FOOD AND DRUG ADMINISTRATION (FDA)

COORDINATED DEVELOPMENT OF ANTIMICROBIAL DRUGS AND ANTIMICROBIAL SUSCEPTIBILITY TEST DEVICES

Thursday, September 29, 2016

Sheraton Silver Spring Hotel
8777 Georgia Avenue
Silver Spring, MD 20910

Reported by: Dylan Hinds,
Capital Reporting Company

A P P E A R A N C E S

Jane Ambler, PhD
Vice President, Clinical Microbiology
Wockhardt Pharmaceuticals,
Helen Boucher, MD
Director, Infectious Diseases Fellowship Program
Associate Professor of Medicine
Tufts University School of Medicine
Samuel Bozzette, MD, PhD
Vice President, Medical Affairs-Americas
bioMérieux
Bill Brasso
Senior Staff Scientist
BD Diagnostics
Darcie (Roe) Carpenter, PhD
Director, Clinical Affairs
Beckman Coulter (Microscan)
Ed Cox, MD, PhD
Director, Office of Antimicrobial Products (OAP)
Center for Drug Evaluation and Research (CDER)
FDA

A P P E A R A N C E S (Continued)

Ian Critchley, PhD
Vice President, Clinical Microbiology
Allergan
Roger Echols, MD
Consultant
Shionogi
Robert Flamm, PhD
JMI Laboratories
Steve Gitterman, MD, PhD
Deputy Director, Division of Microbiology
Devices(DMD)
Office of In Vitro Diagnostics and Radiological
Health (OIR)
Center for Devices and Radiological Health (CDRH)
FDA
Romney Humphries, PhD
Section Chief, Clinical Microbiology
Associate Professor, Clinical Pathology
David Geffen School of Medicine, UCLA

A P P E A R A N C E S (Continued)

Amanda Jezek
VP, Public Policy and Government Relations
Infectious Diseases Society of America
Kevin Krause
Director and Head of Microbiology
Achaogen
Olga Lomovskaya, PhD
Vice President, Biology
The Medicines Company
Amy Mathers, MD
Associate Professor
University of Virginia
Sandra McCurdy
Field Microbiology Affairs Director
Melinta Therapeutics
Melissa Miller, PhD
Professor of Pathology and Laboratory Medicine
Director, Clinical Molecular Microbiology Lab
Associate Director, Microbiology-Immunology Lab
UNC School of Medicine, UNC Chapel Hill

A P P E A R A N C E S (Continued)

Mary Motyl, PhD
Senior Principal Scientist
Merck
Sumathi Nambiar, MD, MPH
Director, Division of Anti-Infective Products
(DAIP)
OAP, CDER, FDA
Jean Patel, PhD
Deputy Director, Office of Antimicrobial
Resistance
Centers for Disease Control and Prevention (CDC)
Charlene Reed, PhD
Chief Executive Officer
The Foundation to Combat Antimicrobial Resistance
John Rex, MD
Senior Vice President and Chief Strategy Officer
Infection Business Unit
AstraZeneca, plc

A P P E A R A N C E S (Continued)

Daniel Sahm, PhD
Chief Scientific Officer, VP Microbiology Global Services
IHMA

Ribhi Shawar, PhD
Branch Chief, General Bacteriology and Antimicrobial Susceptibility Branch
DMD, OIR, CDRH, FDA

Fred Tenover, PhD
Vice President, Scientific Affairs
Cepheid

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

INTRODUCTORY REMARKS

DR. NAMBIAR: All right. Is this better? Okay. We'll start again. So, good morning, and welcome to the FDA workshop on coordinated development of antimicrobial drugs and AST devices. My name is Sumathi Nambiar, and I'm from the Division of Anti-Infective Products.

So the last several months, we've heard from various stakeholders, clinicians, clinical microbiology laboratories, drug and device manufacturers that there are challenges on many fronts to make antimicrobial susceptibility testing available in a timely fashion, following approval of a new antibacterial drug.

And so, at today's meeting, we would like to understand what some of the challenges or bottlenecks are in making antimicrobial susceptibility testing available in a timely manner once a new antibacterial drug is approved.

We hope that this meeting will provide an opportunity for a robust discussion on this issue and

hopefully identify some potential solutions to address the challenges so that appropriate treatments can be made available to patients.

Just a couple of slides on the microbiology aspects of antibacterial drugs, really from a drug perspective and Ribhi will talk about it from a CDRH perspective.

I think many of you are familiar with this guidance document on microbiology data and it was recently updated as of last month. And this guidance document provides overall information that is needed or the program -- the microbiology program that is needed to support the development of systemic antibacterial drugs.

I'll also touch upon the microbiology section of labeling, and I'm sure most of you are familiar with this, but would serve as a reminder. So subsection 12.4 describes -- which is the microbiology subsection -- describes the relevant microbiology data for the drug. It describes the mechanism of action, mechanisms of resistance, interaction with other antimicrobials, et cetera.

In addition, the antimicrobial spectrum of activity of the drug is described, and we typically call it as a first list and a second list. The microorganisms included in the first list are associated with a labeled indication and microorganisms included in the second list efficacy has not been demonstrated in adequate and well-controlled trials and the microorganism listed here should be relevant to the labeled indication.

This subsection also provides the susceptibility test interpretive criteria and we have a table that looks like this where we provide the MIC criteria and the disk diffusion criteria. And we list the organisms for which we have adequate data.

Again, many of you are also familiar that earlier this month, a new guidance was issued by CDER and CDRH on coordinated development of antimicrobial drugs and antimicrobial susceptibility test devices. You'll hear a lot more about this guidance in Ribhi's presentation next.

The key messages in this guidance are that we really would like to facilitate interactions

between drug sponsors and device manufacturers for coordinated development of new antimicrobial and AST devices. We're willing to consider joint meetings with the drug sponsor and device manufacturer and such meetings will be attended by representatives from both the drug side and the device side. Such meetings can be requested by an AST device manufacturer or by drug sponsor.

I think it's important to note that the review of the drug and the device will remain independent. So review timelines for either product will not be affected.

So we have a busy day today. What we've tried to do is make sure that we hear from the various stakeholders and have a very robust discussion on this issue. So our first speaker today will be Dr. Ribhi Shawar, from CDRH. He'll provide CDRH's perspective on AST devices. We'll hear from Dr. Mathers on the perspective of a clinician and from Dr. Humphries on the perspectives from the laboratory.

Dr. Motyl, from Merck, and Kevin Krause, from Achaogen, will present the perspective from drug

sponsors. Bill Brasso and Dr. Carpenter will present the perspective from a diagnostic device manufacturer.

We have two sections for clarifying questions from audience and panelists and just wanted to emphasize that the forum of this is really to encourage interaction. And we really want audience members to participate, ask questions, provide comments because we find that discussion very helpful. So this is not as formal as an advisory committee. So please do not hesitate to bring up any points you would like to during these sessions.

In the afternoon, we'll hear from Dr. Miller and Dr. Patel about how ASM and CLSI can help with the process. Again, have time for some clarifying questions from the panelists and audience. And for those members of the audience that could not get their questions in during the two sessions we have for clarifying questions, we have 15 minutes set aside for public comments.

So again, we really encourage you to participate. It's very helpful to hear your comments. We have an hour set aside for panel discussion in the

afternoon, and then Drs. Cox and Gitterman will provide concluding remarks.

So before we go to Dr. Shawar for his presentation, I thought we'll take a minute to introduce the panelist speakers. Maybe Dr. Bozzette, here we can start with you.

DR. BOZZETTE: Hi. I'm Sam Bozzette. I'm an infectious diseases doc, and I'm the vice president for medical affairs in the Americas at bioMérieux.

DR. BOUCHER: Good morning. I'm Helen Boucher. I'm from Tufts Medical Center and Tufts University School of Medicine in Boston. I do transplant infectious disease.

DR. LOMOVSKAYA: I'm Olga Lomovskaya. I'm from Medicines -- Olga Lomovskaya, from Medicines Company, vice president of biology.

MR. BRASSO: Hi. I'm Bill Brasso, senior staff scientist from Becton Dickinson.

DR. CARPENTER: Darcie Carpenter, director of clinical affairs for Beckman Coulter.

MR. KRAUSE: Good morning. I'm Kevin Krause, director and head of microbiology at Achaogen.

DR. TENOVER: Fred Tenover. I'm the vice president for scientific affairs at Cepheid.

DR. GITTERMAN: Steve Gitterman. I'm the deputy director of the Division of Microbiology Devices at FDA.

DR. SHAWAR: I'm Ribhi Shawar. I'm branch chief at the Division of Microbiology Devices at CDRH.

DR. PATEL: I'm Jean Patel. I'm in the Office of Antimicrobial Resistance at CDC and I'm the outgoing chair of the CLSI subcommittee for antimicrobial susceptibility testing.

DR. COX: Good morning. Ed Cox, director of the Office of Antimicrobial Products, CDER, FDA.

DR. CRITCHLEY: And good morning. Ian Critchley, vice president of clinical antimicrobial at Allergan.

DR. MOTYL: Mary Motyl. I'm senior principal scientist at Merck.

DR. MATHERS: Amy Mathers, infectious disease physician at University of Virginia.

DR. HUMPHRIES: I'm Romney Humphries. I'm section chief of clinical antimicrobial at UCLA.

DR. REED: Charlene Reed, CEO, The Foundation to Combat Antimicrobial Resistance.

DR. MILLER: Melissa Miller. I'm a clinical microbiologist at UNC Chapel Hill and I'm here as the chair of the Committee on Lab Practices for the American Society of Microbiology.

DR. NAMBIAR: So many thanks to all our panelists and speakers for taking the time to be here today. Dr. John Rex could not join us in person. So we are hoping he's either on the phone or via WebEx. So Dr. Rex, are you on the phone? Maybe not.

DR. REX: Yes, I am here.

DR. NAMBIAR: Oh.

DR. REX: Thank you.

DR. NAMBIAR: Very good. Thank you. So with that, we'll move on to the first presentation of the day by Dr. Ribhi Shawar, who serves as the branch chief in the Division of Microbiology in the Office of In Vitro Diagnostic and Radiologic Health at the Center for Devices and Radiologic Health at FDA. Ribhi, welcome. I'm not sure how to get this out. You can -- it's not escaping.

(Setting up presentation)

FDA PERSPECTIVE ON ANTIMICROBIAL SUSCEPTIBILITY TEST DEVELOPMENT

DR. SHAWAR: Good morning, everyone. Again, this is Ribhi Shawar, so that goes on the record for those who are transcribing.

Welcome, everyone. Good morning, and thank you for coming here. It's a great day outside, so, you know, comfortable inside. Thank you, Sumathi, and thanks, everyone. This is a topic that is dear to everyone's heart. So let's get started.

Here's my outline. Pretty much, I'm going to give an overview of the AST landscape. Many -- everyone in the room here is very familiar with it. But this is just important so that everyone gets on the same page. Discuss the concerns that Sumathi already alluded to. Many of you all are also very familiar with those. And also, highlight some of the FDA initiatives, including the latest guidance on coordinated development, and provide some examples of the timelines based on data that we actually have seen at FDA.

So here's the landscape. Devices come in various shapes and sizes and the landscape is also changing as the future goes on. Disk diffusion devices, dilution-based devices such as agar gradient diffusion and the devices that of course measure MIC based on either a visual read and/or automated, whether it is requiring algorithm-driven or some other mechanism.

And the reason I'm mentioning this is -- excuse me -- although it's very familiar to everyone, is that there will be differences and I'm hoping that we'll also hear more details about how each of these represent different challenges for device manufacturers as they develop them.

Not too much of a discussion today about other ways where we arrive at deciding whether an antibiotic is going to be useful or not for that particular organism. Detection of resistance is clearly another way.

But we're not going to touch too much on it, except that it somehow spills over in the sense that some of the reference methods that are used are

pertinent when you are evaluating, let's say, either a growth-based culture media that has antibiotics in it or any of the culture-independent measures of measuring molecular biomarkers, et cetera. So just keep that in mind, that some things there might be in need of addressing.

The regulation, again, boring topic, but this is pretty much what -- how we work and what governs us. All AST devices in the general sense of what we're talking about today are Class II, require review and a 510(k) premarket. They are non-exempt. They are subject to, according to the MDUFA timelines that have been established, to 90-day review cycle. That cycle starts the minute a submission hits the door at CDRH.

The regulations, I listed just a couple of the more important and relevant ones to the discussion today. There are other regulations that govern, for example, other molecular devices and other culture media that contain drugs in them. But this is the most important for us today. And studies and the data that are presented are also governed because this is a

Class II -- or these are Class II devices, are governed with a special controls guidance that we refer to all the time.

It's a Class II special controls guidance that lays out many of the parameters and the studies that are needed. And I'll highlight a little but more about that in the coming few slides. But there are other guidances, as well as Sumathi already alluded to, the microbiology-related topics from CDER as well. And there is several -- there are several CDRH/CDER combined guidances, including the now available coordinated development guidance.

So just for the sake of sort of putting side by side, if you will, the kind of things that happen when a new drug, let's say, is being looked at in order to become an approved drug, and of course the parallel to it is what susceptibility test devices might be applicable.

So again, the left-hand side -- your left hand -- yeah, left-hand side of the screen shows the antimicrobial drug timeline. And those -- the activities, you know, some may spill over from one to

another. So this was just mainly my way of illustrating the kind of activity that happens. So don't come talk to me after and say, no, that's not really in phase II box. This is in phase I.

No, so but the point being that, you know, everything starts, you know, early. You have R&D, mechanism of action, et cetera, from the drug side. And as you move further down, you learn more about the drug. You learn more about the methods. You have reference methods. You reference CLSI documents. You do all of that.

And there are new answers, as many of you are aware, for each drug where it might need something special. It might need -- keep that in mind because that may impact some of the timelines that we're talking about as you begin to learn more about the drug.

But anyway, on this slide, I'm showing what happens, for example, in the case of disk. And what I'm describing is what happens today and things may need to be changed. Things may need to become better or what have you. But this is actually an

illustration of where information about the disk is coming in during the review time at CDER. And the bottom line with all of this is that once things are set and the drug is approved, there has been -- or there would have been a lot of data that has come into CDER.

So according to the guidelines that we have now, what happens is that that data becomes the basis on which now CDRH relies when a sponsor comes in and requests a 510(k) clearance for that particular disk. So in this case then, once a device manufacturer has done all of their R&D before that and they come into CDER, CDER reviews the data.

That data comes into CDRH. And it is only coming in referencing the drug label that just got approved. CDRH consults with CDER to make sure that everything is okay, that there has been no issues identified. And based on that, the disk manufacturer gets their clearance. We cannot give a disk manufacturer clearance unless they submit something to CDRH. That's the timeline for a disk.

This left-hand sort of remains the same.

Now, this is talking about MICs and they are different obviously. But the -- what we have currently is that, for example, a sponsor -- so the activities have happened on the drug side. Now, we're talking about what could happen, or how it happens at the CDRH.

We have had sponsors come into CDRH and come and ask to contact us with questions about their device and how their plans are. But all of that right now sort of happens after the drug gets approved and that's why we're discussing things here today, to see what ways we can possibly help out in that regard. The review cycle remains 90 days, but once the device comes in for submission to CDRH.

This, I provide this just also so that everybody is on the same page, not to discuss too much of any detail here, except to say that for an AST MIC-based device, pretty much these sort of four categories that you see in the left-hand column would require a clinical testing, clinical meaning in a clinical laboratory.

Two clinical sites can be outside and the industry can have some testing at their site if they

can provide clinical isolates that are fresh or stock. There are details that are provided in the AST guidance about those and we have recently also modified some things and offered the guidance on the use of isolates for that.

But the rationale for this is, as you can see, you have a clinical testing. You have a challenge set in order to address specific resistance mechanisms, for example, in order to understand how the device performs. There is reproducibility, as this is a requirement really for many devices and also quality control because those are usually -- is the way that you can tell that testing has been conducted in a good manner.

There is -- you see on the slide here, you probably have already read it while I'm talking, but there is a rationale for each of these cases. And again, this is just a snapshot. You can read more about it in the guidance document. But the idea is that we want something robust to evaluate the device since it's going to go on the market for use in patient care.

So this is the gist of now we're talking about. Sumathi already alluded to who the players are. So I will not repeat that. All of them hopefully are represented here. And if not, you can carry the message to others who are not here.

The main two topics of which only the bottom one I'm going to talk more about, but spend one minute maybe about old drugs and where the breakpoint change issue has been lingering for a while. To highlight, CDRH is mandated to consider clearance, or when a device comes in for clearance, only when breakpoint changes have made it into the drug. In other words, at drug A, the breakpoint was 4, 8 and 16 and now it's lower.

It has to make it in order -- it had to make it into the drug label right now before device manufacturer can submit. And this has caused some delays. But again, this not really the topic, only to say about this that FDA is currently exploring options for AST device manufacturers to -- so that they can use up-to-date breakpoint information in their device labeling in a more timely manner. That's pretty much

where we are at with that.

So regarding now new drugs, so imagine now there's a new drug, has coming in. CDER is looking at it and there are activities ongoing, as I showed in some of the slides on the left-hand slide of those two parallel sides. So there is a delay and that's why we are meeting here.

So I thought that perhaps the illustrations in those two slides, this slide and the next one, would hopefully sort of give everyone a basic understanding of the type of timelines that we are dealing with and where those timelines fit.

So just to orient you, this is masked data. There is no mention of the drug and no mention of the device manufacturer. The timeline is in months on the x-axis and on the y-axis you can see whether it's an AST disk or a manual MIC method or it's an automated device.

And the point zero is when CDER said on August 1st or August 21st that this drug is now approved. So we looked at the data that we have for that particular drug to see when did CDRH receive a

submission for clearance for a particular device. And you only need to look at the blue bar in order to understand very quickly how each device is different.

But for example, remember what I said about the disk, where I said that our review is pretty much -- all I need to -- all we need to do is receive a submission from a disk manufacturer in order to get the clearance of that disk. If you look at disk number two, it took almost eight months for that submission to come in.

So the blue lines, if you keep looking at them, that is the -- that is the lag of time that it took a device manufacturer to bring in a submission for consideration at CDRH. CDRH cannot consider anything that they don't have. So those are the timelines that I'm hoping also that some of our colleagues from the AST industry will perhaps highlight so that there are ways that we can understand the reasons why.

I think everyone in the room can begin to think also of ways and why it took longer for one than the other because there are technological requirements

for one that are more than the other. So clearly there will always be that difference. But at least in the case of AST disk devices, that would not have been necessary.

This is now another slide where I have identified the drugs, not the drug manufacturer. But you -- because these are recent data. So the timeline here is just in days. That's the difference just between the two slides. Again, it is just another illustration and you can see the one thing that I did not highlight on the previous slide I will highlight here -- is that you see the green bar is really just the review time that it took at CDRH.

So when you look at the blue, that's time outside of CDRH, cannot do anything about it. the time within CDRH, you can see there were some cases where it is almost within 40, 60, 50 days, 70 days. If everything is good and all the data is supportive, we would clear it.

Again, Sumathi showed this and you can -- if you haven't read it already, I'm sure you read it page to page. But just in case, please look at this. And

the most important thing is this is now a draft document. It is subject to comments. Please provide your comments by November 21st to the docket. So any thoughts, any ideas, we are here to listen and hear from you as the experts in the field.

So again, in the interest of time, I will just browse through very, very quickly on these slides because Sumathi already alluded to what the highlights from this coordinated guidance document -- or what is the spirit of this guidance, whether it was written exactly that way or not. But we will do our best in order to see where we can -- where we can help.

But here are some highlights. This is a draft guidance. It is intended as a general guide and not prescriptive. Drug applications and AST device applications remain separate, for the separate centers. Review timelines are for the separate products and not influenced by each other. And the guidance encourages early interactions among, again, drug manufacturers, AST device and the various centers at FDA.

So for example, you can engage all parties

early in the CDER discussions, CDRH meetings and what have you, the mechanisms of which we can work out. And find and identify where coordinated development strategies and synergies are possible.

Emphasizes FDA's belief that a better coordination of development -- and by the way, this is another important point that I want to highlight, that this is not a co-development because there have been sometimes use of the term that way. We are calling it of course coordinated development so that because we try to bring them together but not necessarily in that sense of it being a co-development.

It provides a flexible mechanism that allows perhaps a close as possible to concurrent review of drug and device. Again, it is not companion diagnostics and that is really emphasized in the document.

Some practical points, respective companies can submit their coordinated development plans in various forums -- for example, pre-IND/IND to CDER, pre-submission -- we call it Q-sub in our case. Pre-submissions are free of charge and companies have used

those. And we have really -- we feel at CDRH that those are very, very useful interactions and actually lead to a better submission when the premarket notification comes in.

Respective companies can again request a joint meeting if that is necessary and the device manufacturer in their 510(k) submission, depending on how the coordination was going, need to reflect and refer back to what things might have been done in the CDER so that CDRH and CDER can consult and coordinate.

Finally, Jean Patel on my right-hand side and I are proud co-principal investigators on this effort that we initiated in order to help the community to have a resource that hopefully will just grow better and with more isolates in it such that those isolates can serve for the community to use. So this is the FDA and CDC AR isolate bank. If you are in this room and you don't know about this bank, eh.

All right, and then, now in summary, just reviewed the concerns and provided insights into FDA experiences. Illustrated with some timelines the issues that maybe we can refer to those slides back

maybe in some discussions.

And I'm again hoping that some of the device manufacturer presentations will go maybe even more detailed to help out with understanding those timelines. And I provided some overview of FDA initiatives and resources. And again, the goal is to benefit patients, clinical labs, healthcare providers and industry. And finally, I would say it really is an example where really it takes a village for this to happen. So, thank you.

(Applause)

DR. NAMBIAR: Thank you, Dr. Shawar. Our next presentation is from Dr. Amy Mathers. Dr. Mathers is an associate professor at the University of Virginia, where she's clinical director of the antimicrobial stewardship program and also serves as the associate director of clinical microbiology.

CLINICAL AND LABORATORY PERSPECTIVE

UNIVERSITY OF VIRGINIA

DR. MATHERS: Thanks for having me. I feel quite passionate about this issue. And I felt like my job today was just to give you a flavor of what's

going in the trenches in terms of management and how difficult this is in practice. So, first disclosures.

As everybody knows, we've had increasing drug resistance. New drugs are coming. And so, that's great that we've had some new drugs, especially for multidrug-resistant Gram negatives. We're happy. I don't want people to think clinicians are not thankful for this. But it's really hard to use these drugs when you don't have susceptibility testing.

And so, there are a lot of issues around not having susceptibility testing or updated breakpoints on automated devices, which is what most of clin micro -- your average clinical micro lab relies on. I'm going to just focus, as an example, on the issues around the Gram negative -- the new Gram negative agents as sort of just how this has impacted practice.

So I figured I'd just start with a case that I had not very long ago of a young woman who was in her early twenties, cystic fibrosis, so has ugly *Pseudomonas* as her main pathogen. And from about 10 days prior to her admission, she had this sputum taken. It's mucoid. So it was done by disk

diffusion. She came in very, very sick, went to the medical ICU, was in shock and, you know, not great options there.

So we put her on intravenous colistin, meropenem and tobramycin. If we had susceptibility testing to other agents, that would have been helpful. But we don't routinely have that available and our send-out lab typically only does it on active patients. So we don't routinely send it anywhere to get it done ahead of time.

She then about three days into her ICU stay developed neurologic toxicity with paresthesias and weakness attributed to the colistin from the neuromuscular blockade. And I didn't feel comfortable continuing colistin at that point. And so, I didn't know exactly what the best thing to do was. But I opted to go, without susceptibility data, which is somewhat gutsy, but I just didn't know what to do for this young woman.

We went to ceftolozane/tazobactam, Cipro and continued IV tobra. She was not doing better. And we cannot get susceptibility testing on non-urine/non-

intra-abdominal isolates from the reference lab that we had been using. Because it's from her airway, they won't do this susceptibility testing. So I didn't know what to do. When she's not improving, do I stick with the new drug, not knowing susceptibility? So these are just some of the stressful situations that are occurring out there.

When you're trying to figure out whether or not you want to use a new agent, you know, you're sort of feeling what I just demonstrated, that the risk benefit of doing that. There's not going to be as much data out on any new agent. So you don't feel as comfortable with failures or the activity. But theoretically, ceftolozane/tazobactam would work better than a lot of other agents for this isolate in vitro at least.

But if you can't have susceptibilities, it's really difficult to use a drug. I know that everybody knows this, and I don't think this should change, but the way that modern infectious disease is practices, as most people in this room know, you use susceptibility data. It's not like there's going to

be a clinical trial on every indication that you would possibly use that for.

For example, meropenem only has indications for skin and soft tissue, intra-abdominal and meningitis. But we use it for urinary tract infections. In fact, it's been a comparator in trials. We use it for ventilator-associated pneumonia. And so, it's fine. There's just too many infinite clinical trials to have. I don't think that's what we would argue for. But just knowing that it's not site-specific, you know, typically where you're using antibiotics. It's susceptibility-specific, how you use the antibiotics.

If you don't have susceptibility testing, what do you do? Well, for group A strep and penicillin, I don't care. I don't need it. And it basically comes down to is there resistance. Is there known resistance? Are there ways for isolates to develop resistance? Because if there's not, then you can be pretty sure that you could just use the drug.

And I think initially with some of the newer Gram negative agents, I think there was potentially

more hope of now seeing resistance crop up so quickly. But I think when you're treating a multidrug-resistant Gram negative, it's difficult to trust that. And now that more literature is moving out and then the recent, you know, development of resistance on therapy that's being seen with some of the newer agents.

In fact, there was a -- in a recent paper, it was retrospective -- not ideal -- but three of 10 of the microbiologic failures to ceftaz/avibactam developed resistance while on therapy. And so, when you're a practicing clinician and your patient is failing therapy, is it because you're not giving enough drug? Is it because they've got a new infection, or is it because there's development of resistance on therapy? And therefore, you really need rapid susceptibility or timely susceptibility anyway when you're in practice.

When you're treating patients that are critically ill, I think this is where a lot of this urgency comes from. And clinicians feel a lot of urgency around susceptibility testing. And this is just an old study that's, you know, over 10 years,

from 22 institutions of patients that had septic shock, so the sickest of the sick patients. And the odds ratio of mortality, if they were given inappropriate versus appropriate antimicrobials, and appropriate was defined as in vitro activity of that antibiotic was given within six hours of identification of septic shock. So it makes a big difference. And so, people don't want to give drug upfront if it's not likely to be susceptible. And if you can't get susceptibilities to figure it out, it's very difficult.

So here's just sort of a timeline of the way that I think about it. So I just tried to assay all the places that I wish I had susceptibility testing when I'm treating a serious infection. I like to be able to look back at the patient's past microbiology and see if it was susceptible to the agent that I'm about to use before I even give empiric therapy.

You reevaluate that empiric therapy at 48 or 72 hours. And if your patient is not doing better, you really do need susceptibility testing at that point because you're looking for resistance and/or can

you reevaluate if you've got the wrong source. And so, you then look elsewhere for a different agent. Also, in terms of sort of stewardship, your patient's doing better but you need that susceptibility to really target the pathogen that they have and get rid of all the other empiric therapy that you don't need.

So this is a very busy slide, and I'm not going to go through the entirety of it. but I wanted it to be available to you guys to review, although the print's quite small. So I felt like I was representing a lot of physician's voice in this issue. And so, I didn't know exactly what to do. There wasn't much in the literature.

But I reached out to eight different physicians from different practices that I personally knew. So already it's totally not random at all and it's just people I knew, and asked them what their -- what they felt like their impact at their different hospitals around the country were. You can see there I put university -- the top four university respondents and the top bottom two are community respondents.

And basically, this column here, the impact on use of a new agent is you can see here, it's pretty much impacting use of these new Gram negative agents. Most of the respondents -- I didn't ask them specifically about any one agent. But most of the respondents were referring to ceftazidime/avibactam or ceftolozane/tazobactam. It's having a huge impact on use, missed opportunities, not using at all because they can't get susceptibility testing.

And so, the only place where it's being used widely is somewhere where they're releasing the research use only data into the chart or to the clinicians in real time. The person who responded to me though also said this situation is horrible. And so, I felt like that was worth quoting. But it's not easy out there.

And then, the other thing that I asked clinicians around the country is what is your impression of research use only, when a lab tells you that they've got a research use only piece of information on an isolate. What do you do with that? And the clinicians that responded, or their

colleagues, said, yeah, I use it. I use it for clinical practice and it seems to work pretty well.

So I don't know what to say about that. But it's just concerning to me as a micro director and we had initially personally started by doing the research use only and releasing quietly in desperate times. But we don't do that anymore and we send them all out. But now there's a delay and it's really impacting use.

So I just also wanted to leave you with this table of is there a delay and, you know, when you're doing the research use only or the send-outs and there are some of the delays listed and then some of the clinicians' feelings about not being able to get susceptibility testing unless it's research use only.

And every lab where they had been doing the research use only and then taken it away, the clinicians are really frustrated and don't understand why that is. And then, this last one, the turnaround time on their susceptibility testing was three to four weeks. And so, she felt like that was not meaningful in the chart or that she just didn't feel like she could use the drug.

So in summary, susceptibility testing is central to the way that we practice modern, in-hospital infectious diseases. And we really, really need for these new drugs a way to test them and for updated breakpoints, a way to use the best of the best data clinically. And without a way to do it in a clinical micro lab, your average clinical micro lab, it makes it very difficult. So thank you so much for your attention.

(Applause)

DR. NAMBIAR: Thank you, Dr. Mathers. So we'll next hear from Dr. Humphries on the perspective from a laboratory. Dr. Humphries is a section chief of clinical microbiology and is an assistant professor in the Department of Pathology and Laboratory Medicine at the School of Medicine at UCLA.

UCLA

DR. HUMPHRIES: All right. Thank you. In here? All right. So I'm going to give the perspective of how this all plays out in the lab. And, my declarations.

So again, I'd like to start with a case

because I think this is sort of how we encounter these situations day to day. So this case was a 62-year-old lady with advanced pancreatic cancer who came in with vomiting and fever after surgery. A CT scan showed fluid collection in her liver, inflammatory ascites and blood cultures that were collected at that time grew Gram negative rods.

And so, we in the lab got a call from the infectious diseases service at the time saying, you know, this patient has had a history of carbapenem-resistant Enterobacteriaceae in the past. Is there a way to test ceftazidime-avibactam for us as you're testing the rest of your susceptibilities?

So you know, when we look at what the lab -- labs in the United States look to for guidance on susceptibility testing, it really is the Clinical Lab Standards Institute. And CLSI does give guidance to labs that they should be able to test additional agents for those isolates that are resistant to all or nearly all drugs that they test on their routine drug susceptibility test panels.

And ideally, this would be done in-house,

or, if needed, be sent to a reference lab. And the reality we're faced with today is almost none of us can do this in-house and there are very few reference labs that are available to do such testing. This is actually also a requirement of the College of American Pathologists, which is a group that many clinical labs in the United States are certified through.

So if you take a look at what labs are doing today for susceptibility testing, by far and away it's automated susceptibility test systems. Vitek and MicroScan hold the majority market share over Phoenix and Sensititre. But most labs are putting isolates on these automated systems and reporting out results this way.

Rarely, labs will use an alternative method, maybe for a difficult organism or perhaps for a drug that's particularly difficult to test or if there's no claim for a drug/bug combination on their routine AST method, they may in some cases use an alternative. And so, Dr. Mathers gave an example of this with the *Pseudomonas aeruginosa*. If they're a mucoid isolate, many labs that serve cystic fibrosis populations would

do disk diffusion for those.

I will say that doing different testing for a lab is a pretty big endeavor. You're talking about a lot of additional quality control, training, not to mention bringing up these tests, which I'll talk about in a moment. And so, most labs prefer to use their system for everything they can. And this is particularly true for those smaller community hospitals.

So when we look -- again, I'm going to focus on Gram negative agents because I think the problem is most critical for these. But these are what we have today as options for these agents. So there are disks available that are cleared. There is an MIC method, which is through Sensititre for both drugs.

These are available, but only on custom panels. And so, if a lab wants to order these, they must order at least -- and there's a typo there, it should be a thousand or 500 of these panels in order to get this drug. And so, that's a pretty big commitment for a lab, especially for these agents. And many would not go that route because they are

fairly costly as well.

As far as reference labs goes, there's one that does susceptibility testing for these agents and that's LSI. A big problem for us in California is they are not licensed to test Florida, New York or California patients. And so, for patients in those three states, this is just not an option.

In addition, there are delays. If that lab finds the isolate to be resistant, they are going to repeat test it and that is associated with an increased delay, when really we want those resistant results as soon as possible. So it is an option, but in reality, there are several limitations to this.

So I too kind of reached out to my colleagues to see how people are dealing with this situation today. And so, these are a couple of different microbiology lab directors in the Los Angeles area. And so, the small community hospital that has no specific microbiology director are using the research use only Etest for these drugs. They've never done a verification study to show that this test works. But they've been checking their quality

control and that's been okay. and these -- they report these results to the chart with no disclaimer.

The private hospital, which has a PhD microbiology lab director, they perform the research use only test after they've verified the performance. And they go through the extra measure of prior to reporting the result, calling the physician and explaining to them the limitations of research use only testing. I think this is really above and beyond. Most people who are using these RUO tests are not doing this. But again, it kind of speaks to those labs that have these higher capabilities of having PhD level or MD level microbiology director.

The county hospital that I queried simply cannot test these. Their hospital has a policy that they are not to use any research use only test whatsoever. They cannot send it to the reference lab because they're not licensed to test California patients. And then, the other two contract reference labs they work with, which is ARUP and Quest, don't test these agents. So they have zero options for testing.

And then, finally, I queried one of the large reference labs in our areas, and again, they cannot test because they found the disk reproducibility to be poor. And again, by policy, they cannot use research use only reagents.

So you know, one question I had is there are FDA-cleared disks for these drugs. So the question was why not just bring on that disk. And so, people who responded to me said they found the reproducibility to be poor. Their physicians wanted an MIC, not a susceptible, intermediate or resistant result.

And finally, and I think this is a big one, you know, as Dr. Mathers mentioned, we use a lot of these drugs for more than the packaged label indications. And an MIC means something, but a disk zone means absolutely nothing to a treating physician. And so, if there's no disk breakpoints -- for example, the Enterobacteriaceae and ceftolozane/tazobactam -- there's no value in using a disk if that's what you're being asked to test.

Just to touch briefly on what a lab goes

through to bring on a new susceptibility test, we are required through CLIA to do a verification study. This includes tests that are FDA-cleared and this is testing that is done in-house before we start patient testing. I want to emphasize that just doing your quality control testing is not sufficient for this.

A lot of labs have the misconception that just running QC is enough. But it's not. The lab must test an accuracy panel of a minimum 30 isolates and the CDC/FDA resistance bank is a great resource for that for some drugs, but not all. And the lab also must do some precision testing of at least five isolates in triplicate over three days.

So this maybe doesn't seem too difficult. But I'll tell you most hospital labs are crippled at the thought of doing a verification study like this. They really have big concerns about designing the studies, as well as executing them and resolving discordance, which will of course happen is another big issue, in particular if you don't have a reference lab that you can send isolates to for confirmatory testing.

And so, a lot of the labs, you know, when we talk about even bringing on new breakpoints, they just don't even bother because this step is too difficult for them.

A couple of other considerations we have when we bring on a new susceptibility test, we need to write a new standard operating procedure that includes things like when we're going to test, how we're going to interpret any special reporting considerations. We need to work with our IT group, which is actually probably the rate limiting step in the whole thing, to add this to our panels, building the interpretations, developing an interface.

Developing your quality control plan, which as of January of this year includes the use of an individualized quality control plan, which is a risk assessment specific to that test and a plan based on that risk assessment, which is a pretty big process. Training and competency. So to give you a sense, at my institution, and we bring on a lot of new tests, it takes us six months to a year to bring on a new test. We can fast track things a little bit if there's an

urgent need -- for example, if there were an FDA-cleared test that we were going to bring in for one of these drugs, we would fast track it a bit. But some of these things just can't be sped up, including the IT part.

So if we go back to our case, this patient actually had a ceftazidime/avibactam-resistant isolate. And we tested it in my lab by reference broth micro dilution. We obtained avibactam powder to do so. But this is not the typical situation for labs.

And so, if you go back to our labs, if they're using a research use only test, likely that result would be reported three days after the routine susceptibilities are known because it would be something done after the fact. And we're really not sure at this point how well research use only tests do to detect resistance.

A lab that can't use research use only tests and doesn't have a reference lab to send it to, they'll never find out this result. They would just never know and the physician would be left probably

using this agent empirically for this patient and this isolate in particular was a KPC producer. And then, a lab using a reference lab probably would receive this result a week after and maybe with further delays. Because this isolate tested resistant, this lab is going to do confirmatory testing to make sure that was an accurate result.

So I think that there's, you know -- there's really a dire need for us to have FDA-cleared tests. What labs need is these tests on automated systems because the majority of us are using those and bringing on ancillary other testing is very, very difficult. So, thank you.

(Applause)

DR. NAMBIAR: Great. Thank you, Dr. Humphries. So we'll now move on to the next session, where we'll hear from the experience of the pharmaceutical sponsors. The first speaker in this session is Dr. Motyl, who is a board-certified clinical microbiologist from Merck. And prior to moving to Merck in 2000, she was the director of medical microbiology at the Beth Israel Medical Center

in New York City. So, thank you, Dr. Motyl.

PHARMACEUTICAL COMPANY EXPERIENCE/PERSPECTIVE

MERCK

DR. MOTYL: Okay. Thank you very much. So it's a pleasure to be here to -- I'll be one of the representatives from the pharmaceutical company. And -- okay, this is a problem when you're short. Ah, yes. Sorry, sorry, sorry, sorry.

Okay. So what I wanted to say a little bit is about myself. And prior to my coming to Merck in 2000, I was a director of a large medical microbiology lab in New York City. It was a laboratory that handled over 600,000 specimens each year.

So I really was very much aware of the issues of breakpoints, new breakpoints, old breakpoints, RUO versus approved tests, the fact that there were a multitude of device manufacturers because they would all come and visit me and also the problem of the lag between the time a drug was approved and when it was available on an automated device.

And the thing that was different though that at the time -- so recall I came to Merck in 2000. And

I was at Beth Israel from 1990 to 2000 -- is that, you know, we had a very active infectious disease group and very academically inclined. And we had an agreement that if there were results from RUO devices, I would be able to give them that data because they would know how to interpret it.

I was also able to do susceptibility testing on isolates that possibly weren't in the given labels. And that was based on an agreement with the infectious disease department. So how things have changed in the last few years where most hospitals, most laboratories can't do this any longer and don't do this any longer.

On the other hand, so those things have changed dramatically. On the other hand, when I first came to Merck, Invanz, or ertapenem, was first approved then in 2001. And it was almost three years before it could be tested on a susceptibility device. And how little has changed since then, because the numbers are still the same. That time delay of around two to three years still exists now almost 15 years later.

So Zerbaxa (ceftolozane/tazobactam) was

approved in December, of 2014. But there is no automated commercial device available to test for susceptibility to this antibiotic, as Dr. Humphries has said and Dr. Mathers has said. We have manual tests available.

We have a disk, manual Sensititre panel is also one, gradient diffusion strip. But they were approved also about one-and-a-half years after Zerbaxa was approved. That meant for a year-and-a-half or so, there really virtually was no way to test for susceptibility to this new antibiotic. So we really need to close the gap between antibacterial drug approval and the availability of susceptibility tests.

So some of this, you know, we keep hearing over and over again from all of the stakeholders in this process. Why is it important that approved AST devices are available? It is really critical for clinicians to make decisions for patients where there is limited options, as both Dr. Humphries and Dr. Mathers have mentioned, especially for those multiple drug-resistant Gram negative organisms where you can't predict the susceptibility by any kind of a surrogate

test.

So the FDA-cleared tests are required by hospitals for patient reporting purposes. MDs are reluctant to use an antibiotic that the hospital can't test for and are reluctant to use information from research use only devices.

And frankly, if -- even if a hospital does request RUO devices from us, they have to sign terms. They have to agree actually to terms and conditions stipulating that the RUO will not be used in determining therapeutic options for patients or for other diagnostic purposes. That really does stymie the process. That really does stymie the availability of critical information for the patient.

So RUO devices do have a limited ability -- limited utility and are not a bridging solution, although probably more discussion really needs to occur around what kind of data could possibly be shared with clinicians from RUO devices.

Approved susceptibility testing devices are also very important to understand the local ecology. There is such a big effort these days about, excuse

me, antimicrobial stewardship programs. Many hospitals are instituting these new programs and how are the decisions to be made if there's no way to do susceptibility testing and determine your local ecology?

And finally, it's important to have approved susceptibility devices to be able to detect the emergence of resistance, especially when a new antibiotic comes out. It is critically important to know whether there's a pattern of resistance development or not.

So what are our goals? Our goals are to ensure that the providers have access to manual and automated susceptibility tests as quickly as possible. I mean, manual tests are very important, as I've been mentioning, to be available as quickly as possible because at least that's an option. It may not be the one that hospital labs favor, but it certainly is an option to be able to use these devices.

However, we've heard from all of the previous speakers that the end users prefer the automated tests. So really the goal for all of this

has to be to speed the commercial development of the automated susceptibility testing devices. That should be our not only long-term but short-term goal.

So why are there delays for the availability of commercial susceptibility tests? So this is really a multifactorial problem. There are certainly internal delays from both the drug sponsor and the device side. I mean, having been intimately involved now in the last year on getting Zerbaxa on susceptibility testing devices, it is clear that just the process of signing these initial agreements is something that is interminably long.

We have templates. They have templates. The templates go back and forth and discussions go on and on. Legal gets involved at both ends. You know, six months, eight months pass and, you know, the dots -- the dots aren't dotted and the I's aren't dotted and the T's aren't crossed still. And this is maddening. But this is an internal problem that needs to be worked out but certainly does add to the delays in the approval process itself.

Now, in addition, there's the complexity of

the development process itself of the different devices. There are development cues. Susceptibility testing companies can only develop so many drugs in a given year. And at a time when new breakpoints have been applied to old drugs, now they've become bombarded not just with new drugs but having to update the breakpoints on the old drugs.

So there are development queues. And you may make a queue that year, or maybe not. And you may be bumped to next year. That adds another year. A device may be approved but most of them are very heavily reliant on software.

This is no longer the day when you can just lift the plate up in the air and read the MIC. You have to rely on the interpretation by a computer. And the software update may take some time later, to occur sometime later. The update may be once a year, every other year or every year-and-a-half. The device may be ready. Software might not, add time to it.

And then, finally, there's also the commercial availability of the devices. So the device may be ready. The software may be ready. But you

need to get groundswell in order to get the device manufacturers to manufacture plates or panels with your drug on it.

So it also becomes a negotiation. Real estate is very limited on these panels, you know? and device manufacturers are not going to make a panel just for you and they're not going to kick off your competitor off of the panel. And so, it is, you know -- and I hope I'm not sounding facetious. But it becomes a problem and it becomes a very intricate problem of negotiating and discussing and that takes time, in addition to that.

And of course, there's what we've been talking about here today is also the timing between drug approval versus device approval. And we've heard already that this requires approved FDA breakpoints and the device is approved only after the drug is approved.

So when you put all of these different factors in, you can see where the delays potentially are and also potentially where the solutions are. I did want to bring up also the delays in updating of

new breakpoints for old drugs. So I did mention that might block up a queue for the device manufacturers because all of a sudden now they've become bombarded with having to change the breakpoints on old drugs.

And within the last five or six years, there's been a really concerted effort to change the breakpoints on the old beta-lactam drugs, now using PK/PD. And that took a great deal of discussion, took a great deal of anxiety on the part of man different people. But certainly the CLSI was able to accomplish this task, at least to a great degree.

So now all of us and the device manufacturers have to do that in addition to everything else. Now, if we think though -- I mean, what makes me upset though is if we think that that was an important thing to do, to change these breakpoints because in fact the old breakpoints were not appropriate and could have led to patients being mistreated if a physician relied on the old susceptibility breakpoints.

Then, how can we possibly be standing here today and just accept the fact that it takes two,

three, four, five years maybe for even these new breakpoints and old drugs to make it on devices. I mean, if it truly was a medical issue, then why are we waiting? How can we possibly justify that?

So how do we work with device manufacturers? Now that I've almost beat up the poor device manufacturers, how do we actually work with them? So we obviously have to as a pharmaceutical company -- and I really don't mean to -- I think the device manufacturers are doing a phenomenal job. I just think that they are bombarded and overwhelmed.

We have to work actually with all the device manufacturers because as has been mentioned also, there are any number of automated systems. There are different preferences for specific systems in a specific hospital. So we have to work with all of these.

In addition, though, what might not be appreciated is we also have to work with device manufactures ex-U.S. and we have to -- there are certain devices that are only available ex-U.S. There are certain cards and panels that are available only

ex-U.S.

So if you consider the process and the complexity of the process of getting your drug on a panel in the United States, you know, multiply it by two or three times if you have to now also have your drug on panels ex-U.S. So what are the -- some of the resources that we share with the manufacturers?

Certainly the costs and the costs for developing a new antibiotic on a panel can be as low as in the thousands of dollars to several million dollars. And I'm not sure. I mean, from the pharmaceutical point of view, we feel that we're paying a lot for the development. But possibly we are not.

And this is I think a situation where if there is better cooperation and better working together with the device manufacturers to really understand what their true costs are for development, then maybe there is a path forward there as well. Maybe the $2 million for an automated device is only a tenth of what it really costs. I really have no idea.

But if we were more transparent and were

able to work together better, maybe we could address this kind of a situation as well and help expedite the development and the approval process.

Now, we do share information with the drug -- - with device manufacturers. We do share the indications, the organisms that are being sought, some nonclinical data and the estimated time for submission. We also recently for Zerbaxa deposited a panel of very well-characterized bacterial isolates with the CDC with MICs and molecular mechanisms of resistance. And we've had these isolates characterized to the level of efflux pumps and porin defects and so on.

And I think this is probably a very excellent resource, these panels that the CDC has now. And I think even possibly more than just sharing of the clinical isolates because clinical isolates from the clinical trials, let's say, would tend to be susceptible. I mean, they are not going to be covering all of the different resistance mechanisms.

So I think together with sharing some clinical isolates from the clinical trials, the

resources that the CDC now has and hopefully will expand on should be able to cover all of the different resistance mechanisms that are so critical to new antibiotics.

So some improvements to the working relationship, and we've -- first of all, we've tried to improve some of our processes on the paperwork internally. We actually have a Zerbaxa susceptibility testing development team. And really, there's probably about 10 of us and we regularly meet with each of the device manufacturers either by teleconference or WebEx or at every meeting that is available.

We sit down and we regularly follow progress and try to expedite any delays. We've even set up a powder committee, if you will, because then we found that one of the hang-ups within Merck itself was the availability of powder, whether it was from a -- by a device manufacturer or an investigator.

It could take weeks, up to months to get powder and there are some laboratorians that are fully capable of doing manual -- or set up their own MICs

and yet it might take months to get powder out and we've tried to expedite that as well. And some of what we've figured out also is in the future, if any new drug that is in development -- so one of the things that some of the device manufacturers have requested is that we come and visit them and give them basic information about the new drug that's being developed.

You know, and we're going to expedite this. We're going to make this different in the future. we're going to -- whether it's going to be by teleconference or WebEx or something, we're going to pass all of this information to all of the manufacturers at the same time. I mean, we really need to at every level try to expedite the process itself.

So what are some of our learnings with -- so we had something that's in development and that is imipenem/relebactam, MK-7655A. It is in phase 3 development. So we have, and please don't laugh, an aspirational goal of imi/rel being on automated devices no longer -- no later than six months after

approval. So I know this is aspirational. But we are working really, really very hard.

So we've initiated all of the contracts concurrently with the Zerbaxa contacts. As I mentioned, we've simplified the process for powder availability. We also -- this is another team then that meets with the device manufacturers to address issues and problems and to push the development.

We also have a large panel of imipenem/relebactam susceptible and resistant isolates that have the mechanisms of resistance fully characterized. And you know, we plan to submit those to the CDC to be an available panel. And we're really looking forward to these meetings with CDER and CDRH and the device manufacturers to push this along.

So what are some of the potential challenges to co-development and the risk to the device manufacturers? You know, some of this has been covered already. Some uncertainty that a new antibiotic will be approved. Manufacturers have development queues and a queue may be booked up. Old and new antibiotics, as I've mentioned, compete for

time and resources, at least in the last probably five years with the changes to the breakpoints, to all of the beta-lactams.

The device manufacturers have been completely bombarded with having to make changes. The adoption of a new automated AST panel may be slow as well. You know, panels and cards are expensive. Laboratories may hesitate to change or discard old panels, kind of use them up, if you will.

Resistance panels that might be separate from a routine panel could be expensive and not widely utilized. And as Dr. Humphries has mentioned, QC and validation needs to be performed. And then, there's also the integration with the Laboratory Information System that may be required. All of this takes time and this all adds to the delays.

There's a return. You know, so the return on investment for new panels and cards devices is low. Device manufacturers are not incentivized to expedite development, in part because there may be low demand in the beginning with a new antibiotic.

Now, although antibiotic resistance is

considered such a key issue, you know, medical societies, hospitals, quality assurance organizations have not prioritized the availability of AST devices to be available promptly. It's something that we know about. It's almost like a secret internally.

But I don't see a groundswell in the literature -- in the medical literature -- saying why are these things not available six months after a new drug is approved. And I think we need much more, more activism on the part of these different societies in order to address the situation.

So in the last few years, drug sponsors and prescribers have been encouraged to address antibiotic resistance. So sponsors were encouraged to innovate the GAIN Act, incentive discussions, the IDSA's "10 by 20", all kinds of different guidance documents on expediting development of new antibiotics.

However, there are no similar incentives or mandates for the AST manufacturers. So you know, there is no "10 by 1" -- you know, 10 new drugs in one year. There is no -- there are no financial incentives. It's as if we have -- we have -- we are

trying to address one part of the problem. But we are not addressing and not helping out the device manufacturers with respect to expediting the development process from their end.

So we really welcome the FDA draft guidance. We do think that earlier collaboration is going to be a very positive thing. We do like the idea of joint meetings with the device manufacturers. And we do really hope that the professional and quality assurance and medical societies will become more actively involved in this question and trying to solve this.

Now, we do recognize it may be difficult to achieve current drug approval and device approval. And we are looking actually for more details in the guidance or as a result from this guidance, including how to -- how to provide critical susceptibility device -- susceptibility data to physicians during this gap period while we're trying to figure out how to shorten that time between development of a drug and development of a device.

How can we help the laboratories and the

physicians? What can -- what can laboratories and physicians do with respect to RUO tests or isolates that are not in the label? And we do need much more discussion to incentivize the device manufacturers.

Maybe explore the possibility of something like a BARDA-like mechanism or reimbursement or so on. But it really is all of us that are involved. And I'm glad that Ribhi brought up it takes a village. And I thought maybe I shouldn't say anything about it taking a village because this is a presidential year and who knows who stands for whom or whatever.

But it really does take a village, you know what, because it does not just take, you know, the pharmaceutical company. It's not just the FDA. It's not just the hospitals and it's certainly not just the device manufacturers. You know, we are in almost like a perfect storm where every piece of this process needs to be amended and fixed.

And I think only by the application of our joint smarts, our joint efforts and our joint willingness will we be able to solve this. And I hope that we do in the short term. Thank you.

(Applause.)

DR. NAMBIAR: Thank you, Dr. Motyl. Our next speaker is Kevin Krause, who's from Achaogen. And he serves as the director and head of microbiology and oversees microbiology-related R&D activities at Achaogen. So, welcome.

ACHAOGEN

MR. KRAUSE: Okay, great. Thank you. Good morning, everyone. Firstly, I'd like to just thank the FDA for the opportunity to be here to speak on behalf of the pharmaceutical industry. Disclosures there.

So let me begin by saying this is a very exciting time to be in antibacterial development. There's a lot of great progress that has been made over the last few years that have been driven by a few defend things.

First, there's been some significant progress made on the regulatory science side. We're seeing drugs approved much faster for those that meet unmet medical needs. We've recently seen ceftazidime/avibactam approved using the 505b2 pathway

based on phase 2 data, other streamlined development pathways and expedited NDA reviews.

And in addition, there has been a new spirit of collaboration and innovation brought to the space. The FDA and EMA have been increasingly working together. They've been great partners in this process. We've seen progress made with passage of the GAIN Act on the legislative side. And we have additional -- we have additional partners available to us through groups like BARDA, the ARLG and NIAID broadly, various CDC initiatives, CARBAX (ph) and others that are coming forward.

So all of that has created a new era for us to bring drugs to market faster. However, as we've heard, we're only doing part of the job at addressing an unmet need. It is only partially helpful when we're bringing a drug to market faster, but we don't have AST available at the same time. And as it stands now, new drugs are launching faster and faster.

But there are no commercial AST tests available for most of these drugs. And that leads to a reluctance on the part of the physicians,

appropriately so, to use new antibacterials when they don't have susceptibility testing available.

So the goal then should be simultaneous approval of the drug and the device. We can shorten the timelines we have now, but we really need to get to a place where the drug and the device are approved at the same time.

So I wanted to focus today on three fundamental challenges that I see, and that I've seen over my career in what it takes to bring an AST to market. And I'd like to describe those challenges. I'll talk about the causes of them, some of the effects, and then I'll offer up some solutions for consideration.

And those three are, of course, the delay between drug and AST device approval, how we can work towards eliminating that delay, the effect of updating -- making updates for marketed drugs is slow, so both on the breakpoint side and on other areas where performance needs to be improved. And then, how we can work towards seamless integration of communication between pharma and AST, which already happens to a

certain degree, but then also work with our colleagues at FDA more closely.

So if we begin with the first challenge, so the lag between drug and AST approval, this lag is really creating an unnecessary obstacle to the provision of high quality patient care. We have an urgent unmet medical need to treat MDR infections and we're bringing drugs to market faster. But really it's becoming increasingly difficult to identify the patients that would benefit from these new antibiotics if AST is not available. This leads to -- and we've already heard some of this. This leads to inappropriate antibiotic selection and frankly drives poor clinical outcomes for these patients.

Conversely, it really doesn't allow the pharma company to allow timely feedback on how our drugs are performing when they go out there into the real world after launch. We don't get timely feedback on what new clinical data might be appropriate when drugs aren't used to a significant degree. And we don't get real-world information on how our drugs perform with respect to resistance patterns and how

reliable the AST methods are. And I don't mean just automated methods. I mean does our MIC reference method actually work. Do our disk tests work? We don't get that information in real time so that we can course correct if the drugs aren't used routinely.

And so, I would say that the regulatory innovation that we've applied to streamlined antibiotic development really needs to be applied to the AST side as well so that we can get this information faster.

So I wanted to offer a real-world example from my past and that's the timeline for ceftaroline, or Teflaro. So we began -- I used to work at Cerexa. We began discussions with the AST companies in 2008. It was actually before my time there, as the phase 3 studies were just getting underway and those discussions continued through the phase 3 program. and you can see there when the NDA was submitted and reviewed and Teflaro was approved in October, of 2010.

Immediately, or relatively soon after approval, we had one of the disk manufacturers get their disk FDA-cleared. And then, Sensititre panels

and other disks came online a bit later. There were some technical challenges with ceftaroline that led to a little bit of a delay with some of the disks. Typically, these would be approved a bit sooner than the timeline you see here and tame for e-tests.

However, it took almost four years for the three automated systems to be FDA-cleared. And there were a number of reasons for this, which I'll come back to later. But you know, this is really, really a significant challenge for a company trying to sell a product when, you know, there's essentially no susceptibility testing left and no one really understands how to use this drug.

This example has been quoted in a few different places over the last year because it's really the most contemporary drug that has a long lead time and where all the AST devices are available. But what's never said is that the dates that are shown here, which are publicly available, are the dates when CDRH cleared the device.

But it took another 12 to 18 months to actually commercialize these panels. So we say four

years, but it was really closer to five-and-a-half or so before all these devices were available. And that's driven by customer demands and requests and some other things. But also the information that's required to update the software on these devices.

So ceftaroline was out in the world for five-plus years before the full suite of AST devices was available. And that is a typically timeline for a drug that was developed under a traditional timeline. Ceftaroline was developed using four registration -- phase 3 registrational studies, two in each of two indications.

And although that seems like, you know, it's sort of the opposite of what we want here, we want to get drugs to market faster. That longer development time actually gives the AST companies longer to develop their panels, right? So they had more time to work through all the data that they need to require.

So then, what happens when we accelerate drug development? Well, if we think about Avycaz, which was just approved, well, a year-and-a-half ago or so based on phase 2 data, because it had the

potential to address an unmet medical need, there was no way for us to accelerate AST development. We found a way to get the drug to market faster. But at the time, there was no way to accelerate AST.

So as of this month, when I checked, putting this presentation together, which was 19 months post-approval, there were only disks and TREK Sensititre available. The drug's been out there for 19 months and there's essentially no way for most clinicians -- and we heard that already this morning -- to test the drug that was approved earlier because it was meant to address an unmet medical need.

Okay. So what would we want? What would be the ideal situation to address this? I think the key thing is to have simultaneous review of an NDA and the 510(k) package for each of the device manufacturers. That currently does not happen. Currently, 510(k)s are submitted only after a drug is cleared and approved.

And so, a few things that we could consider doing to help loosen some of the requirements that drive that. The first is using phase 3 central lab-

derived data for investigational devices that are tested alongside the reference method as an alternative to the requirement for fresh clinical organisms for a 510(k) package.

It used to be many, many years ago that we would use things like e-test strips in our phase 3 program to gather more data compared to the MIC method. And that was for the pharma company to make sure that we were developing the e-test strip in a way that made sense.

But that data was never used as part of a 510(k) package. It was moistening the pharma company kept to themselves, in part because we were often told that that data could not be submitted. It could not be a surrogate for the data that it was required to collect as part of a 510(k).

At least in my experience, that sort of approach has fallen off. I don't think we do that type of testing as much anymore because it's expensive. But you know, certainly getting data from a central lab on contemporary clinical isolates side by side with a reference method is exactly what is

required of the 510(k). It's just that it's done in the context of a clinical trial rather than done separately by the ASP company after the drug is approved or during the phase 3 program.

In addition, I think we should also think about revising the rules for data requirements for species that are in the approved package insert only. There are certainly situations where some isolates -- some species could be used as surrogates for others, especially among the Enterobacteriaceae.

You know, if you only have *Citrobacter freundii* in your label, *Citrobacter koseri* is probably going to behave exactly the same way and you should be able to use that if you didn't get that in your label as a surrogate. Same goes for different species of *Klebsiella* and others. And so, just loosening those rules a little bit I think would greatly help the AST companies bring their products to market faster.

I'd also like to propose that we consider establishing AST centers of excellence as part of a national surveillance program. And there's been calls for a national surveillance program in different

flavors over the years. But I think here specially for AST, this would allow us to test drugs earlier in development on a standard platform that -- and a level playing field. And this would allow us to identify resistant organisms sooner.

Every time we develop a drug, we don't find resistant organisms early in surveillance and almost never in our clinical program. but they immediately appear when the drug is launched. So they're out there. If we had a national surveillance program, we should be able to find those resistant organisms sooner.

And that would -- that would really allow the AST companies to push the bounds of the performance of their product and to more appropriately decide what their error rates are early on. This would allow us also to expand the publically available clinical stock and challenge sets that were previously described.

Those isolates, if they come from national surveillance, could be contributed to a depository that's available publically. And another added

benefit is that we would understand the true spectrum of activity for new antibiotics. We heard that drugs are often developed for a couple of key indications against a limited set of organisms.

But they get used for all sorts of things that are not formally studied in the clinical trial. And so, this would allow drugs to be tested, at least for in vitro activity against organisms that are more rare and things that the pharma company doesn't specifically pursue.

And then, lastly, I think we should consider a limited use labeling approach to 510(k) clearance for AST diagnostics. If a -- or excuse me, if an AST device has most of the data that is required for a 510(k) clearance -- for example, using the data from a phase 3 study -- why not allow that to be used in a limited use setting? We do that for drugs. Why not do that for diagnostics, especially diagnostics that are meant -- that are used for a drug that already has limited use labeling?

Okay. The second challenge -- so, as we've already heard, making changes to AST devices is slow

and it hampers development of AST for new drugs. And I have a few examples from my past that I can describe here. When we have outdated breakpoints, as Mary nicely highlighted, those changes were made for a very specific reason. And when they are not implemented, we are then continuing to make poorly informed treatment decisions that lead to potentially worse outcomes if the diagnostics don't change the breakpoints.

But right now, there's a significant lag time between breakpoint changes at the FDA and CLSI and actual implementation. And this is driven by the fact that it takes a long time to college the data that's needed to make those breakpoint changes. There's a pretty significant burden of requirement on the AST company to collect data that -- to make those changes and it strains the limited resources at AST companies and it limits the ability to develop new drugs.

So two examples from my past are with telavancin. We were in the middle of developing the automated systems and the first VSRA -- the

vancomycin-resistant *Staph aureus* isolates popped up. Well, it turned out that the automated devices had difficulty detecting those isolates. There was also a breakpoint change that occurred with that and telavancin AST development was completely stopped while those changes were made.

And the same happened with ceftaroline AST development when issues popped up with piperacillin-tazobactam. Now, nobody would argue that vancomycin and *Staph* or piperacillin-tazobactam and Enterobacteriaceae isn't a huge public health concern.

So certainly those things need to be prioritized. Those changes need to be prioritized. But there has to be a mechanism where developing new drugs in the background can continue to move forward while those changes are made and that would happen if those changes were made more quickly.

There was a paper that came out this month that I thought was particularly interesting in the context of today's discussions from Bartsch, et al., and it was in the *Journal of Clinical Microbiology*. And it talked about how -- it talked about the

implementation of the new -- the new carbapenem breakpoints for Enterobacteriaceae. So these were changed in 2010 by the FDA and CLSI. And as of the writing of this paper, they had still not been implemented on most major AST systems.

And so this group, it's an epidemiology-focused paper, they took data from Southern California. They surveyed every hospital in Orange County and basically built a population model and extrapolated that data forward. And they talked about CRE carriage rates in the United States.

And their estimate was that between 2010 and 2015, there are 8,500 additional CRE carriers in the United States because those are patients that had exposure to other patients with CRE who were not identified as patients with CRE and therefore contact precautions and other things were not put in place.

So you know, an additional 8,500 patients walking around with CRE that are colonized because they were exposed to another patient is just not acceptable and it is a major public health concern.

So how can we expedite these changes then

that desperately need to be made? Well, again, I talked about AST centers of excellence and national surveillance. That same program can also help more rapidly identify problems with AST and with breakpoints.

Currently, at least in the way that I understand it, identification of performance issues for AST often come through a series of customers sort of highlighting issues that they've seen. And then, there's a discussion at CLSI and then there are breakpoint changes that are made over time.

But if we had sort of a sentinel group that was looking at things in real time, they might more quickly identify any potential issues. And so, if you know about the problem sooner, you can fix the problem sooner.

This same group can then also monitor the performance of AST devices once launched and make sure that the breakpoints that are set at launch make sense and that they actually lead to the appropriate clinical outcome.

Dr. Motyl alluded to this a bit. But I also

think there's a role for ADT products that group new antibacterials, specifically cards that come with the automated systems.

If you were to think about a resistance card that just had all the new agents on it, so all the new anti-CRE agents, that might segregate those drugs from any changes that needed to happen to sort of older legacy drugs, if you will, that are on the standard panels. It would isolate them. It would sort of keep them separate.

And you know, we may only use those cards in cases where an MDR pathogen is identified. But that's where these drugs should be used anyway. So you would go to that card and get that susceptibility result when you have patients similar to those that were described earlier.

And then, that would allow some flexibility on updating that card more regularly. It wouldn't have to maybe fall into the same development cycles that we currently see.

And then, lastly is to just develop more -- a broader range of antibiotic dilutions during

development. You know, right now, when a breakpoint change is made, there's a whole bunch of work that needs to go into changing that because often there isn't data on the MIC -- the specific MIC dilutions that are now representative of the breakpoint.

So if we identified a lot -- or if we developed a lot more dilutions up front, even if it was 10 years later, that data -- you could go back to that data and see what the performance at different breakpoints was and at least use that as a foundation to begin to change breakpoints. And I think that could save a lot of time.

Now, we already sort of do this in principle. Currently for a lot of the automated systems, the pharma companies will pay for development of multiple calling ranges, as we call them. But it's an optional approach and it's frankly very expensive. Every time you add another calling range, you're doubling the cost.

And so, a lot of companies, especially small companies, opt out of this approach. But there might be some happy medium between those two that would help

facilitate more quickly changing breakpoints.

And then, the final challenge, so lack of communication between pharma, AST, device developers, CDRH and CDER. So we've heard talk today about the possibility of having joint discussions between these groups. But that rarely, if ever, occurs. So in fact in my career I haven't ever seen that occur for the four drugs I've worked on.

And I think this is a missed opportunity for information sharing and coordination of activities. You know, and I'll talk about some of the potential benefits of this in a minute. But the one thing that immediately pops out is agreement on tentative breakpoints that can be used for development of the automated AST devices to help expedite those systems.

Currently, it also leads -- this problem also leads to setting of breakpoints, using investigational devices, specifically Kirby-Bauer disks, but in some cases dry-form panels before those devices are reviewed and cleared by CDRH. So you know, we have to -- we have to walk a fine line there. If we had coordinated communication, coordinated

review of a 510(k) and an NDA, it may help streamline and eliminate that problem.

And then, alignment between pharma and AST companies. So you know, we often start talking very early, phase 2 or earlier. But it takes a long time for development to begin. And I'll come back to some of the reasons for that in a minute. But you know, it can take two to three years from the time we start talking to the time development actually starts. And there are some very good reasons for that. But there's also some solutions.

And part of that is driven by the fact that pharma changes its mind or discovers new data. So we may provide a reference method and then change it later. That completely derails the AST development process.

And so, there's ways to more robustly develop things up front that would help. And there are also examples where AST companies have run into technical challenges that the pharmaceutical company can help alleviate. But if those discussions don't happen, we can't help.

Okay. So just to highlight some of the -- well, and there's a lot of them, a lot of the moving parts that we all have to coordinate when we're thinking about developing an AST device. So first of all, there's a significant amount of resources from the pharmaceutical side that need to go into development of an AST device. You of course need people who know what they're doing.

So you need dedicated and experienced personnel from the pharma side who know how to manage not only this process but can manage multiple partners, multiple companies, multiple device streams. So it's essentially a project management role with technical aspects on top of it.

There's a significant financial investment from pharma. In the current drug I work on, I went back and looked and we've spent so far more than $2.5 million across all the devices. Now, that's not a lot of money in the context of drug development.

But for a small company, that's a significant investment and that's money that's spent at risk up front. So you know, thinking about ways to

de-risk some of that spend is helpful.

And then, once we do all that, we need to match our timelines for drug development to those of the AST devices. We often don't talk about how those timelines match up until we find out that we can't get our drug developed for a period of time because we're off cycle. And then, there are limited spots available for development at the AST side.

So all of that happens in the background. But then, there's a significant amount of data that we need to collect on the pharmaceutical side. Each one of these requires a study or multiple studies and a significant amount of money. And I won't go through all of them. But you can see that there's a lot of them. And if any of these change during development, it can detail the entire process. So better communication as things move along can help streamline that entire process.

Okay. So earlier and better communication between pharma and AST companies. I think clear discussions of data and issues along the way can really help facilitate everything. We need to figure

out a way to expedite the contracting process from both sides.

Again, across three companies and four drugs, I've seen the same or very similar timelines. You know, two, three years to get a contract up and running. And there's reasons for that and a lot of it has to do with misalignment of incentives across AST and pharma or just the time it takes to negotiate these things with multiple companies.

I think one way to do that is to schedule regular calls to discuss progress and issues. This rarely happens at this point, at least in my experience. There is no joint steering committee. There is no joint discussion that happens at regular intervals to talk about what's going on.

I think there's opportunities to leverage the CLSI and the Susceptibility Testing Manufacturers Association to facilitate these broader communications. Often pharma comes to the STMA at the CLSI meetings, gives a onetime presentation and that's the last time we talk to the STMA as a group, at least until maybe breakpoints are set or something along

those lines.

All these things would allow broader understanding of each other's perspective. I think there's just a lot of -- a lot of better communication that can happen.

And then, thinking about bringing the FDA in to joint meetings. I think there's an opportunity -- well, for drug development, we have regular meetings that we need to have at certain milestones in drug development. And those don't exist for AST.

I think it would be reasonable to suggest that we might consider having joint meetings that include the AST at regular milestones, maybe pre-phase 2/3, pre-NDA or pre-510(k), to talk about what's going on and make sure that we're all on the same page and that things move together a little bit better.

At those meetings, we can discuss potential pathogen lists and tentative breakpoints, if we can gain agreement on all those things, I think, and allow the AST companies to move their development forward using an agreed-upon tentative breakpoint that, if that breakpoint changes later and it's within, say, a

dilution, that that won't make the AST company start completely over. If we have agreement up front to that, I think there's an opportunity to streamline things. And that will make timelines and the AST queue and all sorts of other things more transparent.

And then, I think we need to allow the FDA to tailor AST development pathways for each drug as an individual drug. We do that for drugs in certain circumstances, especially in the context of an unmet need. But I haven't seen that happen on the AST side.

And so, today, you know, I see this as a call to action. This is the first step. We need simultaneous approval of drugs and AST devices for new antibiotics. There's a lot of very smart people in this room and I think, you know -- and a lot of innovative people. And I think there's a lot that can be done here if we all put our heads together and thought about how to do things differently.

We need to enable pharma, AST companies and the FDA to work together on ways to bring devices to market faster. And that includes increased regulatory flexibility on data requirements, so things like

streamlining of data requirements, increased flexibility in the types of isolates that are required and used in 510(k) studies and new avenues for AST devices -- AST device labeling to include limited use statements.

I would also strongly encourage Congress and Health and Human Services to think about ways to create financial incentives for AST development. Dr. Motyl talked about some of those. We've done that successfully on the drug development side. But currently, those incentives do not exist for AST.

And so, today is the first step. We've made great strides forward on how to streamline drug development and we need to bring the AST devices along with that to enable simultaneous approval of drugs and AST to better serve the patients who desperately need the new antibiotics that we create. Thank you.

(Applause)

DR. NAMBIAR: Thank you, Kevin. And many thanks to all the speakers for keeping to time. So we'll take a short break and maybe regroup in about 15 minutes. Thanks.

(Whereupon, the foregoing went off the record at 10:43 a.m., and went back on the record at 11:02 a.m.)

DR. NAMBIAR: All right. So in the next 45 minutes or so, we'll hear the perspective from the diagnostic device manufacturers. The first speaker for this session is Bill Brasso, who is the senior staff scientist with BD Diagnostics and has been there for over three decades. So, thank you, Bill, and welcome.

DIAGNOSTIC DEVICE MANUFACTURER EXPERIENCE/PERSPECTIVE

BD DIAGNOSTIC SYSTEMS

DEVELOPMENT OF COMMERCIAL PRODUCTS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING

MR. BRASSO: Thank you very much. Thank you, and I'd like to welcome everybody to the CLSI/AST subcommittee meeting. Oh, wait. Wait. No, that's not -- although most of the same players are here.

Would like to thank Dr. Shawar, Dr. Nambiar and all of the FDA for allowing us to come here together. It's been great presentations. It's a good thing I actually looked up the word repetition. And

it said it's very good practice because repetition process provides the practice that children need to master new skills and ideas. So kids, we're going to talk about AST devices.

So this is our presentation. And Dr. Carpenter and I have worked together actually on this in a move for solidarity for the AST manufacturers. Let me see if I can get this right. There we go. This is just a short agenda that we're going to do.

I'm going to start out with an introduction and talk a little bit about commercial AST development. Dr. Carpenter is going to talk about some of the challenges we've had and some of them that you've already heard from some of the other speakers. So it was great. We didn't even have to put plants in the audience. They've already helped us incredibly. And then, proposals and suggestions for moving forward.

So first, just quickly about myself. As I've mentioned before, I'm a senior staff scientist with BD. I've been there for 31 years, 20 of those years in AST development, so have worked a little bit

on this. Also been a past president of the STMA and currently an active member, which are most of the AST manufacturers.

So a little bit about the STMA, which some of you have seen just the acronym -- Susceptibility Testing Manufacturers Association. And these are the member companies that are involved. And hopefully, you are using if not one or more of our systems in your laboratories. But this is a group where competitors get to come together and actually make a difference.

We've been organized since 1994, have regular meetings twice a year at the CLSI AST subcommittee meetings. After is a separate meeting and it's amazing how much competitors can get together in one room and talk about things that are so common to them and work towards solutions.

The accomplishments that we have in the STMA, we participate in the development of updates to FDA and CDRH guidance documents with the FDA. We're advocates for some of the recent antimicrobial resistance legislation in the U.S. Congress and we're

working on the ADAPT Act and 21st Century Cures. We act as liaisons and representatives for AST industry on standardization committees such as CLSI, USCAST and EUCAST.

We do this in working groups, also ad hoc working groups and we're also involved in document reviews. We're involved in roundtables with pharma companies to introduce new drugs. As Kevin mentioned, the pharmaceutical companies will usually come at least once, and that's true, it's usually one time to one of our meetings to introduce us to their new drugs.

We maintain a database for all the antimicrobic codes. Just in case you always wonder where those three-digit codes come from, the STMA actually holds the database for those codes. And the pharmaceutical companies will come to us and ask for a new code when they have a new drug. And we're also a central mechanism for supplying antibiotic bulk powders.

So a little bit about AST systems. The devices provide therapeutic guidance to physicians, as

you know, and the clinical laboratory to determine the susceptibility of the bacterial pathogen, if the infecting organism is resistant to the drug of choice or drugs of choice and to detect emerging resistance through surveillance. Most of our labs, as you know, use automated systems for AST. Some still use the manual methods though, such as disk diffusion and actually making broth microdilution panels and macrotubes.

This is us. This is the commercial AST methods and, as I said, hopefully you recognize one or more of these that are in use in your laboratories. I should have said something about the -- but I won't, no. We're all together.

So start out first, we want to talk a little bit about the different methods. And it's the Kirby-Bauer disk diffusion method is one of the main ones for AST. We've already heard that that's used to develop in the development of new pharma offerings early on. The principle is pretty much every one knows here, but it's a Mueller-Hinton agar plate is inoculated with a standardized suspension. You place

the antimicrobic disk on the surface. You incubate overnight and you read the zones of inhibition and interpret the results using a standard, such as the CLSI standard. And most of these disks, or just about all of them, are prepared commercially.

Then, the next is our broth microdilution method. And this is one that we'll focus on a little bit more in this talk because most of our automated systems have to do with that. The principle is a microtiter plastic tray is inoculated with a standardized suspension in a cation-adjusted Mueller-Hinton broth. You incubate it overnight in ambient air. You read the MICs and interpret the results. These are prepared either in-house or commercially. And usually, the agents are dried, frozen or lyophilized.

So you've already seen a couple of these slides. So I hope I have the number -- the years and the amount of time correct in these. But this is just, again -- and again, repetition is very good, kids -- this is talking about the development cycle for a new pharmaceutical. Usually takes one to 10

years in the preclinical development stage. Right after that, an IND supplication is usually submitted, which takes about 30 days.

There is clinical development, which can take five to 10 years, or at least in the past. Regulatory approval can be fairly early, I think earlier than one year I've heard, but up to two years. And then, post-marketing surveillance. And the clinical development is usually divided up into three different phases.

During those first -- that first and second phase is where the pharmaceutical company will develop its disks and its reference brother microdilution method. So those are done fairly early on, working with a disk manufacturer to provide RUO disks. This is going to hopefully for the pharmaceutical company result in an NDA submission and review after phase 3, which can take about three months to as much as five years I've heard. And eventually, they are looking for FDA approval.

So also in this process, there are now possibilities from the FDA that have allowed for fast

tracking. The FDA has developed four distinct and successfully approaches to making new drugs available as rapidly as possible. Priority review, breakthrough therapy, accelerated approval and fast track. I won't go through these. I'm not an expert on these. We can talk to Dr. Shawar afterwards about them.

But -- and there's even a rolling review, which a drug company can submit completed sections of their NDA for review to the FDA rather than waiting until every section is completed. So these are available right now to the pharmaceutical industry. But I must say that AST manufacturer and device manufacturers do not have something like this in place.

So for the AST manufacturers, first, if we're talking about disk development, this usually -- now we're talking about commercializing the disk. So this will usually start, as I said, with an RUO product early in phase 1. But that disk development might take as many as four or five years before it actually -- all the disk manufacturers have that drug developed on their disks. It usually starts in phase

1 and then it's incorporated into the pharmaceutical company's phase 2 testing.

All of the CLSI M23 studies need to be done before any clinical testing is done. So, and to develop a new disk from scratch -- this is for research use only -- the customer, which is the pharmaceutical company, has to provide the specs for the labeling and development. And this includes the product description, the concentration of the drug and also deciding that very important disk code.

Other critical information that's needed at that time from the pharmaceutical company is how is this compound, this powder -- is it sensitive to light? Is it sensitive to moisture? How about temperatures? When you go to dry these disks, is the drying temperature that's used in some of our manufacturing processes going to actually start breaking down that compound?

Is the compound water-soluble or is a different solvent system required? Solubility is very important because you want to make a -- you have to have a homogenous solution when you're preparing these

cards. You don't want cards with different potencies of that powder on them. And, what are going to be the QC test strains? They should be the ones that are usually used from CLSI and the ATCC. But do they have ranges yet? Have they been developed? They're usually developed in the RUO stage and then passed on to the other companies.

Do all of the other companies -- are they able to get those same test ranges with their disks? It's very important. Usually there are three lots of research use only disks that are made for testing the potency, QC and performance and stability. And then, later on, when you want to convert that disk to an IVD product for sale, there are other files and documents that are required.

Now, for the AST development. The AST development -- so this is for the broth microdilution test has already been done in usually phase 2 and phase 3. Actually how that's done, how you prepare the drug for that testing is actually published in the CLSI M100. And this is what talking with the pharmaceutical manufacturers and consulting the M100

document is how the AST manufacturers usually first start their development efforts.

We want everyone to memorize this slide. This is all the steps that are involved usually in many of our AST development. They will be a little bit different for the different manufacturers.

But starting up at where it says antimicrobics selected for development, working all the way through those development, where we're doing our stock solution development, our data reviews with developing challenge set, testing organisms, QC testing and making sure that they're acceptable all along the way or you have to go back and repeat.

Before you're actually manufacturing panels for clinical trials, you have to do internal testing to convince your own regulatory group in our companies that you're ready to go to clinical trials. And let me tell you, that's not an easy one. They can be as hard as the federal agencies, and should be.

Then you get to go into your actual clinical trials. That takes quite a while. You've already developed your algorithms, your preliminary

algorithms. After you come out of your clinical trial, if the data is acceptable, you're finalizing your algorithms. You're putting on expert rules.

And then, you have to go through medical and marketing and your regulatory again for approval before you can even consider going to the FDA. And this usually -- once you go to the FDA with your product, it usually takes about three to nine months. And the whole process, just getting there, can take one to 3.5 years for a lot of the AST manufacturers.

So for the AST development, the pharmaceutical companies usually approach the manufacturers during phase 2. And some of the manufacturers, as has been shown, can begin a little bit early. They can develop in phase 2 and they're involved in providing even reference broth microdilution panels. Others of us wind up starting about during phase 3 so that the clinical trials will hopefully coincide around the NDA submission.

Considerations for selecting a drug for AST development -- so what do we think about -- when a pharmaceutical company approaches an AST device

manufacturer at the STMA meetings or coming to our particular companies, what do we ask? Does this antibiotic look promising to make it through the NDA approval process? That doesn't happen all the time.

Does the drug address a current public health issue? Does the antibiotic require special conditions, additives, special handling that's going to make this development for our particular AST device a real challenge? Has the AST manufacturer already begun or are they in the middle of an AST development cycle?

And this is where business decisions come in. And I think this is an important one that's been mentioned already, that a pharmaceutical company would love to walk in the door to BD and say, we want you to do our drug right now. And you know that that just doesn't -- isn't going to be able to happen because all of us have a multitude of different products besides ID AST products.

So those of us in ID AST have to make a very good case that we need the resources, the finances to be able to go in and start the development on these

drugs. And other, are there any other pressing issues, which has also been mentioned, which Dr. Motyl alluded to. Are there some new breakpoints that have come out?

When the new cephalosporin breakpoints came out from CLSI back in 2004, I believe, or '05, it really threw the AST companies for a loop. We had to stop development of all new drugs and it took quite a while. And as you know, not everybody has these, the cephalosporin and the carbapenem breakpoints even available on their systems yet. And that's many years. Many different things caused that.

But the thing to point out is that it gets in the way literally of new drug development. Is it necessary? Absolutely. But sometimes these things are what can block starting development on a new drug.

Now, just a little bit about clinical trials, and you've already seen some slides from Dr. Shawar. So I'll go through these fairly quickly. But you must receive -- for each drug and each indication, you need to receive -- you need to submit a premarket -- a 510(k) and receive clearance on that to be able

to put it on your device.

So for each antibiotic and indication, a separate 510(k) is required. So what's recommended in the AST guidance document for this? Well, you need at least three sites. And one of those can be internal. So these are external sites where you're going to do your clinical trials.

You need at least a hundred organism from each site, a hundred from each site and 50 percent of those have to be fresh isolates right now and 50 percent stock isolates. You also need at least a 75 strain challenge set. You have to do -- and that's for the accuracy part of your study.

You also have to do reproducibility part of the study, which is usually running 10 organisms in triplicate for three days at each site. You follow the interpretive standards that are in the FDA guidance document, although you can use usually CLSI standards as well.

You have to have stability for three lots with real-time data on those. You have to have QC available that you have to submit on the reference as

well as the test device. And this involves CLSI strains that are testing -- you need at least 20 results per site and at least one QC strain has to be on scale and on scale meaning that it has to be within the boundaries of the dilution range that you have that you're testing at those clinical trial sites. You have to do inoculum density checks.

And also, there are many other recommendations that are made so that you can get approval. And then, for this, once you put all of your data together for those three sites, analyze that data, you have to have these kind of numbers. You have to have at least greater than or equal to 90 percent essential agreement and categorical agreement.

You have to have a VME rate for the number of resistant isolates as your denominator of 1.5 percent, less than or equal to 1.5 percent. And your major error rate has to be less than or equal to 3 percent with your susceptible isolates. You also cannot have a growth failure rate of greater than 10 percent.

The reproducibility has to be at least 95

percent or greater and also for your QC performance has to be 95 percent or greater for those organisms listed in the CLSI document. This is very important. It's required for not only the overall performance, but for each individual organism or organism group.

So you have to have all of these for your *E. colis* that are in that study. You have to have all of them for the *Kleb* pneumos. You have to have all of them for the *Pseudomonas aeruginosa*. If you don't, you're going to receive a limitation for that. You have to have it overall too.

But it's very important to know that you have to have it for each group or what you get is those ugly little Xs that you get on your reports and that you wind up calling the AST manufacturer to say how come I can't get a result for *Proteus mirabilis* in a particular drug.

And then, lastly, commercialization. And this is something that Kevin pointed out when he said that even though the device manufacturers might have gotten clearance on one of those drugs, it took four-and-a-half years. It was another year-and-a-half

before they received them on panels. So drug X is ready to be introduced on a panel or a card. Well, we need new catalog numbers to be designed. We have to get a product name. What are we going to call this?

It's going to be a new Gram negative NBPC50 negative breakpoint combo, something catchy. For the companies with many products, you have decisions on those older products. Are we going to obsolete some of those? There could be still data that's maintained in software of our customers that they can't -- they can't handle that. They have to keep the data that they have.

You need to update the product label information, your customer labeling. This includes box labeling, panels, cards, your package insert with the instructions for use has to be in every box and has to be accurate and changed every time a new drug is added. There's a therapy guide that has to be updated and also expert systems guides.

The letter to the customer usually letting them know what's going on with this new product that's coming out. Why do I have to have a new product, a

new catalog number? I just got one a year ago. Well, if we want to get these new drugs on panels, these are things that have to be considered. And the notification of the new codes to interface with software vendors, LISs. We know how that can be, just trying to get those to work correctly.

So, and finally, building inventory not only because -- building the new inventory but getting rid of that old inventory that you now have that you have 20,000 cartons in your warehouse that your manufacturing folks are saying, wait a minute, I'm not taking this on as scrap. So you have to reduce that as you're making your new inventories.

And finally, software installs and training. So at this point, I'd like to turn it over to Dr. Carpenter to tell you a little bit more about some of our challenges. Thank you.

(Applause)

DR. NAMBIAR: Thanks, Bill. So Dr. carpenter has been a member of the micros and product team for 10 years and now part of Beckman Coulter. Thank you.

ANTIMICROBIAL SUSCEPTIBILITY TESTING: CHALLENGES TO GETTING TO MARKET

DR. CARPENTER: Thank you. Yes, this has definitely been a collaborative effort, and I got the short straw to talk about all of the issues. But thanks to all the previous speakers because most of the issues that are in my next couple of slides have already been brought up. So again, back to repetition.

Challenges that the device manufacturers have with antimicrobial drug sponsors is phase 3 strains can't be used as part of our AST device manufacturing clinical trial studies. Another challenge, as was previously alluded to, the lawyers between the pharmaceutical companies and our AST manufactures can take months to agree on wording in a legal contract. So that is a predecessor to even just getting the powder that we need to be able to start our development process.

And then, as the antimicrobial drug sponsors go through their formulation process and their development process, if they change a formulation, if

they change a process in how they make the drug or change that frozen reference process because they find that stability issues, solubility issues, then our work has to be redone. So it invalidates what we've done to date and then we have to rework those efforts.

Then, we also look at, which has been alluded to previously, that some -- not all the antimicrobial agents that start in phase 1 end up with NDAs. And so, then we can -- if we start too early, we could put time and effort into developing something that's never going to end up going to market.

And then, back to those lawyers again, when you have an antimicrobial agent that's sold to another pharmaceutical company, we have to start the whole contract process all over again. And then, to complicate that even more these days, a particular antibiotic may be sold in Europe by this pharmaceutical company but in the U.S. it's another pharmaceutical company, which also creates a lot of challenges for us.

Having said that, there's been a lot of recent positive changes. Working with the STMA, I

think we've improved our relationship with the pharmaceutical companies significantly in the last few years and we are now getting the invites and the regular coming and presenting of these new agents to all of the device manufacturers. However, you know, we should be thinking about do we need to have them come back more often. And maybe we need to have more improved cadence to those discussions.

And then, we're now seeing the drug sponsors creating organism sets for us, which we're able to get once the contract process is through, which are helping us create better challenge sets and have those resistant organisms or those unusual organisms available for testing.

When we're looking at challenges with the FDA approval process, you know, the current process does not allow us to even submit a 510(k) until the NDA has been approved. So there is a -- you know, a stop point in the existing process. And the breakpoints and the indications of organisms are the last part of the NDA process through CDER.

So we can't finalize our data processing and

finalize our algorithms and indicated organisms that we need to include in our data sets until that information is available. We're also very limited to our testing on what is in that package insert. So as I alluded to before, with some of the closely related species, you know, if we encounter them during our clinical trial, but it's not on the package insert, we can't include that data in our submissions.

The current acceptance criteria does not take into account the inherent variability of the frozen reference method. And to exacerbate that even further, if the breakpoints are around -- the wild type is around the breakpoints, that makes it even harder for us to meet that acceptance criteria.

Here's an example of some data for one particular isolate with one particular drug that is using just the CLSI frozen reference method, following the M7-A10 guidance, working within the parameters that are currently there. And you can see that, yes, we have a nice mode at 0.5. But the range of MICs range from 0.25 to 8. And when you look at this data, at the parallel columns are two rows of antibiotics --

of the antibiotic on the same panel. so these are set up just side by side on one panel at the same time and you still get this amount of variability with the frozen reference method.

There has been an ad hoc working group at CLSI that looked to try to refine these parameters even further to help maybe reduce this. And it was determined that they could not be reduced further.

Continuing on with the 510(k) criteria, the current design requirements do not allow for this variability in the reference method. The current guidance does not allow for a range of MIC values to be compared to for a single isolate. If you look at the ISO document, they do allow for some repeat testing, which helps deal with the resolution of discrepant isolates.

The testing -- the data collection required, again, is the same for all inoculation methods, all read methods for all phases of the study. And a separate 510(k) is required for each procedural option.

Testing requirements have expanded over

time, which has resulted in longer clinical trial times. And part of this is due to the restricted organisms. Personally, I had one clinical trial. I had two agents on it and there was no overlap. One was MRSA. One was MMSA. So now, I've just doubled my clinical trial time because there's so much limitation on what the organisms are that we could test.

Items that are missing in the current guidance document but are now expected to be part of what we submit is having minimum number of isolates per species. If we don't have -- if we don't encounter enough of a given species, even if it's an indicated organism in the fresh, we may not have enough to be able to get an indication. We're now being asked to have a restriction of stock isolates to be less than three years old. So then again, that restricts our availability of what we can use.

More requirements for data to be on scale. This is particularly hard with new agents. When these great new drugs come out, and if it's a really good drug, most of the isolates we encounter during our efficacy phase are susceptible. Well, if they're

really susceptible, the dilutions are very low and it makes it hard to get that on-scale data. The application of the acceptance criteria to each individual group as opposed to just the overall performance of the product. And we're now starting to see requirements around molecular characterization.

We are also dealing with expanded data requirements when we're looking at breakpoint changes and having to go back and basically do a full clinical trial again to collect the needed data to be able to request a breakpoint change. The fresh isolates being less than seven days causes restrictive ability to collect the isolates that we need.

You know, some hospitals have their workflow that they won't allow us to have an isolate until they've finished the workup. So we may not be able to get that isolate until day six, seven or eight. Well, at day eight, it's not of any value to us. It limits our ability to work with reference laboratories. I worked with Quest at one point to try to do this and we found out there was one day a week that they could send an isolate to us that would be able to be within

that seven-day window based on weekends, transportation, when they worked, when we worked type of thing.

When we're dealing with species that are not frequently encountered at the particular site that we chose to do our clinical trials at can also cause us challenges, getting the minimum Ns we need to get the claims we want. And as I already said, the new agents are often very susceptible.

As an AST device manufacturer, we're balancing multiple demands. We have the new antimicrobial agents. Then we have the breakpoint changes. And then, we have to look at it and say, you know, is this something that's a significant public health threat? And then, how much demand is there for the customer for a new agent? If it's a ME2 and very similar to something we've already developed and already have commercialized available, how much need is there from a commercial perspective for that drug?

New antimicrobials typically have few resistant organisms. So then again, we're not able to have MIC values over the entire therapeutic range that

we're trying to get indications for. And again, this is further limited by the product insert. Fast-track status has been made available for the drug manufacturers -- yeah, for the drug manufacturers. But there has not been anything similar for the AST devices.

ANTIMICROBIAL SUSCEPTIBILITY TESTING: SUGGESTIONS GOING FORWARD

MR. BRASSO: This is in the true spirit of tag-teaming. So what are our suggestions moving forward? To continue meetings like this today. It's taken a long, long time to bring a meeting like this together and I really -- we both, you know, thank Dr. Shawar and the FDA for finally bringing us together and submitting a new document, putting a new document out for this coordinated effort.

DR. CARPENTER: Coordinated development between the drug -- the AST manufacturers and the drug devices would be beneficial that we'd be able to, you know, maybe use some of the phase 3 isolates as part of our clinical trials, be able to use -- so then we'd be looking at a situation where we're using the same

isolates that were used to develop the drug are being used to develop the device. And that would be beneficial.

MR. BRASSO: To have the antimicrobial drug sponsors create challenge sets for us that would help us, subsets of their phase 3 study isolates. They have a lot of the organisms that are resistant that we could -- would really help us out in our studies. We would love to have FDA involvement in these to approve the challenge set, to approve a challenge set that we can use across the different device manufactures rather than each one of us coming up with our own sets.

Making it large enough to replace the efficacy and challenge testing under the current guidance. The challenge to this is, well, if somebody makes that, if the pharmaceutical company makes up that challenge set, would they be able to make it available to all the different manufacturers?

DR. CARPENTER: And looking at a concurrent review drug and AST device process. As it is now, we cannot submit it until the NDA has been approved. One

of the challenges from the device side to doing this is if the breakpoints or the indications for species during their review process change, it would require the AST device manufacturers to reprocess our clinical trial data or may invalidate some of the data that we have collected.

MR. BRASSO: We're not going to move as much now. Revising the current FDA guidance document. So this is the one that's currently is dated August 28, 2009. So fast-track opportunities for AST device manufacturers for the clinical trial and its requirements would be a terrific benefit to all of the AST manufacturers. To allow reporting of MICs for organisms not in the product insert. This has already been mentioned a few times.

To allow approval of MIC reporting when the breakpoints are not available for a particular organism or a group. Revise the requirements for removal of limitations. Currently, this requires almost the same amount of time to go out and do a -- you have to do a 510(k) normally and it's just like doing a new drug development. Revising the

requirements when a breakpoint is changed for a particular antibiotic.

And allow for replicate testing to compare to the range rather than the mode of that particular organism. This has come up and we feel that this will alleviate some of the inherent variability issues in the broth microdilution reference test, and it takes into account this variability.

DR. CARPENTER: So additional changes that we think need to be made is to allow for this repeat testing to reduce the data requirements. You know, make the data requirements part of the primary method and then maybe the alternate inoculations or the alternate read methods would have a different set of criteria than the full data set. Allow the CLSI QC ranges to be used in addition to the FDA QC ranges in our data submissions.

More use of the CDC/FDA antibiotic resistance -- the AR bank -- and to use that to provide challenge sets for when we're looking at breakpoint changes and that we would basically do a breakpoint change based on a challenge set that was

available to all of us. And this would only apply to products that didn't require a design change to accommodate the new breakpoint change.

MR. BRASSO: For the new guidance document that just came out, that we do have -- all of us have the opportunity to provide comments up to November 21st. I have that memorized now -- of this year. Drug sponsor and the AST device manufacturer should be and hopefully can meet together with the FDA. This would be very important for us, for logistics.

This could result in five different meetings. Can we all get together? Can we arrange that? Hopefully. A sponsor or an independent person would be representing all AST device manufacturers. That seems to probably be a better way than to try and get all four or five, six of us in the room at one time. And probably just one meeting for all of the AST device manufacturers.

Does this change when the AST device manufacturers can submit their 510(k)? That would be wonderful. That's one thing we're looking for. What happens for breakpoint changes? This really isn't

addressed in the document. But maybe going forward, it will be something that we can put into our suggestions for that.

And also, just to mention that we want to try new test cases and we're looking for pharmaceuticals to come and help us with this. Melinta Therapeutics has already volunteered with a new drug that they have that they would like to try this process once we get it solidified.

DR. CARPENTER: And then, again, to continue to support the 21st Century Cures Act, which allows for a greater flexibility for the FDA in carrying out its duties for updating susceptibility test interpretive criteria for drugs and devices.

MR. BRASSO: And for our conclusions, and I should say that Dr. Carpenter and I were actually thinking about giving each other t-shirts, that I would wear a MicroScan t-shirt and she would wear a BD t-shirt, just for solidarity. But in our conclusions, the AST device submission process has had small changes over time resulting in significant changes to the AST device clinical trials.

DR. CARPENTER: But we're very optimistic that the current process can be improved. And meetings like today is a good step in that direction.

MR. BRASSO: We need more coordination between the drug sponsors, the FDA and the AST device manufacturers. This is vital for all of us in order to close this gap between getting the AST devices and the pharmaceutical companies close to that NDA approval.

DR. CARPENTER: In order to make these changes, it's going to require that we make changes to both the draft guidance that was just released this month and then also to the existing AST device guidance.

MR. BRASSO: A fast-track process has worked for the antimicrobial drug sponsors. This process would provide assurance of quality AST device results while providing accurate commercial AST methods to clinical laboratories sooner.

DR. CARPENTER: And the current process has, as we've heard already from our clinical colleagues, you know, with the current process, we're limiting the

use of these new drugs because they're not on formulary. They don't have AST results to be able to come up with an antibiogram. They don't know what to do with these agents. So they're not using them.

And then, on the flipside, we also have patients being treated with these antimicrobial agents maybe not in the best method out there because they don't know what the -- because they don't have the approved device to be able to determine what the MIC is.

MR. BRASSO: Thank you very much.

(Applause)

DR. NAMBIAR: Thank you, Bill, and thank you, Dr. Carpenter.

DR. SHAWAR: For the record, they just shook hands.

CLARIFYING QUESTIONS FROM AUDIENCE/PANELISTS

DR. NAMBIAR: So I think we'll open the session up to questions, comments from the panelists and certainly from the audience as well. So I see that we have a question there.

DR. SAHM: Yeah, Dan Sahm, from IHMA. I

have a question and a follow-up statement. Can somebody tell me the scientific rationale for needing isolates less than seven days old, when in fact all the data that's generated in NDAs, both in clinical trial and surveillance, are on isolates that are older than seven days old?

DR. GITTERMAN: That's a very -- excuse me. That's a very good question. I would turn it around and I'd say rather than having FDA explain the rationale for every piece, you've raised a very good question. And I think that there is a docket for this meeting, correct? Is there?

DR. SHAWAR: Yeah, there is an open --

DR. GITTERMAN: Or during the public comment. This is invaluable to us as well because it's an opportunity to hear feedback. I would suggest to you and, you know, people you represent to make that point and scientifically -- because there are a basis for what we do everything. We don't do it capriciously.

But by the same token, that may have evolved over time and that this is not the time that that

occurred. I would suggest to you submitting the evidence or the scientific basis for an alternative proposal and we would be glad to review it, get back to you and whatever changes we could make, if it's justified, absolutely.

DR. SAHM: Well, thank you. I just -- my basic question was you don't need it for clinical patient data. Why do you need it for devices? But we can submit it that way. And I would also suggest -- I don't want to speak for others necessarily -- but there's a player in this group that wasn't mentioned that I think could help a lot.

And that's companies like JMI and IHMA. We have a continuous replenishment of data at isolates with known resistance mechanisms that are being studied around these new drugs in development that could feed into your assays and development that are all right in parallel with what's relevantly going on in the clinical trials. So that might be worth using as another resources in these processes, just for your consideration.

DR. GITTERMAN: Just to comment, that's an

excellent suggestion. And I have the privilege of making a few closing comments hopefully briefly at the end of the day. But the fact is we are listening to everything.

And again, I would propose going back and perhaps being more concrete and saying this is how it could be in the process. And again, with the STMA and the groups that likely will respond to this meeting, everything's on the table. Not everything obviously. But many things are on the table and things have evolved. And if you have a reasonable suggestion and could see why that process would work, later I might comment on this in sort of a bigger context. We would love to listen to it.

Everybody in this audience -- I can't speak for the entire audience because most of them didn't introduce themselves, nor did you ask the audience to introduce themselves at the beginning. But we all have the same goals. The clinicians want these out there. The device manufacturers want to make them available. The drug manufactures essentially.

We all have the goal of the public health.

And anything that you could suggest that makes this process, you know, assures safety and efficacy and at the same time makes it easier, less burdensome and expedites it, we are absolutely in favor of. So please, make us an offer.

DR. SAHM: Okay. What was that address to submit my offer to please? Again, I didn't get that.

DR. GITTERMAN: Right. Well --

DR. SAHM: I didn't get the website. Thank you.

DR. NAMBIAR: Amanda, you had a comment?

MS. JEZEK: Yes, just a quick comment. Hi. I'm Amanda Jezek, with the Infectious Diseases Society of America. And I just wanted to say that IDSA is greatly supportive of these efforts to speed AST devices to market and the comments that Dr. Mathers made earlier this morning are very reflective of what I hear from our members across the country about the urgent need for more of these devices to help guide patient care and to implement antibiotic stewardship programs.

And this really couldn't be happening at a

more timely point in time, as stewardship is becoming such a national priority. Just this morning, CMS announced a final rule requiring stewardship programs in all long-term care facilities. So this is tremendous progress and we're really going to need these tools.

The second point I wanted to just briefly make is I heard a number of folks mention the progress we've made in getting new antibiotics to market in the last couple of years. And yes, we definitely have made progress and it's something IDSA is very excited about.

But I do need to underscore that there's significant unmet need for new antibiotics to come to market. And we do think that getting new ASTs to market and hopefully getting a better process for ASTs can be helpful on that point as well because we know certainly pharmaceutical companies want to know that these devices will be around to help make sure that physicians can use new antibiotics.

And we also hope that the more tools that we have for stewardship, the more comfortable FDA will

feel in allowing for more streamlined and flexible clinical development programs for new antibiotics. So I know folks mentioned the need for more medical societies to be engaged in this effort and just want to say IDSA is a very excited partner for this. So, thank you.

DR. NAMBIAR: Great.

DR. TENOVER: One of the things I didn't hear mentioned -- over here -- today -- sorry -- oh, Fred Tenover, from Cepheid. One of the things we didn't talk about is in the absence of having susceptibility tests available for specific drugs is using mechanisms of resistance, either phenotypic or genotypic, to inform the clinical about things that the could either rule out or rule in.

So for example, if you -- if you had an isolate, you couldn't test it against Avycaz, but you knew that it had a metallo-beta-lactamase, you could tell the clinician that information. And so, you would know that would not be an appropriate drug.

And so, I'm wondering whether those -- whether either phenotypic or genotypic, even old

things like the modified Hodge test, are ever used, ever communicated to the clinician to help guide those therapeutic decisions in the absence of a specific MIC or disk diffusion result, if that would be helpful.

DR. NAMBIAR: So, back to Romney?

DR. HUMPHRIES: Yeah, I guess I can speak to that a little bit. So up until very recently, as you know, Fred, there have not been FDA-cleared tests for that type of indication.

Again, a lot of -- if you're talking about differentiating, for example, a metallo-beta-lactamase from a different type of carbapenemase, it really does need to be a molecular test because there is nothing endorsed by CLSI that would do that. And again, most labs don't have the capability to develop their own molecular tests for that indication, although there is the one now that is available on market.

DR. NAMBIAR: Helen, did you have a comment?

DR. BOUCHER: So I just had a couple of comments. The presentations were excellent this morning. Thank you all very much. I wanted to speak about the stewardship concept again because I think we

can't overstate it. And I'm sorry about my voice. The need to protect these antibiotics that we have is so great and a lot of us have been speaking about this for years.

And I think that can't be emphasized -- even if you look at a drug like ertapenem, I was interested that that was raised because when ertapenem was approved, we were so thrilled to have this option. And we all assumed it was going to work against ESBLs like imipenem and meropenem, based on the in vitro data that we had.

But we at our institution had three patients who failed ertapenem, kidney transplant patients with urinary tract issues. And it wasn't until we forced the issue and did the testing that we found out that the particular ESBLs were resistant to ertapenem but susceptible to imipenem and meropenem. And then, the practice would change. And this is before we ever had automated testing.

So we treated a number of patients inappropriately and could have induced more resistance. And I think that notion that in these

desperate cases that we all have that Dr. Mathers pointed out -- we've all been there and done that -- the risk of inducing more resistance and then potentially spreading it can't be overstated. So having availability of these tests and the data, whatever data we have in terms of susceptibility on the organisms that are known is really important to public health and to the health of our patients. So I think that's really important.

A second issue is do we ever use Hodge tests and other things. At our institution, we're fortunate. We have a really great micro lab who works with us closely and an investigational lab. And so, certainly we can get a Hodge test done and other things. It takes time, usually longer than we have to make treatment decisions. And it's limited by the resources that we have at the time.

So certainly having real susceptibility and/or approved molecular tests would be far more optimal. Thanks.

DR. NAMBIAR: Thanks, Helen. A comment from the floor? Maybe if you can introduce yourself and --

thank you.

MS. MCCURDY: Sandra McCurdy, Melinta Therapeutics. I volunteered to see if we could get delafloxacin as a test case with disk, gradient strips and dry-form panels. But when Dr. Humphries said that it would take six months to a year to get a new test incorporated into the lab because of these QC requirements, I'm now very concerned and I'd like to know if there's anything that could be recommended to reduce or help clinical labs with this process.

DR. HUMPHRIES: Yeah. So I think this is something that the CLSI has worked extensively on to provide guidance to labs on how to do these verification studies. And again, I think it's hard for us that work in larger academic centers to understand what the smaller hospital-based community labs are really faced with. It's exceedingly difficult for them.

In many cases, you know, it may be a supervisory, even a bench technologist that needs to go to the effort to design these studies and to do them. And so, you know, the six months to a year, a

year would be switching systems. Six months would be maybe bringing on a new disk or e-test. But it is something that can be in certain cases fast-tracked if there is a clinical need, if we're hearing from our physicians that they need this data. But I do think that having enhanced very basic guidance for these smaller labs would be of benefit as well.

DR. PATEL: So at CDC, we've leveraged the FDA-CDC AR bank to help with this and we've done this in collaboration with sponsors. So specifically we have had sponsors deposit isolates with us for in-house validation of ceftaz -- or I'm sorry, the Merck drug and then also ceftaz-avibactam. And so, we can make these panels of isolates available for a hospital laboratory to do the in-house validation.

I think combining an isolate resource with, you know, instructions on how to do the testing would be a tremendous resource and more rapidly incorporating these tests.

DR. NAMBIAR: I think there's a comment there and then, Roger, you'll be next.

MS. BERKELEY: I'm Lynette Berkeley (ph). I

wanted to make two comments. First of all, thank you very much. The presentations were really very, very good and enlightening. You know, we are living in a global village, according to Ribhi. That's what we live on. And microorganisms can come with their host within one day from somewhere else in the world. I am wondering if the device manufacturers take into consideration isolates from different countries in preparing their devices.

DR. CARPENTER: Absolutely. One of those things, when we develop our challenge set, we'll look at what -- we'll look at the publications and see what resistance mechanisms have been published and where they're coming from. And then, we will make efforts to get isolates in from all over the world.

MS. BERKELEY: Okay. Thank you. The other -- I wanted to just ask a question. The requirement for having seven -- for using organisms that are seven days old, I wondered if the thought behind that could have been subculture to prevent the organism being sub-cultured too often, because if it's sub-cultured, then the genetics will change. And I don't know what

anybody has to say about that.

DR. LOMOVSKAYA: Let me just -- let me just try to elaborate on this point because I think I actually sent in response to Fred's comments -- sent exactly about this couple of days ago because nobody would argue that biologically subculture would affect -- can affect what you get.

However, we are not looking at biology here. We are testing devices for performance. So from this perspective, whether something changes due to sub-culturing, it is important but not for testing of device performance.

From this perspective, it was really not clear at all why there is this requirement, which can slow -- which slows down the testing process, period.

DR. NAMBIAR: Yes, Ribhi?

DR. SHAWAR: This is Ribhi Shawar. Can you hear me? Can you hear me?

DR. NAMBIAR: Yes.

DR. SHAWAR: Okay. Sorry. This is Ribhi Shawar. So rather than getting into the details of a response about seven days or frozen or stock, I think

all of these can have their own scientific rationale for why they got in. There were -- as we learn more, we adapt and we change.

And if there is a big rationale about removing let's say such that requirement or any other, we'll be willing to listen. We have adapted to our requirement the many STMA -- manufacturers have communicated with us through a document that we sent to them answers to certain issues and results have been important issues that really have helped in my opinion in advancing the testing.

But for the audience, I think -- and everyone else who might -- (inaudible) -- there may be aspects that you would like to address, like I don't want to have seven days. I want to have 15 days.

But when you're considering the thought process about coordinated development, think of the low hanging fruit and think of the areas where if I improve that, where would be the best area I could focus in order to shrink down that lag time.

And if the seven days is one important aspect of it that actually could shorten the time of

development from the device side, we've seen all the steps that the device side have said that they needed and the drug side that they needed and the agreements and all of that.

I think there are many, many areas that could be potentially more impactful on that time to coordinated development, which is the topic of this meeting.

DR. NAMBIAR: Thanks, Ribhi. Roger, and then we'll get to you.

DR. ECHOLS: My name is Roger Echols. I'm an infectious disease physician and consultant with Shionogi, which has a Gram-negative product in late development. You know, first, just to reiterate, the presentations were spectacularly done. I've been recently introduced to the whole world of devices and have traveled and met with many of the manufacturers individually. And I understand the problems. I think there are solutions. But that's going to have to, you know, come with some -- a lot more work.

The one thing that I want to make clear from my perspective, representing a company trying to get a

drug to market to meet an unmet medical need quickly, is that, you know, using the terms phase 2, phase 3 and the idea of we're collecting hundreds and hundreds and even thousands of clinical isolates is really not the case anymore.

Pivotal data is really phase 2 data. There are no phase 3 programs for these streamlined developing drugs. You can call them phase 3 if you want. But they're really relatively small studies and consequently there will be relatively few clinical isolates on which to determine -- (audio break).

(Whereupon, the foregoing went off the record at 12:26 p.m., and went back on the record at 1:32 p.m.)

DR. NAMBIAR: -- Melissa Miller and Dr. Miller is a professor of pathology and laboratory medicine at the University of North Carolina Chapel Hill School of Medicine. And she's also the current chair of the ASM Committee on Laboratory Practices. Thank you.

ROLES AND RESOURCES IN COORDINATED DEVELOPMENT

UNC SCHOOL OF MEDICINE

DR. MILLER: Thank you, and thank you for inviting us -- inviting us here to give ASM's perspective on the issues we've been discussing this morning. Here are my disclosures, none of which are relevant to what we're discussing today.

Just a little bit of background, for those of you that may not know. The American Society for Microbiology is the largest single life science society. We represent over 47,000 scientists and healthcare professionals and our mission is to promote and advance the microbial sciences. And this is done through a variety of methods -- conferences, publications, certifications and educational opportunities.

And many of our members are individuals that are directly responsible for overseeing clinical microbiology, immunology, molecular diagnostic laboratories, individuals that are licensed to do the testing in laboratories, industry representatives and researchers involved in the development and the performance of new technologies.

The Committee on Laboratory Practices, of

which I am the current chair, is concerned with issues that involve science and technology of microbiology laboratory practice that's either directly or indirectly controlled by the government, an agency of the government or an accrediting or standards-setting private agency. So that's kind of the background of where I'm coming from.

ASM has a long tradition of being involved in antimicrobial resistance efforts. I've just provided a link for you if you're interested in seeing some of the issues that we follow. I've listed some specifics just in the last couple of years. As recently as last week, the president of ASM, Dr. Sharp, participated in the UN General Assembly, which was really a landmark opportunity to speak on antimicrobial resistance. Our membership had put together a petition, a letter and we had representation there.

We have provided recommendations to both presidential candidate campaigns and have heard back from one of the two. I said nothing. We have supported antibiotic incentive amendment to the

National Defense Authorization Act. We have participated in the Presidential Advisory Council on CARB through a working group meeting, responded to AMR rapid point of care diagnostic and participated in the White House Antibiotic Stewardship Forum. So we're very committed to this problem of antimicrobial resistance, which directly leads to what the issues are we are discussing today.

And so, in kind of prioritizing, and this is not necessarily in order, kind of where ASM falls in terms of the impact of the issues we're discussing, number one is patient care. So the significant delay between availability of new antimicrobials and the approved susceptibility methods negatively impacts patient care. As we've heard, physicians are reluctant to use a new antimicrobial without susceptibility data. And because of this, as we heard, drugs may not be used at all. And so, MDROs may not be treated effectively.

Empiric treatment of MDROs without supporting susceptibility data is not without consequence. So new antimicrobials may not be

effectively restricted, and it depends on how each institution from a stewardship perspective is structured. But in some cases, the susceptibility is required prior to use of a new antimicrobial or before a drug gets put on formulary. So this could lead to increased antimicrobial resistance and loss of activity of some of these agents.

Results from a reference laboratory, if available -- and we've heard the limited availability of this -- may not return, and I love the term, in a clinically actionable timeframe. So this may -- and they may also restrict trusting to FDA-approved indications, which we've had some discussion about.

So the research use only verbiage is a problem for clinical laboratories. As we've discussed, initial testing methods that become available are limited to disk and agar gradient diffusion strips that are labeled as research use only. It's research use only. So companies require us to sign a statement and usually it's the director personally that's signing the statement that products will not be used for clinical care.

We may also be required to report our data back to the company and some of the membership of our committee commented that we don't have the time to do this. We understand the importance of doing this. But there are laboratories that simply don't have the time to do this.

Many clinical laboratories either cannot report RUO results at all, which we heard in Dr. Humphries' talk, or some institutions, it is considered research, require IRB approval or consent of the patient before doing these tests. And some laboratories just don't have this capability or the desire to go through that process. Laboratories cannot bill for RUO tests and tests may be unreliable in performance or provide misleading results.

Third is transparency, and I've heard this word already today. More transparency is needed between companies and clinical laboratories. So companies may revise or reformulate their research use only disk or agar gradient diffusion strips before they are FDA-cleared. And so, labs will then need to re-verify test performance. Disks and agar gradient

diffusion strips might be provided for verification studies, and I heard from many laboratories that once they need additional tests to do additional susceptibility tests in their lab, they could not get anymore disks or agar gradient diffusion strips. It's not available.

So we've heard already about the verification of new methods. Clinical laboratories struggle with how to verify new antimicrobial susceptibility tests, particularly when there's no reference available to compare results.

So Dr. Humphries also talked about that CLIA requires new test verification and ongoing validation of accuracy. Reference laboratories are needed to provide this service. But it may be too expensive for some laboratories to routinely be checking their susceptibility tests with reference methods.

Some pharmaceuticals in the various drugs have provided reference testing. But I think it's pretty clear that they can't do this for all of us. A designated verification panel of organisms with known susceptibility profiles is needed for verification or

validation for each new drug. And I hate to break it to the very proud co-PIs, many laboratories do not know that these strains exist and that they can get them. And further, I think many laboratories don't even know which strains to request.

So I think the idea that we've discussed during the discussion, I believe, of having a very specific verification panel with instructions about what to do would be very helpful for clinical laboratories.

So automated testing devices, we've also spent some time talking about this. So we need a process to fast-track antimicrobial placement onto AST devices. So an expedited process similar to the qualified infectious disease products under the GAIN Act is needed for adding new drugs to previously approved antimicrobial testing devices and panels. And although these QIDPs are being expedited, this is great, we have new drugs, laboratories cannot perform susceptibility testing. This is a major obstacle.

So the co-development and FDA review is obviously what this workshop is all about. And the

ASM states that the availability of accurate susceptibility test methods should be coordinated with all new drug applications. And the key to this, and it has been mentioned several times, this cannot delay the development or approval of new antimicrobials. So it's not that -- just that we're looking for having them approved or reviewed at the same time. We want them all earlier, so not to extend the time of the new antimicrobial review.

So ASM's role, and we spent some time within the society discussing this. This is not something that in the past we have been involved in. but we have interfaced with the FDA on numerous occasions. And we're certainly committed to working together to solve this important issue for clinical laboratories.

Experts from our membership are willing to serve on working groups to develop and implement a solution, whether that's these centers of excellence -- we certainly have laboratories that we could identify to be part of such a program -- or an ongoing working group to solve these problems.

Once a proposed solution is agreed upon, I

think that oversight of the process is really needed. It's wonderful that we're here today in this workshop and discussing proposed options. But we need to make sure we follow up on these actions and that with time, this is monitored and that we're really seeing the effect of the solution in terms of getting approved AST devices.

Another thing that was mentioned earlier is advocacy, which ASM has a strong history with as well. And so, in collaboration with other organizations, this is something that we can also commit to. So with that, I'll hand it over to Dr. Patel.

(Applause)

DR. NAMBIAR: Thank you, Dr. Miller. Dr. Patel is deputy director in the Office of Antimicrobial Resistance at CDC and also chairs the CLSI Subcommittee on Antimicrobial Susceptibility Testing. So, thank you, Dr. Patel.

CENTERS FOR DISEASE CONTROL AND PREVENTION

DR. PATEL: Thanks to FDA for inviting me to participate in this workshop. I am pleased to announce that I am the outgoing chair of the CLSI

Subcommittee for Antimicrobial Susceptibility Testing. Dr. Mel Weinstein will be the new chair and he's working very hard. It will be an easy transition. He'll begin his first meeting in January. But today -- and I also wanted to acknowledge that this presentation was developed in discussions with Mel and also with Glen Fine, the CEO of CLSI.

So I'd like to describe how CLSI can help with this process. But before I do that, let me just say a few words about what CLSI is. CLSI is an internationally recognized standards development organization. That means that this organization meets the criteria set by the World Trade Organization for a standards development organization.

The process is a -- the decision-making process is a consensus process and this means that there is representation from government, professions and industry, that this representation is balanced. Meetings are open to everyone. There is a commitment to transparency. Meeting materials are publically available. Interests are balanced. And conflicts of interest are fully disclosed.

The CLSI subcommittee that I'll refer to is the Subcommittee for Antimicrobial Susceptibility Testing. This is a group that develops a number of documents, and I'll describe those in a moment. This subcommittee works all year long. The working groups meet by teleconference throughout the year. But we have two face-to-face meetings, on in January and the other in June.

We have about 200 people who attend these meetings. I agree with Bill Brasso. This meeting feels a whole lot like a CLSI meeting. I see a lot of familiar faces. These meetings are open to all. The subcommittee has official liaisons from a number of professional organizations. Those include -- and many of our liaisons are here today. But the professional organizations include IDSA, ASM, CAP, STMA, SHEA, the hospital epidemiologists -- let me make sure I'm not forgetting -- the Infectious Disease Pharmacists Society and the APHL, the public health laboratories.

So the CLSI subcommittee sets standard methods for antimicrobial susceptibility testing and these are the reference methods by which a commercial

device is compared for FDA approval of a device. The reference methods most commonly used are frozen broth microdilution and disk diffusion testing.

Recently, this -- we have had to consider variations of the standard method for antimicrobial susceptibility testing. And this happens when a new drug is being developed that requires adjustment of the standard susceptibility testing method. We don't do this lightly. We would only alter a method if it's really needed.

But we've identified that case recently for two drugs. In one case, we wanted to ensure that the susceptibility testing method demonstrated the optimal activity of the drug, the kind of activity that would be expected when the drug's used in vivo. And in another case, we wanted to ensure that there was reproducibility of the susceptibility testing method. And if there's not good reproducibility, then you're not going to have a good test.

CLSI sets standards for in vitro susceptibility testing criteria and quality control. So these are the data standards for establishing an

MIC breakpoint. The data standards for establishing a disk diffusion breakpoint and also the data standards for developing QC ranges of the reference method.

I wanted to highlight this QC range issue because this is where we first learn about new drugs that are coming to market. Manufacturers of new drugs come to CLSI's subcommittee very early to establish QC ranges for their reference method. And this is often before -- often happens before the drug is named. But once the drug is named, then it appears in the CLSI glossary. And it is through this method that we first become aware of new drugs and then we track the progress of these drugs as they go through the developmental process.

The CLSI subcommittee also sets standards for -- not only for testing but for interpretation of the results. So for setting breakpoints. And that means that at our meetings, we have experts in developing data for antimicrobial -- for breakpoints, for applying breakpoints, for prescribing antibiotics. It's really a place where all the experts come together to discuss these issues.

The folks attending CLSI meetings are representatives from healthcare and that means prescribers as well as the laboratorians who develop antimicrobial susceptibility test results. There are representatives from industry and that includes pharmaceutical industry as well as device manufacturers. STMA has a regular meeting that coincide with the CLSI meeting. And there are representatives from government agencies and that includes CDC as well as FDA CDER and FDA CDRH.

And we have official members from FDA appointed as advisors to the subcommittee.

So I think CLSI can help by being a convener and by helping to track progress toward coordinated development of devices and drugs. So specifically, we have all relevant parties attending the CLSI meetings already. We can create a space for those groups to meet together, especially as this coordinated development progresses.

And we can do this through a variety of mechanisms. But one that we've discussed is forming a specific working group and perhaps an STMA-led working

group where pharmaceutical companies can meet with device manufacturers to discuss the issues of developing an AST device. I think this can be -- we can work with industry to ensure that this can be done in a manner that protects and proprietary information that is -- that has to be discussed as the process of this development occurs.

We also can track the progress of the drugs so that all folks are aware of the new drugs that are in development and where they are in development. We're already doing this kind of unofficially. But we can make sure that that information is shared with all. And we can also track the results of this effort and how long it takes for approved devices to come to market as a result of this coordinated development.

Before I wrap up, I just want to put my CDC hat on for a moment and also mention our efforts in developing antimicrobial resistance lab network. This is a new effort from CDC and it is the process of developing public health laboratory capacity to detect and categorize antimicrobial resistance. I think this is a new resource for antimicrobial susceptibility

testing and for resistant isolates.

In this capacity, we hope to bridge the gap between the kinds of data that are generated in a hospital laboratory for managing a patient and the kinds of data we need for a public health response to antimicrobial resistance. We'll be collecting the most resistant isolates from hospital laboratories and categorizing them within this new laboratory network.

The idea is to generate data for action. So these are data that are linked to prevention programs, both in a healthcare institution and within a state. And those prevention programs are meant to address new resistant problems and implement interventions that reduce the number of resistant infections. With that, I thank you for your attention and I look forward to the discussion.

(Applause)

CLARIFYING QUESTIONS FROM AUDIENCE/PANELISTS

DR. NAMBIAR: Thank you, Jean. I think we'll open it up for discussion and questions either from the panel or from members of the audience. Anyone who couldn't get their question in, in the

earlier session is welcome. Yes, Roger?

DR. ECHOLS: (Off mic, audio out) 3:33:27 Jean, thank you --

DR. PATEL: Thanks. So at the CLSI meetings, we do have official representation of EUCAST and our new representative is the new chair of EUCAST, Christian Giske. So he will attend his first CLSI meeting in January. Through this official representation on CLSI, we have worked toward harmonization to the extent possible.

I think we still have a long way to go. Most recently, CLSI raised the issue of these differences in disk mass. This is a place where, especially for these methodological differences, I think it's very important to harmonize here because these differences can potentially create errors in laboratories where there might be confusion about what disk to use. And I think we made good progress so far.

So for example, we have agreed that moving forward, CLSI and EUCAST will not use different disk masses. We will use the same disk mass and there

won't be a difference.

I do think we have to go back and look back at the differences that exist now and work toward harmonization there. I would say that harmonization can happen when there are sufficient data to fulfill an M23 requirement for establishing a disk diffusion test. And it also has to be changed that improves performance, isn't just the status quo.

I do think that there are areas where breakpoints could be harmonized. We have worked together on a number of issues. And those have been specifically the colistin breakpoints that was done in collaboration with EUCAST.

And then, most recently, the *Neisseria gonorrhoeae* breakpoints and ECOFF values were done in collaboration with EUCAST. I will tell you that the CLSI subcommittee would like to do more of that. And we're hoping that we'll hear the same things from EUCAST.

DR. SAHM: Dan Sahm, from IHMA again. I had another question. But what you just brought up, Jean, is an interesting point. If we're going to coordinate

the disk masses, how do we go about that in new disk development? Now we're talking about getting Europe on board before we go ahead with the process, which could add to the timeline, because currently it's been done in the U.S. only.

And then -- I'm not saying it's a bad idea. I'm just wondering what you think it will do to the timeline of coordinating establishing initial disk masses.

DR. PATEL: So I would say that this is -- this is somewhat dependent upon the sponsor. And I think the sponsor needs to, you know, begin their development, their disk diffusion test development with a disk mass that we'll all stick with.

I'll say the CLSI -- or I'm sorry, EUCAST has a very nice document that describes strategically how to pick the right disk mass. I think it's good guidance. I think we could use that and all agree to the same disk mass. But I do think it kind of begins with the sponsor.

DR. SAHM: Okay, and the other question I had was with regard -- IHMA from time to time helps

people with -- get RUO products distributed so local labs can do testing. And this may be a question for Melissa. But one of the sensitive points that our sponsors run into is this viewed by agencies as promotional, putting their drug in hospitals pre -- you know, at RUO stages for testing.

And it does come up from time to time and nobody seems to have an answer as to whether or not there's any liability for a promotional activity there, because it does take money and somebody's got to pay for it. and if a drug company is paying money to have their drug tested, it could be viewed as promotional. And it's just an issue that comes up.

DR. MILLER: Yeah. I don't really have an answer to that. I think the perception of a conflict would certainly be there and it would have to be reviewed by the medical staff before doing something like that. And it's going to be institution-specific as well, so --

DR. REED: I think that very issue though is what has stopped those of us that can do reference broth microdilution from doing it because, again, the

drug company cannot pay us as an institution that may be prescribing the drug to do testing for other hospitals. And to be honest, that's really what has prevented us completely from doing testing for outside clients.

DR. PATEL: Other comments? We have plenty of time for comments. Yeah?

MR. FLAM: Hello?

DR. PATEL: Yes?

DR. FLAMM: Hi. This is Bob Flamm. I'm from JMI Laboratories and we do contract testing for many of the drugs that are in development as well as commercialized products. And I commend the FDA for putting this workshop together. I think it's extremely important and long overdue to have the stakeholders together to deal with this problem of the lack of diagnostic tests.

I think we've seen there are a lot of steps in the process that take a long time and there are many opportunities at each of the steps to reduce time, and I think that all has to be done. And they are in essence interconnected in that timeline.

One aspect that I haven't heard much discussion about, but I just urge people to think about as they go about correcting timelines along the various steps, is the effect of -- the effect of these regulations and guidances on companies who are doing earlier development. And that is that many of the companies discovering compounds these days are small companies.

And so, when we as advisors or consultants tell them that this is an important process to consider, having a marketed product available so that patients can actually see these drugs, they're not all that concerned about that. They tend to view that as the big drug companies' problem, who's going to buy the drug from them. And they really ask the question must I do this or is it a nice to have in the development process.

If I -- will it delay my filing an NDA if I don't have a diagnostic device available or can I continue my process with the clinical trials and save this money and someone else can spend it later and I'm not at risk? So I think anything that we can do to

remove the barriers, sort of the onerous cost that it is to get diagnostics developed will be very beneficial as we try to urge these smaller companies to start thinking about this process.

And not only will it be nice to reduce the cost to them if they begin development early, also I think co-development is a great approach at urging them. But I think any guidance that urges the development will be useful because, frankly, one of the questions would be, well, I looked at the micro guidance and it doesn't say I have to do this, do I have to do that.

So whether it's a requirement or just urging and urging in meetings along the way, I think that would be very beneficial because this model of smaller companies taking a molecule up through phase 1 or phase 2 will probably continue. And when money's tight for them, this is one of those things they tend to put on hold.

DR. PATEL: Thanks, Bob. That's an excellent point. Ian?

DR. CRITCHLEY: Yeah, I mean, actually

coming from a sponsor, one of the most valuable insights that I've gained today was actually from our clinical colleagues down the table from me. And you know, we've talked a lot about the manual devices. We know that for the automated systems, that's probably going to take longer and it may be a stretch goal if we can get the approval of those devices to coincide with the approval of the drug.

But one thing that did concern me about what I heard this morning, particularly with the disk testing methods, you didn't feel that comfortable or confident with the reproducibility. And how do we deal with that and how does CDRH -- if there's a performance issue -- is it a performance issue or, you know, it's just a concern that it's not working for you.

DR. HUMPHRIES: I think -- so that wasn't my own personal view. That was views from others when I asked why aren't you using the disk and that was feedback I got from the large reference lab and also two of the hospital lab directors. So I think, you know -- I think we need to make it a lot easier for

labs.

I think as soon as possible after a product becomes cleared, there should be a disk that is available for clinical labs to use that is FDA-cleared. And I think that there should be very clear guidance and strain isolates that are available to labs so that it comes as a package deal. And you know, in the clinical lab, we have companies help us with verifications all of the time.

And so, I think this is something that could be done to help speed up access to the disk. Ultimately though, we do want an MIC. But you know, obviously it's going to take a little more longer to get it on the automated devices. And so, honestly, at this point, anything is better than the current step. But I think it could be stepwise.

DR. CARPENTER: Yeah. I would just iterate the same, that a disk would be much more helpful than having nothing. I mean, an MIC, sure, that would be ideal, especially when you're trying to figure out what to do PK/PD-wise on a new drug. But we would be delighted with a disk and in our own lab, one of the

barriers has been having enough isolates with reference values to test the performance in our own lab. And so, on the new agents -- and so, that's been a barrier for us. But clinicians would be happy to have SIR.

DR. CRITCHLEY: And you know, another question while I've got you as well, we mentioned, you know, to fill the void right now, we're using reference labs. And I think both Allergan and Merck are using LSI.

Should we be helping other -- like Quest was mentioned, ARUP. Should we be working with other reference labs to try and -- you know, is there anything we can do to help fill that void? It looks like in California, you can't use LSI. But could you use one of the others?

DR. HUMPHRIES: Yeah, absolutely. So how it works in clinical labs is we typically have a contract with one or more major reference labs. And so, the big players would be LabCorp, Quest and ARUP. And so, I think working with those three groups would certainly provide access to testing to the largest

number of patients possible. But again, early access. And for whatever reason, the larger reference labs have really taken a long time to bring up this testing.

And in particular it's an issue for patients in California, Florida and New York, where there are additional regulatory requirements for doing testing with those patients and LSI doesn't have those licenses at present.

DR. PATEL: Jane, and then Helen?

DR. AMBLER: So I just wanted to go a little deeper from where Ian was taking the conversation because I want to lead on from Ribhi, that this is the low hanging fruit. Disk seems to be easier to get to approval. I don't know if the AST manufacturers want to comment why is it so difficult for pharma to get disks to do their initial M23 studies because this is the first thing we have to present to CLSI. And it says in the new guidance M23 document that we should have disks from two disk manufacturers.

My company has presented two compounds, had great difficulty finding two disk manufacturers to be

able to do that in a reasonable timeline. And we've had to present the data based on one.

The other comment I'd like to make is -- so I arrived in America in 2002 and was introduced to CLSI. What we have seen now is we need these products. How do we get them? We've had to turn to Europe and European manufacturers and other devices to bring them in. I don't know if anybody wants to comment on that.

DR. PATEL: Do we have any responses before we move to other comments?

DR. ECHOLS: Just to reinforce what -- I mean, the disks -- you think the disks are the simplest way to go forward. But the number of manufacturers that make disks are relatively small. They're not always easy to work with and some really don't care.

There's no motivation to -- whether it's financial or otherwise, to get on board early to make disks that might be available at the time of launch. It's just -- it's not on their radar, and I'm talking about the biggest of the big.

DR. PATEL: Thank you. One more comment about the disks and then we'll move on.

UNKNOWN: Yeah. I would like to second that. I have one disk that I was told I wouldn't have until 2019. That's a long time for a disk.

UNKNOWN: That was one disk.

DR. PATEL: Romney, and then we'll move on to other comments, I think.

DR. HUMPHRIES: So I guess that's the one thing that worries me through all of these discussions. I think there's many little steps that we can take to speed up process.

But at the end of the day, if the priority isn't there from a business standpoint to bring these drugs onto commercial AST devices, all of the things that we're talking about today aren't really going to make much of a difference.

And so, I'm not sure how we can prioritize getting susceptibility tests made from a business standpoint. And obviously that's a very difficult ask. But at the end of the day, I think that the diagnostic manufacturers have to recognize that this

is a very big priority for the U.S. market.

DR. PATEL: Bill, and then Dr. Bozzette?

MR. BRASSO: I think that's a very good question, Romney. I'm probably not the best person to answer. But I think one of the ways is to look at what happened with the pharmaceutical industry, that there were certain incentives.

There were groups that came forward such as BARDA and other organizations that provide some incentive ways and the FDA stepped in and said we have -- we can provide fast-tracking. And that provided some impetus that obviously at the top levels of the pharmaceutical companies also said, hey, antibiotics?

I mean, they're busy making other drugs that are more of a priority that they can make a lot more money on. So for all of a sudden them to start focusing on antibiotics, that's very important. There's no reason why our industry can't do the same thing, if we have the right incentives. And we're surely going to bring what's been said at this meeting back to them. So --

DR. PATEL: Okay. I'd like to just wrap up

this conversation and then we'll move on to other comments. So. Dr. Bozzette, you're up.

DR. BOZZETTE: I wasn't going to talk about disks.

DR. PATEL: Oh.

DR. BOZZETTE: I was going to respond to the comment about, you know, I've learned a ton today. It's really been an amazing talk about speeding timelines, using existing platforms and existing constraints on resources, which is kind of what we have in front of us. But there's also a drive towards simultaneously perhaps developing new platforms so we don't get stuck.

And secondly, trying to raise the constraints that diagnostic companies operate under. We've heard a lot of them. You know, there are regulatory constraints. There are mostly capacity constraints. So how do we approach that? I think the many kinds of stimuli and programs that have been designed for pharmaceuticals are very suitable for use in this industry.

I mean, it's very simple. If we want to

have sustained increased capacity, there has to be a steady source of revenue. It can't be up and down, bit by bit. And the revenue perhaps should not be tied to volume of sales. There are market entry bonuses, guaranteed markets, those sorts of things that again are being proposed for pharmaceuticals but would work for diagnostics as well.

And then, there's lowering the development cost. And that can be done again through prizes, maybe not so much, but doing grants, public funding, by co-funding with pharmaceutical companies. I know pharmaceutical companies believe that they're probably paying quite enough. But we still face these constraints given the current payments.

So I guess what I would say is I think maybe another meeting about expanding capacity and developing new technologies would be appropriate. But between now and then, I think we could advocate for generalizing some of the same stimuli and incentives that have been developed for drugs to diagnostics as well.

DR. PATEL: Thank you. I'd like to go back

to some raised hands previously. I think Helen and Olga, in that order, please.

DR. BOUCHER: So I'll -- sorry, I'll try to comment on two things. One is the clinical, so back to Dr. Humphries' comment. I think as a clinician, anything we can have locally is optimal. So the send-out lab is great, but it takes -- a week is good really to get data.

So we have to make treatment decisions in a data-free zone. And then, we're stuck for a week. We can call and beat them over the head. But they're not going to give us the answer usually for at least a week. So I think that the disk, or getting it on the automated system is really important.

And I'd just offer again that in 2016, with the evolution of budgets and things at our hospitals and regulation, fewer and fewer micro labs are even willing to do disks. You know, I'm hearing now from colleagues around New England. So I think that's just important to factor in as we think about our patients.

In terms of the incentives, I think that the notion of de-linkage, you know, is gaining traction.

So de-linking return on investment for antibiotics from how much is sold is definitely gaining traction globally. And that was even brought up in some of the UN conversations.

And that's great, and I think if we can bring that to the diagnostics, that would be great because there isn't going to be a market for a diagnostic for Acinetobacter, right? I mean, we don't have enough cases. We never will. So anything we can do to further that discussion I think would be positive.

DR. LOMOVSKAYA: I just wanted to make again in part scientific comment about this low hanging disk fruit. So in reality, in some cases, there is a confusion, for example, why, for example, disks are not correlating very well, could be difficult to develop because of a lack of correlation.

In some cases, it is true biology because bacteria on the plate are growing very differently and expressing different resistance mechanisms. The bacteria growing, for example, in liquid media. And if you are really clearly defining -- it is our task,

sponsor task really to clearly define all these issues when you can have a problem. And if you show drug manufacturers all these reasons why, for example, this particular disk or this particular situation is not working and providing clear biological data, it could make it much easier.

So that just wanted to make a comment that potentially it can help. But in general, I cannot personally absolutely agree more that incentives should be given to manufacturers because all other things are kind of common sense. They're easy to solve. We can release this regulation, that regulation, seven days, 15 days. But what needs to be done is really help manufactures to move faster.

DR. PATEL: Fred Tenover?

DR. TENOVER: Thanks. This is Fred, from Cepheid. I wanted to get back to the issue of testing bug/drug combinations that are not in the label because clearly as a clinical microbiologist, this is something we want to do to help clinicians choose drugs. But I'm just sort of wondering about the practicality and the legal issues of doing that. If

the lab starts testing Serratiae, then there really are no data on Serratiae or Acinetobacter or Burkholderia. There's a clear clinical need to do this and we want to do this.

But on the other hand, I get a little worried about encouraging laboratories to start promoting drugs off label. So part of me says we have to do this. It's obvious. But part of me says, gee, are we putting clinical labs at risk by telling them that any bug/drug combination is open for testing?

And I'd just be interested in hearing from some of the pharmaceutical folks about that because if there's really not an issue, if it's a small issue, then we should do this. But if it's really putting labs at risk, then they should know that.

DR. PATEL: Thank you. Any other comments? Mary?

DR. MOTYL: I just wanted to say something about costs and I thought that was a very good comment about possibly we don't recognize the actual cost for the development of the devices. And so, we may personally feel that we're paying a lot. But we

actually don't know the actual cost.

And I think what was very helpful for the drug discovery efforts when John Rex and colleagues went through the whole development process, which actually showed that there's no reason whatsoever to develop an antibiotic because you're actually never going to make any money.

So I mean, I think that was really very valuable. And we don't really -- we know the process and we hear the intricacies of the process. But we don't understand the costs and I think it would be very helpful. And I know each company has a different cost structure. I do understand that.

But it would be very helpful for us to really understand, you know, what is it that these things are costing because, I mean, you could get -- I mean, frankly, one gradient diffusion strip costs a teeny amount of money. Another gradient diffusion strip costs a great deal of money.

Now, where is the difference? You know, and I think it would be very helpful to understand.

DR. REX: Well, you know, I agree with you.

But I think it also depends on what you mean by cost and what you mean by price, which are, you know, obviously different things. But cost is not just the physical cost of the labor and the machine. It also entails incorporating the risk that nothing's going to happen, that you'll never see a return and a number of other factors.

In addition, you know, I think price is kind of the same way. The price has to be good enough to knock other things out of the queue or good enough to expand capacity based on that increased revenue stream. So it's -- I agree with you. We need to work together on that.

But it is a tough issue that I think that my management probably won't be including increasing capacity much without additional sources of revenue or ways of lowering costs. That wasn't a policy statement. It was my sense.

DR. PATEL: A question at the microphone? And then we'll go to Kevin.

MR. ANIGA: Yes. Kunik Aniga (ph), Johnson & Johnson Global Public Health. As a sponsor, we go

through a lot of -- a great deal to, you know, develop drugs for unmet medical need. And the regulators, FDA particularly, who is also in a great deal of effort to accelerate approval of those drugs so that it becomes available to people -- to patients who need them the most.

And after the approval, we keep developing drug susceptibility testing. And when we get to the end of that phase, we want to talk about device manufacturers. And the answer we hear is the market is too small, right? Or the best we can do for you guys is to develop a lyophilized product and we just let people know it's there. But it's not going to be a device.

But yet, we're hearing today that clinical laboratory will need to test these isolates. Especially I'm talking about TB particularly, which is not much in the scope here. So is there something that FDA can do in terms of making access to those non-approved devices to clinical laboratories in those circumstances? It's a little bit out of the scope, but it's not that much out of scope.

DR. PATEL: Thank you. Kevin?

DR. GITTERMAN: Oh, I thought I was being called on. That's a very good comment. And let me just -- if I can just reflect a little bit, even though everybody knows the answer and -- or from what I've heard today. But perhaps I'll address his comment.

MR. ANIGA: Thank you.

MR. KRAUSE: Thank you.

DR. SHAWAR: Can you come closer or either bring your mic closer?

DR. GITTERMAN: Okay. Can you hear me? Okay. Seriously though, there's really three issue at heart to some extent. There's the regulatory issue and this was raised before. What can we do? You know, we're not omnipotent. I mean, we have very strict -- we have a lot of lawyers and the fact is we have to obey the regulations. And statutes have to be interpreted. We have limitations.

Second thing is policy. What can we do and what creative ways and what ways that can be supported can we do. And then third is, as has been expressed,

is what can people do outside the agency. And there's been talk all around the table about advocacy. I hate this term because no one's defined it and there's many different ways to define it.

But I would suggest, again, one way we all think about it simplistically is market failure. And when we -- again, don't shoot me for that. I know there's different ways to define it. But let's look at drugs. Everybody -- I think a number of people have complimented CDER, as they should be, because they've been effective and groups have been very effective in changing the approach.

The problem was recognized. But a lot of the things I've heard as, quote, "solutions" -- fast track, QIDP, et cetera -- are regulatory solutions. They are not something that Ribhi and I could go back, as much as we'd like to, and say, guess what, we're going to have a fast track solution. And a lot of this actually goes down, just to support people who talk about advocacy, goes down to -- back to HIV and DDI.

Someone -- Dr. Echols, thank you -- when,

you know, there's a lot of demand -- it was Dr. Bozzette. Excuse me. I know they both don't look old enough to have been there. But in fact, they were. And it was -- you know, there was a lot of advocacy. Again, going back to another comment I think Dr. Romney made -- and I won't confuse people who spoke -- about seamlessness perhaps taking a different model.

There's been a lot of discussion about supporting drugs. I mean, we could look at drugs, sort of MDROs, you know, differently than we can about normal practice. But there's not a lot of economic incentives for MDROs. Some people have said, and I don't want to get into it, that these are drugs that should never be used.

There's no model, no matter what John Rex says, of developing a net present value for a drug that ID is going to encourage not to use. And to some extent, it's not of course true for diagnostics. Diagnostics are a step before that. But they're not going to be heavily used diagnostics unless resistance becomes very, very common.

And perhaps the model has to be different.

Perhaps, you know, instead of -- and again, I'll apologize to the woman who just spoke -- manufacturer's drugs. Maybe the model has to be very different, that people have to be using their advocacy in groups that are out there like PACARB (ph), talking about diagnostics have to go in the fold and to talk about drug development absent diagnostics as unacceptable.

And if there isn't market -- I'm going to use these words wrong -- market forces, and I think Dr. Bozzette commented on it. Someone else just commented on it a second ago, that -- and I apologize -- that there may not be any money for it, for disk manufacturers. Well, then somebody else has to support it because it's a public health necessity.

And I just want to say -- but my opening comment was -- there are things -- and this is circling back to your comment -- there are things FDA can do. And again, I cannot tell you more strongly how we would really appreciate, you know, scientifically based solutions, whether they're low hanging or high hanging, that we can help this

process.

We would feel a lot better at night being the solution instead of the problem. But there are limitations to that. And regulatory answers -- I'm sorry, regulatory or legislative would be a better way, solutions, you know, may be the only way to truly solve it. But in that interim, people who could suggest concrete actions that we could pursue.

And again, I don't want to empathize more. I can't -- you know, we can't go into detail. But we do a lot of work trying to address some of the concerns that have been expressed, to use it with all of the tools that we have because we're not impotent. But we're not omnipotent either. So I really appreciate the comment.

But it may take the people around the table and not us to have that outside influence, people in PACARB, people who can really say, you know, we've only been focusing on one half of the equation. And that's just my two cents as a regulator.

DR. BOZZETTE: Well Steve, I think you make a really important point, that regulators do in fact

have tremendous influence over the cost of development and that some sort of fast-track mechanism, for example, or some of the things that we've heard today even about the age of the cultures that can be used, you know, eventually will translate into a lower development cost. And that will cycle through and increase the capacity. So I think you're spot on.

DR. GITTERMAN: Sam, I absolutely agree. And again, and I say this with, you know, really being completely open because -- well, that we really do want to listen and we clearly -- that is clearly within our policies because, you know, obviously there's no perfect science.

You know, there's no, you know, religious tome that says this is how, you know, the Ten Commandments of device development. And certainly, you know, we've all learned a lot over the years. But there are things that are completely outside of our scope.

And diagnostics that do not have a net present value are not going to be developed regardless of that. And it would be -- you know, a lot of the

thinking, obviously there's a tremendous amount of brain power around the table and in the audience, could really start analyzing and say what are the places that we just can't do it.

We just can't do it. And this is where money has to be -- you know, has to be developed because there's not going to be a regulatory solution. We can't -- you know, as good people -- and I think like all of industry sometimes we like to -- you know, people like to bad mouth.

But the fact is I've met very few people in industry who really do not care. And most people come to industry with tremendous backgrounds in public health, like Dr. Tenover and others, and like Dr. Bozzette, coming from academics. But it's still a business. And a lot of people are not going to do it for the public good.

You know, a lot of diagnostic companies do not make a tremendous amount of money. There's no home runs in diagnostics. So I agree with you, Sam, and we absolutely want to make any change that we can. We are going to work at it.

But there are things outside of our control that, you know, it's -- that we're going to appreciate, you know, other groups, advocacy groups that can advocate, of course for the right things. But it's a challenge. It really is. Sorry.

DR. PATEL: Okay. Kevin, and then we'll go to Charlene and I think Ribhi.

MR. KRAUSE: Yeah. I just wanted to come back to the comments that Dr. Motyl made about the cost structures for some of the development, with the current conversation in mind as well. In all areas of contract research that we do, we're required by law in many cases, or federal financial accounting laws that require us to understand exactly what we're paying for.

According to Sarbanes-Oxley laws, we are not allowed to prepay for more than a very small percentage of work that is done. And the place that we often get stuck in negotiating contracts with AST companies is on exactly that and the not completely understanding what exactly it is that we're paying for. And certainly there are proprietary aspects of

the cost structures of each company's price structure.

But as Mary pointed out, there are pretty significant differences in pricing and cost for homologous -- somewhat homologous devices. And this gets worse when we try and go to organizations like BARDA and ask for funding. If we can't explain what we're paying for, it becomes very tough.

And so, I think even if costs were to increase to accommodate the risk and the economic burden that the AST companies face, I think without that transparency, it's going to be tough. It's going to be tough to sell paying some of the costs as things go up, and again, trying to include organizations like BARDA.

DR. REED: Well, this is probably a pretty good segue to introduce or reintroduce the foundation to the group here. There have been a lot of really good thoughts and input and I think actually forward thinking going on. So the mission of this foundation is to facilitate the discovery and the development and access to antimicrobial therapies and diagnostics. And the foundation is -- has been set up and is an

independent, unbiased third party.

So interestingly, as such, the FCAR is putting together and hosting what we call the ASTC, the AST challenges working group. And the purpose really is to expand to a larger discussion all the challenges around ASTs. You know, what happens within CDER and CDRH is a part of the picture.

It's how reimbursement occurs, how it occurs globally for a business case, for all concerned. How does it get adopted by the clinical microbiology labs? You know, all of these things are interrelated, yet separate siloes.

So we -- this group includes interest in looking at the regulatory issues, as in today, coding and reimbursement, commercialization issues, adoption by the clinical microbiology laboratories and the participants who have agreed to be a part of this at this time come from the FDA, from CDER and CDRH, therapeutic and diagnostic companies.

We have payers and coding experts. We have clinical microbiologist, practicing ID physicians, representation from the NIAID through ARLG and the

CDC. And our goal is to get the global issues on the table and then determine how we can work together and with others to solve them.

It may be there are working groups formed out of this coalition. We don't know yet. But to the original -- the original statement, it takes a village. But you know what? You've got to get the neighborhoods together.

DR. PATEL: Thank you. We'll have a comment from Ribhi, and then we'll go to John Rex on the phone.

DR. SHAWAR: Thank you. This is Ribhi Shawar. Just a comment and also a question. Regarding disks, the idea was that if we look at disks the way they are currently being done as perhaps a way to look at it and let's say it's working, there are issues. There are cases where it just doesn't come or what have you.

But the review happens earlier and because of that, the action is earlier. Well, the action cannot happen until a device comes in. And we've heard issues that there may be just the device company

isn't interested in bringing it in. So that -- I'm glad -- well, I'm actually saddened to hear that but glad that the timelines that I compared were one device manufacturers came in about 30 days or two months whereas another one didn't come in until a year to submit their application.

So that was the idea. Is there something there that we could potentially learn from and with all the ideas that have been thrown out? My other sort of comment and question is I've heard a couple of times about incentives and about perhaps even need for legislation, which Steve really articulated well, that it's not really within what FDA really can do.

But I heard things like fast-tracking and doing things like that. I'd like everybody to go back and think about the couple of slides that I presented where you can see where the timelines are and where the delay is. So if you -- if there would be -- let's say there's a fast track and, okay, let's say instead of 90 days for a review of a 510(k), it's going to be made 60 days.

Let's just go on and saying something like

that. Well, first of all, it's not going to happen. But in the -- in the realm of all of these delays, I want to be able to see where can we possibly work where we can bring that action about a device closer to the time about the drug. And that can only happen by working earlier and coordinating things with all the caveats that we talked about.

But when we mentioned fast-track -- and so this is kind of my question, is can we be more specific or perhaps in comments to the coordinated guidance as to what specific things can possibly be done at FDA that could bring that closer, given the regulatory timeline that is set forth.

My timeline starts at the time that document control center receives an application. And my timeline, if everything is good with that application, is no more than 90 days. In fact, our average is -- I wish I had drawn the average. But our average probably is even like 50 or 60 days. We really don't like to sit on -- I mean, we have excellent reviewers and managers to really make sure that that happens.

DR. PATEL: We're going to go to John Rex

and then we can take more comments from the room.

DR. REX: Great. Thanks. Am I reasonably clear?

DR. PATEL: Yes, you are clear. GO ahead, John.

DR. REX: Okay. Thanks. Many thanks to the organizers for a great meeting and I'm really sorry I could not be there in person. And as noted, drug development has been streamlined, with more work underway. But today's presentations, excellent presentations, have made it clear that we need to do this for AST. Actually, I don't think I've ever heard such a clear and comprehensive coverage of the problem. Many thanks to the speakers.

What I've heard today suggests to me that there are three problems here that we need to tackle in parallel. First, we've heard about device development problems that are often very logistical in nature. Developing a new test takes time. Validation is best done once a breakpoint is truly known. And there is a time and workflow problem that has to be solved around this. This is going to require a lot of

hand-in-hand working, especially to ensure that disk-based methods are promptly available, at least from regional reference labs.

And you know, I recognize in passing a disk is not an MIC. But that actually -- to my way of thinking -- is something of an advantage because they force a bit of thinking about the fact that even though we express MICs in µg/mL, they're not really physical measurements. I kind of like the idea of expressing MICs in millimeters. That makes you really think about what PK/PD means.

So anyway, the solution to this first problem seems to focus mainly on earlier co-working -- work focused on validating across a narrow range of candidate breakpoints and some simplification of some of the regulatory requirements around isolates. I'm not an expert about frozen isolates versus fresh isolates. But I certainly see the point.

And I'll mention here that we've been talking about a similar sort of problem with studying some difficult infections. In the case of nosocomial pneumonias, we've been struggling with how to get

people enrolled in those studies quickly before they have too much other therapy. And we're actually taking the novel tact of getting consent from people before they develop pneumonia, should they develop pneumonia, to be in the trial.

And the way I heard Mary Motyl talking about the work that they're doing, that's the same sort of thing that we all need to be doing in this area. We need to be really pulling this work far, far forward. And I know that's already being done in many places but maybe not by everybody.

The second problem -- the second thing is we have a problem at the interface between the label for the drug and the label for the AST device.

For practical reasons, new agents can only be studied in a few specific indications. And the number of organisms that will be found in those studies is by definition finite and the programs are getting smaller, which means that the numbers are getting smaller.

But patients present regularly with problems that absolutely require extrapolation beyond the

defined coordinate in the label. Infections will occur at body sites that have not been and may never be studied.

Similarly, infections may be due to bacteria not yet extensively and possibly never extensively studied. There's really only one systematic solution here. And that's to return to the path that has worked reasonably well for years. Experts in micro and ID are trained in the process of integrating susceptibility testing, PK/PD and knowledge of bacterial and disease pathogens to make choices.

I'm reminded of something I was taught many years ago, that MD stands for makes decisions and you've got to do it now. The solutions here are going to require thinking about labeling language for both the drugs and the devices. I know there are payer and legal concerns about using drugs as off label.

But I think we're going to need to respond with label language that reflects the clinical reality of the need to act and the need to avoid obstacles to the use of newer drugs. It's time to revisit some of the ideas about labeling that we've previously debated

for unmet need drugs. And George Drusano recently reminded me that not using the best available drug is, in many ways -- it's worse than bad stewardship.

It's digging the hole deeper because you're actually perpetuating driving the resistance to these existing agents. It really is unfortunate to see new agents not be used where they'd be appropriate.

The third issue is one that's larger than this conference today. But it weaves into the other two. And so, I think you've got to mention it just sort of to acknowledge it and that's the problem of cost of reimbursement.

There's a fundamental tension between stewardship and sales-based reimbursement that has to be resolved. And perfect answers don't get exist. But they're going to be grounded in thinking about the fire station or the fire extinguisher metaphor for antibiotics.

In this model, the micro lab is the smoke detector. The physicians are the firemen and the antibiotics are the fire extinguishers. The fundamental tension is that we want to have the full

complement of fire detection and firefighting capacity. But we also realize that the correct number of house fires per city per year is zero. Stated in the language used last week at the UN, we're going to have to find ways to de-link innovation reward from actual usage. And as I say, it's a big problem. We're not going to solve it today.

So putting it together, my summary is that it's critical that we work together to solve the piece of this problem that is within our gift. To do that, we're going to need to accept the reality of imperfect tests and imperfect information.

And I think everybody has a role to play in removing the obstacles and a certain amount of uncomfortable, out-of-the-boxes thinking is going to be required about how we talk about this and how we share this with our colleagues. So, thanks very much for letting me participate by phone and back to the -- back to the meeting. Thanks.

DR. PATEL: Thanks, John. Bill?

MR. BRASSO: I wanted to direct my comment, if I could, to Ribhi, to the proposal that you just

made, which I thought was very good. And I think that's what we need is to start -- you know, now that we've all talked about it, we know what the issues are. It's time to, you know, get down and find some -- what can we do.

Is there something concrete that we can even do here today that might make a change? One thing that you said, which was very important, was that even if you -- if the FDA changes from 90 to 60 days, what does that really mean in the grand scheme of things if it's taking us 40 months to develop a drug? And that's just 30 days extra.

So one proposal that we have that was in one of our slides that maybe we could do something concrete here is to development, we had asked for -- to be able to use the same organisms for -- that were used by the pharmaceutical company to establish the breakpoints, that we could ask that the pharmaceutical companies create a challenge set of organisms. Those organisms would be used by all of the device manufacturers. That saves money right there.

That saves money from each pharmaceutical --

or from each AST device manufacturer from going out and developing their own challenge set, which takes a very inordinate amount of time to find those resistant isolates, to test them consistently, that you're not getting MICs all over the place. So that saves time there.

And then, it would save time for the FDA, I believe, because the reviewers would know that one consistent challenge set is coming in for all four devices. They would be able to -- I'm not -- maybe you could even compare them across. But when you know those isolates that are coming in, you know what the expecteds are right off. That should take a little bit less time for the reviewer.

So maybe that does even shave a day off of the review. So if those are concrete ways, which is what we're looking for, I'd like -- I mean, that was one of the proposal that we had. And I'd like to, you know, really try and have people think about that one. Thanks.

DR. PATEL: Thanks, Bill. And I think we're going to move soon to a panel discussion where we

focus on the questions that had been posed to the panel. And I think that will be a good opportunity to really focus on concrete solutions to some of these. Melissa, do you have a comment?

DR. MILLER: I was just going to comment something similarly to Bill, to Ribhi's comment, in terms of fast-tracking. I think you made a very important point in terms of shortening the FDA review may not have a gross impact.

My thought behind the fast-tracking really had more to do with how can we make the clinical trials for the AST devices simpler.

How can this be less onerous for the diagnostic companies, whether it be using certain strains or less fresh strains or all of the details that I don't know that goes through an AST clinical trial, is there guidance that can come from FDA to somewhat minimize what's required for these devices, and that was fast-track it?

DR. PATEL: Ribhi?

DR. SHAWAR: This is Ribhi Shawar again. This meeting is about sharing ideas, not about making

a decision. But I can go on record saying that some of the ideas that were talked about here are also ideas that we talk about, you know, what we ultimately will be able to do and not do, willing to look systematically keeping patient-centric.

We want to make sure that devices that we put out are safe and effective. So we will keep that as our target and we will not change things on a whim like that unless we feel confident that that is not going to be moving us from that target.

But it seems reasonable to think along those lines because it is valuable for us to be able to say use challenge isolates that compare across devices. If they come in within the same timeframe, if they're using the same sets of isolates.

That was actually one of the very first thoughts that we gave when we thought about the FDA-CDC isolate bank was exactly that, that if I'm comparing -- oftentimes, I'm really comparing apples to pineapples to oranges, you know? There is that case. So we thought why not, you know, have those kind of panels that would serve both for the drug side

when they are developing as well as for the device side.

So before I sidetrack too much, these are good ideas. Let's, you know, have them more, you know, thought of and more refined in order to be able to do that. But before I close, we have certain plans that we are working on and both comments from here, from STMA, from device -- from dug manufacturers can help us in our future plans. So please submit your ideas.

For example, we are doing for the AST guidance document, this is a special controls guidance document. We cannot change things in the special controls guidance document easily because those special control guidances and the requirements that are set there came as a result of a down classification from a class three to class two devices.

So those are strict requirements that are set forth. However, STMA knows this and others -- and other manufacturers know this, that we've been working through issues and clarifying things. So with that in

mind, we have a -- we are working on what we call a frequently asked questions guidance document where we're going to specifically address things that are maybe not so clear in the class three guidance document was written back in the late '90s.

But with the idea that how can we streamline things better within the confines of what a class two special control guidance is. So keep that in mind. There are things hopefully that will be coming in order to clarify things. And I would absolutely love the idea of being able to compare -- not to get rid of clinical testing. Let's just be clear on that.

There has to be some fresh clinical isolates tested, no doubt about that. But if panels -- and as we move forward -- and thanks to Jean Patel and her group at CDC -- we would love to keep adding to the bank. And you know, the more isolates, the better.

The more refined they are, the better. And the more we can demonstrate where this is valuable for everybody, the more your tax dollars are at work. That's all.

DR. PATEL: Thank you for that. A comment

from Mary, and then I'm going to have a call for any other public comments before we move to the panel discussion.

DR. MOTYL: So just one tiny comment. You know, obviously this challenge set idea is great and we have deposited 30 isolates and we've told already the vendors with whom we are working that those isolates are available.

I mean, the one thing that we are getting back from -- or actually I've been contacting them. Do you have enough? Is this enough for you? And they're waiting actually for the FDA to say is 30 isolates enough. Is 50 isolates? Just to have -- you know, I know.

I mean, we're in a vicious circle. But then, we'd be more than willing to deposit another 30 isolates or whatever. But we need to really all try to help each other out. And if we -- you know, if you give us the guidance, we'll certainly help out the device manufacturers.

PANEL DISCUSSION

DR. PATEL: Thank you for that. Another

call for any public comments? Thanks. I think we'll move on to the panel questions. Sorry. For these questions, I think we have had discussion on some of these topics.

But this is an opportunity for the panel to dive in a little deeper on some of these questions. And there are two. The first one has multiple parts. And this is about coordinated development of new antimicrobial drugs and antimicrobial susceptibility devices. It's needed to facilitate -- is needed to facilitate the availability of AST devices coincident with or shortly after drug approval.

The first part is what information is needed by the device manufacturer, and when, to facilitate more timely development of AST devices. What are the challenges to obtaining this information and what are some potential solutions? And I'm wondering if we should take each part at a time. Maybe we can pause and actually focus on this first one.

So it'd be good to hear from the panel. And I think a key question here is not only is what information is needed by the device manufacturers, but

when. When would device manufacturers be willing to start with the development process?

DR. CARPENTER: Darcie Carpenter, Beckman Coulter. I think the biggest thing is the breakpoints and what organisms we're going to use because the sooner we have that, the sooner we can start developing. If we don't know that information or it's preliminary and it might change, you know, those have big impacts on the size and the amount of data we have to collect for our studies.

DR. PATEL: So I have a question. As a drug's being developed, there might be a broader range of organisms and those get narrowed as the -- you know, once a drug is actually approved. Can you kind of give us more information on how that impacts your development?

MR. BRASSO: Sure. With some of the newer drugs that have come out for Gram positives, we have gone and developed challenge sets with a lot of different staff species particularly with the Enterococci, you know, for when we talk to the drug companies at first. They have a much broader group of

isolates that they're targeting. And then, when the drug gets developed or goes through the FDA and receives approval -- I got that right -- the drug gets approval -- it's only -- the breakpoints are only for *Staph aureus*.

So that was a lot of work that was done ahead of time by the AST manufacturers. Now, you take it the other way with the discussions we're having now with, well, wait a minute, maybe we should be able -- we should be looking at some of those other organisms. Well, then that becomes helpful. So when we can only submit most of our data would be *Staph aureus* isolates. Then, what happens to the rest of that data? So --

DR. PATEL: So a good question is how could that be helpful? Would it be helpful for those other organism to actually set, for an example, an epidemiological cutoff value in the absence of a breakpoint when we develop those kinds of data for organisms that might not be in the drug label? So, I'm seeing some nods.

DR. CARPENTER: I think -- I think having

that data potentially available, understanding that there's not a clinical breakpoint would still have great value potentially. It would have to be couched and a lot of education go out around that. But that's really valuable data that could be used and potentially could be used, in my mind, by a device manufacturer with an ECOFF or with -- depending on there's no breakpoint.

DR. PATEL: Right.

DR. TENOVER: Right, and I think it goes both ways because if the data clearly show that a drug has no activity against an organism group, if it's a cephalosporin enterococcus, those are very -- as important to get out there as they are where it may have potential activity, just not proven in a clinical trial.

DR. PATEL: Great. Helen?

DR. BOUCHER: I'll just make another plug for stewardship. You know, in the setting of stewardship as a condition of participation, we're going to have the ability to have experts interpreting the data and using them, as many of us already have

the luxury of having now. But that's an added safeguard to the appropriate use of such data.

DR. PATEL: And Ribhi?

DR. SHAWAR: Ribhi Shawar again. I think I want to sort of trigger one other important point here about information and when.

Device manufacturers have to decide on what concentrations they want to put on their device and really state being limited and more drugs are coming, I'm pretty sure that there will be a timeframe that you -- device manufacturers will need to know sort of that -- you know, are we talking about, you know, 228 or are we talking about 0.521 or what type or breakpoint could we be having.

So maybe from you, Bill or Darcie, somebody, look -- at what point in time it's really critical for you to have that information so that you can design something, so that it can be -- coincidentally be evaluated, let's say, by the time that the drug trial is being done.

DR. CARPENTER: Darcie Carpenter, Beckman Coulter. There is limited development we can actually

do without the breakpoint. It's that simple because we don't know how that performance is. To your point, we often -- because of now having requirements of having on-scale data, you know, we take to clinical trials a series of dilutions much broader than what we ever think we're going to put on a medical device.

And then, to also potentially have that data again if a breakpoint changes in the future. I think it's more to the point of what you were asking earlier, Jean.

You know, if I go to clinical trials with four organisms, thinking I'm going to get those, so my 300 isolates are, you know, 25 percent of each and then you remove one of those organisms, you've now cut my challenge -- you know, my efficacy set by a quarter.

And now, I don't have enough data to be able to submit. And that's where it comes back into having a direct implication to our clinical trials. So then, I have to go back and collect more data, and that takes time.

DR. PATEL: Right. So if I hear you

correctly, you're doing a clinical trial with a range of organisms with a requirement to hit this critical amount for FDA approval. But then, if the number of organisms that are in the label get cut, you have to go back and do more clinical trial testing to up the numbers of the organisms.

DR. CARPENTER: Correct.

DR. PATEL: Okay. Romney?

DR. HUMPHRIES: So to me, this again speaks to the value of being able to have both the organisms in that group one and group two approved on an AST device because labs will certainly be using it to test that.

And if you identify some issue with that specific drug/bug combo, but that information's, you know, just put aside because it's not going to be part of the ultimate label, that really doesn't serve anyone I would think.

And so, I think that it's still really valuable data that you're gathering. But unfortunately, you're sort of penalized because you have to go out and test more isolates as a result.

DR. CARPENTER: But I don't know how much of that data we're actually collecting because we're having to wait until we get the NDA because we're not taking the risk. And so, we wait until we have the NDA label so that we only go out and look for those. And so, unfortunately, we're not looking at the ones beyond what's on the package insert.

DR. HUMPHRIES: Right, and so those other bugs are never really tested --

DR. CARPENTER: Correct.

DR. HUMPHRIES: -- to see if the device works at all for them, which I guarantee clinical labs are using those devices to test those bugs. They're tricking the system. And so, you know, again, this is kind of -- it's an issue.

DR. PATEL: Bill?

MR. BRASSO: Just Ribhi, with the question you asked about the dilutions, about how we set up our dilutions, so when we first talk to the pharmaceutical companies and they will say that we will ask what are your preliminary breakpoints, what are you shooting for, we'll usually go many on -- many dilutions on

either side of that. So sometimes 10, 11, 12 dilutions that would be on our original development.

Now, when we develop our drug -- where it becomes very critical is in the early development, when you're starting to set up your formulations, which are different -- just in case anybody thinks that you can take an antibiotic powder and put it in one of our systems and make it work just like that, that does not happen.

These are completely different environments than the -- in our panels than even in the broth microdilution reference method. So they are a little different. When we do that, when we're setting up our formulations and then testing thousands of organisms against these formulas to see which one's best.

At least in the -- in the case of some of the manufacturers, they're developing algorithms at the same time. Those algorithms are targeted around the breakpoints.

So you try and target the susceptible breakpoint that you were given by the pharmaceutical company and a couple more on either side. But you

can't possibly get the performance exactly the same on all of them.

So it kind of -- you're rolling the dice and hoping all along this way that those breakpoints are going to hold, even though you're hedging your bets and trying to be aware of what could happen. But, so to answer your question, when very early on, it's good to have that information.

DR. PATEL: Okay. You helped me. I was going to ask a naïve question, that if you're actually validating data for all these different dilutions, can't you just, you know, adjust the -- it be a simple re-analysis of existing data when you get the final breakpoints.

But you're saying that that's not the case because there are instrument algorithms involved and actually calling the breakpoint.

MR. BRASSO: Correct. Perfect, and it is -- it is the case that you just state for the reference broth microdilution and for some of the AST manufacturers that do not count or require a little bit more of the software in the algorithms to be able

to get a more rapid call on the MIC.

DR. PATEL: Thanks. Fred?

DR. TENOVER: Fred Tenover, Cepheid. Since the guidance also mentions molecular methods, let me just jump in and say there are data that we need for molecular methods early on too and we have been involved in several clinical trials now and helping to enroll patients.

We're not so much concerned about the organisms as we're concerned about what clinical specimens you want to do because most of the time we do direct testing out of clinical samples. And this is something I think is sort of a novel idea for a lot of the pharmaceutical companies because they're thinking drugs and bugs and we're thinking genes and sputum versus blood versus urine.

So I just wanted to get that out there as well for those of you who are thinking about ways to enroll patients earlier. That's what we're thinking about on the molecular side.

DR. PATEL: Ian?

DR. CRITCHLEY: Yeah. I was just going to

ask our device colleagues -- and I don't know if we do -- but I mean, could the sponsor help? Usually before we submit our NDA, we do benchmark or baseline surveillance before approval because then that allows the agency to monitor and track what's happened after approval.

And I don't know if we do or if we don't. should we provide you with that benchmark surveillance information? Because that would give you the MIC ranges for a large population of organisms. It would help you with the dilutions. It would be a national representation of, certainly for the U.S., on what we're likely to see. So it would give you a heads-up.

DR. CARPENTER: And that's collected before?

DR. CRITCHLEY: Yeah. We usually submit in our NDA a --

DR. CARPENTER: Okay.

DR. CRITCHLEY: -- what we call a benchmark surveillance in the NDA.

DR. CARPENTER: Okay.

DR. CRITCHLEY: And then for five years post that, we use that to monitor and track changes in

susceptibility.

DR. PATEL: Thank you. Jean?

DR. AMBLER: So I think -- it's Jane Ambler again. Ian, that's a really great point because I know for the CAZ-AVI submission, you know, we spent to a tune of like $5 million on surveillance data. We had all the molecular characterization of those organisms. We had the antibiogram. You know, had you been able to provide panels for us, we could have tested it using your panels.

And you know, we worked with the IHMAs or the JMIs of this world. And if we can share or come together, because I think we're collecting very similar data, it's to compare versus the reference method. If we could do half of that with your panels, I don't know. we need to come up with a way that we can streamline this to help each other's needs.

DR. PATEL: Olga?

DR. LOMOVSKAYA: I also would like to argue that when we provide AST manufacturers with provisional breakpoints, those are pretty solid. So a lot of work comes into setting these provisional

breakpoints based on PK/PD work. So when we are doing it, those are not just numbers and they're definitely based, you know, again, on a lot of work.

Moreover, some of us also hedging our bets and in fact setting -- kind of going into double breakpoints, saying we're paying almost twice to in fact develop two breakpoints at the same time. So I would say that a lot of information is available. And again, provisional breakpoints, usually not so far away from actual breakpoints.

DR. PATEL: Great. Thanks for a great discussion. Are we ready to move on to B? Are there ways drug companies and device companies can interact and collaborate more effectively during drug development to achieve concurrent development of a single or multiple AST device?

And I think we've heard ideas about testing device panels as a part of the drug development process. I've heard that from a couple of different folks. And it might be good to discuss the validity of that idea. Of course, there's a risk inherent in that, and that is that the drug will fail during the

development process. But there's also just, you know, huge potential benefit of efficiency there. Sam?

DR. BOZZETTE: I guess I would -- I hate to state the obvious. But you know, early and, you know, robust collaboration and maybe some of these fora where groups of device manufacturers or groups of pharma companies can get together and inform each other about what's going on in each of the areas and, you know, start to make the individual contacts and the contracts.

And I think we're hearing a lot about how people on both sides are trying to intensify the collaboration and keep it, you know, moving forward. And I think companies are very amenable to that. We -- I expect you do too. We have people whose job it is now -- relatively recently have people whose job it is now to interact with pharma and make sure that we're moving the ball. And some of the people in the room are working with some of our people in fact.

DR. PATEL: Bill?

MR. BRASSO: Sorry. I don't want to dominate on these questions. But one thing, I like

the idea. I'm trying to think of how the logistics would work because we have -- there are different manufacturers.

And one of the biggest things is what we're talking about is for a pharmaceutical company to walk in right now and say we have drug x, we want all of AST manufacturers to stop what you're doing, develop our drug right now, same time. Get ready to start, which would be absolutely fantastic.

Unfortunately, we know that there might be one of us that's ready. So does that unfairly give an advantage to that particular AST manufacturer? Possibly. But if the drug fails halfway down the road, that's a deterrent rather than a good thing. So I like the idea. I'm very interested to follow up on this and try to figure out how the logistics would work with this.

DR. PATEL: Thanks. I think it does come down to logistics. Darcie?

DR. CARPENTER: Yeah. You know, I think that's going to be the one thing we haven't talked about today is basically the business objectives at

that particular time for each organization, the AST device manufacturers and the pharma companies. You know, we've had that situation where we've gotten FDA approval for a drug.

But our next software release is OUS. And because our business -- you know, and it just happens when it falls and when we're doing things. And so, I think it's more than just logistics. And some of that from the business priorities is going to be hard to streamline or get on the same page.

DR. PATEL: Yeah. Fred?

DR. TENOVER: I'm just wondering. This may come under 1(d) more than 1(b).

DR. PATEL: Go for it.

DR. TENOVER: But I'm just wondering about ARLG, BARDA or things like the NIH clinical trials group that provide disk development on a contract to do this where that's their sole purpose. And if companies are having a really hard time finding a disk manufacturer, then that may be a very good investment for the government, to be very targeted and to provide that specific service.

DR. PATEL: Disk manufacturing?

DR. TENOVER: At least a start for the interim.

DR. PATEL: Yeah.

DR. TENOVER: At least as an interim basis to get things going and then as other manufacturers have time available, then it could be transitioned. But early on, like the, you know, PK/PD studies that are done by the clinical center and other animal work that are contracted by NIH.

DR. PATEL: Ian?

DR. CRITCHLEY: I don't know if this fits in (b) or (c), but one of the bottlenecks that Kevin talked about this morning was it's not necessarily about the timeline of approval of the 510(k) submission, but the big lag between the approval and the commercialization. Is there anything that we can do to help with that? You know, 12 to 18 months is a long time.

DR. PATEL: Bill?

MR. BRASSO: Just to go along with one thing that Darcie was saying, that I'm sure all of the

manufacturers have had and also the pharmaceuticals companies have had, is when we say we just started a new phase or cycle of development. You just missed the boat. And that could mean a significant lag.

Unfortunately, we can't -- you know, we all try and hang on as long as we can before we start a new cycle. But once that starts, it's hard to go back and bring a new antibiotic in.

DR. PATEL: Yeah.

MR. BRASSO: So, and that causes some of that lag, Ian. That's --

DR. PATEL: So I'm wondering if it would help for industry to plan for these kinds of studies, if there is a consistent tracking mechanism of drug development and where these are at and that would actually change the planning structure that happens within a company.

I know what it's like to work in a big organization and get them all to work together. I'm a government employee. So I imagine that, you know, similar challenges in industry. But we all need to plan and information is key. Kevin?

MR. KRAUSE: Yeah. That's exactly what I was going to say and I wonder if there's an opportunity to leverage the STMA meetings to have, you know, every pharma company come, you know, give some updates on where things are at and then you guys can plan -- you probably can plan over three or four years out what's going to be coming your way, if we give you the timelines that we're working against, which you often don't know.

And I think just more broadly, increasing communication. I mean, we've heard several examples now just in the last 10 minutes of things that you weren't aware that we were doing surveillance. I actually had never heard the piece that you mentioned about if we drop a species, how that actually affects you. I know it does affect you, but I never heard that level of detail.

And so I think, you know, when you ask us to provide a list of species, if we knew the consequences of getting that wrong, I think you might get different answers from people, from some companies on some occasions. So just increasing that communication

through whatever mechanism possible.

DR. PATEL: Darcie?

DR. CARPENTER: You know, another point, when we start a development process too, we are not the frozen reference method. And you know, our manufacturing process does things to the drugs. And sometimes we don't find out what those are until we get into development.

So just because this drug is similar to this drug does not mean that our development time is the same for those two drugs. One drug may take 10 times more formulation cycles to get it to work versus another drug. And like I said, they could be very similar because it's sticky, because it doesn't handle our -- you know, our dilution process. It doesn't handle our drying process.

All those different things are, you know, things that we don't find out until we start playing with it.

DR. PATEL: So from the pharma companies, any barriers to getting powder to device manufacturers to work out these issues at an early time point?

DR. MOTYL: So, we did. I mean, we did have terrible powder issues because we actually didn't even know who had the powder. Is it in this facility or that facility? But you know, that was part of what we streamlined. So we now have one place for powder for investigators as well as device manufacturers. But it was a nightmare. I mean, that definitely was a nightmare.

But actually, you know, I wouldn't dismiss Fred's idea. I think that's like a really innovative idea. You know, I think disks are incredibly low return on investment for the device manufacturers and we all have the tales of woe of not being able to get two disks.

I mean, there has to be another resolution for these things that are so critical early on to have available and then -- and then, you know, concentrate the device manufacturers on the automated devices and not get stuck in with disks.

I mean, it really is out-of-the-box thinking. But boy, I really like that a lot. So I also like the idea -- I like everybody's idea all of a

sudden. I like Kevin's idea too about the STMA tracking. And you know, I just wonder -- so you all are different companies.

So I don't know that even in your close circle will you be able to say, well, we can't develop, you know, Kevin's drug because it's sticking to our plates. But Mary's drug, we can develop because, gee, it's like, you know, soluble and air even.

I don't know if you're going to be able to share that kind of information. But I actually do like that idea too of some sort of tracking mechanism of the development of drugs and so that -- so that even you internally know, you know, I can do three more or I can't do two or something. I think these are all very good ideas. I love them.

DR. PATEL: Great. Melissa, and then Romney?

DR. MILLER: I was just going to get back to the point of different device manufacturers being on different cycles. This is a problem for clinical laboratories because if only one manufacturer is able

to then work with pharma for that particular drug and where company x is AST, it's very unlikely for us to validate and bring in a company y AST system just for this one drug. So just a reality check there.

DR. HUMPHRIES: My comment was along those same lines. I mean, it's a huge endeavor to bring on especially the automated AST systems. A disk, maybe you could get away with.

But then, the question I had is, you know, if ARLG is manufacturing disks, how are then those to be distributed? You know, it becomes a bit of an issue. But I think a coordinated trial with several of the disks would be a good first step right off the --

DR. PATEL: So you're saying that even once a drug is available on a commercial device, you might not buy the panel just because it has that new drug on it?

DR. HUMPHRIES: I think -- so if I have device A and they have a new panel with that drug, then probably I would. But if I have a device B and device A has the panel, there's no way I'm getting a

device A just to test that one drug.

I mean, it's a big endeavor. It's a big capital equipment purchase for these things. And the verification and IT logistics of having two different systems in the lab is very difficult. I honestly don't see any, you know, clinical labs doing that.

DR. PATEL: Can I ask a question for clinical microbiologists? So there's a lot of -- you know, there's limited real estate on automated susceptibility testing device panels. And sometimes you don't want to give up an old drug just because a new drug is available.

Are you getting to the point now where you have to test multiple panels for a single isolate or would you move to an alternative susceptibility testing system like a disk?

DR. HUMPHRIES: I think it depends on where you are. In Los Angeles, we see a lot of resistance. And so, being able to test these newer drugs is really important to my lab. But I know labs in other cities where they don't encounter this as often, they're happier to test as needed kind of the next day,

knowing of course there is a delay. I do think though for most places for these new drugs, they would be testing them on a disk at first at least or an e-test if it was available sort of on demand.

DR. MILLER: I'll just say we're in the minority of Romney's pie chart in the beginning in that we are disk diffusion users. And that is to give us the flexibility to make our own panels, to add these disks when they become available for this very reason. But we are the minority.

DR. PATEL: Yeah. Good. Well, I would welcome the panel for any other comments for the other questions that we have here. We have kind of dived into all of them, which is good.

Are there other technical, administrative or other challenges that exist for drug device companies, and how can those be addressed? Also, how can agencies, standards setting organizations and others facilitate coordinated development? Any issues we haven't discussed? Fred?

DR. TENOVER: Getting back to the infamous list two, I guess it sort of falls on CLSI and EUCAST

to develop those breakpoints for those things that don't have FDA indications and the willingness to do that because there is that clinical need. So it's one thing to be able to test and determine an MIC.

And I think one of my favorite comments from my years at CDC was a surgeon who called me and asked for an amoxicillin MIC on a staph and I said it was two. So it was resistant. He said, two? He said, oh, is that on a scale of one to 10? So MICs aren't always the bottom line.

We need to be able to turn those into S's, Is and Rs for some clinicians. But then, if that's not in the label, then somebody else has to do it, which means that FDA has to come to an agreement with CLSI about how we handle these data.

And I think we can't ignore those data. I totally agree with Amy. We just have to move beyond this. And the question is how do we do it in such a way that everybody is appropriately served and we don't go horribly off-label?

DR. PATEL: Yeah. Roger?

DR. ECHOLS: Thank you. Roger Echols. Just

there's one item that has not been brought up so far. I'm not sure if it's the appropriate time, but let me try it. And it has to do with whether there's an S, an I, an R or just an S and an R.

In other words, is there an intermediate breakpoint? And what I've been hearing from various organizations is an effort to go towards S and R and eliminate the intermediate breakpoint, particularly since many of these new drugs are only -- there's only one dose regimen.

So you don't have a dose for UTI and a dose for skin and a dose for HAP/VAP that's different. It's one dose for everything. And I've heard from EUCAST that if there's only one dose, there's no intermediate breakpoint.

But then, I hear from manufacturers that when you eliminate the intermediate breakpoint, it makes it that much more difficult for them to meet the specifications that they have to do to get approval by the device side of the FDA.

DR. PATEL: So I'd like to address that with my CLSI hat on. This does reflect a difference

between the two breakpoint setting agencies. So I'll say at CLSI, we normally set an intermediate breakpoint because one of the definitions for intermediate is technical variability. And there is a technical variability in the gold standard of at least a single doubling dilution.

So an MIC of two and an MIC of one are essentially the same result. And really, an MIC of 0.5, 1 and 2 are essentially the same result and fall within the accuracy limits of a test.

When -- and that is by far and large why the intermediate breakpoints are set. It also does help the device manufacturers meet the performance criteria established by FDA. Having room for technical variability in applying the breakpoints is essential to meet those performance criteria.

There are occasions where CLSI will not have an intermediate breakpoint. And that is if the susceptible breakpoint is at the upper limit of the MIC distribution and we know at the next dilution there are resistant mechanisms present and PK/PD data or clinical data indicating that isolates at the next

dilution will fail therapy and we try to keep those to a minimum. But that is different than the EUCAST approach to applying breakpoints.

DR. REED: I just -- to comment, for a clinical lab as well, not having an intermediate breakpoint makes verifying an AST device for a drug/bug combination very, very difficult and I've seen many labs that will not adopt something if there's no intermediate because any error you get is a very major, major error.

And they have a hard time understanding that if it's right at that breakpoint, maybe that's not as severe of an error than, you know, ones at the bigger extremes.

DR. SHAWAR: I just want to say technical point, many here will understand -- maybe some people more than others. But recently, STMA approached us at the CDRH side of devices with trying to come up with sort of a, quote, "scientific solution" to this issue when you only have -- you either have very major errors or major errors and you only have 1.3 percent to get past that criteria.

We've come up with a reasonable solution to that and provided that to STMA where we look at the -- right at the area where there is essential agreement. But let's say that's where all the errors occur. So we report those as errors, but that has not resulted for us to say, no, we can't clear you for that, realizing that, as Jean just said, there are technical issues. There are other issues.

But that's really -- so that's one of the -- I just want to emphasize that there are collaborative efforts that go behind the scenes that may not be very obvious to everyone. And this is one of them.

DR. PATEL: Can I ask has that solution been put -- been applied?

DR. SHAWAR: Yes.

DR. PATEL: And it resulted in an approval of a device with an SR, single dilution? Steve?

DR. GITTERMAN: Yeah. I would just make the point that -- I just wonder if we're going around this backwards. I mean, I'm almost offended -- I say that word with quotation marks -- that the idea that we'd be doing something to sort of meet FDA's or some type

of regulation.

The goal should always be the public health. And if S and R -- thank you, the patient -- and if S and R has more clinical relevance and is the right thing to do, then we need to change the way we approach it. and I of course, you know, value Ribhi's trying to do this. But the fundamental issue should be what is the right thing to do.

DR. PATEL: So --

DR. GITTERMAN: And it shouldn't be what we're asking for if that's not the right thing to do.

DR. PATEL: So perhaps I wasn't clear. But when CLSI does include an intermediate breakpoint, it's not just to help a device manufacturer get FDA approval. It's because there is evidence of technical variability. And you know about the technical variability and the reference method. Yeah.

DR. GITTERMAN: Well --

DR. PATEL: Yeah. Any other comments?

DR. CARPENTER: I think it's harder to hold the AST device manufactures to a more stringent criteria than what the frozen reference itself can do.

And that's -- you know, when you get to that S and R, you start getting into that realm.

DR. PATEL: Yeah.

DR. CARPENTER: But I agree. You know, the intermediate is because of technical variabilities, not because we need it to be able to get our devices approved.

DR. PATEL: Right.

DR. CARPENTER: It has to do with correlating to a reference method that has that much variability.

DR. PATEL: Yeah, there's no reason to ignore the technical variability that exists if there's no clinical reason to do so. Okay. Let's move on to the next question, unless there's more here.

In situations when a new antimicrobial drug has been approved but a commercial AST device of any type has not yet been cleared, how can clinical laboratories provide reliable information to clinicians about appropriate use of the antimicrobial drug?

So I think we've had some discussions on this. There are definitely concerns about using research use only tests within a clinical laboratory. That's a huge challenge for microbiology laboratories. Yeah, Romney?

DR. HUMPHRIES: I think, you know, in spite of the delays associated with reference labs -- and there's no doubt you would ideally want the test done in-house.

But at the very least, to have regional reference labs, perhaps through the public health system -- I'm not sure -- that could perform testing for labs for these critical cases before an FDA-cleared commercial device was available would be a big step in the right direction because, at present, that just doesn't exist.

DR. PATEL: Yeah, and I think that would be an excellent use of this new lab capacity.

DR. TENOVER: And I think also if we broaden our thinking beyond Gram negatives and include Gram positives, then we have a lot of molecular methods that are already cleared, like for detecting mecA and

mecC and a lot of the new drugs, at least cephalosporins, could probably use those molecular results to predict the potential outcome. And you'd get those answers in an hour.

The number of markers for resistance in the Gram negatives is growing. They're on Nanosphere and they're on BioFire and Cepheid has products. And I think those are sort of slow to come because people clearly don't know what to do with the data. And I think there's a lot of physician education that needs to go on to tell people what the value and what the utility of those molecular markers is.

But I think there are probably more that are coming. And again, those are results often available within an hour that, again, we can put the algorithms together to predict likelihood, probably more of failure than of success of a drug. But still, in the absence of any other AST data, I think those would be very valuable.

DR. PATEL: Thank you. Ribhi, and then Bill.

DR. SHAWAR: Ribhi Shawar. So what I'm

about to say is really not with the FDA hat on. So nobody go out there and say FDA suggested this. Reference panel -- the reference MIC panel is where most of the experience is during all the phases of the drug trials. And there will be successes and failures and modifications and additions and whatever until it now gets optimized.

So all the data that supported the drug trial came from that method. So now that the drug is approved, if there was an entity that were to provide these frozen reference panels to entities that can do the testing in a timely manner to provide for the patient, it's almost like the disk idea. You know, but in this case, now we are providing an MIC.

So we recognize -- CLSI, FDA recognizes CLSI methodology and all of that. So therefore, that is why when that method gets developed and for this particular drug, CLSI would say, you know, this is the additive, this is how you do it. So everything is set.

In other words, so it's unique really from a perspective of a new drug or new diagnostic method

where you have the experience and you have a method that is, quote, "reliable" except in cases where it's not, where it's -- you know, well, when it's difficult, you have disk -- you have the drug not able to be reproducibly working for disk.

And CDER therefore does not put a disk criteria or CLSI would not put a disk criteria because there are problems, not because of anything else. But anyway, you know, I will stop here. But again, I want to emphasize for the record that this idea has nothing really to do with FDA endorsing it.

DR. PATEL: No. At CDC, we think about that issue a lot. We prepare our own frozen broth microdilution panels. And we think about how we can make that be a resource when it's -- when there's a critical need. Bill?

MR. BRASSO: With the question that's been brought up, I was wondering if I might be able to change it a little bit to say when an antimicrobial drug, and specifically colistin, is not available in any commercial AST devices, which they are not in the United States because there are not FDA breakpoints

for colistin, which is why you don't see it on any of our devices.

But yet, the drug is used. It is available on some RUO panels. But I heard today that RUO is not the way to go, that a lot of times you can't use that data. Yet we know that colistin is used in every hospital in the United States. So how does that -- in looking at this, how does that provide reliable information to the clinicians?

DR. MATHERS: So just a couple of comments to this. So the colistin question is a good one. But a couple of comments to this. One thing that I would request for clinical labs is that when there is a reference lab, that they not turn away based on origin of that organism.

That would be very helpful to labs, that if they'll test -- even though the drug was only approved for intra-abdominal or urinary, that they test other sites if possible because that's just the way that infectious disease is practiced. And it's already difficult. So that would be one request.

And then, I think also as new panels become

available, I think we would have been able to do RUO or feel more comfortable with RUO reporting if we had another method such as the bank if there was available isolates where we knew what the MIC should be or what the results should be in our own hands in the lab and could just do a mini lab validation. And that's why we're afraid to use the RUO.

So with the colistin, we are going to go forward, just for an example. We are going to go forward and use colistin RUO from Sensititre plates. But at least we can use the AR bank to validate that within our own lab and validate the performance to that degree.

DR. REED: I think it kind of speaks to the issue we're faced when things are labeled as RUO. And I don't know that that's necessarily the most appropriate labeling for something that's a reference broth micro dilution. Sure, there's no Enterobacteriaceae -- you know, there's no FDA breakpoints for colistin. And so, that's why we can't get an FDA-cleared test.

But again, if one could show that the

essential agreement was good, that would get us so much further ahead because the reality is clinical labs are testing colistin by disk diffusion, which does not work. And so, the data that they're giving their clinicians is completely meaningless. And they're really using colistin in absence of any meaningful information.

So again, I think that having that research use only labeling puts us at a very difficult situation, A, from, you know, a liability perspective because we do sign something that says I promise I will never report this on a patient's chart, and I personally take on that liability if I sign that.

And then also, from a billing perspective as well, we can't bill for those. And so, it's very difficult to justify all this extra testing that we can never get reimbursed for.

So I know it's a difficult ask. But you know, the reasoning behind having research use only on a reference broth microdilution or frozen form panel that's sold just because there's no breakpoint doesn't totally make sense to me.

DR. PATEL: So are you saying if there were -- so for example, if you can't set a breakpoint, we've encountered this in CLSI where we have rules about setting breakpoints and you can't set a breakpoint where you have absolutely no PK/PD data, no clinical data and all you have is MIC distribution data.

And then, you set an epidemiological cutoff value. And that's what we have for colistin and Enterobacteriaceae. You know, do you use an epidemiological cutoff value?

DR. REED: I wouldn't use an ECOFF for colistin and the Enterobacteriaceae. But there are CLSI breakpoints for Acinetobacter and *Pseudomonas aeruginosa* -- not FDA breakpoints, but CLSI breakpoints.

So there is a source by which the lab could interpret a test, you know, in a lab-developed kind of situation that has good essential agreement. At least then you're providing useful information to the treating physician.

Now, where there isn't a breakpoint, I think

that again would be one where I would phone the physician and explain, you know, this MIC is above what's normal for this group of organisms. Take that and consideration of the fact that we don't have a clinical breakpoint and what's going on with your patient and use your judgment, as they do every single day. So --

DR. PATEL: I'm going to turn to John Rex on the phone and then we'll come back to comments on the panel. so, John?

DR. REX: So, John here. That was a really interesting discussion about this question of how do you -- what would you use instead of RUO. And it makes me think about what we're talking about doing with drugs themselves where we've had this notion of what we've called an LPAD drug and language about you should only use this when your patient has limited or no other treatment options.

And you know, I have no idea whether there's a way to adapt it. But so the principle exists for that kind of language because that's really what we're talking about here. You're only doing this because

you're stuck. You're not doing it just -- you're not doing it for fun. And it should be done, you know -- but it is appropriate under the circumstances. It's actually worse than not doing -- to facilitate it. so that's my thought, something like LPAD, but for AST devices.

DR. PATEL: Thanks. Thanks, John. Melissa?

DR. MILLER: This may be a naïve question. But would an ASR application here be appropriate or could it be appropriate? Because the research use only label really ties our hands of many laboratories to where it's grossly impacting patient care.

Some labs just will not use research -- or cannot. Their institution has a policy not to use research use only reagents devices. I don't know where the ASR rule falls into this and if that could be applicable to these panels, for example.

DR. GITTERMAN: This is a difficult discussion because obviously, you know, people are discussing the RUO. But that's in a very specific context when the RUO is far -- you know, a much, much broader point. I'd raise the sort of concern I have -

- I had raised -- I had mentioned earlier.

There's regulations that -- you know, things that we can do about through FDA and there's things that have to be done regulatorily, like as John had mentioned on the phone, LPAD, you know, that's a regulatory solution, a lot of these things.

When people are talking about different approaches to using RUO and language, you know -- I can't remember it off the top of my head, but specifically says for RUOs and not for clinical use or treating a patient. That's beyond, to be perfectly honest, the discussion that could be had around the table. That really falls back into the advocacy. What can we do in the bigger sense?

And there's also the question of, you know, again, we're getting into the third rail of anything FDA could ever discuss, which is LDTs and laboratory validation and things outside of the regulatory framework. And that's what I'm hearing a lot of this discussion now. I think it's valuable and I think there's aspects to it. but it's going to be very hard for us to give a regulatory solution within the

confines of what we can do now.

We would certainly welcome any proposals within what we can do. But I'm not quite sure altering the RUO framework. Regarding ASRs, that's interesting and perhaps -- I don't think -- because that's such a sort of narrow area, I'd be welcome to talk to you afterwards. I'm not sure it would be a general discussion.

If I could just make one general point because I had a smile on my face when Dr. Humphries had talked -- had mentioned this concept of regional labs. And you know, you have to go back a hundred years almost. But before antibiotics, what did we treat with? And you know, we treated with antiserum or arsenicals. But that wasn't, you know, a catchall. And sulfonamides didn't actually make it to America before that.

But the only treatment was, you know, antibody therapies or serum therapy. And you know, the captain of the Man of Death at that point was Pneumococcus. And New York state had established a series of regional labs so they could serotype

Pneumococcus as rapidly -- promised one-day turnaround such that they could get you -- because type-specific -- that was the big argument in those days because you could use general serum or type-specific serum for Pneumococcus.

But they were going to turn it around in one day because that was the great public health innovation of the time. And just a factoid, the person who invented the rapid serotyping method that made it work was Jonas Salk, 20 or so years before he did polio.

But the fact is I'm so struck by that because they could do this a hundred years ago and we would -- you know, I have trouble getting, you know, a device we don't have in our hospital across the street, which has a major medical center.

So I really like that suggestion and that's more from a public health standpoint. What can we do in a general sense to provide better care for our patients, completely outside of this. So, I'm done.

DR. PATEL: Right. So we call it the antimicrobial resistance lab network. Yeah. Ribhi,

then Darcie, and then I think we're going to move on.

DR. SHAWAR: Okay. Just wanted to have a clarification of what we're talking about. This is with regards to the methods and where there is a breakpoint or there is no breakpoint.

So I want to differentiate between cases where maybe there's not a breakpoint, maybe CLSI has it. Maybe FDA doesn't and maybe -- you know, so it falls into that RUO realm where I am applying a test of some sort to give a result and I don't want to do that.

But more specifically talking about let's say a new drug where there are not all these problems. Okay, we know what the organisms are. We know what the breakpoint is. It just got approved and -- but there is no testing method for it. The reference methods that are applied are methods that labs can do. And I think I can -- maybe people around the table who know more about this can correct me.

But we are not looking at those, or we do not consider these as LDTs. In other words, it's a reference method. You're applying a reference method.

As long as you have it made in a way that is matching what CLSI does and you're using a drug and you're using the interpretation of what's in the drug.

So to that, I distinguish between that and let's say an RUO for a drug that may be in Europe and it's not in the U.S. and that kind of thing. So just so that we are talking the same language.

DR. PATEL: Thank you. Darcie, and then we'll go to closing comments.

DR. CARPENTER: And this probably goes right into your closing comment. You know, the thing that I think at this point worries me the most is the things that we haven't thought about or the things we haven't talked about. I think we've talked -- we have a group of ideas and we've talked a lot about those ideas.

But we've heard a few new ideas and I think, you know, all of us need to go back and think about that and process that because it's the things we haven't talked about or haven't thought through the full implications of changing this piece and what it's going to do that still needs some more work.

DR. PATEL: That was a great closing

comment. So we'll move on to closing comments from FDA and I'll turn it over to Dr. Ed. Cox.

CONCLUDING REMARKS

DR. COX: All right. Thanks, Jean. And thanks, everybody, you know, for a series of excellent presentations and really excellent discussion today. And I think, you know, getting everybody together at the meeting today has really, you know, increased our collective understanding of both our own fields and the fields of others. And I think that's really important.

You know, in any, you know, situation where you're trying to overcome challenges or come to solutions, clearly getting an understanding of what everybody's facing is sort of, you know, a very important first step.

So, and I do think, you know, from all the challenges that have been identified, you know, there's a number of things that we all need to work on to solve to overcome the challenges we face here. And I think we've each got sort of our own list of things, if you will, from over the course of the meeting.

So I know I've been keeping track of a number of areas where, you know, I think that we can make progress. And I think, you know, there are also, you know, a number of items where I think each of the respective stakeholders here in essence can make progress.

So you know, we look forward, you know, to achieving, you know, the goals that I think we each have in mind for ourselves to be able to get there, to working together, to working with you to improve the situation here.

You know, recognizing that, you know, this environment of, you know, drug development, device AST, device development, the impact on the clinical community, you know, all the other pieces that go along with this, we kind of all have to find a way to work together to improve the situation overall for patients.

So with that, I will conclude. I don't know. Steve, you may want to send some well wishes. But before I do that, I just want to thank everybody for coming and, you know, we look forward to

continuing to work with you and, you know, getting to solutions on all of the challenges that we see before us. So, thank you. Steve?

DR. GITTERMAN: I'm usually -- I completely second, of course, everything Ed said. I don't think I can do it as articulately. But since this is actually my time, I'm going to talk for just a couple of minutes. I just took some scribbles down.

The first thing I just want to clarify is I misspoke earlier -- really. But there is not a docket for this meeting. There's a docket for the guidance, correct? Okay, now instead of giving me that big frown -- but so you can submit -- because if we said -- you know, you could stretch it.

If you said the guidance is coordinated development to get devices out earlier and to some extent somebody believes the actual clearance process for guidance is one of the problems, anything's on the table and we'll look at it and it goes into the public record. And it's very, very valuable to us.

And again, I would emphasize that sometimes when they come through in one organized form, it's

much easier for us to deal with. And you know, again, I don't mean to put pressure on any one group. But please use that mechanism if you can. If you feel really -- you know, real compelled and you don't want to put something in the public domain, Ribhi -- R-I-B-H-I --.shawar@fda.hhs.gov --

MALE: Could you give his home phone number just in case?

DR. GITTERMAN: Yeah, I'll be glad to do that. And you -- he's -- you know, that's for effect. The fact is we would welcome it. I'd be glad to give you my email as well because good ideas are always welcome and --

DR. SHAWAR: My out-of-office says contact steve.gitterman@gda --

DR. GITTERMAN: That's true. No, but the fat is it's true. It's not that -- well, I'll talk about this in a second. One quick thing, second point. I have just a few quick points.

The talks were sensational. I mean, people obviously put a lot of thought -- obviously there's a lot of angst about this and people probably saved up

these ideas for years and have been waiting for that forum to get them out.

But I particularly liked -- and it's not to separate out -- Dr. Brasso's last couple of slides when he was playing tag-team, where he listed a whole bunch of issues. And I was really struck by that because the fact is we at FDA have talked about and are trying to move forward on almost every one of those issues.

But it's really tough. And getting these perspectives, all the perspectives and working cooperatively -- because we all have the same goal -- would be tremendous.

So you know, we are welcome to go forward and if we have to have another meeting, perhaps a different forum or different mechanisms, we certainly -- I'm talking about this side of the house because I think if we're talking about that side of the house, Sunita will -- oh, by the way, deserves a tremendous round of applause for doing so much behind the scenes. Did you introduce yourself? What? Or did I steal Sumathi's thunder by not doing it? But behind the

scenes -- in any case -- right.

DR. SHAWAR: -- give that out after.

DR. GITTERMAN: Yes. Thank you. Just to clarify one point, one of the major points of the guidance is there is no restriction now at this point on waiting for the drug to be approved. One of the points of the guidance is you could come in before it's approved.

Our mechanism is you don't even have to pay for it unless the drug's approved. Now again, as was clearly said, that would be contingent on the drug being approved. But one of the points in the draft guidance would be to try and get rid of that barrier so that -- because a number of people mentioned it.

We want to get rid of that so there is a mechanism to come in early when the drug is still in review and to take advantage of the synergy. That's just clarifying it because it came up on a number of points.

And again, to make another point about the draft guidance, it's coordination is king. That's really the point of the entire guidance, to try and

emphasize that we will do anything we can to aid coordination.

And when people talk about five different groups and things, I thought it was a tremendous statement. Somebody made it, that maybe there could be one representative that's authorized by both the drug and -- you know, the drug manufacturers but one device representation to come to meetings and, you know, is accepted confidentially.

But whatever mechanism we have, you know, we will try and work with it. and the guidance, of course, says you can request this on the CDRH end. But of course you could request it on the drug end. It's a given. You know, we're happy to meet with anyone.

A couple of things I heard. The idea of a clinical trial center is -- you know, is a tremendous idea. And again, I would emphasize -- the ARLG came up a number of times. Somebody mentioned that there was never a report -- an independent report analyzing the drug -- the device development process. And in fact there is one under development. And just having

had a look at some of it, clinical trials are a big piece of it and AST is certainly a smaller subset of drug trials.

But you know, that should be something on the table, something that decreases cost, is not biased towards any manufacturer and again can somewhat delink -- I love the person who mentioned delinking because that's really something we're talking about, fundamentally delinking the cost of something that may not be a good incentive to overcome -- and again, it's the wrong word -- but what could be conceived of as market failures.

Okay. A couple of -- a couple of quick points. Again, I would make the point of regulation versus policy versus outside efforts and again in comments please feel free to try and separate these out because, again, as we talked about, advocacy can make a big point. And anything's on the table. We want to listen. But things we listen to, we're going to be more responsive to things we could do something about.

Is there anybody from the gray sheet here?

No? Okay. this is not for the transcript. But you know, just thinking out of the table, what could we do? One of the problems we're talking about and something I'm hearing -- and I think Dr. Shawar nicely said -- is there's a difference between at the onset and information we learn going on, that we don't know enough and we're delayed catching up all this information early on.

And I think, and again it's a blur, but people were saying, well, can we have a fast track? We have some mechanism to do it. Well, that's tough for us. You know, we don't have, you know, under the regulations two different tiers. We don't have this type of process. But we could all think out of the box.

This is not a proposal, okay? Everybody raise their hands and swear it's not. But thinking out of the box, we have a lot -- and there's a regulatory issue. We have a lot more control over PMAs than we do over 510(k)s. PMAs give us a lot of options in the post-marketing arena that 510(k)s don't. Maybe the STMA wants to say, look, we know PMA

is a little more burdensome.

But that's something we could work with. But maybe they would say, great. Now, let me tell you, form the drug side, no device manufacturer ever said I would want a PMA. You know, you'd be shot on site. That's like -- you know, that's just -- that's like walking into the DNC and saying, yeah, I think Trump's a good man.

No, but the fact is if you guys talked about it and said, look, here's a solution. We'd be willing to do this. And maybe, you know, there could be some support, you know, some way to do it. And that gives FDA the powers they need to do things differently. It gives them the sort of post-marketing hook that we can't get through the present mechanisms and that might be a way to do it.

But I'm just suggesting that as something out of the box that nobody's ever come up to us and said, yeah, that could work. And we would be glad to discuss it. The fact that you're nodding gives me great -- you know, because I have tremendous respect for everyone around the table.

Last thing -- I know. He's telling me to hurry up. Quick. Our issue and every one of our guidances, benefit risk. If you're making comments, think about benefit risk. Good science, which is everything we're based on, versus being overburdensome depends, you know, what your perspective are. There are two sides of a long -- you know, a long divide. Make the point for benefit risk.

Again, we talked about advocacies. Dr. Echols said try to make it a seamless process, you know, looking for incentives. And what I really like about this discussion is nobody mentioned the five-minute diagnostic to do everything.

But you know, we do have -- we are doing a lot of things. There's the -- you know, that Dr. Patel has played a key role in, the -- I think I just said something I shouldn't have said. There's a -- you know, there's the prize, you know, again, which is quite a bit of money, that, you know, if somebody comes up with this five-minute diagnostic for that prize, it's -- you know, it's quite the incentive.

There's a lot of efforts we're doing, which,

you know, again, blah, blah, blah. Thank you again for engaging. A lot of people came a long way. Clearly everything was so thoughtful. I'm astounded. I'm going to be stealing from your slides forever and you're not getting credit.

But I will turn to -- we do respond, don't we? Yes. I can assure you she ended up having to email both Ribhi and I. But we got her an absolutely definitive answer. And we do -- you know, again, you know, we are patients too. All of us are patients.

The very last point. I have a personal sort of family emergency going on. I apologize having to constantly check my BlackBerry. Luckily there's no split screen and having to step out during the meeting.

But it was not, you know -- it was not in any way, shape or form to show disrespect, actually if I've insulted Dr. Echols. I only meant it in passing. I hope nobody felt disrespected. Dr. Patel?

DR. PATEL: Actually, I'll turn it to Sumathi?

DR. NAMBIAR: Yes, I just wanted to say

thank you to everybody, the panelists and speakers and certainly to all of our audience members for attending and for actively participating in the discussion.

But before I conclude, a special word of thanks to Sunita Shukla, associate director for reguatlry science, who did a lot of the background work and I think pulled together a very successful meeting.

And we look forward to continuing discussions and dialogue on this topic and finding a way forward. So, thank you all and safe travels for those of you that have come from far. Thank you.

DR. SHAWAR: A round of applause for --

(Applause)

(WHEREUPON, the foregoing adjourned at 4:02 p.m.)

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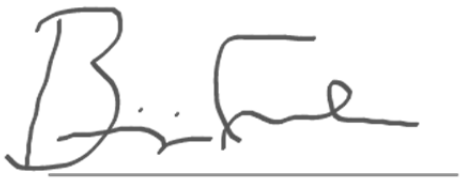

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