at 2012, 2013 and 2014, many of those actually don't get WHO-endorsed

until much later. Just the process in that is very extensive. And then there are others, like Alere q, that have dropped out of the market as well. So, there are challenges there.

But looking at probe-based GeneXpert assay, it was FDA cleared in 2013. So, a few years later FDA was able to get that cleared. It provides results in sputum, as you know, in two hours. It identifies TB and determines resistance to rifampin. But more recently the ultra-cartridge has just been released. It is as sensitive as culture but there is a downside to this and it has a slightly lower specificity, and I can talk specifically about that a little later. There is a new Omni form factor that will probably be coming out next year for point-of-care applications, and that's what it looks like. So, you can use a cell phone to operate that. And the year after they're hoping a new XDR cartridge will expand the drug menu, so that you can start looking at fluoroquinolone as well as aminoglycoside resistance.

But the question that came to me early on is how well are these tools actually being utilized in

countries? And here is a trial that was recently published out of the ieDEA program. This is an NIH-funded epidemiology cohort looking at HIV/TB-infected individuals. And just to note that although HIV individuals should be tested with TB, only about three-quarters of this in a programmatic setting that is well funded were actually tested with TB. And out of those, it was only 80% -- actually, 80% were tested for AFB smear microscopy, and shockingly only 5% actually were tested with GeneXpert, even though the majority of the sites had access to the test.

This isn't just a one-off type of observation; there is also a number of work that's in press now from Madhukar Pai's group, and the purpose of this slide here on the right is that he's looking at the number of smears that were done in country versus the number of Xpert cartridges that were procured in that country for that year. And this just gives you a very rough, crude estimation on how much GeneXpert was actually done within countries, and the countries are listed on the left-hand side, although you can't see them. What's important to see is that in the bar graph on the very

right-hand side, closer to the left, the lower the ratio the more Xpert that is being used. And the only country that really is replacing smear microscopy with Xpert is South Africa. Almost all the other countries are using this as a research type of tool.

And why is that? That's a good question. I think a lot of it has to do with cost; a lot of it has to do with political will. But there are also other concerns, such as discordance and concordance assays between these various different ones. This is a paper that was published a few years ago, but it does provide an example of how discordant some of these different assays, whether they be liquid culture, solid culture, GeneXpert, other molecular-based tests, or even some laboratory assays.

So, why the discrepancies? Well, there are some phenotypic issues known for some drugs, especially for ethambutol and pyrazinamide. There are unknown rare or unique single nucleotide polymorphisms, or mutations, that can be picked up in one assay but not in the other. The critical concentrations are often poorly characterized, and we really don't have a good

idea of the epidemiological cutoffs for MIC detection as well. And there is low-level mixed population in many of these circumstances which result in heteroresistance, and I'll get back to heteroresistance in a little while. But first I want to talk a little bit about next-generation sequencing, which is where I want to spend most of my time, because this really is an all-in-one type of tool. We can identify TB, drug resistance, virulence determinants, and because of the way TB is transmitted in a population, it is oftentimes clonal. So, it's really important from an epidemiological standpoint to understand the genotyping, evolution, population structure as well as the phylogenetics. And all of this can be done with next-generation sequencing.

And when we talk about next-generation sequencing, oftentimes we're talking about whole genome sequencing. It's one of the most comprehensive ways in which NGS, or next-generation sequencing can be done. However, it is culture-dependent. As a result of that, it's slow, still fairly expensive, because you're using both culture and molecular at the same time. And

because it is so comprehensive, it's a huge amount of bioinformatics that need to go in with that.

More recently a lot of people have been turning to targeted amplicon sequencing primarily because you can sequence the sample directly, so you don't have to rely on culture and, as a result, simpler, it's a lot faster. You can actually do much deeper sequencing and you can do several hundred different loci at the same time. The weakness, of course, it's not as comprehensive and you have to have prior knowledge of the targets that you're going to be looking at. And, finally, you do need some additional optimization. It's not a really well characterized assay as of yet.

So, as a result we need for a comprehensive, standardized database to provide a priori information regarding these drug-resistant loci and mutations that are associated with drug resistance, and that's really the remit of ReSeqTB. And it's not just finding out what these mutations are, but it's the interpretation of these mutations that is really holding a lot of the field back. And this is where we think that we're

differentiating ourselves from other databases that are already out there. So, we have predefined a number of different criteria where we take a look at a very basic statistical approach to the date, looking at p-values, likelihood ratios, looking at homoplasy as a next step to determine lineage markers, ensuring those are not included in this analysis.

And then there's a number of expert rules, where we take a look at each individual mutation and determine whether that mutation is associated with increase in the minimum inhibitory concentrations, whether that's also associated with an adverse clinical outcome, and then go back and look at some functional genetics to confirm that those observations are also true.

So, sequencing has been done in clinical trials. This has been shown by a number of different speakers. Looking at transmission of multidrug resistance, looking at relapse versus reinfection, drug resistance. But I do want to spend a little bit of time on heteroresistance. And, again, heteroresistance, really what this means is a presence

of a small number of organisms that are resistant to an antimicrobial drug within a population that is susceptible to that drug. And this actually may explain why we're seeing some failure to eradicate an infection in some patients that seem to be actually treated with appropriate antibiotic drugs. And the reason for this may be that the sensitivity of detecting heteroresistance is different for the different assays.

So, Sanger sequencing, line probe assays, it's around 30% to 50%. Whole genome sequencing can go a little bit lower, 5% to 10%. Culture, which is our standard, standard methodology, typically 1%, but often -- actually, it can go down as low as 1%, but typically 3% to 5%. And targeted sequencing actually can get much lower than that at 0.01%.

Targeted amplicon sequencing, and the one that I'm going to be mentioning is a single molecule overlapping read or the SMOR assay, can reduce sequencing error rate and that's how they're able to get down to that low amount. And this also has the potential to identify populations of resistant bacteria

with sensitivity that exceeds the current gold standard, and that's almost a problem when we're looking at clinical trials. So, is that a false positive? And so, the only way to really take a look at this is to take a look at serial samples of an individual that is under treatment, and this is a published -- a study that's recently been published by John Metcalfe and Rob Warren. This is a patient out of Moldova who is MDR-positive. And what they've done is tested, taken some samples throughout a period of about four years. They have tested amikacin DST both phenotypically and genotypically, and then did their SMOR assay. And the bottom line to this is that you can actually detect very small numbers on the first 2011 time point in the SMOR assay, that it's less than 1%, but it's susceptible for the DST assays. And then obviously, it becomes positive once those numbers increase above 10%.

So, I really concentrated mainly on the pathogen side of the equation, but there is the host side as well, and so can NGS be used to assist host pharmacogenomics? And the answer is yes, it can.

There's a number of genetic variations for specific targeted human genes that can be associated with drug-induced liver injury or with, on the other hand, on the right-hand side, greater drug exposure. And the result of this, if you can start doing a systematic review and start taking a look at what's available in the literature, and this is by no means comprehensive, but you can start seeing that there are a number of genes that are associated with having a number of different SNPs. And those SNP frequencies oftentimes population-dependent, but they do have an effect on adverse reactions.

So, if you increase levels of the drug, obviously, you approach maximum tolerated dose, accumulation of toxic metabolites and adverse events. So, you can probably predict some of those. If the levels decrease, however, you could reduce treatment efficacy, incomplete eradication of bacteria, prolonged treatment, and potentially relapse. Alternatively, you can actually increase the chance of developing drug resistance. So, this may be some mechanisms that could be more characterized better in clinical trials.

So, in conclusion, culture remains a challenge. I think it's still a very important tool to keep in mind that is within our armament, but we need to start optimizing other tools that are much faster and quicker to get that type of information to patients much better. And we need to be able to optimize those tools. From a clinical trial perspective, sequencing assays, I think, are a couple of things that we can do. One for the pathogen side is resistance prediction, and one from the host side is predicting adverse events.

There are a number of biomarker assay tools that are still in development. I'm not going to go through these in the interest of time, but I will mention that the treatment-monitoring assay, the prediction of cure versus relapse, and the biomarker LAM tool is something that my colleague, Debra Hanna, will present next.

I'd just like to acknowledge members of -- my colleagues at Critical Path Institute, as well as our partners, and they're listed on this slide. Thank you very much.

DR. FARLEY: Thanks very much. We're going to

hear next from Debra Hanna, who is the executive director of the Critical Path to TB Drug Regimens initiative led by the Critical Path Institute and funded by the Gates Foundation.

DR. HANNA: Wonderful. So, thank you to FDA for the opportunity to speak today on the role of the Critical Path to TB Drug Regimen initiative in facilitating drug development for TB. I was asked to make up a little bit of our time today and fortunately that is very doable, because you've heard from many of our critical experts and partners who contribute to the CPTR program, Eric, Payam, and others today. So, if I skip over a few slides, I'm happy to answer any questions you might have during the discussion session about those particular projects.

So, for those of you who aren't familiar with the CPTR initiative, we are a public private partnership that was launched about seven years ago, now with the focus of the remit to accelerate the development of entirely novel regimens for TB. So, specifically we're interested in helping our partners move forward the combination of multiple new agents

that haven't been individually approved.

The areas of focus, primarily focus for CPTR really are around the advancement of new drug development tools, which include biomarkers. I'm going to talk about one exciting program today. And the way that we do this is really taking an evidence-based approach so that we're ensuring that we're applying the most robust scientific framework around evaluation of these model systems.

We're really at an important part in our lifecycle as a CPTR program, so we're in the midst of evaluating the work we've done over the past six years and applying for a new award with the Gates Foundation. And through those discussions and through discussions with our partners we've really decided that we're going to hone in and refine our work specifically on advancement of these preclinical methods, drug development tools, which also include modeling and simulation components. A big part of the theme of my talk today will be the importance of collecting, curating, aggregating data across multiple different sectors and contributors within our program. I'll talk

about how we do that in a moment. And really focusing on developing pathways for new treatment regimens that include drugs that are not yet individually approved.

We have a large number of members and partners that participate in our organization. I've described it here at the bottom of this slide. In this graphical depiction, what I'm showing you on the outer side of this circle is all of the different sectors that do participate in the work of CPTR. So, we have large pharma, biotech companies, small pharmaceutical organizations; we have academia, government institutions, patient advocacy groups. And, importantly, this infrastructure supports the work that we do because we provide a neutral ground for data collaboration, again, which is underpinning for all of the model and methods work that we do. We provide a legal infrastructure that allows for the safe sharing of those data. But as importantly, it's a neutral opportunity for the members of our consortia to interface with regulatory agencies, which for our programs include both FDA and EMA, and I'll talk about a couple of projects where that has been critically

important for advancing our projects.

So, I talk a lot about the evidence-based evaluation of methodologies. And the reason that we use that terminology is that in the CPTR program, and really in this community here in the room, we're very focused on how you apply these different methodologies for making drug development decisions. There's a lot of important and wonderful work that are done in these model systems to drive future research and scientific hypothesis, but we care specifically about applying the rigor to give developers confidence that they can use these data to make robust decisions about derisking compounds.

So, this is just a quick slide to tell you about the framework that we use, which is called the Qualification Pathway. Both FDA and EMA have a strategy for the qualification of novel drug development tools, and two points that I want to make on this slide is that you begin all of these projects, including hollow fibers, sterilizing mouse model, LAM biomarker work, that I'll talk about, with a definition of a context of use statement. And what that really

means is that we're making a very clear statement about how a particular method should be used to make a particular decision in the drug development pathway. And that's a lot harder than it sounds.

And depending on the context of use statement, that will drive how much data is required to prove that context of use is true and applicable. And so, this is the approach whether we pursue formal qualification or not that we use to assess methodologies in the program.

So, I'll skip a couple of slides here. I do want to mention very briefly the importance of data collaboration within the context of this consortia. So, one of the very first deliverables of the CPTR program was to develop with our partner at CDISC a TB therapeutic area data standard which allows us to aggregate clinical trial data across multiple sources. And for those of you who are moving forward with new drugs that you hope to register, you know now that you have to collect all your clinical trial data using that standard to submit to FDA. And so we as a consortia develop that standard. We implement it within the course of our consortia, and this allows us to evaluate

preclinical data that is shared by many of the collaboratives in the room with clinical outcome data to really assess productivity. Marco has already told you about our ReSeqTB data platform, and I do want to briefly mention another partnership between CPTR and WHO, where we have -- and TB Alliance, where we have aggregated the Phase 3 quinolone-containing trials and made those fully publicly accessible to everybody in the room and researchers across the globe to ask important questions about those data sets.

So, this is really a great summary slide, if I needed to just, in one slide, describe to you what we're doing in CPTR now. So, our original remit from the Gates Foundation was to assess in this drug development paradigm gaps in our understanding of either how to choose the right drug to put in earl combination studies, how to choose the right dose, or translatability among steps. And we found a couple of big gap areas that will not be a surprise to any of you. We have focused a lot of our efforts in preclinical methodologies, as you've heard about today, because we think it's critically important for these

new drugs moving forward that we understand very crisply as much as possible about the PK/PD relationship that individual drugs will have and also how those will behave in combinations.

So, we turned our focus first to the hollow fiber system. We're now working on a similar assessment of the sterilizing mouse model. I will say in this critical preclinical to early clinical study transition phase we have hit another important milestone, which is the development of physiologically-based PK model to help describe potential drug penetration in the granuloma of adult patients. This is based off the South African population. This model is fully developed. It was developed based on the data repository that we have in hand, including preclinical data from Veronique Dartois, the hollow fiber system data, the Baylor labs. Also, Eric Nuermberger's data. This model is publicly accessible. We can provide it, we can also provide training to any developers interested in applying the model. But very important to understanding translation from preclinical space into early clinical studies. There is also a big gap

and a very expensive leap and time-consuming leap between Phase 2b studies and Phase 3, and so we're doing a lot of mathematical simulation work around understanding quantitative assessment of time to positivity, as Payam mentioned earlier. Chuck talked about the importance of population PK. He's leading a project with CPTR to develop that model and make it accessible.

We're doing a lot of work with Rada Savic's lab at UCSF and Eric Nuermberger to understand mechanism-based implications in developing new drugs and drug combinations. Happy to talk about any of those in detail during the discussion.

So, this is a dangerous slide, as we found out earlier this morning, but the good news is I don't need to spend a lot of time on it. Just simply want to say that, yes, we did a robust assessment of the in vitro hollow fiber system and for a couple of reasons. One, we know that we needed to improve that PK/PD understanding, and this was one methodology that was going to generate intensive quantitative information in that space. But as Eric had mentioned, this model has

been used for the past decade in lots of different anti-infective programs, as well as TB, but really as a research tool. And so, we had a lot of work to do assess predictive accuracy. He told you about the outcome of that work, but what I do want to mention is he mentioned two important points. Questions remaining around reproducibility of the model and the ability of other laboratories to take up this technology. So, 20 months after -- for the 20 months following the qualification with EMA of this methodology, we did intensive studies around -- in trying interlab reproducibility for the hollow fiber system. And we will be publishing on that soon. We're so confident with that work that several of our pharma partners are now working with us for the industrialized application of their new chemical entities in combination going into filings.

In terms of uptake into other laboratories, we've also developed a laboratory manual with several experts. That laboratory manual will be fully accessible for those who want to start up systems like this in their own facilities and want to reproduce

studies.

So, I'm not going to spend a lot of time on the sterilizing mouse model work, but to simply say that we're applying the same kind of approach. So, I think that there is a false assumption that because there is so much data in the sterilizing mouse system because it has been such a pivotal methodology in drug development decision-making in TB, that we may have had more standardized data, or more standardized systems, or had done this predictivity analysis with a mouse model as we did with hollow fiber system, but that's not true. And so, we are at the point where we've collected all of the important data that we think we need in order to do that predictivity analysis and literally within the next month we'll kick off that statistical analysis plan.

So, I do want to spend the last few minutes of my talk specifically focused on the LAM pharmacodynamic biomarker program. This was alluded to in a couple of different talks earlier this morning and really is one of the areas of most energy CPTR right now, and I think for really just cause. We've talked in several

presentations today about the high-unmet need for real time assessment of efficacy in TB drug development trials. We really do require a tool that can assess early bactericidal activity and sputum culture conversion endpoints, which we know are recommended by regulators in real time or as close to real time as possible, allowing for quick decision-making.

There are lots of bonuses that come along with that, like reduced cost and reduced time for trials. We've heard from Payam, we've also just heard from Marco, that we need to be able to have methodologies that are easily implemented in laboratories where these clinical trials are run. And if at all possible, methodologies that aren't affected by contamination for measuring burden sputum or impacted by drug carryover effect.

We've talked about the potential value of EBA. We know sputum culture conversion is very important, but there are a lot of issues with these, including the number of different laboratories, which is very, very minimal, that can do -- or trial sites that can do EBA studies. And there's lots of problems with

contamination, and then the time to grow up cultures from sputum.

So, through our partnership with Otsuka and through CPTR, the LAM biomarker has come forward. We know that lipoarabinomanna is a major cell wall component and may have developed a new immunoassay, which is an ELISA-based methodology that measures LAM in sputum. The good news is that very specific for LAM from Mtb and doesn't have cross-contamination with other oral bacteria. And there is strong correlation between sputum LAM and colony-forming units, as well as TTD. Two wonderful qualities of this is that the data to date say that it's not affected by contamination or drug carryover, and it offers much quicker testing, approximately five hours, which we can agree is better than six to eight weeks.

So, we are taking the qualification approach with FDA on this specific pharmacodynamic biomarker, and I've talked to you about the importance of defining a context of use statement. So, we have done that and we have actually submitted a full letter of intent with all of the data that are available to date on this

specific pharmacodynamic biomarker, and submitted that letter of intent on June 9th of this year to FDA, and we are continuing conversation with them.

Context of use, incredibly important. So, this one I'm going to read, right, because we choose our words carefully. LAM is a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum. A decrease in LAM sputum likely affects the reduction of bacterial load in the lung. This pharmacodynamic biomarkers should be considered with other microbiological measurements, such as culture, as a real-time evaluation of treatment response in clinical trials that patients with pulmonary TB and positive smears and cultures, such as 14-day EBA trials, clinical trials of pulmonary TB up to 56 days, or clinical trials to provide evidence for early decision-making in adaptive trial designs. And so now it's our job to coordinate all the data that supports this context of use statement and execute the statistical analysis plan, which will result in the submission of a briefing book to both FDA and potentially over time, EMA.

So, the envisioned impact, which is really the punchline of this presentation and I think what many alluded to as an important pivotal game-changer within the TB regimen development space is what a real-time pharmacodynamic biomarker could do for this field. So, again, we are not proposing this as a surrogate biomarker for culture, but now we can get a real-time assessment that with confidence we know can measure the decrease of bacterial load in sputum in patients within the course of clinical trials?

So, you've heard about the length lf clinical trials in that the typical strategy is regimen EBA trials followed by a Phase 2b study, which is most likely two-month sputum culture conversion, and then moving on to the very labor-intensive Phase 3 pivotal endpoint studies. And between each of those phases there is a 12 to 18, 18 to 24-month delay in working with regulators in countries where these clinical trials were designed. So, that is a huge time sync for these different programs. And also, you're losing the understanding that you have within individual patients across the course of a clinical trial. And so, Patrick

Phillips has done and proposed some work on potential seamless adaptive trial designs that could be implemented should a qualified pharmacodynamic biomarker that gives you a real time assessment could be implemented within the course of these trials.

So, one of the aspirational goals we heard about earlier in Erica's presentation was a more seamless trial design, where you could have a single program and continual enrollment, and that's the aspiration of the application for a biomarker such as LAM, should the data warrant that type of qualification decision. We at CPTR work together with Patrick and others in the room to do a landscape analysis and actual mathematical simulation of the impact and implementation of a biomarker like LAM if qualified, and that work will become one of the core projects of CPTR going forward.

So, with that thought I will just end with a thank you to all of our partners and collaborators, and just continue to put in a strong pitch for data collaboration and top partnership, because that's what makes CPTR possible. Thank you.

DR. FARLEY: Thanks, Debra. Robert Wallis, you are invited to come right up to the podium. In the Federal Register notice for this meeting, we invited folks who wanted to, to provide some very brief formal comments, and Bob took us up on that. So, he has about a five-minute, five-slide presentation. We'll hear from him right now.

DR. WALLIS: Thank you very much. I'm delighted, actually, to take up some comments from Payam and to talk about this question of moving from Phase 2 to Phase 3 more efficiently. I think all of you are familiar with this work that we did while I was still at Pfizer, looking at results from 24 trials from 20 to 40 years ago, of 58 regimens, almost 8,000 patients, in which we identified month 2 culture status and treatment duration as predictors of relapse. There was a rather simple mathematical equation. What was interesting about it is our ability to then go ahead and subsequently validate this, using independent data from six studies, 12 regimens, involving another 4,000 patients, and that's what I want to talk about here.

So, the way I'm showing these data, the

observed relapse -- the observed recurrence rate on this axis, the predicted recurrence rate on the vertical axis, this scale is Logit transformation, which takes a proportion that can range from 0 to 1, and stretches it out from negative infinity to positive infinity. It's a very useful transformation for this type of analysis but it's not very intuitive. So, for each of the corresponding values I have the percentage here represented in the inset. And obviously, a perfect prediction is this 45-degree dotted line here. And then here at 10%, this is my personal threshold for the limit of acceptability for relapse rate. We can argue about whether it should be higher or lower. It's a reasonable guess.

So, what we first looked at was for the three fluoroquinolone trials. We wanted to predict the results of the four arms, experimental arms, from five Phase 2 trials of six fluoroquinolone regimens, and this is the prediction, exactly on target.

The relapse rates in all eight arms of these trials were then predicted based on the month 2 culture results and the duration of each arm, and I'm showing

these results here. So, in green are the six-month arms, and in pink are the four-month arms, and this was published in 2015.

We have two new studies to add. One is the TBRU treatment shortening trial. This study took 390 HIV-negative patients with noncavetary disease at baseline and negative culture at month 2, and randomly assigned them to six or four months of treatment. From my perspective, this study succeeded, actually, in showing that low relapse rates in this population were consistent with what we thought in advance. So, 1.6%, this is the six-month arm, and 7% in the four-month arm. So, a 7% relapse rate in a four-month regimen actually is pretty good, but unfortunately the study failed by finding that duration was a predictor of relapse, which for reasons known only to the investigator was contrary to the study's hypothesis. In any case, the predictions were quite in line with what they should have been.

And then, lastly, two additional studies of a single arm, open label studies of the Bangladesh regimen in Niger and Cameroon. The month 2 positive

proportions were 6% and 13%, and they followed about 150 patients in total for one year, and no relapses were detected. And these show up over here in blue. These were assigned a value of 0.5% relapse rate because values of zero are not permitted, and we had originally used this method for small studies with either relapse rates or culture-positive rates of zero in the original publication. But these -- this estimate, there is some uncertainty, could be further in this direction, further in that direction; we'll have to wait for larger trials. But in any case, this overall result I think is quite impressive.

This is what the database looks like now. Seventy regimens, a distribution of less than six months, six months, and more than six months, and a distribution of African studies and global studies.

And these are the p-values for the parameters for the equation. And I want to point out, this is 10 to the minus fourth to 10 to the minus fifth. This is very striking. And if anyone wants to play with a simplified version of the calculator, it's online here at my website.

So, the conclusion, the model is accurate, R-square value of greater than 0.9 in this independent dataset, and it's generalizable. And by that, I mean it remained accurate under previously untested conditions. So, the fluoroquinolone results were predicted without fluoroquinolone data. The TBRU study results were predicted without any information about host data, and the MDR results were predicted without any MDR or clofazimine data. Does this mean that it will continue to be similarly useful in all studies in the future? I don't know, but this is a reasonably impressive track record.

None of the studies in the training dataset and very few in the validation dataset excluded recurrent disease due to reinfection. And this presumably introduced noise into the predictions, and you would think that accuracy would be increased if we had had the ability to look at true relapse.

The data right now are insufficient to create a similar model using time to culture conversion and liquid medium or one including baseline parameters, and I think collecting those sorts of data and

incorporating into this sort of model should be a research priority. And I would be particularly interested in incorporating the sputum LAM assay into this sort of model. I think that would give you an outstanding approach to informing the required duration of new, potentially shorter regimens, and that's my five minutes. Thank you.

DR. FARLEY: Thanks very much. We absolutely promise that you will get to eat lunch soon. But we wanted to turn our attention, to have a short panel discussion and opportunity for some questions and answers and interactions. And as folks think about question they want to follow up with the speakers, we've heard a lot of good information this morning, as well as discussion points they would like to bring up, I'd kind of like to remind the panel that our focus today is development of drug regimens. And what you'll hear this afternoon is that evaluation of those regimens, once we move into efficacy studies, the benefit of each of the components of those regimens has already been understood. And part of that has been through in vitro and animal work as well as PK, and so

we invite you to focus discussion around lessons learned and approaches going forward, and things that developers ought to keep in mind, based on our experience, to help move the field forward. So, we invite the panel to open the discussion, and then if the audience wishes to participate, you just need to stand at that microphone and we'll see you. Thanks.

DR. COX: So, Eric, you talked some about the animal models and the animal models are sometimes helpful but not always correct. As far as TB regimens, a whole new regimen somebody is constructing, how confident do you feel from the data that you might get from animal models that you're able to select a good regimen to effectively treat patients with TB? Your thoughts?

DR. NUERMBERGER: Well, I think it really gets to the justification for doing the kinds of evidence-based assessments of these methodologies so you can understand exactly how much confidence that you can have in these tools. So, I don't think we're at the point where we could say with supreme confidence that we can adequately predict a contribution of each agent.

Certainly, within the preclinical setting it's relatively straightforward to demonstrate the contribution of an individual drug with the kind of factorial designs that are quite amenable. And the better one can demonstrate that with -- by showing dose response and efficacy at exposures that we could justify as being clinically achievable the more powerful that is.

I think an important question is when -- we look at a variety of different endpoints, and I would, again, generally have the most confidence in looking at -- in proclaiming a contribution if we can show that the component contributes to bactericidal effect, contributes to sterilizing effect, contributes to suppression of resistant mutants that are resistant to other companion drugs in the regimen. So, the more preclinical endpoints one can bring to bear and demonstrate activity or contribution, the better. So, I think that's an important aspect of it.

DR. COX: Do you think the mouse model, with further research, can it be pushed so that we can squeeze more water from the stone, as far as

information we get from it, or are there inherent limits in what the mice can tell us?

DR. NUERMBERGER: Yeah, I mean, it's a model, but I think that if we -- if we really look objectively at what we know on either side of the equation, what the mouse model has yielded and what the clinical trials have yielded. I think it's difficult to argue that the mouse has provided false or misleading information.

I think the key issue is how we interpret results that come from the model. And if you look at these REMox regimens as an example, there were increased bactericidal effect in mouse models, there was a relatively small effect on the treatment duration, and I think that was wholly consistent with the REMox result in the sense that there was demonstrated increase in bactericidal effect. But whatever effect size there may have been on treatment shortening, it was not a two-month effect. And so, I don't think the mouse gave us bad data; I think it's -- we were -- we as a group, in moving forward with a trial like that, we're perhaps in hindsight overly

optimistic, but that was based on some of these, you know, at the time, recognition that many patients do well with four months of standard therapy. And there were other rationales for moving forward with a Phase 3 trial at that point, building capacity and, you know, and there weren't a lot of other regimens to push forward at that time. So, I think obviously, the mouse model was also not the only reason that that trial went forward, so we have to think about the decision-making in that context.

DR. SPIGELMAN: You know, a common theme to me, and it applies here and it applies to a lot of other areas, and I'll get into it maybe in the afternoon a little bit, is distinguishing between what we can learn qualitatively and what we can learn quantitatively. And I think that's basically what Eric has been saying.

And if we look for over-interpret -- if we look for having to derive truly strict quantitative data from a lot of these, we're going to be disappointed and, to a certain extent, throw out the baby with the bathwater. If we realize that

directionally or qualitatively there is a huge amount that can be learned, then I think it can inform steps moving forward. But I think we have to be careful in terms of what the expectations are in terms of quantitative relationships.

DR. HANNA: I would just add, to underscore a point that Eric made during his presentation, I don't think we've ever said there is going to be one single model that gives us all the answers that we need. And I think this is where we think pairing the quantitative system in the in vitro PK/PD model with more qualitative data that is assessed in the appropriate mouse model, those two pieces of information together will be important.

DR. NUERMBERGER: And I certainly wouldn't have wanted my comments to suggest that I think the mouse model is a be all, end all. I think it's just as suggested. And I think there are plenty of opportunities to continue to improve. And, again, incorporating information that may come from Kramnik mice or marmosets or other caseous models with respect to how well drugs are partitioning into various

important places. I think there is very good rationale, at least, to believe and certainly opportunity to demonstrate in these types of models that there may be compartmentalization of certain drug effects. And maybe there is a rationale for putting a drug in a combination just because it's only one of two or three instead of all four of the drugs that really achieve the kind of concentrations that you think you need in the caseous portion of a lesion.

And so, I think there are ways to build on that and certainly ways to continue to try and enhance our quantitative understanding. I think it sounds pie in the sky at the moment, but I think there is no reason to think that we can't continue to build and move closer and closer to quantitative appraisals of what various preclinical models can tell us in an integrated and comprehensive way. But that work has got to start somewhere.

DR. COX: And I guess one more part of this, too, is that to the extent the animal models and the other tools are used to inform choices that then go forward in clinical trials, you'll be able to have that

feedback and that database will grow over time to further increase the understanding of what can be concluded from those various different preclinical models.

DR. NUERMBERGER: That's absolutely right. If we're not asking these questions and thinking about how we want to answer these questions right now, then we won't be in a position to capitalize on these kinds of opportunities. And it's critical because a lot of the new drugs coming forward now are different in the sense of their physical chemistry, their PK characteristics, and they don't necessarily act like the isoniazids and the pyrazinamides. And so, it's a really important stress test for the preclinical models.

DR. COX: Chuck, can I ask you, you seem to be hinting at TDM. Do you want to say anything more about that?

DR. PELOQUIN: I appreciate the fact that you picked up on that.

DR. COX: And how would that work? I'm just sort of curious, your vision on this?

DR. PELOQUIN: So, if you get on an airplane,

someone is flying the airplane, typically, right? Or if you get on a bus, somebody is driving the bus. And if you're giving drug therapy and you're not going to do surgery, then you want to get the most out of that drug therapy. So, either you're controlling the therapy or its controlling you. So, if you give standardized doses, which is generally what's done, that broad spectrum -- I gave the example of rifampin from 0 to 45, that's what you're going to get. Now, it would be convenient of that wasn't the case, but unfortunately it is. And we have similar data for all the different drugs.

So, if you wish to -- and I would suggest doing it early, before you select for drug resistance, if that's going to happen. If you can get even just two blood samples in an individual patient for the drugs that you're using, you have a snapshot of what's going on. If you have the MIC, you might be lucky, and their organism is very, very susceptible, and you might not need to push the drug really hard. On the other hand, the patient's isolate might have an MIC that goes right up to the epidemiological breakpoint that we use

clinically and in which case you might have to push harder. And if you know that, then you have a good idea of how hard you're going to have to push and how much toxicity you might be expected or willing to tolerate in that situation.

DR. COX: So, it seems there are two laudable goals that we heard about. One is you want to get the dose right, you want to get to an exposure that's actually going to be able to treat the patient. And the other is the idea of sort of a pan-TB regimen, in essence, something that is simple that you could administer to patients that doesn't -- you know, ideally not have to do testing for either drug toxicity and all. So, it sounds like what you're describing would be something where you did some testing early on to see how you're doing with dosing, maybe adjust it once, do one more test, and then hope at that point that you're on autopilot for the dosing and you're going to achieve exposures that would remain constant throughout. Fair or --

DR. PELOQUIN: Well, hope is not a strategy. What I would say is that if we have drugs that are

immensely potent relative to how much is required in a patient. So, if your AUC to MIC is in the thousands, because you have an incredibly potent drug, then you probably don't need therapeutic drug monitoring, because you're way, way above it. But that's not true of virtually any of the drugs that are being looked at right now as experimental drugs or the drugs that are in clinic. And we're really much more in a situation that, for example, our lab does TDM for patients with fungal infections, and fungi can't even make up their mind what they are, they're a yeast, they're a hypha, or whatever. Yet if you're treating a transplant patient, they get TDM for all their immunosuppressants and their antifungals. And now in our intensive care units we're measuring beta-lactams because the MICs are getting higher and higher and the concentrations are all over the place with all the things we do to patients in the ICU. So, TB is not quite as extreme as those cases, but there is still a lot of variability, and up until now we generally don't control it.

About 200 different centers around the country send samples to my lab. There are several labs in the

US that can do this, and there are several labs in Europe that can do this. So, it's not impossible to do it. That's all I can say.

DR. COX: So, one other thing, and just so folks sort of have a feel. So, what we're going to try to do is we're going to break for lunch at 12:55. So, we'll do about five more minutes with the panel this morning and then we'll -- that way we can start the afternoon session on time, and we can finish on time, which I think will be really important. So, if anyone has any burning issues they want to surface for the morning, please do so now. Mel, please.

DR. SPIGELMAN: Chuck, only because I know you so well. More is always better and apple pie is great. Have you come up with a clinical trial design that would actually test what is the obvious, you know, true hypothesis that therapeutic drug testing really does yield better clinical results, more cross-detective results, etc. in TB? Because I think as a next step to actually ever get to the point of implementation is frankly having clinical trial robust, prospective data that quantifies to a certain extent the benefit.

DR. PELOQUIN: The closing number of studies that I showed, showed the consequences of low exposure of the drug, and the last two, the high rifamycin studies, showed the advantages of high exposures of the drug. So, I think actually the data are there in clinical situation. Now, as far as testing, TDM versus not TDM, could it be done? Yes, it could be done, but that's a little bit more challenging. But I think from the clinical trial data, it's pretty clear that, again, unless you're going to do surgery, you're relying on the drugs. And what the drugs work through is a pharmacodynamic parameter, and you can identify that preclinically and then you can optimize it. So, in a clinical trial you could get early concentrations and feedback.

So, it's just like flying a plane -- you direct the plane where you want it to go and then you get feedback of whether, as you turn the plane, if it actually went where you wanted it to go. You can get that information with serum concentrations, adjust the dose even in a clinical trial. I'm not saying it's easy; you'd have to have the assays probably close to

the different centers, but you could do it. HPLC is not a new tool. I was using it as an undergrad, and that's a long time ago.

DR. SPIGELMAN: Yeah, but I think, again, not meaning to belabor the point, there is a difference between frankly retrospective cherry-picking with data to show what could be considered obvious if somebody malabsorbs and doesn't get the drug, they're probably not going to do as well, to prospectively actually quantifying basically almost even cross-benefit. Do you do it for everybody? Do you wait until somebody doesn't respond? If you do it for everybody, with which drugs? How do you intervene in terms of the changing? What difference does that make ultimately? So, I do think if you want to change policy and ultimately really impact systems, it's just necessary to go that next step.

DR. PELOQUIN: Well, I'm open to doing that. As far as the studies, obviously, I had a finite time to present, so I don't really think that they're cherry-picked, per se. I think the most recent rifampin and rifapentine studies really encourage

people to look at those in great detail, because it's telling us that without good PK you don't get PD. But, conversely, with good PK you get excellent PD. So, again, I refer you to those papers.

DR. COX: And it sounds like, Mel, maybe what you're suggesting would be a randomized trial where one arm got TDM and the other did not, and then the question is, are the outcomes different between the two groups, yeah.

DR. SPIGELMAN: Yeah, I mean, that's the most obvious, sort of off-the-hand clinical trial design, but I'm sure when people would sit around and think about it, you might be able to come up with something better, but that sort of data, to me, would almost be the next step.

DR. LOBUE: I mean, I think the issue from a program standpoint is ideal versus good enough, and we might need those level of data to make those type of programmatic changes. Because unlike the University of Alabama football program, TB -- even in this country, TB programs are not that well resourced or funded. And while you made the point, well, if they're contributing

to the development of drug resistance, that would make up for the cost, but in fact we really don't see a lot of acquired drug resistance in programs that really start patients on the right regimen at the right time and do good directives or therapy.

DR. PELOQUIN: What you say is true. I think where you could see an advantage would be the duration of the treatment. So, if you optimized early, you might be able to get back to more what was seen in the BMRC trials, whereas, you hit them hard, you hit them early, which is really the mantra in HIV. Hit hard, hit early. And that's not really what's done in TB. We just sort of use the standard regimen, and that regimen by itself is not really optimized. It was sort of, this was good enough at the time, and decisions were made. You know, the BMRC was not highly funded and they had only so many things that they could do.

So, again, I think however we approach this, the PK and the PD are essential components, because that's now drugs operate. And if we have the opportunity clinically to optimize it individually, that would be fantastic. And that's really what we do

with other disease states. With diabetes, we don't give everybody 10 units of regular insulin three times a day regardless of the glucose being 300 or 30, and we don't give standardized doses of warfarin. And you can go down the list, so we don't give standardized doses. TB is one of the exceptions where we do.

DR. FARLEY: Great. Well, we're going to break at this point and we promise to get to you this afternoon first thing. So, we're going to try to resume at 1:35. That will be Dr. Higgins' talk, the FDA talk. You don't want to miss that. And we'll see you all in about 40 minutes. So, thanks very much and we'll have more time for talking this afternoon.

[Lunch break.]

DR. SPIGELMAN: I'd like to initially, for the first talk this afternoon, introduce Karen Higgins. Karen, as I think most of us know, is the statistical team leader that supports the division of anti-infective products at the FDA and has clearly been involved in so many of the programs that have come before the FDA. Karen, thank you.

DR. HIGGINS: Thanks, Mel. So, I'm going to

go over some regulatory issues to think about when designing your adequate and well-controlled trial for TB regimen development. There is a lot to talk about, so I'm going to kind of briefly talk about a lot of things. My main point, and it's something I'm hopefully going to repeat a lot, is every TB development program is different, so I highly recommend that you come into FDA and talk about your specific program, because there are going to be a lot of nuances.

But I'm going to talk about some regulatory requirements, including substantial evidence, accelerated approval, and added contribution of components of the TB regimen. And then I'll go into some of the clinical trial design things to think about, including patient population, control, endpoints and statistical analysis. My focus is really going to be on efficacy.

So, the FDA has required since 1962 to have substantial evidence of effectiveness to approve a drug. That is outlined in the Code of Federal Regulations, and it discusses adequate and well-

controlled trials, which you probably all heard, since it's plural, it's been meant to mean two or more trials. However, in 1998, the Clinical Effectiveness Guidance came out as part of the FDA Modernization Act, and in that it kind of opened the door a little bit more and gave situations where one adequate and well-controlled trial would be sufficient, along with independent substantiation of the findings. And in TB we often find that that would be the case where we would have one adequate and well-controlled trial plus a large amount of information from EBA trials, and plus studies in animal and in vitro.

But keep in mind the importance of adequate comparative safety information. So, sometimes one trial might be appropriate for efficacy but it wouldn't lead you to quite enough adequate safety information. So, that is always something to keep in mind. Sometimes, if there is not a large enough safety database it could lead to some kind of a limited use indication.

So, the accelerated approval program is something important to think about when developing a TB

regimen. This allows for earlier approval of drugs that treat serious conditions that provide meaningful therapeutic benefit over existing therapies. So, it uses an accelerated approval endpoint that is reasonably likely to predict clinical benefit, but in itself not a measure of clinical benefit. And, of course, the whole point of the accelerated approval program is it can considerably shorten the time required prior to receiving FDA approval.

A sponsor would then be required to conduct a post-marketing study to confirm the anticipated clinical benefit. If it's confirmed, then they would get full approval; if not, it potentially could remove the drug from the market.

So, some things to think about regarding accelerated versus standard approval for TB regimens. I kind of have a couple of thoughts on this slide. One thing we should think about as kind of the impact of the regimen is it's a high impact regimen. And, if so, you would tend to think more towards accelerated approval, and that would certainly be the case for MDR treatment regimen that is more effective or less toxic,

or an XDR regimen that has fairly good efficacy.

But an additional thing to think about, not only is the regimen high impact but, kind of, how much complete information do we need? And the more complete information you need, the more maybe you'd think towards standard approval. And something I would think about would be for a drug-sensitive regimen we really may need information on the final long-term outcome before switching patients from a highly effective standard regimen of the HRZE. So, in that case, even though a new drug-sensitive regimen with a totally new treatment regime would certainly be high impact, it might not be appropriate for accelerated approval because we would really want information on that long-term endpoint.

For an MDR regimen, if the test regimen has a markedly shorter duration, it's quite likely that we'll want to have an endpoint past the end of treatment. So, again, that would give us some estimate of relapse rate to make sure patients wouldn't be at a high risk of relapse if they were on this markedly shorter MDR regimen. And once you have that information, that in

fact might be evidence of clinical benefit, so that might just automatically lead you more towards standard approval. But this just kind of underscores, again, the need to come in early and kind of talk about your program and your drug, what you're going to be studying and maybe what the best plan for approval would be.

So, an example of accelerated approval is bedaquiline. It was approved in 2012 for the treatment of adults with MDR pulmonary tuberculosis. It was an add-on trial where patients were randomized to bedaquiline or placebo for 24 weeks. Patients received best available therapies for 18 to 24 months. The accelerated approval was based on time to sputum culture conversion, where there was a superior effect over placebo. But due to limited safety and an increased mortality on bedaquiline, it received a limited use statement saying to reserve use when an effective treatment regimen cannot otherwise be provided. And, again, the sponsor would need to conduct a confirmatory trial assessing patient survival, clinical resolution of tuberculosis, and rate of relapse at a later endpoint after patients have

completed TB therapy.

So, something to consider and that we've discussed today already is this combination rule, since we have a multiple drug regimen. So, the combination rule as stated in the Code of Federal Regulations states that two or more drugs may be combined into a single dosage form when each component makes a contribution to the claimed effect. So, you need to know that if you're going to give patients an additional drug that that drug is actually adding efficacy and not just potentially adding toxicity. That's been interpreted to mean a factorial design trial, which can be -- grow huge if you have multi-drug regimens. So, just in this little example of a two-component regimen, you'd need at least a three-arm trial, and you need to show the superiority of the combination to each of the individual components. So, that could be a high hurdle.

So, in 2013, the guidance on co-development of two more new investigational drugs for use in combination talked about that, and talked about how a factorial designed clinical study is certainly

preferred, but that in some cases it may not be possible. And in those cases, which TB is likely one, because you wouldn't want to give patients a regimen that is not fully effective. That perhaps information on the added contribution of the components could come from in vitro and in vivo animal models, Phase 1 or early studies, where the clinical study would assess the full regimen. So, in many cases this might be what we can do with TB development.

So, just to keep in mind, you could develop a TB regimen as a fixed dose combination, where all the components of the regimen are formulated together into, say, one tablet. It could be co-packaged in, say, a blister pack, or they could be individually packaged but labeled to be used in combination. And I just wanted to let you know that pretty much the efficacy and safety requirements will be similar for those three situations.

So, some things to consider for designing the TB efficacy trial. The main one is what is that TB regimen you're looking at, and is it a new, completely new regimen or is it really a new drug kind of being

added to a regimen that's already out there? So, for example, if it's a new regimen, if it's a high impact new regimen, for example, three or four new drugs with new mechanisms of action to treat TB in four to six months; that would be a high-impact brand-new regimen. Or, similarly, two new drugs with new mechanisms of action possibly paired with an older drug. If the contribution of the effect of the components could come from an earlier phase of development, such as EBA trials in animal models. Then the clinical trial could assess the efficacy of the regimen as a whole.

But on the other extreme, let's say it's a new drug being developed, for example, a new drug to treat MDR-TB given on top of the best available therapy, or a new drug to replace one drug in the standard drug-sensitive regimen, then it's more of the development of a single drug, and the efficacy of that single drug we will likely need to know from a clinical trial. And just an example, bedaquiline was that case. Of course, these are kind of two extremes of the spectrum. You could fall somewhere in between there, so, again, coming into discuss it with the division early on would

be helpful.

So, the patient population of your clinical trial could be drug-sensitive TB, MDR-TB, XDR-TB, or any combination or all combined. And, as mentioned earlier, different patient populations might lead to different routes of approval. So, the expectation is that you would conduct a randomized, controlled, blinded trial. There are some cases where blinding is just not feasible, so the trial should really be then conducted in a blinded manner however possible.

The control treatment would really depend on the patient population and the regimen. So, for example, if it was a drug-sensitive TB trial you were conducting, we would expect that standard six-month HRZE regimen is the control. For MDR-TB, it would really depend on the resistant patterns and the location where it was studied. For XDR-TB, given the poor outcome and long duration of treatment, it might be possible for a drug with great effect to have it be assessed in a single-arm trial with an historical control group. I worry about mentioning historical control groups because they are the weakest of the

controls. It's nonconcurrent and it's very difficult to have a confidence that the patients in the historical control are comparable to the patients in the trial that would have XDR patients. So, again, I'd come in early and we'd talk about how best to come up with an adequate historical control for that.

And I just want to mention briefly, again, like was done for bedaquiline, for a single new drug for MDR/XDR, you might use an add-on design where patients are randomized to either an optimized background regimen plus the new drug versus optimized background regimen plus placebo. And this is really a placebo-controlled trial. I know over time this is likely going to be getting more and more difficult to conduct as therapies for MDR-TB improve, but I just wanted to point that out.

So, we've talked about endpoints already this morning, but there are early endpoints that people would measure -- sputum culture conversion at two or six months, say; time to sputum culture conversion. But keep in mind these early endpoints really don't test whether the planned duration of the regimen is

adequate.

The late endpoint is the one we consider kind of the final or the ultimate endpoint in measuring TB efficacy. Sustained culture conversion 6 to 12 months after treatment ends. I'd say the timing of the endpoint really should be based on time from randomization and it should be the same for the two treatment arms. So, even though I'm referring to it as it is approximately measured at 6 to 12 months after the end of treatment, that should then be defined in the protocol as a time from randomization.

And you should capture the reason for failure, as in treatment failure, relapse, reinfection, if you're able to differentiate the two, and if you've lost the patient.

And then the last point I want to talk about is just the analysis of the clinical trial. Obviously, it depends on the specific clinical trial in your hypothesis, so you could assess it using a superiority analysis or noninferiority analysis. You all pretty much understand superiority analysis, but it helps to then go on to explain noninferiority once I've walked

through this a little bit.

So, superiority is really the gold standard of assessing efficacy. It's determined by showing the test arm is better than the control. And really since an add-on design is a placebo-controlled trial, it would be an automatic analysis for an add-on design.

And here is just a figure to represent the superiority design, where I have a number line which captures the treatment difference between test and control. On the left, it's in favor of control drug; on the right it's in favor of the test drug. The diamonds, the point estimate from the trial, and the parentheses capture the 95% confidence interval. So, in this case for superiority, that confidence interval would have to be completely to the right of zero, demonstrating that the test is superior to control.

Now, moving on to noninferiority, efficacy is now determined by showing that efficacy of the test arm is close enough to a known effective control. So, two key points in that sentence are close enough, how close it has to be, and to a known effective control. So, how close it needs to be is the noninferiority margin,

which is labeled as M here. And this is all greatly detailed in the FDA Guidance on Noninferiority Trials.

So, this margin, M, depends on two pieces of information. One is how effective is that control, and that's called M1, and the other is just based on clinical judgment, and that's how much efficacy we would be willing to lose. And the margin can't be greater than either of those two numbers.

So, in this case it's the same number line, where on the left is still in favor of the active control, and right is favor of placebo. But now that confidence interval doesn't need to be completely to the right of zero; it's a more relaxed test. And you're actually -- it can go down to up against that margin, which is the limit of how much the new test regimen can be worse than the active control. And coming up with that margin for TB can be very difficult.

So, it depends on the specific trial design, including the patient population, timing and definition of endpoint. And it really depends on what that active control is. So, in the situation that I mentioned

earlier, if it's a test regimen, if you're going to test the efficacy of your complete test regimen to the complete control regimen, and that means you kind of determine the added contribution of the effects from previous Phase 1 or animal studies. Then you need to understand that the effect of the whole control regimen, which is highly effective in TB. So, that M1 that we've estimated would be really very large and should be fairly easy to estimate.

So, for instance, in the drug-sensitive TB study, HRZE versus no treatment is going to be very large for patients. Similarly, for MDR-TB, best available therapy for MDR-TB is going to be really quite large compared to no treatment. So, when it comes to estimating a noninferiority margin for testing a test regimen to a control regimen, it's going to really hinge on that clinical judgment of how much efficacy you're willing to lose. It still might wind up being a small number, but at least it's -- there is no data, you are able to come up with a number and then you conduct your study.

And just keep in mind, this is often for kind

of this high impact regimen, which might be better in terms of treatment duration or sputum culture conversion or toxicity, but we'll still want to make sure that you're not losing too much on that final clinical endpoint, which is why we're assessing it for noninferiority.

When you assess noninferiority of a test drug to a control drug, it's much more complicated. Because you have a multi-drug regimen, the efficacy of any one of those particular drugs in that regimen is going to be fairly modest compared to the efficacy of the whole regimen. So, in this case it's going to be much harder to conduct the trial.

An example would be, let's say you'll have a new drug and you want to replace ethambutol in the drug-sensitive TB regimen. So, you're going to randomize subjects to HRZX as the new drug versus HRZE. In order to determine that FX has efficacy, you need to understand how efficacious ethambutol is in that drug-sensitive TB regimen, and that is going to be very hard to estimate from the literature.

Another option would be, let's say a new drug

added to drug-sensitive TB regimen, but the regimen is shortened by two months. In that case, it's a little bit easier because your drug would kind of be replacing the last two months of therapy in a drug-sensitive TB regimen. And there is some data to show that that has a fairly large effect. And that's actually in the TB, the draft TB guidance. It's in the appendix, a justification for how you would do that.

So, just in conclusion, adequate and well-controlled trials are required to determine the efficacy for TB regimens or drugs, and you really need to put together good evidence on the contribution of each drug in a regimen.

The pathway for approval depends on the impact of the regimen. Accelerated approval is possible. It's also possible it could lead to a limited indication if you have limited safety data. Development of a single drug will lead to a different study design than development of a full regimen, especially with high impact. And it's important to discuss development program with FDA as early as you can. Thank you.

DR. NAMBIAR: I think we have a couple of minutes, if there are any clarifying questions for Karen.

DR. LIENHARDT: Yes, thank you very much. A very, very short question, please, Karen. For the early endpoints, sputum culture conversion, you mentioned that you would like to see sputum culture conversion at two or six months. What is this or? Can you please tell us? What does it depend upon?

DR. HIGGINS: The or was just listing some possible early endpoints. So, I think that would also be something to discuss with us in the development of your program.

DR. LIENHARDT: Okay, there was nothing really due to the fact that you want two-month culture conversion if it is drug-susceptible TB and six months if it is MDR, or was it really more on type of appreciation of the investigation arm and what the regimen might be?

DR. HIGGINS: Exactly.

DR. LIENHARDT: Thank you.

DR. NAMBIAR: So, we move on to our next

topic, which will be New Approaches to TB Drug Development. We hear both from a developer and some of you are presenting industry. So, it is my pleasure to introduce Mel Spigelman, who is the president and chief executive officer of the Global Alliance for TB Drug Development. And prior to joining TB Alliance, Dr. Spigelman was at Knoll Pharmaceuticals, which is a division of BASF Pharma. Thanks.

DR. SPIGELMAN: Thank you very much, and definitely thank the FDA for convening this meeting. It really is fantastic to see the attention being given to TB. So, the first thing that I've done is change the topic of my talk a little bit from new approaches to TB drug development to the past, present, and I should say potential future approaches. So, I took that liberty first, and I think you'll see why.

Disclosures, I work for the TB Alliance. And now let me first start with what, from my perspective, as being with an organization that is responsible for developing new therapies for TB, the approaches that we see as being relevant, if not mandatory. And this may be different depending on organizations and where

people come from. But a common anchor of what we've always believed and frankly I think may be the situation in all other diseases around the world, and therefore I've labeled this as being an approach that has existed in the past, although more so recently, in the present, and I think will continue even more so to be important in the future. It starts out with maybe what could be viewed as a truism, and that is that we have to ensure explicit clarity on exactly the problem that we're trying to fix with the development program. And it has to provide very practical, cost-effective, and implementable solutions for the identified problem.

And one of the subsets of this is especially where it deviates a little bit from something like an FDA charge, getting regulatory approval is necessary but not sufficient in order to justify a TB drug development program. Now, that doesn't mean that the solutions have to be optimized, but they do have to have a net compelling benefit to patients, to payers, and to healthcare systems. Now, I would say that this is really important in developed countries that are resource-starved, but I think for any of us who follow

or are involved in what's going on even in the United States, this is certainly true here in the US, too. Not from an FDA perspective of approving something, but for having it actually do something in the real world. Let me give a couple of concrete examples that might raise a little more clarity on what I'm trying to say here.

The first one is an example, and that's actually a real-life example, that if -- you know, would one substitute a drug in first-line therapy but not shorten the duration or increase or decrease the side effects?

Now, it's interesting, about 10 years ago, or something like that. It was a while ago, Mark Goldberger, who, you know, Ed's predecessor at the FDA, we were in the first meeting I had with the FDA and we were presenting, actually, in a four-month regimen. And he asked, well, why don't you just study a six-month regimen with a drug substitution, you know, and if it works, if it's safe, if it's effective, etc., etc., you can get the drug approved. And I was sort of dumbfounded from even having been in the TB world for a

while, because I said why would we do that? It would, you know -- yeah, you would get the drug approved, but why would we do it? He said -- obviously, if anybody who knows Mark, he was trying to be helpful, you know. The goal was to get the drug approved in TB.

Now, so that may not be that controversial, but the second example, which I think could be more controversial for discussion at some point is, does adding an additional drug to poor second-line regimens with the only obvious advantage being getting higher sputum conversion rates but no other advantages, does that offer a net benefit?

You can get the drugs approved. We've seen two drugs globally get approved on that basis. Does it offer truly a net benefit, if you really consider all of the sort of accompaniments that would go along with that type of development program? So, that is past, present and future. Let me now get down to the real present of what are we really doing in terms of the development programs that we have, at least the TB Alliance. I want to just present two programs, or two approaches that we currently use, one of which has

already been gone into -- both of them have already been mentioned.

So, these are specific -- right now, not new approaches, but things that we do. The first one, and Cathy put this slide up earlier, I think, as part of her presentation, is an approach that we really designed -- I think it's now about seven years ago -- when we really were looking for what we called a unified pathway for moving really -- and at that point we were thinking of pretty much of a straightforward start at the beginning, go to the end process. We started it with a pretty intricate preclinical program that defined preclinically -- and Eric can speak to this because he was involved from the beginning -- that we had at that point in time a basket of about 10 different drugs. And we said, look -- and they were either in late development or late preclinical or approved drugs seven. And we said, if we took all combinations and permutations that made sense, which regimens would surface to the top as being the most effective or the most promising?

That was done in parallel with standard Phase

1 type of work. And if a drug could pass Phase 1 work, then it would go into a straightforward two-week -- and, again, I don't like the term EBA. We try to get away from that early bactericidal activity, because, frankly, the real benefit as we see in two-week studies of single drugs is dose ranging. Because there's almost no other chance from a practical point of view to do much in the way of dose ranging for TB drugs. And obviously, it's critical to figure out what dose do you want to work with and -- as opposed to almost every other disease. We can't do dose ranging from a practical point of view when we get into late stage Phase 2s or Phase 3s, not to any appreciable extent.

Now, the fact that it has to kill bugs in human beings is clearly critical, but it's not the old days of a two-day EBA to click off yes, no, does the drug kill bugs in people; it's really to try to figure out what's the dose that we want to bring forward that we can at least convince ourselves a little bit that it is the optimized dose.

Then the -- what we designed then was saying, okay, before we go much further, we want to take two

weeks and look at a two-week combination program, and this is all intertwined with the preclinical work and with the Phase 1 work. So, clearly, this has to be done not just based on a single go/no-go criterion, but really on the total profile. If you have two or three drugs with similar toxicologic issues, you know, that's tough to think you're going to push those forward, etc. And similarly, is the benefit -- is there any evidence of synergy preclinically, etc., and then moving into a two-month regimen and then moving into a three-month regimen -- or into a definitive Phase 3 trial.

So, this approach, and also the advantage here of what we tried to integrate, and this is another important piece of it is, we were looking for regimens that could cross over between drug-sensitive and conventionally what was called MDR-TB. At least MDR-TB, so we were looking at novel regimens that one could obliterate this distinction. And that raises all sorts of difficulties of how to design those trials when you get especially into the later stages. How do you fit -- you can't randomize MDR patients, for example, to HRZE as the control group?

So, without going into all the details of how we finally decided to move this whole paradigm forward, we figured out a way that made sense that if the MDR patients do just as well as the DS patients for all intents and purposes, that would be convincing -- with the same regimen -- that would be convincing and enough proof that it was valid in both.

Now, it's been raised by other regulatory authorities, also, on the issue of do you really need that or do you simply have a regimen that says you want to use it in patients who are sensitive to the known entities in the regimen, but it's irrelevant what their resistant to. So, again, that's a nuance that went into the whole consideration of designing this path forward for developing regimens.

Now, about three years ago, four years ago at the most, we started thinking about, well, could we do it a little differently? Because by now we had at least two totally novel drugs that we had access to, and a third one that wasn't totally novel but for which there was almost no preexisting resistance, and said could we sort of skip all of this stuff and kind of

just go to the end and potentially then move backwards? And that was really the genesis of the Nix trial, where we said, okay, you know, have access to bedaquiline, we've got pretomanid, we've got really good early data on those two. We've even used those two a little together. We knew from other people's work that linezolid certainly appeared to have activity in TB, although it had some side effects.

Now, note that these three drugs had never been used together in a single patient, to our knowledge, and I'm pretty much 100% sure, and we said, look, in the XDR-TB population, we can go right not to a two-month sputum conversion or to have a regimen that may have efficacy, but we can't really even tell people how to definitively use the regimen. But based on the mouse data that Eric had generated with us, and based on other data, we really said let's be a little conservative in the sense of maybe this regimen can cure in four months, but that's maybe going a little too far. And we frankly arbitrarily said let's treat patients for six months, XDR-TB patients for whom the risk-benefits seem to be justified. And obviously do

this in a well-controlled clinical trial in the sense of the oversight but not in the sense of a control group in the clinical trial. And, frankly, not look at any surrogate endpoints. Look at two-month, actually, at the end of the day cure rates in these patients, understanding full well that this trial could have blown up in the first 10 patients by virtue of either toxicity or lack of efficacy, or anything. And we said let's try this as a different approach, and that's what I think people have heard about now in the Nix trial.

So, if we look at what are the present approaches that we see in terms of developing new therapies, new regimens in TB, I think for us, at least, we can either kind of move forward with the approach that I showed initially, or in a sense move backward. Because the next step actually with Nix is now that we think we see compelling evidence that those three drugs work in the XDR-TB population, obviously, we're still doing that trial, but we are already starting an optimization trial of that regimen to move backwards. And by that, I mean it would be difficult, although not impossible, certainly, to use the regimen

in MDR-TB patients. I would say it would not at all be justified to even consider that regimen because of the linezolid in DS patients. But if we can optimize the regimen in terms of safety, especially, then one could move backwards, so-to-speak, and move it into MDR and move it into drug-sensitive patients, and have that as the path, development path to get one regimen that would suffice for all patients.

So, I think both of these approaches are viable. I think we've already moved regimens forward and backwards now with both of these approaches. So, with that, let me now move to the next question is, what's the story with new approaches? Because everything I've talked about so far, to me, at least, are what I would call old or present approaches.

So, I don't have to spend a lot of time on this, because I think we've really been talking about it for most of the morning. Clearly, the lack of the instantaneous readout of response severely limits the implementation, at least in my opinion, of different types of adaptive designs that could be put into drug development.

Now, clearly, we've heard about the LAM assay, which could serve a tremendous purpose in that regard if it truly were -- you know, if all the data falls in place and it's scalable, etc. But right now, we still don't have that instantaneous readout that could give us the ability to really pivot very quickly from Phase 2 to Phase 3, etc.

The other point that really is a problem, and I think I tried to bring this up a little bit in the morning discussion is, we don't have a predictive quantitative relationship between Phase 2 readouts and Phase 3 readouts. So, when we look at culture conversion and we really try to then design Phase 3 trials and ask the specific questions of, okay, well, what are really the specifics? Are we going to do a four-month experimental arm, a five month, a three month, three-and-a-half months? We don't have the data preclinically that give us a huge amount of comfort that we're picking the one point. And that, I think, is still a limiting factor. But I think we have to be careful not to, you know, as the saying goes, throw the baby out with the bathwater. Because, again, I tried

to mention this morning, preclinical models are predictive; they're just not quantitatively predictive the way it would ideally be desirable to have them. And what do I mean by that? This is a slide that Eric showed, so I'm not going to go into it in terms of if we look at mouse relapse experiment data and then we apply that to a variety of regimens that have been studied in the clinic -- and, again, the slide that Eric showed this morning from his data. Whereas, I don't believe, and I'm sure Eric doesn't believe it, if a regimen cures in a mouse in four months, will it cure in four months in man? That still is a bit of a leap of faith, in my opinion, whether it's four-and-a-half, five, etc. But what really is convincing in terms of the preclinical data is the rank order of the duration, so that in fact from everything we've seen, if the preclinical mouse model, and we still have yet to be able to add on to this hollow fiber and other modalities in terms of preclinical data. But the rank order of efficacy and of predictiveness in man really appears to hold up, at least in this five regimens that are on this page, for which Eric also showed the data

this morning. So, I do think we can learn a huge amount from the preclinical models; obviously, never enough.

So, that brings us, really, to the next question of, okay, speculating now on what are potential future or new approaches that could be used in TB drug development? And I really put these out as really just sort of very abstract thinking at this point. Because I have to tell you, there's not a huge amount of real thoughtfulness or real concrete proposals behind them, but just to throw out a couple of ideas. Oh, and also, before that, I really want to add, because I think we're all aware of this, is that approaches to TB drug development are going to be highly dependent on any advance we make. So, an approach, for example, like Nix could totally go away almost if we're successful in XDR-TB patients. When we have a four-month regimen, if TBTC and ACTG trial, for example, works and our new standard becomes four months, we've got a whole new ballgame, then, in terms of how to predict for a three-month or a two-month, etc.

But having said that, and absent either having new technological advances or having new breakthroughs with new approvals for different regimens for either DS, MDR or XDR, there are two ideas that I just wanted to float by everyone and obviously for discussion as we see fit. One is the concept of large, simplified clinical trials. These are -- for those of you who are old enough, like me, to remember the concept of large, simplified clinical trials was in vogue really around the '80s and '90s in terms of, you know, the issues around the cost of clinical trials, the complexity of clinical trials, and could they be made somewhat bigger but with less data collection and all of that? And I'm not sure that we can't do something along those lines in TB.

I think -- you know, I won't do it justice -- you know, Payam brought up the fantastic point this morning that just going through the culture issues in Phase 3 clinical trials is a bear. I mean, it is a nightmare and fully agree with everything that Payam talked about and give credit to what TBTC and ACTG have done in terms of trying to standardize them. But then

I raise the issue that if we really had big enough studies, do we have to do culture, or can we live with very few cultures at the end of therapy, for example? Even with different labs doing them somewhat differently but with larger numbers that truly would separate out something that work from something that doesn't.

And this goes all the way along the lines, for those of us who have the 100-page case report forms and all the ancillary tests, etc., etc., that really eats into a huge amount of resources, is that could we be thinking about larger but simplified clinical trials that could even be done in some of the better TB programs that exist around the world, etc.? So, that's just one idea to float.

And the other idea that I wanted to float by is, should we be thinking about in a Phase 3 type of design, looking at multiple arms, and we could talk about having large, relatively large or noninferiority margins that look at multiple time points for cure. So, that if we had a -- and then, in doing that, we could potentially look at the shape of that cure curve

and not just each one arm by itself in terms of generating more data.

So, if we did trials, for example, with a three, four, five -- and I'm just arbitrarily picking these numbers out there. You know, if we did a trial that had a three-month arm in it, a four-month arm, a five-month, and a six-month, even, or not -- if we get a six-month, and obviously a control arm, could we potentially, in a study like that, deal with the issue that we don't have the translational power to know that this will be a four-month regimen, this is a five-month regimen, this is a three-month regimen? And we put all of our eggs into that one basket when we roll the dice on designing that clinical trial, knowing that if we get conservative, like I said on the earliest example, we go with a six-month arm and almost know for sure that we'll get the drug approved, but that's worthless.

On the other hand, if we get a drug approved, or a regimen approved for a five-month or a four-month, but, you know, it really could be a three-month regimen, that would be a shame, because that's another five to seven years of a clinical trial to actually

feel comfortable with that after we've proven that it's either a four- or a five-month regimen.

So, this would take a much more sophisticated statistical expertise than certainly I have, but to be thinking about would such a design be feasible and practical in terms of dealing with the problems that we have and the limitations that we have as of today?

So, anyhow, that's -- thank you very much for the opportunity, and hopefully at least generate some feedback later on this afternoon.

DR. NAMBIAR: Thanks, Mel. Our next speaker is Charles Wells, who is an associate vice president and head of development for infectious diseases therapeutic area at Sanofi. And prior to joining Sanofi he was at Otsuka, and before that spent a few years in the CDC. Thanks, Charles.

DR. WELLS: Good afternoon, everyone. Can you hear me okay? It's a great pleasure to be here this afternoon to speak with you about perhaps a little bit different perspective on drug development for TB from industry. And as was mentioned, my disclosure is that I work for Sanofi. And I was asked to speak about

these points in thinking about my talk. In particular, approaches taken from industry-based development programs. And as you'll see in my talk, I kind of look at it from the period before 2005, building up to when the new drugs went into development at that time point. And then up until -- okay, sorry, this is always a problem, logistics, for people who are 6.5 feet tall. At any rate, I will talk about this sort of breakdown of periods for development, especially focusing on the two new agents that were approved three or four years ago, the regimens that were studied and why; the trial design endpoints; nuances of combination development from the perspective of taking single agents through development; challenges and barriers in development programs; and then kind of moving forward to registration and beyond. And I think many things that went on during that period apply to what we're looking at today.

So, the first really important point to make about industry's perspective is expediency. The clock is ticking. There's -- time-limited patent protection for molecules in development for TB takes 10 to 12

years, so there's a rush ahead to try to get something through the development pipeline. And also, too, because of competing resources internally, you really have to give a reason to believe to the key stakeholder to make decisions about appropriation of resources for projects. And so, you really need a quick path to and through proof-of-concept and then bold and grand plans for later-stage development to keep people engaged and committed.

Unfortunately, the biology of tuberculosis, as we've heard all day today, works against expediency. It's anything but that, and if you think about previously with TB trials coming up to the time that the new agents were developed, treatment at six months, two years of follow-up to chart relapse made a lot of sense from a public health perspective and for patients, but it's a huge challenge for developers. Animal models and early bactericidal activity studies are great early tools but they have limitations, as we've heard again and again today.

And then sputum culture conversion as a surrogate marker, which I'll talk a little bit more

about. Important help in moving the new agents that came through ahead faster, further and faster. And there is no doubt, earlier sputum culture conversion means something clinically for the patients' overall trajectory if they're treated long enough and, of course, it's important for public health. But when? Two months? Three months? Four months? Six months? Even now, 10, 12 years later, there is still some debate about when is the much meaningful time point?

And then most importantly, as was said again and again today, practical considerations of using that for trials slow contamination capacity for laboratories to support trials.

So, the other important thing in industry, at least from my experience, is all roads lead to the target product profile and what your label will look like at the end of development. And so, that serves as the blueprint for development throughout the process, and so you should really have a very good idea of where you're headed at the very beginning of the process, and you will be held very accountable to that throughout the process.

So, just briefly, this is a very simplified, scaled-down TPP, but you're looking for, if it's a new drug or new regimens, novel mechanism of action that's active against resistant strains that are in circulation. In terms or target patient population, at a minimum it should be good for multidrug and extensively drug-resistant TB patients, but as a base, then also good for drug-susceptible TB patients as well.

Skipping down to efficacy, where M and XDR-TB are concerned, the new agent added to or the new regimens should be superior to the existing treatment that can be achieved. And then also because of the degree of toxicity for treating MDR and XDR-TB, it should be safer.

So, a little bit more focused now on M and XDR-TB, and it's interesting, because XDR-TB wasn't even defined until 2006 or '07 -- 2006, I believe. So, looking at them collectively as an opportunity for development, it is clear there is an unmet medical need for better efficacy, and shorter, easier and safer regimens. And the idea in the mid-2000s, that this

population could be a great entry point for development was really laid out very nicely in a paper by Dr. Sacks in 2008, where I quote, "Exploring efficacy in the setting of drug-resistant disease may present a certain opportunity," and, "The possibility of accelerated approval based on the surrogate endpoint might be feasible." So, that really set the stage on how to approach development for the new agents that were coming through the pipeline at the time. And this, ironically, could actually confer efficiency for development and hasten the arrival of new drugs to patients who really needed them. Yes, faster to market, but even more importantly, faster access for patients.

But now to -- so, it's one thing to sort of have the sort of blueprint and the pathway forward, but it's another thing to execute it. And so, I really want to highlight what was going on at the time that the development programs were going on and getting launched for the new drugs, because I think it's really important to keep these things in mind and think into the future for development.

So, what had been identified in the late '90s and early 2000s that drug-resistant tuberculosis was going to undo all the great progress that was being made for global TB control. And within the auspices of the Stop TB Partnership, the Green Light Committee mechanism was established to help the rollout and expansion of treatment for MDR-TB in helping programs build better services and support for treating patients reliable drug supply, quality drugs, and as importantly, laboratory services to support their treatment and care. And as you can see, a whole list of things were going on -- limited diagnostic capacity. There were a large reservoir of chronic patients, those that had already been treated with some combination of second-line treatment after several cycles of TB. Weaker second-line drugs were available, like ciprofloxacin. And as the initiative got underway and progress was made, by about 2005, in total globally there were about 20,000 patients that had been brought onto good quality treatment that could even be accessed for possible development. And also, of course, since there had been no new drugs for TB in 40 years, no new

or novel drugs, there was limited experience for doing clinical trials and most definitely with GCP.

So, in these earlier years, after the Green Light Committee was launched, some of the earlier programs, the best rates that you could see two months' sputum culture conversion of 30% cure, and the best prevalence was about 60% to 65% with some exceptions, and mortality was about 10% to 20%. So, this was the backdrop for the new agents.

I want to highlight here from one of those programs, data from Latvia. These survival curves indicate sort of the heterogeneity of patient populations, and I think it's very informative now, looking forward to the future, some of these breakdowns of patients. And in this analysis, you see that for patients who have never been treated for TB before and are started on MDR-TB treatment, the respond fairly well and fairly quickly compared to those who have had previous treatment with second-line drugs, which is the top dotted line curve.

So, leading into the 10 years that it took for bedaquiline and delamanid to be developed and approved,

bedaquiline in the US and Europe, and delamanid in Europe, it really did stand to test that the Green Light Committee site served as a great network and had the laboratory support to lead to the development of the agents. And I think in a paper by Carol Milnick that suggested this idea of using these sites, that they could be a great platform for development, really held true.

At the same time, there were stringent definitions that WHO released requiring multiple cultures to confirm sputum culture conversion and cure. And as you can see, the basic design of the trials was, as has been discussed, an optimized background regimen plus a test agent versus the optimized background regimen. This was actually outlined in Dr. Sacks' paper in suggesting that we follow what had been done in the HIV development community.

And looking at the effects on sputum culture conversion for the six months, the way that the trial was designed for bedaquiline, you can see the differences there. And then for delamanid on the two-month sputum culture conversion endpoint. And, of

course, because of the accelerated approval, processes for these drugs, they had limited datasets and so they wound up with restricted labels in very specific patient populations for which they could be used. The irony in all this is that they were putting combinations with drugs that had never been formally evaluated for MDR-TB. But I don't think their approval was the end of the story; I actually think that was the beginning of the story. Because what has followed since is that those drugs have actually gone on to be included in drug-drug interaction studies that would evaluate their use together. And then they've been incorporated in treatment optimization trials that I'll talk a little bit about later. So, in fact, that's the beginning of the odyssey and perhaps even the experience with the bedaquiline trial informed to some degree the Nix trial.

So, where are we now versus 10 years ago, or 12 years ago? So, treatment capacity has expanded. There are a lot more opportunities for patients now. More than 100,000 come onto treatment annually. This is woefully short of the 400,000 or 500,000 that should

be on treatment, but it is much improved from earlier in the story. There are also a decreased population of chronic patients now. Those that have gone through iterative rounds of treatment, there are not as many of those patients most likely now as there were before.

Better diagnosis. We can go for months now down to days to know that we have a drug-resistant TB patient, and that has had a huge impact independent of the drugs being better available. And then now we have better drugs. Moxifloxacin and linezolid and clofazimine from the existing catalog, and then the new agents themselves. There is also some very good experience looking at MDR-TB patients without previous second-line treatment who can be treated with a shorter course regimen for MDR-TB that was tested out initially in Bangladesh with cure rates of 88%.

And so, I definitely think, when you think about where we are in patient populations for development, the WHO report does state that 52% treatment success is what's been achieved overall annually. But that doesn't tell the whole story about the treatment programs that have been well established

and are doing great work in taking care of patients. And so now I'll call your attention to a publication shortly, but in fact, some of these more mature programs can achieve treatment success of greater than 80%, and even for XDR-TB patients, greater than 60%.

I want to highlight this study from Peter Cegielski and a whole sea of colleagues called the Preserving Effect of TB Treatment Study published last year. This is a multinational perspective cohort study, over 1,000 patients, nine countries and 26 sites, and basically all of these sites receiving essentially the same treatment regimen. But what this study was designed to do was to ask the question, did the Green Light Committee mechanism essentially prevent the emergence of additional resistance to second-line drugs? And the answer from the publications is yes, but what it also gave us an opportunity is to really look at treatment in a prospective way and what can be achieved by better programs and better lab services.

So, if you look at the top there, you can see that in sites in this stud that received Green Light Committee approval and went through the effort to build

programs, very high cure, 83%, versus those sites that did not go under the same sort of development, 59.8%. The same for the labs. Labs that had more capacity to do second-line drug susceptibility testing had higher performance than those that had labs with less capacity. And then lastly you see the breakdown there of outcomes for patients based on previous treatment history.

Also, too, another great publication from Korea, which shows, in addition to programs, what the newer drugs or the repurposed drugs could do. Shows in this nice study that over the course of three different cohorts evaluated, the treatment success went up from 54% up to 84%. And improved outcomes were mostly associated with the frequent use of later-generation fluoroquinolone and linezolid in the third cohort. And linezolid in particular was used for those patients who were refractory to treatment at three to six months. And about one-fifth of those patients were XDR-TB patients.

And even where XDR-TB is concerned, things have gotten better. They are still woefully away from

where the need to be, but this gives you an idea that things are changing. And I call your attention to the top study there. Sorry for the busy slide. But this is from colleagues in Korea in collaboration with NIH, who did a nice controlled study looking at the benefit of linezolid, basically as monotherapy for chronic XDR-TB patients. And in that study, they achieved six-month sputum culture conversion at 87%, and cure rate of about 71%, with about 11% having -- developed resistance.

Equally of interest in Peru, in the lower left-hand corner, our colleagues there building a strong program over the years, showed that for XDR-TB patients who had good laboratory services and access to the drugs, they could actually do quite well with those patients.

And then lastly, the trial that was used for the registration of delamanid, about 15% of the patients in that study were XDR-TB, and as you can see, there was an improvement of sputum culture conversion at two months and mortality at the end of 24 months of treatment.

So, looking to the future in terms of where we're headed, I think it's very encouraging what we've heard this morning, that advances in the nonclinical realm to improve translational accuracy for the selection of the development of new regimens is very encouraging. It looks like advances have been made with models in the Kramnik mice model, marmosets. A lot of encouraging data coming out of that that could help early on know if we have something or not. And these models are hopefully going to provide better details on drug synergy, antagonism, cross-resistance and whatnot.

So, just kind of taking what I took -- what I presented about the period of development for the two new agents, how do we look at patient populations now moving forward? So, clearly, there is still a lot of room for pre-XDR and XDR-TB patients to do superiority trials, but what are the appropriate comparators now? We have regimens with linezolid -- or should we have regimens with linezolid, bedaquiline, delamanid and/or clofazimine? For MDR-TB patients that don't have resistance to fluoroquinolones and injectables, maybe

now the standard should be the nine-month regimen, and so on.

And, again, I really don't have to go through all the details of this slide. It's the challenges of culture-based assessments for endpoints for trials in assessing treatment effect. So, I won't, in the interest of time, I'll skip over this, because it's already been stated this morning.

So, bottom line is, we need new tools. And I think there is some very encouraging developments that have been talked about today, which I think makes the future look a bit brighter for expediency and efficiency in getting new regimens developed, the PET/CT imaging holds great promise. And then very, very exciting today, what was presented this morning and then at a webcast with Resist-TB about a month ago, on sputum LAM. And if it holds that it's a quantitative marker that can show potential pharmacodynamic trends, if this assay holds up, this could really revolutionize things for the future. And there I've cited the trials that are ongoing in evaluating this, and it's going through the

qualification process.

So, now a little bit more about trial design. It's been talked about a lot already, so I'll only be adding very little to some really great points made earlier. But just, again, keeping in mind that with conventional design it can take up to 10 years, and you have your standard Phase 1 program, your sort of proof-of-concept, which is a combination of EBA studies and the two-month combination studies. And then onto your Phase 3 program with fixed, balanced randomization. Very, very slow, steady progress of development. But maybe now is the time to investigate adaptive trial design, and some really innovative things are already going on in terms of either using Bayesian adaptive design as is being used in the endTB trial, or the multi-arm, multi-stage design MAMS that's been used by the PanACEA consortium for evaluating high-dose rifamycins for revisiting treatment.

Both use information, sputum culture conversion during the course of the trial to adapt the trial, and Bayesian perhaps has more efficiency if you have more than one regimen in the mix that you're

evaluating, that you're trying to move forward, whereas, MAMS may be more efficient if only one regimen is going to make it through. But both have more efficiency that conventional design.

And just a little bit more in thinking about adaptive trial design and the endTB trial. Again, I mentioned that the two new drugs were evaluated as a single agent added to an existing regimen, but then -- and the story really didn't stop there. And I think this is a very exciting indicator that in fact the story was just starting. Once the benefit-risk profile of these new drugs had some degree of establishment, then they could move into these trials to be evaluated I combination with other agents. And as you've seen here in the table, the various agents include bedaquiline, delamanid, clofazimine, linezolid, fluoroquinolones and pyrazinamide. And in this Phase 3 study they're examining these five new regimens compared to the WHO control regimen, which is following the guidelines for treatment that WHO has. And here at the bottom you can see the efficiencies that some simulations attached to that trial have suggested it

might have.

And so, taking all of this together, this slide was presented already this morning, so I don't need to go through the details. But something like this is really a game-changer at the point -- at the risk of being cliché, for the future of development, and regimen development in particular. And so, with LAM applied to an adaptive design approach can see the light of day, I think it could really change things for the future. So, I'm glad to reinforce the message from Debra earlier this morning.

So, lastly, I can't stress this enough and it's been stated by Dr. Higgins. In looking to the future and working on your plan and your development strategy, early engagement of authorities is essential. Seek critical feedback on design of programs and trials in the face of a very steadily, rapidly evolving field, and pay attention to what they tell you. Really listen and work together. Questions about patient population, the comparator arm, endpoints, follow-up, trial design, combination rules, you know, are there efficiencies for that, that Dr. Higgins presented earlier. All of these

conversations can help really, really improve the likelihood of success for getting things through development.

And then just a couple of final two points here. It's very, very encouraging in thinking about taking your development program forward to multiple authorities for review and potential approval that the possibility that they're harmonized and that your program could fit the needs and requirements of various authorities is really important. And it's very encouraging, in fact, that the EMG, the PMDA and the FDA have been in dialogue and have reached an agreement to align certain data requirements to stimulate development to fight any microbial resistance, which TB would fall under that category, I hope, an protect global public health.

And, finally, despite how it's categorized or what list it makes or doesn't make, TB is and should be a priority pathogen in the fight against AMR. And the pull and push mechanisms that are being entertained for AMR more broadly are the lifeblood to TB, and I hope that TB doesn't lose out in this juggernaut that is AMR

now. And it's ironic, too, when you think about it, that Jim O'Neill's report about AMR, one of the largest parts of the story that he tells in that report is drug-resistant tuberculosis. So, with that I'll end, and thank you very much for your time.

DR. SPIGELMAN: Charles, thank you. I think because of the pressure of time, let's move on. Next speaker is Andy Vernon. Andy is the chief of the clinical research branch of the Division of Elimination at the US CDC, and has been involved in clinical trials for, oh, a couple of decades at least.

DR. VERNON: Yes. Thank you very much. I'll echo the sentiments of others who have preceded me here at the podium in thanking FDA and encouraging their continued engagement in this domain. The opinions I'll express are those of myself and not of my agency, and my conflicts of interest are declared here.

I'll move quickly through the overview of TBTC. I think most of you are familiar with us. I'll talk a bit about our approaches to research, talk about specific considerations on the role of individual drugs, where there's a couple of examples from our

work, and end with some comments on our work with other networks as well.

As you know, we were initially funded in the early '90s, reorganized and are housed in the Division of TB Elimination. And we've enrolled about 16,000 patients in trials since '95. We are focused on regimens and research that is programmatically relevant, and we take that particular piece seriously, so there are elements of the areas we're talking about today that are not particularly applicable for our group. We began as a domestic consortium but have become international, as you are aware. And over the past 20 years we've conducted a number of studies in various domains including several Phase 3 studies, diagnostic studies, a number of mostly Phase 2b studies. We placed a large emphasis on pharmacokinetic work.

We have been collaborating with others in our studies for 15 years or more now, and in particular have collaborated a good deal with the ACTG.

These are studies we've engaged in over the past eight years, and our current group of studies are

shown here, an observational platform study that's ongoing, a study of dose optimization for levofloxacin in treatment of MDR, which is a collaboration, actually, with NIH. And our current Study 31, which is a collaboration with ACTG. We are hopeful to move forward with a study of a new pediatric formulation for rifapentine, and for a six-week LTBI regimen late this year or early next year.

As you know, we're organized like other consortia. We have a number of working groups and a core science group which bring forward concepts for consideration by the group, and then adoption as full protocols to move forward.

We've undergone a couple of efforts to review our programs. In 2007, a decade ago, we had a formal external review, which -- whose members encouraged us to continue in the path of doing targeted Phase 2 trials, leading the way to Phase 3 trials, and to continue our efforts to collaborate with multiple partners. A retreat in 2012 emphasized the importance of treatment shortening in drug-sensitive TB, as well as treatment shortening in treatment of LTBI. We have

continued with interest in a variety of these other domains, including drug-resistant TB, but our capacity in this latter domain is a bit limited at the present time.

As I said, our studies are programmatically relevant. They're expected to drive guidelines, to have domestic as well as international relevance, and to help establish clinical excellence in program settings. Our core science chairs have repeatedly emphasized the importance -- I had this conversation with Payam in the past month -- the importance of a robust Phase 2 engine to identify promising regimens. Our Phase 2 working group called CRUSH TB addresses this need, and we have worked with MRC statisticians and others who emphasize the importance of Phase 2 now with their proposal, as you know, Patrick's here, for novel Phase 2c approaches.

We pay very close attention to murine results. Every TBTC meeting now, at least for the past decade, has invited a report from the murine TBTC at Hopkins. And so we consider this an important part of our efforts.

As you know, considerations about the role of individual drugs were based early on the population hypothesis put forward by Professor Mitchison and colleagues at the MRC initially. And he and they proposed specific roles for the activity of anti-TB drugs, focusing on bactericidal activity, sterilizing activity, and drugs which were important in the prevention of acquired drug resistance. And we have, in the work that we and others continue to do, we have more or less continued to focus on these important elements.

However, in recent years we've begun to realize that it is considerably more complex than we had initially thought. The work of Veronique Dartois and others have emphasized that individual drugs might penetrate, as Chuck and others have mentioned today, into different compartments at different rates to different degrees over different time frames and by entry into different compartment components, all of which makes it very increasingly difficult to predict what will be the impact of individual agents or regimens.

I want to provide briefly two examples from work we've bene involved with in the effort to sort some of this out. Over the past 20 years we have worked intermittently but largely with, in particular, with rifapentine, a long-acting rifamycin, as you know, with -- shown here in the yellow, to illustrate its PK curve difference from rifampin, shown in the bluish-green.

In Study 22, we found that relapse rates varied substantially in patient subgroups, in patients with both cavitation and positive sputum culture at two months. Rates of relapse were 22% in the rifapentine arm and 21% in the rifampin arm, and with neither the rates were about 1.9% and 1.7%, a substantial difference that influenced our 2003 guidelines domestically.

TBTC investigators 17 years ago, reasoned that the group of patients who were cured with a continuation phase of once-weekly INH/rifapentine were paucibacillary, and thus similar to persons with LTBI. Murine data available at the time supported this logic. It was thought that LTBI patients were likely to have

even lower bacillary loads and that increasing the dose of rifapentine from 600 to 900 would further strengthen the combination against LTBI.

British experience in the Uganda Preventive Therapy Trial with three months of isoniazid and rifampin suggested that the three-month, once-weekly LTBI regimen was reasonable. And, as you all know, that expectation was borne out and the results were published in 2011, showing noninferiority and really suggesting superiority of the 3HP once-weekly regimen. But, of course, nothing was as simple as it seemed, and one of the problems we encountered was this flu-like and other systemic drug reactions among persons -- about 4% or 5% of persons receiving this regimen.

I was particularly concerned about this as we issued guidelines for use of 3HP and wanted to be sure that we had published, also, information about what to expect and how it might be dealt with in this regard. And I was one of those who was not very convinced that there was much potential for INH to be playing a role in this set of reactions since we knew that rifampin had been associated with a similar problem when used

intermittently previously. However, that publication on hypersensitivity included this note: Given the similarity of published reports of flu-like syndrome associated with rifampin and the reactions seen in this study, one night think rifapentine the more likely cause of these symptoms than isoniazid. However, rifapentine was better tolerated than isoniazid on rechallenge, about tenfold better. In a recent multicenter randomized clinical trial of intermittent continuation phase therapy, participants received 900 mg of rifapentine twice weekly or 1200 once weekly, both in combination with moxifloxacin, and there were no reports of possible hypersensitivity or flu-like syndrome. But it is possible that the lack of flu-like syndrome was due to the regimens or the populations being studied.

Kelly Dooley pursued a couple of pharmacokinetic studies in healthy volunteers using intermittent rifapentine regimens in both and ran into problems with participant reactions. Earlier this year at CROI, Christina Brooks, Alice Pallen and colleagues from the NIH, presented a poster on their initial

efforts to study the interaction between dolutegravir and weekly isoniazid/rifapentine. That study was stopped after four patients had been enrolled because two of the patients had marked hypersensitivity reactions. And so, I thought, well, we're seeing this again.

And then at the ACTG network meeting we were informed that there is now evidence at least for a possible for INH in this reaction -- in this study. Because there was a closed meeting I can't say more about that, but I'm sure it will be published -- presented soon. But it was a reminder to not to leap to conclusions as we try to think about the roles of individual drugs and regimens, and that the complexity of the roles of these drugs is not well appreciated.

The next part of my talk I could begin by quoting Jeremiah, "Oh, foolish people without understanding, who have eyes and see not." I think this has to do with the four-month regimens. I think that the use of two-month culture as a surrogate began with this publication from Professor Mitchison and Professor Nunn, I think -- or, this was a letter just

from Professor Mitchison, I think. "In conclusion, there is good evidence that culture conversion at about two months is a reliable measure of the sterilizing activity of drugs and can be used, for instance, in the development of new rifamycins as an indicator of efficacy long before the ultimate relapse rates are known." I note that he limited that to new rifamycins.

When we looked at culture conversion rates as we were preparing to think about treatment shortening and looking at Phase 2, we initiated this assessment -- Bill Burman led that effort -- to look at how much treatment -- how much improvement in two-month culture conversion meant something. And at the time we thought that, well, there was a 13% increase overall in two-month conversion when PZA was added to regimens. And that was enough to shorten for three months, so we thought a similar shortening might play a role in shortening the current regimen by another 30%. Sometime not long after that and as we were already well into our Phase 2 work, Bob Wallace had published his meta-regression model suggesting that it was going to -- that the culture conversion rates were going to

have to be substantially better to achieve a four-month regimen. As you know, several sets -- four different trials were undertaken, two single site trials, which showed about a 17%, 18% increase in two-month culture conversion, and our two studies that showed very slight or no increase in culture conversion at two months, when moxi was substituted into the standard regimen. And, of course, then the three large studies were undertaken subsequently, which did not achieve a four-month treatment-shortening outcome.

I was interested that Jean-Philippe Lanoix and Dick Chaisson and Eric had published a very nice piece discussing that finding, and what we had perhaps misunderstood in the efforts to look at moxi in this way in CID in 2016. And they went about this by dissecting out the different models that were used according to the different infection models and the different species that were used to predict this. And very consistently showed that if you look individually at each of these, they don't suggest that four months was going to be achievable. They go on to say that we share the views that further development and validation

of more pathologically similar yet reproducible animal models is warranted. We also agree that more predictive biomarkers for Phase 2 trials should be sought. However, the analyses of murine model data presented here and the predictions from the model of Wallis et al., suggest that the principal failure in the development of these regimens was not misplaced confidence in murine models and trials based on sputum culture-based surrogate endpoints, but rather an overly optimistic translation of the output of these studies into expectations of a two-month treatment-shortening effect.

Gerry Davies' group have published in the past couple of years a couple of meta-analysis basically making some similar points about the importance of looking at the Phase 2a and 2b data. The striking feature of the available dataset that they looked at is the variability of pooled estimates of effect for all the endpoints examined. Our review shows that the existing evidence base supporting phase 2 methodology in tuberculosis is highly incomplete, and that it's desirable that a broader range of drugs and

combinations be more consistently studied across a greater range of phase 2 endpoints.

We attempted to do some of this with our Phase 2 work on rifapentine, our Studies 29 and 29X. We discussed and decided to go first with a simpler model of relatively lower dose of rifapentine, no food, no weekend doses, and we failed completely to achieve an improvement in culture conversion. And so, we essentially pivoted without having to resubmit -- without having to completely redesign our protocol added a dose-ranging element and continued forward with the same protocol to look at higher doses with weekend dosing and food and, indeed, found much higher rates of two-month conversion, which encouraged us to move forward with a Phase 3 trial. I show here the, as Chuck pointed out earlier, the issue is exposure and not dose, so that you see that in the red box the groups who had higher exposures achieved very high culture conversion rates on both solid and liquid culture, exceeding the rates in the liquid culture in the standard regimen by 24% to 34%. So, we're now doing this Phase 3 looking at four months of a high-

dose rifapentine-based regimen.

We're also aware that working with Rada Savic and others that there are pharmacokinetic, pharmacodynamic data from our Phase 2 trials that raise that same -- the question once again: Will we be able to achieve culture conversion in the most severe patients? And suggesting that indeed we should be giving continued consideration to some modification of regimens in the face of baseline predictors of severity.

The Nix TB trial of the TB Alliance was -- of course has captured all our attention with very high two-month conversion rates in a previously almost untreatable disease, and high rates of relapse-free cure. I was led to look back at the mouse data supporting this regimen and wondering about the role in particular of linezolid, and I show here the -- one of the murine studies looking at three-month and four-month culture conversion in the regimens of bedaquiline, pretomanid with or without linezolid. And you see this very marked difference in culture conversion at three months, suggesting that linezolid

really is playing a very important role in this regimen. Now, it begs the question of the role of the other two drugs, because we don't really have the data in this study to dissect that piece out, but it is strongly suggestive of a critical role of linezolid. And it's part of my point, that we really need to seriously look at the data that we have already.

A similar point made here in the Phase 2 that was presented by Rod Dawson, the bedaquiline, pretomanid, moxi and PZA study that was presented also at CROI as a poster. And I just note this really important difference, which we've seen in the mouse studies, also. When PZA is active as in the case of PZA-sensitive patients versus when PZA is not active in the PZA-resistant patients, and so the very important role that PZA is playing in conjunction with bedaquiline.

So, a few comments about other networks. As you know, we've been partnering with ACTG on this very large trial now. Dick Chaisson shared a couple of slides on their activities. A very similar set of priorities to those that TBTC have and that make us

good partners from a philosophical point of view. They have a very impressive and very large set of trials already completed or active in a very short period of time.

This is a quote from Dick's slide, which he presented to his external review group earlier this year. "Partnerships are essential for conducting TB clinical trials." I can remember 15 years ago, when it was very difficult for us to find partners, because everybody felt they would be able to do it when they needed it without looking for additional partners. We have a lot of work going on now. The clinical trials landscape is very different from what it was 15 years ago, and a number of fascinating efforts underway.

In conclusion, I just emphasize that we need more and more consistent work in preclinical and in Phase 1 and 2 evaluations of new agents and regimens. And we need to pay attention to those results very carefully. We need more strategically linked Phase 2b, Phase 2c, Phase 3 efforts begun with a successful end in mind and substantially simplifying the administrative environment of major development

efforts. A need for continued and increased collaborations among the major trial funders and networks. A useful step toward this goal might be the consideration for creation of an annual or biannual research conference focused in this area. And then continued efforts by regulatory authorities, such as FDA and international bodies to educate their interested communities and improve the development path. Workshops such as this are a promising step. Thank you.

DR. NAMBIAR: Thank you, Dr. Vernon. Our next speaker is Jeffrey Starke. Dr. Starke is a professor of pediatrics at Baylor College of Medicine, and has been the director of the Children's TB Clinic for over three decades. Dr. Starke will be talking to us about trial design considerations in the pediatric populations. Thank you.

DR. STARKE: Thank you very much. It's a pleasure to be here, and I really want to thank the FDA and Sunita and the organizers and everybody for having me here to talk about this subject. I am a member of the Data Safety Monitoring Board for the PK studies of

delamanid for my disclosure. And I want to thank Tony Garcia-Prats in South Africa, and some folks in the TB Alliance for some help in preparing this talk.

I have a feeling this talk is going to be really different from other talks that you've heard so far today. Ironically, just before Andy's talk I got a phone call about a child that I'm helping out with multidrug-resistant TB meningitis in Texas. And what I came to realize is that we are completely making up how we are treating, and to be perfectly blunt, that child is benefiting from basically nothing that has been talked about so far here today. And unfortunately, that's part of our current state-of-the-art. Some of it unavoidable, some of it avoidable.

So, how does childhood TB differ from adult TB? It's a fundamentally different disease. It develops much more rapidly after infection, particularly in children less than two years of age. It is a paucibacillary form, probably not as paucibacillary as TB infection, but still paucibacillary in the vast majority of children. And only 30% of cases can be confirmed microbiologically.

There is a diagnostic tetrad that really involves symptoms, radiology or physical examination, tests of infection and epidemiology. And there are standardized research definitions which are hopefully used now in clinical trials for those 70% of kids that can't be confirmed microbiologically, but clearly that's a huge limiting factor in doing drug and efficacy studies.

I haven't heard really anybody talk about extrapulmonary disease, and there's a greatly increased propensity for extrathoracic disease in children, up to 30% of children get extrapulmonary disease, especially meningeal and miliary TB. Relapse and failure are obviously very difficult to define because we usually can't define them microbiologically.

Children tolerate drugs better than adults do in general, so that's a very good thing. And fewer children have other significant medical problems, hepatic, renal and cardiac, and so forth, that can affect both pharmacokinetics and the ability to tolerate the drugs.

The two target groups for pediatrics really are kids less than two and adolescents, and you can see

this is based on the pre-chemotherapy era of up to 50% of children less than a year of age who get TB infection will go on to develop TB disease. And up to 25% of them will develop serious forms of disease, particularly meningitis and miliary disease. One to two years of age, 25% will develop disease, and then it goes down, the so-called favored age of children in elementary school. We don't know why that is, but it's been observed in virtually every human population. And then we start to see more cases in adolescent population as well. So, the adolescents and the very young kids are the two biggest groups.

The global burden of TB prior to 2012, there were no global estimates of tuberculosis in children given by WHO, because there was no methodology to develop those estimates. Now there have been several modeling studies, and it's estimated there are a million cases of children, about 10% of the total burden, but only a little over a third of those cases are actually notified. We heard earlier, I think, 23% of cases not reported in adults; well, over 60% of the cases in children probably are never notified.

The estimated mortality of 210,000, that would be 21%. That's the actual measured mortality of children from tuberculosis in the pre-chemotherapy era. I'm going to let that one sink in a little bit. And, of course, that's because we're not finding these kids, diagnosing them and properly treating them.

The global burden of MDR-TB in children, again, estimated 25,000 to 32,000 cases a year, but a very small minority are identified and certainly are not getting properly treated. And, of course, HIV association with TB, even with ART, these kids still tend to have worse outcomes.

LTBI, just to mention briefly, tens of millions of children obviously with tuberculosis infection, at least 2 million probably infected with MDR-TB. Those are our cases of the future. And the estimated child household contacts less than 5 eligible for treatment globally is in the millions, yet this is not being done at all in most of the high burden countries.

Current TB regimens for children are pretty much the same as they are in adults, and I'll be coming

back to that point several times, so I'm not going to spend a lot of time on this particular slide.

What are some of the current knowledge gaps in the treatment of childhood TB right now? Well, PK and adverse effect profiles for existing drugs, I have a kid right now with a very difficult-to-treat infection and I was considering putting him on clofazimine or bedaquiline, and it involves the CNS. I could find virtually nothing on clofazimine levels in the CSF, and he's 5 years old, I have no idea what dose of bedaquiline I would use in him. Even though that drug has been licensed for years, there is zero pharmacokinetic data for 5-year-olds on that particular drug. Very frustrating.

The optimal duration in follow-up of TB regimens for drug-susceptible and drug-resistant TB, we have limited data. Adequate drug combinations in relevant doses for many of the forms of extrapulmonary TB that have been for the most part unstudied. Optimal duration in combination of drugs for TB treatment in children living with HIV, we're starting to get some data, but we're behind in optimal drug combinations and

durations for MDR-TB in children, especially those with so-called minimal disease. We know that regimens that work in adults tend to work in children, but that doesn't help us define actually if we need less drug or fewer drugs, or for a shorter period of time in these children with paucibacillary disease.

So, there are some real barriers to the inclusion of children in TB studies. Obviously, this difficulty of microbiologic confirmation of disease failure and relapse is a huge barrier, huge problem. There is difficulty in performing PK sampling in children, especially infants and toddlers, who are big targets. And especially very important, the developmental pharmacokinetics and pharmacodynamics of young children, particularly in the very youngest age groups, is very, very important.

There is really complacency about the effectiveness of existing regimens. Well, they work, so what do we really need to do?

Trial design issues, what are the proper endpoints? What are the proper sample sizes for children, especially when we start to break them down

by different age groups?

Capacity. We lack trial sites around the United States, certainly, and around the world for actually conducting good studies in children. There has been very little capacity building until recently. Complicated research oversight and some regulatory concerns, which I'll come back to.

And then we still hear this, that we can't do studies in children because it will take funding away from adults. I mean, we actually hear this. Reminding you that children have more than 10% of the disease but get less than 2% of the research funding by current measurements.

Regulatory issues are huge. So, the European Union has a regulation that requires an early pediatric investigation plan no later than the completion of PK studies. The United States, orphan designation, we've already heard this. So, let me tell you in practical terms what this means. When I'm treating a child, even with drug-susceptible TB, I'm taking pills that are meant for adults, we crush them, we maybe put them in a solution, we give them with food, we combine them

together, and I have no idea about the pharmacokinetics under those conditions, and I have no idea about the safety profiles, especially when we get beyond the first line drugs. I would argue that anybody in this room treating an adult under those conditions would almost consider it unethical, yet it's standard operating procedure in pediatrics because of lack of information. And that's one of our biggest problems.

The next two slides I'm just throwing out to show you. If I were to show you this slide in 2010, it would in essence be empty, but there are -- and this is the good news -- many, many trials going on now involving children, looking at regimens for both prevention of disease and also treatment of disease. So, we are making progress in finally getting information. Most of these actually are PK studies and pharmacodynamic studies. There are not as much efficacy studies because of the difficulty of doing those studies in children.

There have been several really nice papers that have been published including children in tuberculosis trials, at what stage is it appropriate

and when should things be done. And this is just an algorithm from one of them about when is it reasonable to introduce children, asking several questions. Is it reasonable to assume that children, when compared with adults, have a similar disease progression in response to intervention? Yes/no. If it's yes, then is it reasonable to assume a similar exposure response with the drugs compared to adults? And so forth. I'm not going to go through the whole algorithm, but the point is, people have thought this out and in general, for tuberculosis, the answer to most of these questions is yes. Of course, there are some differences in disease expression and other things, but in general, especially when it comes to dealing with drugs and drug regimens, the answer to most of these is yes, which leads to a justification of earlier involvement of children in trials.

So, what are some of the lessons we've learned over the years? Well, efficacy, again, difficult to study regimens as opposed to individual drugs in children because of problems with sample size, cost, capacity, lack of microbiologic markers. We realize

that, but the truth is, almost everybody I know in childhood tuberculosis is willing to accept the premise that if it works in adults it will work in children. And so, efficacy studies are not -- I don't want to say they're not important, but they're probably not necessary in order for us to accept that certain drugs and certain regimens may be extremely useful and helpful to use in children. We almost take that off the table.

The aim is to match the PK and area under the curve and other pharmacokinetic and -dynamic measurements in children with those that are known in adults to be both safe and effective, and that's really the major goal of many of the pediatric studies.

We might need efficacy studies for children for some forms of extrapulmonary tuberculosis, and also when it comes to drugs and regimens for prevention, treatment of infection or primary prevention, well, then some pediatric efficacy very well may be important as well. But remember that some children with milder forms of disease may actually require fewer drugs for a shorter period of time, so we agree that's what done

for adults will be efficacious. It's possible we could do less for children and that also would be efficacious, but difficult to figure that out and certainly not when new regimens are introduced or starting to be used.

The general consensus for us, it's okay to enroll children in drug research after the following things. There is a full range of nonclinical studies in adult animals. Safety, pharmacology, genotoxicity studies and appropriate juvenile animal studies do not raise any alarms, any signals or cause for concern. The animal and human studies have substantiated anti-tuberculosis activity, no surprise there. The PK and PD data from adults allow for selection of appropriate PK targets for children where a safe dose has been established, which is around Phase 2a or 2b. I'm talking about drug approval phases now of the drug. And it would be helpful, of course, if there was some data on drug interactions with ARV drugs, since TB in children living with HIV is such a huge problem in many parts of the world.

So, when should we actually begin pediatric

studies? Well, traditionally nothing was done until after a drug was licensed, and I'm sorry to say, but once a drug is licensed, the motivation is gone. And we know this because drug after drug after drug after drug after drug, we have no pediatric data for -- or limited pediatric data. So, we already have proof-of-concept that that simply doesn't work, and as Einstein said about insanity, continuing to do the same thing and expecting a different result pretty much means you're crazy.

So, the consensus is that a pediatric study should begin with safety and basic PK are established in adults, which is usually somewhere between Phase 2a and Phase 2b studies. We also feel strongly that adolescents, and most people are using now 10 years of age and older based on their PK and pharmacodynamics, should be included in late phase adult studies and later on. And you heard a little bit about this earlier today about adolescents being included in adult studies, and I think the pediatric community would be completely behind that concept. And also, begin development of pediatric dosage forms much earlier.

Not after licensing, but during Phase 2a, so that they're actually available at Phase 2 at or around Phase 2b so, in fact, the pediatric studies can begin immediately. We think this is an extraordinarily important concept for new drug development.

Several papers have been published about accelerating clinical drug development. This is one for 2015, and I know it's hard to read things that are like this. But this just talks about both developmental strategy and then some of the challenges that were historical, that are current and that are proposed. So, if we look at developmental strategy, historically there was no specific pediatric development. Kids were given adult doses or adjusted according to weight, but we know that that's an incredibly simplistic way to do things.

Currently, pediatric development is generally initiated once the drug or regimen is approved for adults, starting with adolescents and then gradually moving to children so-called dosage de-escalation. But now what's really being proposed is single-dose PK studies begin as soon as successful Phase 2 adult

studies are complete, and then later maybe multi-dose comparisons as well. And you're going to see a little bit more of this in a couple of slides coming up as well.

For pharmacokinetics and study design, the conservative approach was this step-wise age de-escalation. You would do adolescents and then you would do junior high type kids and then elementary kids, and then finally get down to younger kids. And now I would say within the pediatric TB community, age de-escalation is pretty much accepted as unnecessary for the vast majority of drugs unless there is some specific safety concern, especially for a particular age child. And what I really want to emphasize is that kids less than a year of age and particularly less than three months of age have completely different PK and pharmacodynamics than really any other population, yet we don't even have data for isoniazid and rifampin in that particular age group. And so, we really need to develop that much easier, and these are just some of the suggested age ranges in a consensus panel of pediatric TB experts for how it might be useful to

break down kids in terms of study, but not in a de-escalation but in sort of an all-in approach, in most cases.

Appropriate sample size for PK, there are some challenges here. What is the appropriate sample size for PK within each age group? How many kids do you really need and where do you need to get them from? You need them from different trial sites with different genetics. And how much variation is there, really, that you need to account for in doing these basic studies? Probably single-dose sampling in all age groups and then move to multi-dose sampling as well. Rationalizing sample points, exactly when should blood be drawn and trying to reduce the burden, especially in the smallest children. Drug concentrations of CSF, which in the CSF has been really neglected but is really a very important point for pediatrics. So, those 210,000 kids that are dying, a lot of them have TB meningitis. Use of dosing simulations, which many people in this room know way more than I do. And then, of course, how to do trial design for children who also have HIV infection.

For dosage formulations, they need to be age-specific, they need to be palatable with acceptable taste and acceptable all around, and that needs to be developed while the drugs are going through the approval process.

Trial capacity, we need much more robust network. There is very, very, very little funding to -- relatively speaking -- for trial networks, like Andy talked about, the trial networks that are based mostly for adults.

Incentive for child studies and formulations. Again, there are people in this room that know much more about this than I do, but extended market exclusivity, priority review vouchers and so forth really haven't worked for pediatrics. There is the concept of advance market commitment that may be something interesting to explore. Remember the numbers that I showed you, internationally the potential markets for childhood TB are huge, especially treating tuberculosis infection.

I think it's important to include pediatric experts on data safety monitoring boards and other

things, and requiring pediatric studies for sources of pediatric funding.

I give this example, and I may rankle some people in the room by doing this, but I'll do it anyway. Many decades ago it was decided that particularly in low resource, high burden countries, the thing we were promoting to diagnose TB was sputum smear, microscopy. And the good news, you know, you find a lot of cases and you find the most contagious cases. But by making that decision, it ensured the exclusion of children from international tuberculosis control. I'm going to let that one sink in, too, because sputum is useless in children, next to useless. So, there was no hope of diagnosing TB in children using that as the particular standard. And that's why it's so important to consider pediatric-related things and have pediatric experts at the table when decisions are being made about policy, about science, about study design. How can we design studies to learn the most that we can then apply to children as well?

This is actually from the TB Alliance in showing the traditional at the top, how we go through

the whole adult development process and then we go into the pediatric development process, hopefully, and now trying to combine these things and accelerate them. An accelerated pediatric drug developmental pathway could allow life-saving treatments to reach children sooner than they do today.

And this is just an extension of this, again, from the article by Murray, and I won't go through the entire thing. But it says many of the elements that I've said about when during individual drug development Phase 1, 2a, 2b and 3, we should be introducing various aspects of pediatric drug development, and it's a nice summary slide of all these principles.

So, the overview of the approach. Create regulatory and economic incentives for industry and academia to develop and study pediatric formulations of old and new drugs; create capacity-building for pediatric trials; start development of child-friendly pediatric formulations earlier; start pediatric PK studies concomitantly with Phase 2b studies in adults; establish function within childhood TB community. You know, the HIV people have just passed us by incredibly,

and they have the pediatric anti-retroviral drug optimization group that's been incredibly successful in getting ART pediatric formulations available and distributed throughout the world. So, we need to develop some consensus priorities on these key drugs and formulations for children in TB, identify the research gaps and specific ways of going about trying to approach them.

I'm going to end with a quote, as many people often do. This is from Bill Burman's paper a while ago. First looking at this, "An overzealous attempt to protect some children from the possible harms of research perversely causes harm by either denying access to treatment or through exposing children to the risks of inappropriate dosages of new medications."

This is my life. This is what I do every day. And in general, the people that want to not include children in studies are never the pediatricians, because we know that that means that we're then going to have to use unstudied, unproven drugs and formulations in children once those drugs become available. And I certainly believe in the final quote.

"Children have the same right to benefit from research as do adults." Thank you very much.

DR. NAMBIAR: Thank you very much, Dr. Starke. So, I think we will take a maybe 10-, 12-minute break, and if we can be back by 3:40, that would be great so we can get started exactly at 3:45.

[Break]

DR. SPIGELMAN: [Next is Dr. Christian Lienhardt], who is the team leader for TB Elimination within the global TB program. And Christian is going to summarize, to a certain extent, on the lessons learned from completed TB trials, and also those implications. Christian, thank you.

DR. LIENHARDT: Thank you very much. You're right, Mel, summarize to a certain extent. So, good afternoon, everybody. Thank you very much to FDA for inviting me to come to this important workshop. I really appreciate even more in the sense that when I started the work at WHO to look at how to introduce -- how to make sure that new drugs are being evaluated by the World Health Organization and being proposed for use in countries, which is really related to the World

Health Organization.

I started circulating to the most important, stringent regulatory authorities starting with FDA, and I must admit that the way I've been received here was really extremely welcoming and very warm. And we started an extremely good collaboration, which has led to the fact that when bedaquiline has been approved by the FDA, then at WHO we're ready to immediately embark on the evaluation of the product and the recommendation we could do for the countries for the use of the drug. So, that's, I think, is worth mentioning.

So, in this talk where I've been asked to speak about the lessons learned from completed trials and implications for future trials, I will address the various approaches to trial designs for tuberculosis; mention a little bit about endpoints, some considerations; summarizing all what has been said today; touch upon the new trial designs; and then mention briefly about the work we've been doing at the World Health Organization on target regimen profiles for TB treatment. And relate the lessons learned and suggestions for future studies to how we at WHO

consider that as extremely important for the way we can make recommendation for the use of drugs and regimens for TB patients.

So, it's been a very intense day, so I'm going to try and summarize the best I can. I tried to -- inevitably there will be some (inaudible) things which have been done, but I try to put all of that in prospect. And starting to put in prospects is really looking at the history and, as you can see here, taken from a publication a couple of years ago, is that the notion of development of treatment of tuberculosis has always been in constant interaction both with the amount of drugs, amount of regimens from the very start, in 1946, which was the first randomized clinical trial ever looking at streptomycin for the treatment of tuberculosis and realizing it was leading to emergence of resistance. And since then the history of TB treatment has always been combining, trying new drugs and finding the right regimens. And I think that's important because this is exactly where we are placing ourselves.

So, what are the approaches to trial design?

We have seen that today there are several of those, the classical path in drug susceptible TB, the accelerated approval in MDR-TB, the combination development path, then the unified path in drug susceptible in MDR-TB and on uncontrolled trials. That's again trying to summarize what has been discussed. I'm going to look at those quickly and try to draw the main lessons learned.

In terms of classical path, the way we've been learning in the TB, drug susceptibility has been the three trials which have been carried out to substitute EHRZ control regimen, ethambutol or isoniazid with either moxifloxacin or gatifloxacin. And these were the REMox, OFLOTUB and RIFAQUIN trials.

They were a noninferiority design and a margin of noninferiority was determined by limit of what could be expected to be achieved using reduced duration of the control regimen. Delta was set at 6%, and I quote here Stephen Gillespie in his paper on the result of REMox that was expected to reflect consultation with clinicians in high burden countries and reanalysis of previous trials showing the effect of shortening

treatment to four months without substituting a new drug. And as we heard earlier, it's all about what we can set in terms of control regimen and expectations from the new regimens.

You know about the publication of the three trials and it has been shown already about the results, that none of them were able to demonstrate noninferiority of the regimens with substitution of drug for moxifloxacin or gatifloxacin.

Interestingly, and that brings already to one of the first questions. If you look here at the results, in most of the arms we had a pretty good collection of sputum culture at two months with very high rates in all of the various arms, even though some of them were doing quite badly in terms of relapse, as you can see. And I put on the top here the Study A, which interestingly showed that with exactly the same regimen for infancy phase either for eight months or six months' duration, there were similar conditions at two months with different relapse rates at the end of treatment. So, bringing already questions about the use of the two-month culture conversion as a marker of

treatment outcome, treatment activity.

It's important to try and stop on these two trials and try to reflect on what has been shown, and we have embarked together with CPTR on the meta-analysis of the three trials with a total sample size of more than 3,000 patients. And that has been the place of this so-called TB-ReFLECT, an analysis of fluoroquinolone clinical trials to try and see what we can learn from the trials and what's the failures of treatment they can tell us and how the different arms can be informing us about the way patients were behaving in terms of bactericidal and sterilization activity.

What can be found from this TB-ReFLECT and these are the result which I showed the results shown at the Union Conference in Liverpool last year and now being presented -- is still being worked on. We showed that the failures where in the standard of care and the test arms were mostly associated with insufficient drug levels and mainly rifampicin. So, that tells us already about the importance of adherence to treatment.

The longer duration of treatment as expected

was beneficial and the culture-based predictors were more efficient to predict outcome at four months than two months. But interestingly, what we were looking at was the baseline covariates, and we identified a group of so-called hart-to-treat patients, which showed a higher risk of unfavorable outcome with the following covariates being HIV infected, older, underweight, with a high initial smear in the sputum and the presence of cavity in chest x-ray.

So, that tells us that there might be some difference here within the various groups submitted to the trials. Bias different in the groups and the concept that maybe one duration or one type of trial doesn't fit all. And the one duration for all will need reexamination. So, it's interesting and that work is still ongoing on that to try and see whether this so-called hard-to-treat patients can be identified and might need specific treatment, either treatment duration or dosage.

So, that was the classical path to substitution of one element of the regimen. The other one is accelerated conditional approval on MDR-TB. We

spoke about that also today. That has been the path followed for approval of bedaquiline, but the FDA and similarly by delamanid by EMA a couple of years ago, and no need to go back on those. But what is interesting is that while the two studies provide important information about the safety and efficacy of the two new drugs, they do not provide any information about the best way these drugs could be used within a regimen. And therefore, a series of trials, and just here is an example of all the various trials are trying, among others, to try and see what is the best combination these drugs can be used. So, this is again part of the path being used but with the limitation that we are speaking here about drugs and not about regimens.

So, because of that, there has been a couple of years ago, already the feeling that the development pathway should be looking at combination, and that has been an approach taken by the TB Alliance, and trying to go from the stage of the Phase 2 trials to look around the single drugs, being informed either by the mouse model, trying to go to EBA studies with the

combo, and that is what is being shown here.

So, combo in the Phase 2, 14-day EBA study, and then being led to the 8-week serial sputum colony count, and then if the combo is shown to be statistically better than the control, HRZE being brought into the Phase 3 trials. So, that's the combination development, which has been further refined, and you've seen this slide another time today. That has been refined to the next stage, which is the unified path in drug susceptible and drug resistant regimen development, and that's the path taken by TB Alliance, so that's today.

This unified path has been used for the B-PA-Z-M combination -- bedaquiline, pretomanid, pyrazinamide and moxifloxacin and CO5, who are patients with newly diagnosed drug-susceptible or MDR-TB, sensitive to moxifloxacin where randomized if they were drug susceptible to comparison of bedaquiline, pretomanid and pyrazinamide versus EHRZ. And those who were MDR-TB were receiving the same combination plus moxifloxacin.

The Phase 2 results, which we showed earlier,

showed that there was evidence of substantial additional benefit from the addition of moxifloxacin, and that was an indirect comparison. And the next step would be either a Phase 3 using a four-drug MDR regimen among this group.

So, this is the unified path of being followed, and all of those paths are bringing the main issue about efficacy endpoints. And here I use slides made by our colleague, Gerry Davies, from PreDICT-TB, which shows very well what all the different aspects in terms of what can be detected for considering the bacillary load and over time, and what we are looking at in terms of efficacy endpoints. And the fact that we are always completely condemned by this limit of detection and trying to see what we can obtain in the various development of the bacteria in response to treatment. And looking at either what happens during the treatment in terms of culture conversion at two months or time to culture conversion, and then presence of failure during treatment.

And then after treatments, all those among who might have been shown to have been (inaudible)

developing on recurrence either at early stage or at the late stage with relapse.

And these efficacy endpoints are all the ones which are being collected, and if we look at the Phase 2 studies and here this is a systematical review done by Burnett (ph) and Gerry recently published in CID. And looking at 133 trials with Phase 2a and B outcomes, it has been shown that EBA days 0 to 2 and eight weeks' culture conversion were the most commonly reported endpoints. And again, as mentioned by Andrew earlier, there was striking heterogeneity in the way that the endpoints were being reported along these various studies.

Going back to the fact that we are looking at the two months' culture conversion, the effective replacing ethambutol with moxi or gatifloxacin with first-line therapy was being addressed through various trials, and here I show the slides from the early OLOTUB trial, the Phase 2. Because what interestingly was done here is that the rate of decline of viable colony counts was assessed in repeated cultures weekly over the entire phase of treatment. So, what was being

modeled here was about the rate of decline, where the traditional way is shown here in the study by Conde was to just repeat over time the culture conversion and looking at the evaluation between the test and the control arms in terms of proportions of patients converting or not.

So, we discussed at length about the viability, the validity of the months to culture conversion as the trial level surrogate markers, so it's no need to go on further on that. But what it tells us is the debate is still some hope and where we should consider using longitudinal endpoints as well, because they're for the advantage of being independent of the sampling at time points. There is an unrestricted scale of measurement that are open to greater statistical power and well adapted to cumulative meta-analysis.

This has been used in the PanACEA trial, where the time to culture conversion were being assessed through the various regimens and being shown here for the regimen with 35 mg rifampicin as being much higher significantly compared to other arms. So, there is an

advantage in addition to the time to culture conversion at a very specific time point, like two months, of also considering the dynamic effect of time to event endpoints.

So, I mentioned about PanACEA, so PanACEA was an attempt to integrate to use in tuberculosis, the multi-arm Phase 2-3 trials, which were originally developed in oncology with planned interim analysis. The final analysis is done on the definite endpoint, and the usual Phase 3 bacteriological endpoint of failure or relapse can be used. An intermediate endpoint used to compare each experimental arm with a common control at interim analysis, and the arms are dropped if there was insufficient evidence of benefit using the prespecified critical values. So, the MAMS approach was being used in TB because gave further ability to screen multiple regimens and drop those which are less promising, failing to achieve the specified targets.

So, the feasibility of MAMS has been shown in TB with the PanACEA trial. The arms without evidence of sufficient efficacy were dropped early, thereby

reducing the sample size. There was a slight risk of dropping an elective regimen; however, the trials were shown to be logistically challenging, the culture results for reasons described by Payam earlier. The culture result was low and not being good predictors, so that makes the case for better and real time biomarkers that could be used earlier in treatment. And the question is, would limited data on relapse assist our decision-making process?

So, all that shows that we need real time assessment of efficacy in TB regimen development, and the major issue, as mentioned also earlier today, is the lack of direct readout of response looking at the amount of TB organism being killed. That severely limits the measure of treatment effect, and the lack of predictive quantitative relationship between the Phase 2 readouts, organisms killed, and the Phase 3 readout, the cure. It is unclear how to translate culture conversion outcomes. That has been mentioned as one of the main problem in terms of translating Phase 2 to Phase 3 results. So, we need new biomarkers for conducting measurement of bacterial load in sputum and

the example has been given amply with the LAM assay today.

Another way to accelerate development is the Phase 2c step design in the sense that the culture conversion is limited value and the regimen is likely to be affecting Phase 3. So, a more informal Phase 2 study can be done which includes information on long-term outcomes, and that is what is proposed with a Phase 2c step trial proposed by Patrick Phillips and collaborators.

Additionally, to study the interim duration in Phase 2 and to generate richer data prior to more informed Phase 3 go and no-go decision-making. And the sample size will be similar to Phase 2b study. The novel regimens would be given for the intended duration of treatment -- three months or four months, and the patients being followed for 12 months' post randomization. And then the endpoint being measured would be a composite failure relapse endpoint.

The last aspect of the unified path is the uncontrolled confirmatory trial. So, we had some development recently with the Ebola epidemics and this

paper from Lancet mentioned that the trials of new treatment for Ebola were being justified on the fact that when conventional care means such a high probability of death, 70%, it is problematic to insist on randomizing patients to it when the interventional arm holds out at least the possibility of benefit. Ethical arguments are not the same for all levels of risk. And it was further mentioned that equipoise is a useful principle but it can break down when conventional care offers little benefit and mortality is extremely high.

This is somehow the logic being followed here with the Nix-TB trial about the fact that there was a complete justification in the absence of inefficient treatment to undertake the study with a completely new regimen.

The particular consideration to address for this uncontrolled confirmatory trials. The first is about the arguments being used that are applying for XDR, which is being used, but do they apply similarly, and that's what Mel mentioned about going forward or backward, and here I used the word de-escalation

somehow in quotes is can we apply that from XDR then to the pre-XDR then to MDR-TB? And that is an important question to address up to where can we go? Do we consider that this is a situation of a complete new regimen and pan-TB type of regimen that we can somehow de-escalate on the various groups? Or is that a point where we should start to use an historical control and start to have properly randomized control trial?

So, speaking about that, we at WHO developed target profiles for TB treatment and the idea was to start with the goal in mind. That means that we wanted to try and frame the fact that with these targets and specifications that the developers should meet for the performance of new TB treatment, and it should align with the needs of the end users. So, with this in mind and thinking about the target audience, the pharmaceutical industry, research institutions, product development partners, donors, NGOs, CSO, we thought we would try and address this potential target profiles for treatment regimens. So, here going away from the simple aspect of the drugs but to the regimen itself.

And we placed ourselves in the view that there

would be a scale-up of expert more widely than what was shown this morning, and that's the outcome of testing patients who are suspecting to have tuberculosis will be through Xpert being labeled as either being Xpert-positive or not, so rifampicin-susceptible or rifampicin-resistant. And we place ourselves in this paradigm and developed target regimen profiles for rifampicin-susceptible or rifampicin-resistant. And then we took one further step of the pan-TB regimen that could be given to patients in the situation where there is no diagnostics available.

So, all the three target regimen profiles are being described in this book and they are described in such a way that we show for each of them the clinical indications of the treatment, whether rifampicin-resistant or forms of TB and pan-TB regimen. We list the critical endpoints to be obtained and the way they should be measured. For instance, nonrelapsing cure at two, four, six or nine months after starting treatment. We describe the target populations, like children, adults, persons living with HIV. And we give identifications about the treatment characteristics,

like expected duration, frequency route of administration and the formulation. And for each of those we give other priority or desirable attributes, and the way we place that is to say that some of the attributes should be considered absolutely indispensable and with a go/no-go decision to what's the development of a regimen, whereas, some other attributes would be considered as desirable. That means being in the place for a decision on the type of -- how to say -- sorry, I don't find the words in English now -- when you try and see what is the respective advantage. So, that is what I can say, sorry about that.

So, what about lessons learned? So, if I try to group the various aspects, which I went through very rapidly in this conversation and taking into consideration what has been discussed today, in terms of the lessons learned from the various completed trials, there are a series of implications for the treatment to be used, to be tested, as well as for the design.

For the treatment implication, first of all

and what quite strikingly, the most impactful intervention is to ensuring adequate dosing and adherence to treatment. This is the baseline situation that we ought all of us to ensure.

Looking at the reflect TB output, the importance of rifamycins as the backbone of shortened therapy was reemphasized and underscoring the role of the high dose. And we heard from Payam and Andrew about the various studies TBTC is doing on that.

The patients with high bacterial burdens and experiencing slow decline in bacterial burdens over the initial four to eight weeks of treatment constitute a subset most likely to relapse. And there is evidence that different patient groups may require different treatment duration. The so-called hard-to-treat patients should be or may be considered as a specific population for longer treatment duration and/or higher dose.

And these are implications for Phase 2-3 trials, because it raised a point of knowing whether we need to consider initial patient stratification when we decide to go on to treatment, and that is important to

consider at the time and at the level of the trial.

Spot on to ensure appropriate representation of this population to allow robust subgroup analysis. And then it doesn't prevent us to go for a short for future regimens, pan-TB regimen and the approach between something which is much more individualized, doesn't prevent for looking for pan-TB regimen that can be used in certain conditions.

In terms of design for future regimens, we have seen that an increasing number of potential regimens are being assessed and they need to be able to be reviewed at the same time, so there is an increasing wealth of various regimens to be tested and it will more likely increase in the future.

Alternative adaptive designs enable more rapid differentiation between multiple candidate regimens, but we are aware that there are still logistical constraints that have to be addressed.

And we are aware about the culture conversion with limited value for predicting long-term outcome and the high need of quantitative assays of bacterial burden over time. They need new treatment response

biomarkers.

The uncontrolled studies may have a place, like shown with Nix-TB early in development, and then the question is being posed about what I call the de-escalation or expansion from the specific groups, like the XDR-TB to a group, what Mel mentioned, about going forward or back forward. And the choice of the noninferiority margin needs careful consideration, as does the need of bio-creep.

In terms of PK/PD, we had a series of important discussions today, but the PK/PD analyses are critical. Using drug exposure to understand intermediate endpoints in addition to dose selection is key, and it is important to examine the relation between dose and treatment duration for the efficacy endpoints. So, PK/PD data should be incorporated to build integrative PK/PD models that could reveal further opportunities for regimen optimization, including drug-drug interaction and safety, and improve trial designs.

Lastly, an important point is about data, trial data collection. There is a need of consistency

in collecting clinical data across the trials, and this is needed to expedite integrated learning and the capacity to be comparing between trials and to merge data for further meta-analysis for systematic review.

So, the definition of Phase 3 clinical trial endpoints should be set at minimum with recurrence and relapse. There is a need -- sorry, I missed that. There is a need for global platform independent data standards that enable data exchange and information system, and that's the example given earlier about the capacity to use, for instance, the C-DISC system.

So, we discussed at length about what should be efficacy, but we shouldn't lose mind that safety data are key as well.

So, in order to finalize this type of quick summary of lessons learned, I want to place myself now with the WHO hat and the fact that what we are doing is to issue guidelines on new TB treatments. And we've been using, as can be seen here, the -- we've been evaluating the new drugs and new regimens, bedaquiline and delamanid, and the new shortened regimen treatment for MDR-TB. So, we are using all this type of analysis

and data in order to be able to do guidelines for the countries.

And our guidelines are based on best available evidence. We use the GRADE approach for evidence assessments across a series of questions and outcomes. And there are set criteria for moving from evidence to recommendations.

Our main aspect is what is the best available evidence that can be brought about that ultimately would be benefiting patients? So, we need for clearly and rationally justified approach about the choice of drug combination, design, conduct, endpoints and analyses. We need to have data that we can evaluate, and for that, following the development of the target regimen profile, we intend to develop information to regimen developers that will describe the data that would like to be seen so that we can review evidence for policymaking.

What is important again is to look at -- to be sure that from the time that development of new regimen is being made the appropriate data are being collected, and that when we receive all the data for application,

then we are satisfied that we have the best available evidence. For that we need to have a very strong dialogue between developers, but also between regulators and policymakers. And, of course, down the line we need to make sure that once regimens are being proposed there is full access to the novel products that are arising from research.

So, with this in mind I would like to thank the Task Force on New TB Drug Policy Development that has been putting together the target regimen profile mentioned, and all the colleagues mentioned here who have been helping me in putting together this presentation, and helping me looking at all the various lessons learned from the various trials. So, with that I thank you very much for your attention.

DR. SPIGELMAN: Any questions specifically for Christian before we go into the general question session? No, okay, great. So, we have, I guess, close to a half hour or so for panel discussion or for any questions from anybody in the room, and I guess we probably could open it up, because clearly a lot of the topics discussed this morning overlap, to a certain

extent, with the topics this afternoon, too. So, let me first see if there are any questions from either the panel or from the floor, or topics that you want to clarify.

DR. COX: So, Mel, let me just try and expand a little bit on what you covered in our talk and invite you to comment on it, too. So, and this overlaps, too, with Cathy's talk. It sounds like really the goal of what it is that you're trying to do with regimen development is trying to move forward by leaps and bounds rather than by smaller steps, if I'm understanding things correctly. And you're trying to do it in the most informed way by trying to use the preclinical information as much as possible, whether it be hollow fiber, animal models, you know, recognizing that it doesn't give you the absolute answer, but it allows you to make rational choices that you can then move forward and test in clinical trials. With the hope being that it's not just sort of changing one of the components of a multidrug regimen, but it's actually to try and use maybe three drugs that haven't been combined before, in something totally new.

And, if you don't mind, too, I remember a comment that you made once that I felt was very interesting and I think it underlies what it is that the goal is here, which is if in fact you can -- you know, we think of the terms drug-resistant TB, drug-susceptible TB, and in essence if you can come in with a wholly new regimen, those terms may in essence become somewhat arcane, because new treatment options are available and new mechanisms of action. So, did I get that, right? I mean, and please do correct me, because I think that is one of the newer aspects, I think, that is being brought in the TB drug development through the work of a number of folks, including yourself, and it seems to be one of the ways to get to new regimens and sort of make bigger steps forward more quickly. And not without some degree of risk, but also to be able to change things.

DR. SPIGELMAN: Yeah. So, I think it's a little bit of a cross between what you said in terms of at least the first topic. I think most progress that's ever been made in terms of product development is incremental. You know, the real major, major leaps

are, relatively speaking, few and far between, historically speaking. But, on the other hand, a program or a development plan that's not going to be adopted and adopted wholeheartedly by those for whom it is intended to be used is probably not worth doing. So, it really is walking that fine line between doing the program that has enough net advantages so that the adoption will be rapid and will be significantly desirable by those for whom it's intended, but yet it does not have to be so totally revolutionary.

And one of the primary examples that I can give is that over the last three years or so we were involved in reformulating first-line pediatric drugs, which really is not an unbelievable revolution. It's simply taking -- it was taking three-year-old guidelines from the WHO and getting known technology and enticing manufacturers to actually do the proper formulation, which is not mind-boggling science, to get a pediatric formulation. That really is appropriate, and what Jeff was talking about and, you know, not to be crushing pills for kids, and not knowing what the absorption is like, etc., etc.

DR. STARKE: Do you mind if I point out that that formulation is not available in the United States?

DR. SPIGELMAN: Yeah, I was going to get to that, Jeff. So, I wouldn't call that an unbelievably, you know, sort of tremendous advance, but in the first year this was taken up by well over, I believe, 50 -- or the amount of sales, so-to-speak, or distribution was over 50% of the documented population of pediatric TB in children.

So, I think it's really identifying the combination of what's feasible and what's doable and what's going to actually work. Now, clearly, if in that process, you can totally revolutionize TB therapy, sure, if we can get to the point that we do away with all the old drugs and put in only new drugs that are great. But I think the skeptics are accurate who have said, look, the chances of getting three new drugs not only from an efficacy perspective but from a toxicity perspective, because obviously, that's probably as big a challenge as the efficacy piece of it. Those are pretty high bars to really cross. And we really should certainly be prepared to undertake those but not be

naive in the sense that it's not going to be an easy thing to do. So, that's the answer in terms of threading that needle between significant meaningful change, but it doesn't have to be totally revolutionary.

DR. COX: Interesting. It almost sounds like advice, to some extent, for a financial portfolio, which is you want to balance your risk, to some extent.

DR. SPIGELMAN: Well, frankly, and we also have to balance the ability to attract the funding to do the work, which is not an inconsequential, you know, I think barrier. Because if we could do everything that we would like to do -- and this is just the TB Alliance. I mean, it's the same for -- you know, Charles said it, too. Within a company that's even dedicated to TB, they are not going to get the resources to do everything that probably the TB team would like to do. I think that's probably a fair assumption whether it's Sanofi or anybody else. So, it clearly has to be balanced from that other side of the perspective of where will the funding come from to do the work? And I think that is really one of the major

-- this goes into a different point -- but I think one of the major problems we have in TB is we simply don't have the resources to take enough risk to do enough TB -- to do enough, even, Phase 3 trials to give the feedback to understand what are really the accurate predictors of Phase 2 or of earlier development. And, frankly, I mean, if I look at something like LAM, which is great. It has great potential.

So, what are we -- what's the best we can do right now? We're looking at it against the, quote, gold standard of sputum conversion and of sputum bacteriology, which we know, frankly, without opening that debate right away, is not necessarily a great predictor, but that's the gold -- that's the best we have to measure LAM against. As opposed to having had enough Phase 3 experience and even biobanks, etc., etc., to use them as a predictor, not of an intermediate endpoint, but of a final endpoint. So, that's another area that really is, in my opinion, unbelievably short-changed, because we don't have enough of those trials.

REMox, on the one hand, and OFLOTUB, RIFAQUIN,

etc., were "failed" trials. They weren't failed trials; those trials have delivered an unbelievable fund of knowledge that now informs so much of what we do moving forward.

DR. COX: We often do find that the trials that fail are the ones that oftentimes can teach us very much, and we found that in a number of different therapeutic areas. So, yes.

DR. HUGHES: Yeah, so I'd just like to build on that comment about revolutionary change. Because I think the one example that Charles mentioned briefly but we are closely involved with, with Novartis, we're responsible for clofazimine, which has been mentioned a number of times here, is a very odd case. Because it's really been reserved for leprosy, but obviously, it is getting a lot more use in this area. But a group of dedicated, genius, breakthrough clinicians in Bangladesh really took a revolutionary approach to take an entirely new regimen of seven drugs that they had in the cupboard, all of which had some rationale of why you would use them, and changed the MDR-TB paradigm from 24 months to 9 to 12, roughly. So, glad to hear

Dr. Higgins talk about the importance of looking at breakthrough regimens versus standard of care as well. I think it's very important that we look at that.

Now, how you tease apart the contribution of one of those drugs within seven becomes really quite a challenge, right? So, I think the nonclinical data does become even more important in that case, so I think that is something that we have to always bear in mind. It's not just the EBA study but the nonclinical data, if you can come up with that, is critical.

So, I think for question 1 there, I think that is -- it's going to be extremely difficult when we get into more of these complex regimens and, frankly, I think if you have a regimen that is clearly as good as but much shorter or more convenient or safer, that that should become a way to treat people with this disease.

The other comment I was going to make is related to the other question 1 or question 4, depending on how you look at it, which is the current trial design challenges. So, what we found, right, was we were already to do a very streamlined study, but the amount of time it takes to align with health

authorities and then to get the approval of different sites to get your contract set up, by the time all that was done versus the standard of care, the field had moved, right? And so, what we found was standard of care was no longer achieving -- was no longer 24 months achieving 50% success rates, particularly in the sites you need to go to generate the data with good clinical practice to change -- you know, to inform the field. And there they were getting rates of 75%, 80%, 85%. They were already starting to use shortened regimen. Our own drug was the standard of care when we went in to say, so it becomes very, very difficult. And, again, it's a special case, but I think it's a special case, but I think it's actually informative, because many older drugs are used in TB field and the pace at which the world moves is important to bear in mind.

DR. STARKE: So, I've often thought there is a lot more analogy between TB and cancer than there is TB and many other infectious diseases. You know, they talk about logs of cells, we talk about logs of bugs; they have induction and consolidation therapy, we have initial and continuation. They're all about regimens,

also. For instance, in pediatric cancer they've done incredible things by making sure that all patients are involved in trials. So, my question is, what can we learn from oncology in terms of studying drugs -- studying regimens as opposed to drugs? Because that's largely what they do. It's a question.

DR. COX: I think the folks that are trying to do it in the TB field are teaching us, I mean, to be honest with you. I mean, is there more we can learn from oncology? It's possible. You know, I'm impressed with what folks have been able to do in the TB area with the, frankly, quite limited resources available in this area relative to what's available in oncology. But maybe there are additional lessons that could be learned from oncology and how they approach things. So, I don't know if others have additional thoughts on that.

DR. SPIGELMAN: Yeah, Jeff, I think one of the problems that we have in TB is that we have the history that really limits us. Most of the combination work that, at least I see going on in oncology, is based on pretty much all new compounds and it starts from

scratch. You don't start out in oncology with the standard being a seven-drug regimen that you're looking to tease apart. It kind of grew up, the combination programs that you're seeing now in the modern era, almost like HIV grew up with one drug and then the second was added and the third was added. And it was in a much more rational or semi-rational, orderly process. We're kind of stuck in that we've got poor grade of evidence that defines standard four-drug, five-drug regimens that we somehow now have to tease apart and improve upon, which is a huge, bigger burden than is there in oncology.

If we could learn a lesson and wave a magic wand, though, then what I would say is make TB regimens be payable to the tune of $100,000 or $300,000 per patient and then we'll see a lot more rapid progress in terms of the work being done. But without being facetious, that lack of commercial attractiveness in TB makes, frankly, a lot of what goes on in oncology just nonrelevant to what we're stuck with in TB.

DR. STARKE: I think I was trying to ask sort of a more basic question. We were talking about how do

you determine the contribution of a specific drug to a regimen, and that's what I was wondering if they had some principles that would help. But the way you're describing it almost is where cancer was maybe several decades ago. Although, I've got to say, in pediatric cancer they're still using a lot of the traditional drugs, and so it's not quite just all about new, totally new drugs and totally new regimens.

UNIDENTIFIED SPEAKER: (Inaudible - microphone inaccessible.)

DR. COX: Do you want to respond to that?

DR. PHILLIPS: Can I make some comments on --

DR. COX: Yeah.

DR. PHILLIPS: -- the analogies with cancer? I think, first of all, I'll come back to that point. First of all, I think we have a lot to learn from happenings in oncology. I'm a statistician. Most statistical methodology is done in oncology and we sort of pick out sort of the dregs from there. So, the MAMS, which has been talked about, that came from oncology, and I think many adaptive designs that have been proposed that we've discussed have been done in

oncology. So, we have lots to learn there, and I think the more we read that sort of literature the better.

In terms of the comment that was made about getting data from routine practice, I think one difference in TB trials from cancer trials is the endpoints. So, Mel talked about doing large, simple trials, which I guess are easier to do in settings where the endpoint is something like mortality, which it's a hard endpoint, which is relatively easy to collect that data.

The challenges in TB are patients need to be followed up after the end of treatment. Most of the programmatic endpoints that you've heard presented today are about end-of-treatment cure. There is very little programmatic data about post-treatment, whereas, in trials we need that follow-up, because it's about relapse. So, you need patients to remain in follow-up, which is why it's more challenging just to get routine data to answer some of the questions we've talked about here. And so, I think that's one of the issues. And I think that's also why large, simple trials are more challenging in TB. Or I think it's worth thinking

about how they could be done, but follow-up is so critical in trials that a simple trial would still need to involve very careful follow-up schedules. Even if not many sputum samples are taken for culture, follow-up would be critical.

DR. COX: And maybe I'll just add, too. Folks may recall, too, Rick Pazdur and I, from the head of our oncology office, and I did a panel at CBTR on this very topic. And I can tell you one of the things that came up -- and this doesn't mean you can't learn from the area of oncology -- was really the number of differences that exist between oncology and TB, and why the two fields are different and why it may be challenging to essentially directly translate things over. That doesn't mean you can't learn, but there are differences. It does make it challenging.

DR. MITNICK: Can you hear me now? So, a couple of comments. This has been a really interesting discussion. My name is Carole Mitnick. I work at Harvard Medical School and work with the nongovernmental organization, Partners in Health. On the clofazimine issue, I just wanted to point out that

that new regimen is a standard of care for a subset of MDR patients, that is, MDR-TB patients who have not been previously treated with second-line drugs and whose isolates are not resistant to the drugs in that regimen. So, there are still opportunities to learn about the role of clofazimine in MDR-TB treatment, and also there are still obviously open questions about the optimal dose of clofazimine. So, looking in other populations is another possibility. It's not all lots with the adoption of the shortened regimen in that subset of MDR patients. That's one point.

A second point is just in thinking about the model of scarcity. I mean, I have now been doing TB work for, like, 20 years. I can't believe I can say that. And it's true, I mean, we have always worked within a model of scarcity. But we also have innovated, and I think we shoot ourselves in the foot by continuation to say, oh, we have to be cautious, we have to limit our failures, because there aren't enough resources. So, Mel, you describe three trials that have been considered by some as failures, by others not as failures, and there is still more money for trials.

So, I think we do need to continue to be aspirational, and we do need to not be settling as we have for so many decades. And that's part of the reason that we still have more than 10 million new cases of TB every year and more than half a million of new cases of MDR every year.

So, one of my questions is in the paradigm of the pan-TB regimen, I mean, it sounds to me a lot like where we came from, where the four-drug regimen was supposed to be for everybody. The World Health Organization and other entities discouraged any sort of differentiation in treatment, and now we have at least a half-million cases of MDR every year. So, what is the role in evaluating a pan-TB regimen for modeling or other activities that would try to predict how long such a regimen would be useful, and what the implications would be of having a single regimen that's for what we today call drug-susceptible TB and MDR-TB. It is based on the same nucleus of drugs that is now used for a salvage regimen in the same development portfolio. So, I'm curious about how that fits into evaluation of the pan-susceptible TB regimen.

DR. SPIGELMAN: So, I think there are two separate kind of questions on the table. One I think is really the more generic question, it doesn't matter whether a regimen is approved for DS, MDR-TB, pan-TB etc. There has to be, I think, greater planning for how to protect that regimen for as long as possible within reason. And I'm not sure we've devoted as much attention to that type of sort of oversight of how the drugs are being used. And obviously, that's now a big deal in the whole AMR field, you know, so-called stewardship of antibiotics and all that.

And so, I think that that question is independent of whether a new drug or a new regimen is more limited or very broadly applicable is there has to be sort of more planning for stewardship, so-to-speak, of new therapeutics so that none of them will last forever, but they'll last longer than they otherwise last for.

The other point, at least for me is, what's the real attractiveness of a pan-regimen? The attractiveness to a great extent is that, I think, even if we come up with a really, really great regimen for

something like MDR-TB, there still are a huge amount of structural problems in the way TB is treated realistically in the countries that are most affected. And 500,000 on the one hand is a huge number; 500,000 scattered across a whole bunch of countries and resource-poor environments, etc., etc., still presents a really big challenge to get on top of it. As opposed to if we could present a common regimen that would encompass both what are presently called drug-sensitive and MDR-TB patients, and lump those together into a common treatment paradigm that countries could adopt that would be much easier to give. And that would have tremendous ramifications in terms of the cost structure of the health delivery system; have tremendous ramifications in terms of the cost structure of the drugs by virtue of the volumes. And so, I see it as just a practical way to get on top of the problem of TB in a much, much quicker format than if we continue to -- or if we attack DS totally separately from MDR-TB. That's just a practical issue, in my mind, of how quickly can we solve the problem of MDR-TB. So, I think it's sort of a combination of all of those as to

what some of the benefits are of a pan-TB regimen.

DR. VERNON: I wanted to ask a question about a topic that you raised, Mel, which is large, simplified trials. Payam Nahid and I and others have been discussing for a while now the potential to use a simple, a large, simple trial design to improve our management of INH-resistant TB by doing the trial in resource-rich settings, where simple doesn't mean lacking many of the kinds of data and tools that we would otherwise have in a trial. The potential for such designs to help us with bringing new agents or older agents that lack a current approval in the US, for example, is interesting to us. I wondered if FDA has any examples of having used a large, simple trial design as the basis for approvals?

DR. COX: So, I'm sure there are. I mean, I think of the essence of a large, simple trial is it's usually big, and you're not going to collect a whole lot, but you're going to get an outcome that's important to you. And if it's something that occurs relatively infrequently, then maybe you need a bigger trial. So, there is no reason you couldn't use a

large, simple trial and, depending upon what the problem is, if it's the appropriate design for what it is that you're trying to study.

There have been safety trials in certain areas where people looking at cardiovascular outcomes as an adverse effects, you know, those sorts of things are done. And so, if the large, simple trial is in fact the appropriate trial design for what it is that you're trying to study, then it would be a perfectly fine way to evaluate that issue.

DR. VERNON: Thank you.

DR. COX: Go ahead.

DR. NAHID: I just wanted to raise a point of friction that I would love the panel to comment on, and that's the role the regulatory bodies take versus the role that guideline makers take. And having recently led a couple of guidelines for TB drugs and TB treatment, and being involved in others, some at WHO, it's occurred to me that is there a way to jump that bridge, to bring that gap to be a smaller gap? Because the regulatory bodies want to know what the individual components do. The guidelines committees and, frankly,

the people out there want to know how to use the drug. Is that an argument for exclusively or intensively pursuing regimen development approaches to approvals -- regimen approvals and maybe large, simplified trials would be another, I guess, approach. But what's the panel's thoughts about that, because it's really challenging to make that leap?

DR. COX: So, I will try and make a few comments. It's a very good question, and we do see times when, in essence, drug labels get sort of out of date. You know, the dosing regimen that's in treatment guidelines is different, sometimes the uses are different. And so, if you think about what are some of the factors that can contribute to that? Well, if it's an area where the pharmaceutical company is involved in, say, the initial development of the drug for whatever indications, an then development is happening by groups other than those that actually own the new drug application, that actually own the drug here with us, sometimes there can become a disconnect. I'm not trying to say that that research isn't important; it can be extremely important in some areas. But you can

sometimes over time get this disconnect as drugs age and they become generics. There can also be a disconnect, too, with further study. It's not good for anybody when the drug label starts to get separated from the treatment guidelines. So, to the extent that those that are actually out there doing trials, can continue to engage with the pharmaceutical companies, and we can also engage with both of those parties, we have to do it through the pharmaceutical company, it can help to decrease that degree of separation. So, that's sort of one aspect of it.

The other is that sometimes there are situations where the level of information that's available out there is quite limited and maybe not ideal. You know, low-quality evidence. Clinicians oftentimes are faced with that and have to make decisions. Those writing treatment guidelines may also try and help out in that scenario. So, there may be information that is really of low quality that may be hard for a regulator to look at and say that it meets sort of the standard that we would be looking for in order to give an indication. But clinicians may have

to make decisions, treatment guidelines folks may, too, and that's sometimes another area where you can get a gap.

So, that argues for trying to do good trials, trying to get to good studies before the -- you know, to support the standard of care that's present. If the standard of care becomes sort of non-evidence-based but more just based upon poor quality information because that's all that's available and it's a very difficult situation and people have to make choices and be advised, that's another reason that things can get separated. I'm sure there is more than that, but it is best if the guidelines, the standard of care and what's in the drug label, to the extent that those things can avoid being separated to a great deal, that's usually best for everybody.

DR. HUGHES: Just to follow up on that excellent point there. Perhaps it is something to explore as a community, that circling back between the regulatory bodies and the guidelines makers. I mean, these are people who are using great principles, the WHO, the CDC. These are entities that are taking a

very, frankly, stringent look at the data, to use that word. And whether there should be a mechanism by which these groups talk to each other and circle back so that gap gets closed and usage of the drugs are done appropriately, there is not -- we're not leading providers out in the lurch, because we're telling them to use a drug in a way that it doesn't have an indication for, for example.

DR. COX: Right. I mean, that would be the ideal, to keep that degree of separation as infrequent as possible. It is certainly something where I think the community can work together. You know, the aspiration here would be quality trials that would be available to both those writing treatment guidelines and to those that have new drug applications, so that things can remain congruent. So, it is certainly an aspiration that is laudable and one we should try for. Whether it's attainable is another question, though, because there still are going to be areas where, quite frankly, treatment guideline folks and clinicians are going to be trying to make decisions and trying to provide recommendations when the level of evidence is

just limited. But there are valued treatment guidelines, no question. They do help clinicians.

MS. LESSEM: Thanks. I just wanted to go back to an earlier point, Mel, that you had made about stewardship, because I think we need to be really clear with what we're talking about. The new drugs that we have seen come out for TB are so overly stewarded that nobody is getting them. And they're actually being "reserved" in an attempt to protect the drug, that we're not thinking about protecting patients. And, in fact, we're not even protecting the drug, because only severely resistant cases are getting them, which in some ways is priming the market for more resistance than if we just use them a little bit more liberally earlier on in treatment. So, I don't think that we've seen -- I think we haven't necessarily seen great responsible practices towards using TB drugs historically, but I think with the new drugs, stewardship has gone so far in the other direction, we have fewer than 5% of patients who need them, by conservative estimates, actually accessing the drugs. So, I just wanted to set the record straight on that.

I certainly think countries need to have proper systems in place for diagnosing TB, for being able to see what people are susceptible to, and give them appropriate regimens. But I think stewardship as a blanket term has been thrown around really to the detriment of patients and to the longevity of these drugs. Thanks.

DR. NAMBIAR: I would like to add something to Payam's earlier point about the connection between regulators and policymakers, especially when it comes to issues that Dr. Peloquin explained in his study, that is population PK an variability of drug exposure profiles. Because drugs get approved based on a specific dose, but once they're used in the field, the exposure profile is very, quite dramatically might affect how the effectiveness -- how effective they are in combination with other chemical entities. So, to what point could one consider basing recommendations for use or even the drug approvals on exposure profiles rather than drug doses, and have specific targets that are based on solid population PK rather than dose ranges in kilograms.

DR. COX: Right. So, this is done, and the

way to do it is to design the trial that actually evaluates the drug in such a way so that your dosing is guided by exposure. So, it is doable, and it's just a matter of what is done in the clinical trials that, in essence, for the basis for approval? Are there opportunities if the initial approval was based on a dosing regimen that was a fixed dosing regimen not guided by therapeutic drug monitoring, or not guided by exposure. Certainly, if there is additional data, additional studies that are done subsequently, that could be used to inform the dosing future. So, it's all doable, it's just a question of, in essence, whether it's been done.

DR. HUGHES: David Hughes again. I wanted to come back a little bit to Dr. Mitnick's point in that I did not mean to imply that our journey is over or the party is done. Actually, we are in active discussion with two stringent health authorities, one of them represented here today, as well as we have recently had recognition and ability to import into three countries of high need. And so, we're continuing to work actually feverishly to meet the demand and to inform

that, but at the same time we're looking to get the data.

So, another appeal is both to look more at real world evidence that is generated through single arm or observational studies, but just broad programmatic research to be able to have that in the equation. And also, the broader discussions today about collecting data, better data from the programmatic implementation.

I'm looking at the WHO, who is a very powerful advisory and counselor to some of the countries both on efficacy and safety data, so that we can then move the field forward collectively. Because we're sort of feeling the pain of that weakness in the data collection currently.

DR. GEITER: Yeah, I was just -- you already brought up the CPTR discussion you had with Dr. Pazdur and comparison with oncology. And one of the things that struck me was that he was talking about in oncology they can go for an early endpoint for reduction in tumor size. And if they shrink tumors, they have a drug preliminarily. They then later need

to show increased survival. And so, they've got a very hard endpoint there. We can talk about is it two months or three months, or is it the rate of decline or time to sputum culture conversion, but we do have a microbiologic endpoint that seems to likely predict a favorable outcome. But then at the end we're still tied to a microbiologic endpoint. We really don't have a hard endpoint in TB. It's cure, and what is a cure? Well, cure is, at least in the guidelines, that it's a certain period of relapse-free survival following sputum culture conversion, but that is still based upon a microbiologic endpoint. So, we're a little bit challenged in that way.

It would be nice if we had something else. It was very interesting to see, I think, measurement of mRNA levels that you have a negative microbiologic outcome but you still have messenger RNA hanging around. So, there are obviously some TB bacilli doing something, and if we could develop that into a harder endpoint. And I would just, you know, speaking up for sputum tests, it's what we got and it works pretty well. I mean, in terms of -- you know, if we're going

to go with a microbiologic endpoint, it does pretty well. And that if we could get more rapid results that are equally sensitive and specific, like with the LAM assay or any of the other things that have been provided, I think that as long as we're tied to a microbiologic endpoint, I think that can contribute a great, great deal to the design of trials and the evaluation of regimens going forward in the future.

DR. SPIGELMAN: And now let's turn it over to Ed to final --

DR. COX: Yeah, so we're at the five o'clock hour, so I know folks are planning to head out and catch planes and all that, so I'll keep it very short. But I wanted to thank everybody for joining us here today. I found it very useful; I hope you did, too. And I remain impressed with the degree of accomplishment, the progress that has been made in this area, you know, recognizing that it is not the most resourced area of therapeutics development. But because of the thoughtfulness and commitment of the folks in this room, on the webcast, who have been involved in this area who are not here today, I think

there has been tremendous progress, and I think that's wonderful. And we look forward to continuing to work with the TB community on TB drug development, and I'm sure colleagues and CDRH are interested in continuing to work in those involved in diagnostic development, too. So, we stand ready to continue to work with folks and to try and improve the situation out there for patients with TB. We regulate for the US. We recognize, also, the global implications of a disease like TB and our broader responsibility to the global community, too.

So, with that, I want to thank you all for joining us today and wish you the best, and safe travels.

(Whereupon, at 5:02 p.m., the workshop was concluded.)

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I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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