ANTIMICROBIAL SUSCEPTIBILITY AND RESISTANCE:

ADDRESSING CHALLENGES OF DIAGNOSTIC DEVICES

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Reported by: Michael Farkas

A P P E A R A N C E S

Steve Gitterman, FDA, CDRH
John Farley, FDA, CDER
Romney Humphries, UCLA
Bill Brasso, BD Diagnostic Systems
Ribhi Shawar, FDA, CDRH
Steve Metzger, Accelerate Diagnostics
Kristin Roth, FDA, CDRH
Mike Dunne, bioMeerieux
Daniel Sahm, IHMA
Patricia Simner, Johns Hopkins Hospital
Kimberly Anderson, FDA, CDRH
Robert Bonomo, Case Western Reserve University
Scott Evans, Harvard University
Jean Patel, CDC
Patricia Conville, FDA, CDRH
Uwe Scherf, FDA, CDRH

C O N T E N T S

P R O C E E D I N G S

DR. GITTERMAN: Everybody knows where the restroom is. If you don't, don't raise your hand, just walk out the door and people will -- will tell you.

Everybody knows about ordering lunch? We can order lunch in advance during the break, so you don't have to wait with everybody else, but you will wait anyway, but what can you do?

Okay. Next slide. You know, this is excellent, the slides are improving. The people sit there and they look at events like this and say finally we're going to get something done. But the fact is, everybody's working on this every day. Progress is slow because a lot of these issues are complicated, but I can assure you people here, obviously people out there, are working on this every day. Rome wasn't built in a day and what we're trying to build is really an edifice of antimicrobial stewardship.

We don't -- I couldn't find the slide for that. I Googled antimicrobial edifice,

antimicrobial house, antimicrobial building, nothing fit. But the fact is that's what we're working towards. We're working towards a science, a field, the application of antimicrobial stewardship and the focus today is how can antimicrobials contribute to that.

They've always contributed to that. We've been practicing personalized medicine since the day you could grow anything, but that's what we're here for.

And we have been making, all of us, tremendous progress, exceptional progress, but there's still challenges and there's new challenges because of the progress. That's a good thing. And what have we done just in the last few years? We have the Antimicrobial Resistance Bank, or Isolate Bank, as I've been corrected before, which is a tremendous cooperative partnership between FDA and CDC.

And I believe Dr. Patel is going to be speaking about that later. I'll just give you -- I'll steal her thunder. It's going to be renamed next year The CDC/FDA Antimicrobial Bank. But

it's a great partnership and it's made -- it's addressed what has been a real concern, which is these isolates aren't available and people can't get them and it's trying to -- to accelerate or help address the premarket development of a lot of these devices. A great advance.

We have 21st Century Cures. I didn't want to go through this, Dr. Shawar will be talking about this in a little bit, but we've -- the progress by being able to use standards development organizations for doing breakthroughs is going to take in some cases a year and a half, if not more, in the development of antimicrobial susceptibility devices.

If Ribhi doesn't go into detail, I'll be glad to explain it, but that's a tremendous advancement. It's a great development for drugs and for the public, but it also affects devices substantially.

We have coordinated development, another thing you'll hear about from Dr. Shawar. But again, it's always been the complaint, why can't we do

this, why can't drugs and devices cooperate? Why can't FDA get some of these devices out earlier? And coordinated development, there is a draft guidance, but that is full speed ahead here.

And as I think Dr. Shawar will discuss, it's had a tremendous response and we're really excited about it, and part of the discussion today will be, how can we move forward even faster with this? As things move, as outbreaks emerge, as new resistance mechanisms emerge, we have to have a better process. And I think we've put into place the beginnings of getting that better process.

(Inaudible) I was poking a little fun before, but the President's Advisory Council Antibiotic Resistance is meeting downtown, and if anybody's looked at the paper on their website for today, it's meeting today and tomorrow, they have a number of what I think are very exciting proposals.

Another thing many of these people in the audience have always said is, I'm saying this with a smile on my face, everything for drugs, nothing

for devices. Anybody ever say that before? Nobody's going to raise their hand, but you have.

And in legislation, that is true. You know, there's a lot of incentives for drugs, but some of the proposals there directly are incentives for devices and I think if adopted, have a lot of excitement in terms of addressing some of the major challenges in -- in antimicrobial susceptibility testing. So that's very exciting. We don't know where it's going, but the fact is people are listening. There's a large number of very bright people who have contributed to that report, and that's very, very exciting.

And of course, at the top of the list there's unbelievable scientific advances. It's just -- again, if we all step back and look at where we were 15 years ago, it's a different world in so many ways. And I think some of the challenges we're going to be talking about later during the day are because these didn't exist 15 years ago. The idea of taking a dried spot of blood and doing resistance testing or biomarker testing would have

been inconceivable years ago. And some of the challenges which you'll hear about is because we've advanced so much, because we're testing nonsterile fluids, so a lot of other things. But the progress really just over the last few years, multiplexes for meningitis, more rapid technologies, and it's both molecular and phenotypic, are very exciting.

What else? What are the goals of the workshop? The goal is to inform FDA and everyone else regarding the scientific and regulatory challenges.

Later if we have one of those -- do we have any alcohol I could wipe off the screen so the speakers could see it clearly? Anybody have a clean handkerchief?

But the -- regarding the scientific and regulatory challenges associated with AST -- oh, my gosh. How did the spellchecker miss that? My apologies. We'll change it on the website. You have been spelling it right all these years.

But regarding AST devices, and using molecular

devices, which are AST devices in another form in a lot of ways, and especially novel devices that detect markers. That's one of the goals. We have challenges. We need informed opinions, which we'll talk about in a minute. We have to move forward. This is not something where we could sit still.

We as FDA are not serving industry well. We are not serving the public well. We need to move forward on these challenges. We should be here to help you, not to be a burden.

And this is another brick. We're not going to solve everything today, but we are going to get action items and we are going to move forward. Again, nobody's going to walk out of here today and say this was the best meeting I've ever been to. I could have skipped ID week and just spent today here. But -- that wasn't that funny, really.

But the fact is we should have action items and we should be thinking how are we going to move forward. The agency is very committed to

timeline, to action. It's not just talk. We expect -- you know, we expect progress from this.

And the important thing is we need to move together as partners. The days when FDA and others were considered adversarial are gone. We have to move together. Partnerships are the way to go. We really -- there's a lot of exciting things happening and we all want to do it together and everybody's thinking outside of the box.

Okay? This is the, very quickly, my remaining minute, this is the agenda. I'll be done in -- within one minute. We'll be followed by John Farley, Dr. Shawar will be going through the agenda. Everybody should have a copy of this for the morning.

Interesting topics. Dr. Roth will present the afternoon agenda. And what is your job? Okay. Your job is to shut off your Blackberries -- ah, nobody's affected. Nobody has a Blackberry anymore. See, there's a trick question. But you need to shut off your iPhones, you need to network afterwards and during the break. We have a

docket, anything you could think of, submit it to the docket. We are required by law to read it. So please submit it. The meeting doesn't end today. We really, really want to move forward. Everybody has a role here. Okay?

And with that, I will introduce Dr. Shawar, who will introduce the remainder of the day. Thank you.

(Applause.)

DR. SHAWAR: I don't see John -- oh, John, you're here. Excellent. Thank you. No need to switch.

All right. Good morning, everyone. I'm going to just echo what Steve eloquently said, that we look forward to participation by everyone. We thank everyone, speakers and panelists in the morning and the afternoon. So without further ado, I don't want to take any more time from anyone else. You saw the agenda.

First on the agenda we're going to have John Farley from our sister center, I guess, Center for Drugs, to talk to us about the 21st Century Cures,

implications for susceptibility testing and guidance.

Thank you, John.

DR. FARLEY: Thanks. So for those of you who were following the meeting earlier, you'll note that there's been a last minute call to the bullpen. Sumathi Nambiar, who's much nicer and smarter than I am, actually has business travel this morning and I convinced her that she could not drive to Dulles in 15 minutes in the rain. So she is safely on her way. And I'm going to talk about an overview of the 21st Century Cures Act and the implications for the scientific community that's assembled here.

So I think we all recognize that our process for updating breakpoints and communicating that to folks through labeling is an outdated and an inefficient process, and certainly device developers have had the most challenges in terms of delay. And so one of the things that the 21st Century Cures Act recognizes is that it's very important that the most appropriate and relevant

information be available for the care of patients with respect to susceptibility tests interpretive criteria and tries to -- and we're going to develop another mechanism that will be more efficient.

The process of updating breakpoints will certainly remain an iterative process. It's not instantaneous, but I think the last decade I've been privileged to work with lots of folks in the standards development community and I think we have a very effective partnership going and that that will continue.

And also the Act recognizes that clinically there is a need for interpretive criteria for organisms that are not listed in the indication section of drug labeling.

So currently antimicrobial labeling with respect to susceptibility test interpretive criteria is located in Section 12.4 if the physicians' labeling rule is being followed. And that describes the relevant microbiology data for the drug, mechanisms of action, resistance and

interaction with other antimicrobials.

It also includes two lists to describe the spectrum of activity, the first list and the second list. Microorganisms listed in the first list are associated with a labeled indication and for microorganisms listed in the second list, efficacy of the drug in treating clinical infections caused by these microorganisms has not been established, but they should be relevant to a labeled indication.

So those parts of 12.4 that I've just described will not change.

The 21st Century Cures Act was signed into law on December 13th, 2016. It contains four sections that are relevant to us in particular today. Susceptibility test interpretive criteria for microorganisms and susceptibility testing devices addressed in Section 340 -- 3044 of the Act, antimicrobial resistance monitoring and then Section 3042 on LPPAD (phonetic) or limited population pathway for antibacterial and antifungal drugs.

Section 3040 -- 30 -- let's see -- 3044 of the Act actually modifies Section 11 of the Food, Drug and Cosmetic Act. So regulatory people will start talking about Section 511 and that's why, because it's -- the Cures Act modified that section of the Food, Drug and Cosmetic Act.

Basically we're required as the FDA to establish interpretive -- an interpretive criteria website within one year of enactment. So remind you that that was December of 2016. That website is going to include FDA recognized breakpoints established by standards development organizations, which I'll refer to as SDOs for the remainder of this talk. It will also include other breakpoints where FDA does not recognize in whole or in part a standard, that FDA withdraws in whole or in part recognition of a standard -- that FDA approves an application for a drug for which breakpoints are not included in a standard, which certainly includes the most recent approvals, as you know.

And then a section which hasn't particularly

come up, but is there, FDA determines a product that contains the same -- a product that contains the same active ingredients requires different breakpoints due to the characteristics of the product and such -- different breakpoints are not reflected in this standard.

So the website contains a number of disclaimers because it really sets up a recognition process for a standard, which is relatively new to CDER and it is not the same thing as an indication. It's a recognition of the science behind the standard.

So the website provides information about the in vitro susceptibility of bacteria, fungi or other microorganisms as applicable to a certain drug or drugs. But further, that the safety and efficacy of such drugs in treating clinical infections due to such bacteria, fungi or other microorganisms as applicable may or may not have been established in adequate and well controlled trials in order for the breakpoints to be included on the website. So recognition is not an

indication.

The clinical significance of the breakpoints in such cases is unknown and that the approved product labeling for each drug will continue to provide the uses for which FDA approved the product.

Okay. So you'll see that disclaimer on the website. That is the statutory language that requires that disclaimer.

We'll be publishing a federal register notice not later than the date on which the interpretive criteria website is established. We will continue to review certain breakpoints every six months and update the website as appropriate. When FDA -- when updates occur, FDA will publish a notice on the website. And we're actually anticipating that that updating may be more frequent than every six months. For example, it will need to be updated every time a new antibacterial or antifungal drug is approved.

When a drug is approved based on breakpoints not included in or different from those recognized

or otherwise listed on the website, we will update the website to include the breakpoints on which the approval was based. So new drugs, we -- the breakpoints will not be in 12.4, they will be posted on the website once the website exists.

We'll compile all of our website updated and publish an annual notice in the federal register for public comments. And as Steve said, this is going to be a process where we're all engaged and we're all invited to engage through the public docket submission process, and that is -- is going to continue to be hugely helpful to us.

Now, just one thing that I -- I didn't mention. This recognition process is not going to instantly solve the problem of what you all call, I think, legacy breakpoints. And in my mind, those are breakpoints that we haven't looked at in a really long time. We as the FDA need to have a scientific basis for our recognition. We need to have a scientific rationale. We intend to document that. We will have an administrative record for that.

The standard development organizations have been extremely helpful to us in the past decade, providing information for us to help us understand the scientific rationale for breakpoints. Our microbiologist and Clin Pharm folks at CDER, in conjunction with folks at CDRH, have basically reviewed the breakpoints for every marketed antibacterial or antifungal drug since 2008. That's been a huge accomplishment, and that's the foundation upon which we can build our recognition. But we're going to be continuing to engage with you as the scientific community around these old breakpoints to look at that rationale, understand whether they can or cannot be recognized. Many of them were -- were developed before probability of target attainment and other tools that we now have at our disposal existed.

So that's not going to solve that problem. We as a scientific community are going to need to address that problem.

Let me go back. So for FDA to recognize standards established by a standards development

organization, that SDO has to meet the following criteria. First it establishes and maintains procedures to address potential conflicts of interest and insure transparent decision making. Two, it holds open meetings to ensure an opportunity for public input and establishes and maintains processes to insure input is considered in decision making. And three, permits standards to be made publicly available; for example, through the National Library of Medicine.

Currently we're considering how to apply the criteria to evaluate eligibility of relevant SDOs and we will be inviting formal submissions as to -- from SDOs as to how they meeting this criteria in the near future. And we'll be doing that in a public way.

So as I mentioned, labeling for drugs approved after establishment of the website will actually contain reference to the website in lieu of a breakpoint. So there's actually going to be a hyperlink in a drug label. This is like very innovative for CDER. We are like very hip now.

It's -- it is. It's amazing.

One year following establishment of the website, all application holders, in other words, all of those who own an antimicrobial drug, will remove the breakpoints from the approved drug labeling. We'll be providing rather explicit directions as to how this is going to -- how you're going to do this. We'll give you examples, et cetera. And you'll replace it with a reference to the website. So you'll have a much shorter 12.4. It'll probably end after the second list.

An applicant can seek breakpoints that differ from those listed on the website and we will -- and they'll need to provide data to support that. And we'll have a docket and we'll be able to have, as I mentioned, ongoing public discussion. This doesn't diminish our work, it actually increases it a little bit, and that's okay.

So in terms of Q and A, you might be asking, well, what information should I submit to an NDA if I'm submitting an NDA. Well, an NDA should continue to contain the usual types of information

in terms of clinical microbiology that's needed to support establishing breakpoints and includes surveillance data, activity in vitro, animal models of infection and clinical data.

Will we be setting the breakpoints for new drugs? Yes. If there are no breakpoints established at that point by an SDO that the FDA can recognize at the time of approval, breakpoints should be identified by FDA and these will be listed on the website. The new drug will have a title page that you'll be able to click on and link to.

If an SDO has established breakpoints that the FDA recognizes, then we'll list that recognition on the website instead. This is thinking down the road because I know right now that's not happening.

Can SDOs set breakpoints prior to the FDA? Our position is yes, they can. An SDO can set breakpoints prior to the FDA. It's up to the applicant or the sponsor if they choose to submit that data to an SDO prior to FDA identifying or

recognizing breakpoints.

So just a few words about LPPAD. Section 506H of the Food, Drug and Cosmetic Act is now amended for the -- to describe the LPPAD option. LPPAD would be for a drug that's intended to treat a serious or life-threatening infection in a limited population of patient with unmet needs.

The standards for approval under 505C and D or the standards for licensure under 351 for a biologic continue to need to be met. So the substantial evidence of efficacy standard has not been changed by the statute. We certainly recognize that uncertainty is tolerable when patients have limited treatment options, and that's been the case since the HIV epidemic for the FDA. We publicly stated that and we've applied it, quite frankly, on a number of occasions even in the last year, but the statutory standard is not altered by LPPAD.

LPPAD requires a written request from the sponsor to the FDA that the drug be approved as a limited population drug. There are additional

requirements if it's -- if it's a limited -- an LPPAD drug. The labeling needs -- will be indicating that the safety and effectiveness has only been demonstrated in a limited population. All advertising and labeling will include limited population in a prominent manner. We don't actually have guidance yet on what that means, but prescribing information will contain the statement "this drug is intended for use in a limited and specific population of patients." And promotional materials require pre-submission to the agency at least prior -- 30 days prior to dissemination.

Also Section 3041 of the Cures Act which addressed antimicrobial resistance monitoring describes monitoring at federal health care facilities. A report on antimicrobial resistance in humans and use of antimicrobial drugs and antimicrobial stewardship activities.

So in summary, there really have been significant challenges, particularly in getting the information you as device developers need, and we're trying to streamline that process. The

provisions of the 21st Century Cure Act allow for some options regarding susceptibility test interpretive criteria and will hopefully result in a better process.

The FDA website for interpretive criteria and recognition will be established later this year, and labeling for drugs approved after establishment of the website will simply contain a reference to the website in lieu of breakpoints.

I want to end by acknowledging myself. I'm just kidding.

(Laughter.)

DR. FARLEY: These are Sumathi's slides, as I mentioned. Katie Schumann, who's here, who's been our regulatory lead for implementation of many of the programs that I think have -- kind of the unsung hero of implementing many of the statutes which have promoted antibacterial drug development and we've really made progress together.

I'd also like to acknowledge the clinical microbiologists in the division of anti-infective products of the FDA as well as the clinical

pharmacologists.

As I mentioned, since 2008, and really since 2010, they have reviewed the breakpoint for every single marketed drug, and that's really been the foundation upon which we can build the recognition.

Secondly, I want to thank standards development organizations that have been incredibly forthright in helping provide documentation for why decisions were made. They've really gone the extra mile. And being public about the scientific work that they're carrying out that -- that's really been very useful toward the progress we've made so far, and I'm confident that it will continue to result in progress working together.

So thanks very much.

(Applause.)

DR. SHAWAR: Perfect. Thank you so much, John, for this nice overview. Now we're going to hear -- by the way, we're not going to have questions after speaker. We're going to have the

speakers go through their topics and then, of course, we're going to have the panel discussion afterward with the questions that FDA has.

So I'm delighted to invite Romney Humphries from UCLA to talk to us about their perspective on current reference methods, which I know they use very much at UCLA.

DR. HUMPHRIES: Yes. Yes, we do. All right. Thank you, Ribhi.

And so I'll be talking about some of the reference methods that are used when clearing susceptibility test devices.

So, you know, you may ask why as a clinical microbiologist I'm giving this talk, and the reason for it is at UCLA we perform reference MIC testing for all patients at UCLA. And so we do this by the CLSI, which is also the ISO reference broth microdilution method, with the exception of Enterobacteriaceae from the urine. And so these are just some pictures of my lab. We have an instrument that helps us make these panels. We make 1500 at a time. We do this at least once a

month, usually twice a month, to make gram negative panels, gram positive panels, fungal panels, et cetera, et cetera. So it's a big undertaking.

In this one picture you'll see Kevin Ward. Nobody could do this without somebody like Kevin. He's a very dedicated technologist that works in my lab, and honestly, his full-time job is pretty much making these panels for us.

So like I said, we make a variety of the panels. They are read manually, so we have two technologists in the morning that sit down and read all the MICs through, you know, this very sophisticated device that you see in the picture, which is essentially a magnified mirror. And we also can make custom panels for drugs that we don't test routinely through this process.

So for those of you who aren't familiar with this reference broth microdilution panel, it is the reference standard that is used for the most part for clearance of devices through FDA as the reference comparator. It is well standardized in

that we have standardized media that is used, we have standardized inoculum that's used, testing conditions, et cetera, but there is still some variability. And so this is just a picture of our gram positive panel. You know it's gram positive because of the purple dye. We're very visual in microbiology.

And so essentially what you're reading is buttons of growth on the panels. So you can see right there there's some growth. And so, you know, this is probably not easy to look at without the map to show you which drug goes where, but anyways, you get the sense of what we do.

And so while this method is very well standardized to the best of our abilities, there still is considerable variability from some drug bug combinations.

Oh, and here's the map for -- for the panel.

So if we take a look at the variability of this reference method, and this was data that was done -- compiled by the CLSI susceptibility testing subcommittee where they really looked at

the broth microdilution method, and this was a working group that was chaired by Bill Brasso, who's sitting right here, I see, to my left. And essentially these are data from bioMeerieux where they looked at a single lab and they did nine replicate tests for each drug bug combination. They had three different people read the panels over three days. It was the same lot of panels and they included 91 gram negatives and 79 gram positive isolates. So all told, there were 1927 drug bug combinations.

And so what you see in the graph is the MIC variability that they saw from these isolates. And so for most isolates you would have one or maybe two, up to three MICs that were observed. And this is what we expect. Our essential agreement is the MIC plus or minus a single dilution.

But you can see there are a handful of isolates where you saw four or even more than four MICs, and this is, you know, under pretty much the best conditions possible where you're using the

exact same panels, the same lab, just a little bit of inter-user variability. So, again, we do see things falling outside of that essential agreement.

And so if you simulated from these pooled data, for a sample size of 50 you would expect to be within that plus or minus one dilution 88 to 100 percent of the time. So pretty good, but not perfect.

And so, you know, clinically what does this really mean? And, you know, first off, of course, it's very unrealistic to think that organisms have a single or real MIC. That is just not true. Some strains will behave very well in the broth microdilution methods and others much less so. And where this really comes into play is how close that isolate's MIC is to the clinical breakpoint. And so if you take a look at -- and these are just made up data -- but cefepime MICs, if you had that variability where you see isolates with two or three MICs, but they're well below the clinical breakpoint as is shown in the graph on the left,

it doesn't really matter all that much. However, if you have isolates that are living near the breakpoint, for the same isolate you can get different interpretations just based on the test, you know, replicate. And so in this case, for the graph on the right, for our E. coli strain one, you can see we got MICs of 2, 4, 8 or 16, which could mean that the isolate is reported to the clinician as susceptible, susceptible dose dependent or resistant. And none of this is incorrect, it's just the variability of this broth microdilution test.

So these are some real world data from my lab where we were looking at clinical patient isolates again for cefepime. And so these were tested by the reference broth microdilution method as I described at the beginning on the first day, which was what we reported in the patient's chart. We then repeated the broth microdilution test the next day. And so what you can see for E. coli and Klebsiella is that there were isolates that fell into the susceptible dose dependent interpretive

criteria that were repeated as resistant or as susceptible. And it really, you know, was fairly random across the board. But, again, this just speaks to the variability of the MIC method.

And so, again, I think when we use broth microdilution, we'll really good at calling things very susceptible because there still is variability there, but it doesn't matter because it's far away, away from the breakpoint and we're really good at calling things resistant, but once we start getting into these gray zones, it's a little bit more difficult to have an accurate result.

So when we then take a look at this when we're comparing commercial tests to broth microdilution, and I just pulled these two studies out again that we did in our lab where we were looking at the Vitek test, but honestly this could have been any of the automated susceptibility test systems, or even broth microdilution against itself. What we found in both studies is, you know, a handful of errors. In the first example where we're looking

at Staphylococcus and Enterococcus species, we had 88 errors. And so when we do this type of work, we would repeat all errors by both methods the next day.

And so what we saw in the first case was 45 of those errors resolved upon repeat testing and, in fact, 38 of the 45 errors that resolved were due to the initial broth microdilution result being off.

Similarly, in the gram negative study for the Enterobacteriaceae, we had 37 errors, 21 of which resolved upon repeat testing and 6 of those were due to the initial microdilution result.

And so this becomes a bit of a challenge when you're evaluating systems compared to reference broth microdilution because, again, the MICs will be variable and, you know, upon repeat testing, some of these perceived errors actually resolve themselves.

All right. So things get even more complicated if we were to push the breakpoint into that wild-type distribution. And so this is an

example of cefazolin with E. coli. And so I took the MIC distribution from the UCAST website and what you can see for our wild-type population we have isolates that are living right at the breakpoint with MICs of 2 or 4, or 8 even. And so the problem with this is every isolate that you test is likely to be within two dilutions of that breakpoint and you can see variability within that plus or minus two dilutions. And so as a result, it's very, very difficult to get a test approved or cleared when the breakpoint is right near that wild-type population. And so this is something we've talked about at CLSI is trying to avoid as much as possible, but sometimes the PK/PD just tells you that that's where the breakpoint should be.

As an aside, none of the commercial manufacturers have updated the cefazolin breakpoint for the Enterobacteriaceae on their systems, and, in fact, at UCLA we no longer test cefazolin for the Enterobacteriaceae in part due to this issue. We use it for urine, but that's

it.

All right. Another example of a dilemma is if there is no buffer zone, which is the intermediate. And so just to remind people of what that intermediate category really means, it's, you know, a category defined by a breakpoint, that includes isolates with MICs or zone diameters within the intermediate range. And this is -- those MICs that approach usually attainable blood and tissue levels and for which your response rate may be lower than for susceptible isolates.

So this intermediate category implies the clinical efficacy in body sites for the drug concentrates or when higher than normal doses can be used. And I think we all kind of understand intermediate in that context. But what we sometimes forget, and I think this is very important when it comes to susceptibility testing, is this category is also designed to be a buffer zone that prevent those plus or minus one dilution variability, which is, you know, uncontrolled, to

cause major discrepancies in interpretations; so an isolate that may be resistant one day testing susceptible the next if there's no intermediate breakpoint.

So, again -- and that was directly from the CLSI M100 document. So intermediate isn't just for alternative dosing, but there are examples where we have no intermediate category. And so that includes folate pathway inhibitors as well as the polymyxins. And we recently saw a newer drug, ceftazidime/avibactam, which has no intermediate category, which is causing problems when we look at the disc diffusion test because we just cannot get isolates that consistently test resistant or susceptible and we see very major or major errors.

So here's another example of where this has caused a problem. And so these are cefepime and ceftazidime for Pseudomondas aeruginosa. And so many of you may know that the CLSI updated the ceftazidime and cefepime breakpoints for Pseudomondas aeruginosa as did FDA. However, there is a slight different between the two

breakpoints in that FDA does not have an intermediate category.

And, you know, again, the challenge is you're sort of like walking a tightrope, and this is a picture from when I was in Joshua Tree last where you see people string these tightropes up between the rocks. But I think it's kind of like that when you're doing your susceptibility test if there's no intermediate category. And so what you can see here are the MIC distributions for Pseudomondas aeruginosa and where that breakpoint lives. And so you are sort of right in where that wild-type belongs and any plus or minus one dilution across that breakpoint is going to cause a very major or major error, false resistance or false susceptibility, neither of which MICs are probably incorrect.

Now, if we do both of these things, so we get rid of the buffer zone and we push the breakpoint right to the wild-type we're in even a tighter spot. And this is what essentially has happened with colistin and the Enterobacteriaceae where

we've set an epidemiological cutoff value, so not a breakpoint, because we don't have all the full PK/PD data and clinical outcome data that we need for that, and we no longer have an intermediate zone.

And so these are data, again, from my lab on reference brother microdilution. Colistin is probably one of the most difficult drugs that we test. We are constantly having issues with it. In fact, yesterday in the lab we had a whole conversation about our polymyxin b always being out of QC and maybe we should just quit testing it.

And so if you can see here, we had one panel and we did six replicate wells of colistin using three different brands of cation adjusted Mueller Hinton broth. And so if you look at the first isolate, Enterobacter aerogenes, we had two replicates with an MIC of 0.5, which would be considered wild-type, two at 4 and two at greater than or equal to 8.

Another one is an E. coli with the MCR1 gene,

which, again, if you're not familiar with that, that's the plasmid mediated resistance mechanism for colistin. Two isolates tested wild -- two replicates tested wild-type and four tested not wild-type, but right across that breakpoint. Whereas if you look at really, really susceptible isolates, like our second E. coli, all of them would test wild-type. So, again, you're going to get variability across those interpretive criteria.

So, to put it in context a little bit, the gold standard broth microdilution is not really -- it's not a bad method. It is usually reproducible with one dilution. However, it's not always predictable which isolates will behave and which will not, and there will always be isolates that misbehave when you're evaluating larger collections of isolates like happens when you're trying to develop a test for clearance with FDA.

It could also be, of course, very challenging if the wild-type MIC is near the breakpoint or if there's no buffer zone or intermediate category.

That's something I personally think we really need to avoid doing.

And we may need different acceptance criteria if the MICs are near the breakpoint or if there's no intermediate breakpoint; if we just can't avoid those two scenarios.

And to be honest, I think allowing discrepancy resolution in the submission process is a good thing. I think I showed a couple of examples of how this can be a problem. Even, honestly, if you tried to get the reference broth microdilution method cleared against itself, I think you would run into problems.

And we need -- we may need to further evaluate the broth microdilution method variably for newer drugs because, again, some of these factors are controllable and some of them are not. But going in it's not always apparent what is going to cause the variability in the reference method.

So I want to take the last little bit of my time to go back to colistin for a minute and just talk about this whole issue of clinical

breakpoints and test clearance. And so right now we -- we don't have any FDA-cleared susceptibility test for colistin, and the reason for that is there's no FDA breakpoint, nor, in fact, is there a CLSI breakpoint for the Enterobacteriaceae. What we have is an epidemiological cutoff value which is designed to help monitor for the emergence of resistance, but not to predict clinical outcomes.

And yet, we know in the United States one of the biggest uses of this drug is for carbapenem resistant Enterobacteriaceae. And so how are we going to help our clinicians decide if they're going to use this drug that is toxic when we cannot report out susceptibility test results? And at UCLA, from our experience, just as an aside, about a third of our CRE are very high MICs to colistin, in which case you probably wouldn't want to use it clinically.

And so I just want to throw this idea out, as perhaps we need to think about having tests cleared with ECBs only when that's the only

option, and then have those results reported with a disclaimer. Because otherwise there's no way for us to have these tests available for clinical labs. And like I mentioned, colistin is a good example of this because it's a very difficult compound to work with. And so thinking that clinical labs might be able to do their own broth microdilution for this compound in particular is just totally unrealistic.

And the other thing I just wanted to touch on, and I'm hoping very much, after hearing John's talk this morning, I'm kind of feeling encouraged, but, you know, just this comment about the kind of unlevel playing field that we're on, which is where some of these older tests that were cleared by FDA before 2007 can report essentially isolates with any breakpoint, whereas current tests cannot. And, you know, this is a problem because some of the newer technologies that we really need and seeing developed are at a small disadvantage with FDA in that they can get fewer drug bug combinations cleared on their devices.

And the other challenge that we see happening is that if you're a manufacturer and you know you have an issue with your device, but it's for a drug bug combination that's not FDA recognized, you really can't go back and fix it and have that data resubmitted you won't get that clearance.

And so we know breakpoints are constantly changing and as these are changing, you have this challenge where you may lose some capability with a breakpoint.

And so many of you may know, I'm going to Accelerate at the middle of October, so I wanted to throw this up as an example where you take a look at Acinebacter baumannii on their system versus some of the older systems that were cleared before this rule came into effect. And so there's only two drugs that are FDA indicated for Acinebacter baumannii on the test panel that's tested, which are piperacillin and tazobactam and amikacin, which are not drugs which I think we use, you know, as our first go-to when we talk about treating Acinebacter infections. Whereas if

you take a look at some of the older systems that were cleared before this rule went into effect, they can test the much more clinically relevant compounds. So I'm happy to hear that things -- you know, this -- with 21st Century Cures, we're hoping that we'll move away from this, but this is a big challenge at the present.

Another example of this is with ceftazidime/avibactam, just to kind of drive home how important this change would be, and I really hope it comes out the way we hope it will, with the list 1 and list 2. So this is an example of ceftazidime avibactam where you have the clinical indications on the top. We have breakpoints for Enterobacteriaceae and Pseudomondas aeruginosa, but you'll notice that there's no clinical indication for organisms like Serratia or providencia, which while are Enterobacteriaceae, are not clinically indicated so you couldn't get a test cleared for those as it stands today.

I'm going to skip this because we already heard about that. But I just want to touch lastly

on the other CLSI reference method, which is disc diffusion. And many labs are going to use this in clinical practice as compared to broth microdilution. I think my clinical lab is one of the very few in the country that do broth microdilution routinely by the CLSI reference method.

Discs are cleared by the FDA, but there are some challenges. And so I have this picture here which are, again, some data that we generated as part of a study were doing for CLSI to look at Staphylococcus testing. And there's three different manufacturers of Mueller Hinton agar shown. I've deidentified them so it's Mueller Hinton A, B and C, but I think that even if you're not somebody who's in the lab routinely, you can see there's pretty huge differences in the ability of this exact same strain of Staphylococcus to grow on these different Mueller Hinton agars, and we see this being a problem with the performance of the disc tests as well.

And so, you know, media is -- we recommend

people follow the ISO standard, but I don't know that that's exactly what's happening. Otherwise, we would probably not be seeing such big differences in the performance media to media.

And so this is a challenge is because clinical labs quit trusting the disc diffusion method quite as well as they might because while the discs are cleared, the clearance only requires use one brand of Mueller Hinton agar in the submission and labs don't, you know, use the same company of discs and media all the time. We mix and match just based on whatever is cheapest or whatever our purchasing agreements are, and so this might be causing some of that mistrust with the disc diffusion method.

So I'm there, just on time. Thank you.

(Applause.)

DR. SHAWAR: Now we are going to be delighted to invite Bill Brasso, who is actually -- he's from BD, but his presentation, as you will see in his slides, he is representing the Susceptibility Test Manufacturers Association. So they -- they are the manufacturers mainly of AST devices that

come to FDA for review.

So we'd like to hear STMA's perspective on this topic.

Bill?

MR. BRASSO: Thank you, Ribhi.

I want to take this time to thank Dr. Shawar and Dr. Gitterman for inviting me and allowing the STMA to present some slides and let you know our perspective on this, and then it's all fortunate to follow Romney. A lot of the things that she said I think will be bolstered with some of the slides that we have.

So this will be the industry perspective. And as Dr. Shawar said, even though I work for BD, for Becton Dickinson, I am representing all of the AST manufacturers here, and you can see hopefully on these slides many of systems that are in your laboratories, maybe one in particular that's in many laboratories that I know and love, but I won't focus on that.

So this is the agenda that I'll follow. An introduction sort of to the STMA and talk a little

bit about commercial AST development, the critical challenges and the proposals that we have for addressing some of these.

So for those of you who are not familiar with STMA, you are now. These are all the device manufacturers. They are all listed here. It's amazing that all of us can get together in one room and talk together. This has been going on since 1994 where we met informally a few -- for a few years. And then 2002, actually incorporated as a group and we meet regularly, two to three times a year, to discuss issues that we have collectively and some that we have individually to try and solve our problems together.

We communicate -- some of the things that we do, that STMA does is we communicate directly with pharmaceutical companies for new antimicrobics being developed. We're advocates for antimicrobial resistance legislation in Congress especially, such as the 21st Century Cures Act. We act as liaisons and representatives from the AST industry with CLSI, UCAST and USCAST and have

working groups on a lot of these committees, especially with the CLSI with working groups, ad hoc working groups and document reviews.

We maintain the database for antimicrobic codes. So if any of you have ever wondered where those three-digit codes come from that are on discs, that's the STMA, we hold that database. And also we're a central mechanism for supplying bulk antimicrobic powders.

So talking about some of the communications that we've had recently with the FDA, we participated together in the development of updates to the FDA and CDRH guidance documents. We submitted our concerns and suggested some revisions to the Class 2 special controls guidance document. And this was in a document that's a -- a docket that's listed here. It was back in December of 2016 that we sent that in. A lot of the slides that I have that are coming up will highlight some of the things from this particular docket that we're working on closely with Dr. Shawar.

Also, in September of 2016, last year, we participated in the FDA workshop in Silver Spring, many of you were probably there, where we provided -- tried to provide extensive comments to the FDA draft coordinated development document, and also made suggestions to that possibly for substantial equivalence based on essential agreement only for our performance characteristics.

So now let me talk about, a little bit about commercial AST development. This is our AST devices, as I showed you on the first slide, that you have in each one of your labs. They're used to determine the susceptibility of bacterial pathogen, the -- if the organism is resistant to the drug of choice or other drugs, and also to detect emerging resistance. And today we're going to be focusing, even though there are different systems, we're going to focusing on the automated broth microdilution methods.

So this is a slide that I love dearly that many in this room have told me that they're not

real crazy about, but I always bring this slide along. It shows you sort of from beginning to end in the AST device world and it's kind of a generic one, but shows basically what all of our systems do. And it's divided into separate categories. We actually, in the first part we're doing antimicrobic formulations; in the second part, the preliminary evaluations that we do. So all of this is the work ahead of time. And then we do our preliminary evaluations with the new formulas and go into manufacturing experimental panels and doing QC testing. We then do software development, expert rules and then we get into our clinical trial. If everything looks good at that point, we go into our clinical trials. And this is what the focus for the next few slides will be on.

And then if the data is acceptable coming out of the clinical trials and we can get it through our own medical and marketing groups and our own regulatory approval, then we get to go and present that to the FDA, and eventually, after a long

time, a very long time (laughter), three to nine months of clinical trials, one to -- actually, this should probably be about four to four and a half years sometimes for some of these drugs, to get them actually to show up on panels and cards.

So with the antimicrobial approval processes for pharmaceutical companies, and this happened with the Gain Act in 2012, which we've already talked about a little bit, that the Food and Drug Administration developed several distinct approaches for pharmaceutical companies to be able to get their drugs available to the public as quick as possible. And this was in response to President Obama's initiative for -- the 10 by 20 initiative; 10 new drugs, antimicrobials, by the year 2020. And there have been priority reviews, breakthrough therapies, accelerated approvals, but there really were none of these -- none of these provisions were for AST manufacturers in the game, nor really, when it comes right down to it, in the 21st Century Cures.

There are some pathways that we see in 21st

Century Cures, but no real incentives at this point yet for AST device manufacturers.

So when I was focusing on the clinical trials on that previous wonderful slide that I put up with all those pathways, the one focus was on clinical trials for the FDA submission. These are the guidelines. All of our antimicrobics on our AST devices must be cleared through the FDA and it requires clearance for each antibiotic and for each organism group. And what I mean by organism group is gram negative, gram positive, strep, yeast. But a separate 510(K) is usually required for each one of those.

So what are some of the clinical challenges to timely AST development? Well, for one thing, it's communication with the FDA. I'm going to show some -- some of the next couple slides that are coming up have to do with some of the communications that we've had and the specifics in those dockets that I told you about.

How could fast tracking help us here? There's some ways that -- I think everybody would agree

that if we could get some fast tracking for the AST devices, it would benefit the public and -- and the pharmaceutical companies.

So several highlights -- several requests are highlighted in the next slides. Some could be considered as -- as you're going to see this little apple pop up. This is low-hanging fruit. For those of you who were at the previous meeting in Silver Spring, this topic came up quite a bit. What's the low-hanging fruit that we might be able to grab right away and be able to take care of pretty quickly, that doesn't -- isn't going to need a lot of red tape and paperwork, that maybe we can even get done today. Right, Ribhi?

DR. SHAWAR: You got it.

MR. BRASSO: Also, some of the critical challenges are not only with the regulatory basis on these -- on getting our drugs through. There's also internal challenges that we readily admit there's commercialization which takes an awful long time. I'll go through a little bit of that for those of who aren't familiar with that term.

And also right now the volume of new drug applications and breakpoint changes is overwhelming. It's incredible. So in one way President Obama should be very proud right now because there are going to be more than ten drugs that come out by 2020. I think we're pretty safe with that one. But there's going to be a lot more. And trying to get those drugs on these AST devices is going to be a challenge.

So I've divided this into five main topics for the communication with the FDA, and these are topics that are in the docket, as I mentioned.

So the first one is the extensive nature of the FDA's clinical study -- clinical trial study design. There are many issues here.

And, by the way, these slides are pretty busy, so I'm going to try and hit the main topics on them, but we'll see how we get through in the time allotted. Ribhi did say that I -- he's very happy with allowing me to have some of his time, so…

Some of the issues are with the current requirements for the age of the strains that we

have here, and also the makeup of those strains; how many are fresh, how many are recent. And some of these definitions are new. They're not even really included in the current FDA guidelines. And that could be for a good reason. That could be for working with the FDA and having some of those changes met. But we do need to have those kind of spelled out as we start to do these new drugs.

Also the requirements for the reading or inoculation methods, having that done at all three sites of the clinical trial. So this is talking about your system being able to be read with one type of reader, then maybe manually read or having different ways to prepare the inoculum. Right now each one of those requires it to be run at the same -- at all those three sites and that takes a lot of time.

So we're hoping that with our proposals here that, first, for the current requirements, we've revised some of those definitions for the ages of the strains and the makeup of the overall efficacy

study. And then also accept internal validation possibly for assessment of those secondary methods. As you can see, both of these are some low-hanging fruit that we might be able to address very quickly.

Secondly, the acceptance criteria that we have currently to be able to get a drug to pass and be acceptable, for not only for the drug itself overall, but for each one of the species. You'll know, you're familiar with species limitations, if you're in a hospital where all of a sudden you get a bug drug combination and you don't get a result. Well, these are these limitations that we get.

So some of the issues are the difficult to achieve species specific categorical agreement and error rates. There are wild -- large wild-type populations near the breakpoints with some of these antibiotics.

Dr. Humphries already pointed that out with cefazolin and the Enterobacteriaceae. And these impact -- impact us and they having very lengthy 510(K) reviews, requests for additional testing,

or labeling limitations. And no one, no one, not marketing in BD or bioMeerieux or clinical laboratories want to see limitations. They want to see -- if they're buying a panel, they want to see a result for every one of those drugs. They don't like individual limitations.

So what are some of the proposals? We could use, we could adopt just essential agreement as the primary measure of performance. That way if breakpoints change on a particular drug, you don't have to go back and look over categorical agreement. We really feel that this is something that would be very helpful for us, and the STMA welcomes the opportunity to work with the FDA to better define the acceptance criteria.

Number three was the reference method variability. And Dr. Humphries spent most of her session on this, so I'm going to try and go through this a little bit quickly.

Again, as she reiterated, no AST method is exact, yet currently in the guidance document it assumes that the method is always correct. The

impact of variability of the reference method is significant, and this was pointed out in the CLSI broth microdilution ad hoc working group where we published and presented statistical data demonstrating this variability. And some of that, some of those studies you saw in the slides previously.

The published acceptance criteria from the FDA are not achievable. Now, you'll notice there's another word in red that was crossed out. There was a lot of talk in our discussions with our STMA members that that should remain. Now, I said, no, no, no, that's too harsh. So I took that out, but it didn't come off the slide, so I apologize.

(Laughter.)

And these do not necessarily add to the safety and the efficacy of the product. And I think that's one of the main things.

So I'm going to illustrate very quickly, because Dr. Humphries already showed this, but this is an example of a C. freundii isolate and ceftazidime where the testing was done, this was

provided -- data provided by Microscan. The testing was done on CLSI frozen reference panels with variables. So there were these different variables. But each of these set 1 and set 2 were done in the same -- in the same microdilution panel, broth microdilution panels. The variables were of -- the incubation temperature, plate age, inoculation -- inoculum density, are within the CLSI reference method parameters found in M07. And the CLSI ad hoc working group looked at these different parameters and tried to refine them, but -- to make it better or to reduce the variability, but you really couldn't. There was nothing to reduce the variability. So you can see with this one isolate, the mode is clearly at 0.5, yet there is a spread of the range of this particular organism over five dilutions, depending on which one these -- which of the variables, the parameters, it is tested at.

In a second example, this is a replicate broth microdilution testing of six Serratia marcescens isolates with ceftriaxone. The isolates are going

down here, 1, 2, 3, 4, 5, and you can see that each one in the orange is the MIC range for that particular isolate when it was tested by three different individuals once on each of three days for a total nine MICs. You can see the current breakpoints there for ceftriaxone and how this -- these particular isolates will bounce around. So if you get a reference result that might be at -- for this number two isolate where the X is, at 8, but your system, your test system comes out at 2, all of a sudden you've got a minor error there, and that's a categorical agreement issue that you have right -- right there with those organisms. So you can see each one of these, this would be the only one that probably would not have any problems, but the others could wide up causing categorical agreement issues.

Therefore, when the broth microdilution data is compared to itself and cannot meet the current acceptance criteria, how's it possible for an alternate AST method such as a commercial device to be effectively compared to that and expect it

to meet the criteria?

So, again, these basically are what we just went through, and some of the proposals are what also were outlined by, or mentioned in Dr. Humphries' presentation.

To allow for discrepancy resolution, testing three replicates in the reference method to replace the original reference result with the median of the triplicate reference results. This is -- this is the way it's done currently in the ISO document. And we feel very strongly that that would -- that would be beneficial for us.

And also, we're currently adding -- or the FDA is currently adding trending information in the labeling, which is becoming a bit of an issue with customers in certain instances where they will call and ask in customer service We noticed that when we went to the website that there's some trending information in there. Can we really use this drug? So there are no actual criteria on that trending; that we're asking maybe if we could have that clarified. Low-hanging fruit again.

Low-hanging fruit.

I've only got a couple of slides and a couple of minutes. I'm going to try to rush through these.

We're not able to report all clinically relevant species and CLSI breakpoints so the proposal would be to allow commercial AST devices to report more MIC -- to report MICs for the clinically relevant similar species. And also allow reporting of interpretive criteria from recognized breakpoint standing organizations. Now that's coming out in 21st Century Cures, so we're -- some of these things are coming together. It might be a perfect storm here that is brewing for opportunities for all of us.

And, again, we welcome the opportunity to be able to talk to the FDA about this.

And then one of the bigger challenges, supporting breakpoint changes that happen. Numerous ongoing breakpoint changes from different organizations, not only the FDA, but also CLSI, and throw in UCAST and it's hard to hit these

targets. Extensive testing is required, which requires extensive external clinical trials, costly development, and very costly to implement these in the clinical lab because the clinical lab eventually gets the software updates. They have to do validation studies. They have new QC. So this is not only an issue for AST manufacturers, but when we get it done, it's for the clinical laboratories.

The proposals to provide specialty organism sets to evaluate the AST, all reanalysis of data from the old 510(K)s and allow single site evaluations. There's a big low-hanging fruit on that one.

Quickly, the second part was on AST companies about commercialization. We must reduce our commercialization roadblocks. There is much to do in commercialization. As you've seen in previous slide presentations, once we get FDA approval, there is still a long way to get that device out on a panel. There's new product catalog numbers, new product names. Decisions have to be made on

the older products and adjusting inventories. Updating the product labeling, the box labels, the panels, all of this requires documentation, QC and an incredible amount of following to make sure that there are no mistakes with these as we're trying to get them to the public.

Updating the package inserts with instructions, therapy guides and expert rules, letters to the customer, new software updates and eventually building new inventory while you're reducing the inventory of the old, and getting -- and then calling the laboratories, the clinical laboratories, and saying, hey, by the way, we've got a new catalog number. We're getting rid of that old catalog number. Are you guys okay with that? I hear -- I know you're not happy with that.

One of my last slides is talking about the volume of the new and revised drugs are exceeding our capacity. If you can see here, these are the drugs that have been FDA approved in the last -- since 2010. And right up into last month, where a

brand new drug, meropenem/vaborbactam was just approved. So trying to get -- that's a lot of drugs for the FDA approval.

There's also -- these are the new drugs over here that will eventually be coming between now and 2020.

Also, we have these little Xs that bounce in. That's 29 CLSI or FDA breakpoint changes since 2010. And figuring another new 12 NDA approvals likely by 2021, the volume of the new revised AST absolutely exceeds the capacity for AST development.

Also, where's the business incentive for this for AST device manufacturers? All of us work for large companies. We have a lot more products than just AST devices. So we need some incentives there. And there's actually no additional sales or revenue that comes in for AST manufacturers for changing these breakpoints or switching old drugs out for new ones. So we really need some incentives, it will be very helpful.

So finally, my conclusions. AST device

submission process has had small changes over time, but resulting in significant changes to AST device clinical trials. The current process impact limits the use of new antimicrobial drugs without -- that do have an AST test. The result is that the drug is not available in the local formularies. Patients may be treated with new antimicrobial agents without having an approved diagnostic test. The current process can be improved. More coordination between the antimicrobial drug sponsor, the FDA and AST device manufacturers is vital. Changes will require revisions to the existing AST device guidance and a fast track process has worked for antimicrobial drug sponsors, it will work for us.

So I thank you very much. I'm sorry I went over time a little bit.

Ribhi, I got a dollar and 50 cents for you for that minute and 50. Thank you.

(Applause.)

DR. SHAWAR: Thank you very much.

So if I can have my slides, please. So now,

we've heard sort of clinical lab perspective. We've heard the manufacturer's perspective. So I'm going to cover the FDA perspective and our experience with review of AST device applications.

Which microphone works? This one looks good.

Okay. So this is my disclaimer. The outline of the talk is just to give you a little bit of progress report, if you will, on coordinated development, talk about AST device review and experience, and also reference. You will hear now the theme is kind of building up on reference (inaudible) evaluation from our perspective. And the last bullet has multi bullets underneath it in a slide that will come up later. But we discuss device review challenges and solutions, and I hope that I can convey that there were many aspects that were raised in earlier talks or in earlier discussions than we have actually addressed. So hopefully we can come up with a basket of fruits out of this meeting because we've already done those things.

So just to start then with coordinated

development, the slide is just meant here to illustrate that it will take corporation, collaboration, coordination between the drug side who's developing the drug, the device, who is going to ultimately put that drug on their panels, clearly in communication with the various centers at FDA that coordinate. As John had mentioned previously, we continuously have meetings between the microbiologists and staff in both centers. So the end result, we all hope would be something that would be resulting in improved patient care.

This slide I'm putting up here, it's busy, but only to illustrate that we have developed a process in order such that FDA would be able to somehow facilitate this effort. However, the emphasis on this slide is that there needs to be coordination happening way before so that we can achieve the time of submission as we desire.

So if we start with the middle arrow that's going down, it says "final breakpoints." So that's when, okay, there's a drug and there's a final approval of it. Well, if you want the

device to be available, then all the studies that you wanted to have done should have been done earlier. And that's the main thing really for coordinated development.

So -- but in order to facilitate this, FDA has put some process in. So if a company is interested in submitting an initial submission, saying these are the steps that we're going to do, or that they have already conducted study and say, well, here's the kind of data that we have. We know we don't have breakpoints, the drug is not yet approved. So we can look at that in a pre-submission process. Various paths lead to almost the same position.

The box underneath is simply highlighting that device companies or drug companies, they can do all of this on their own, and if you're coordinating on your own and come time for the drug approval, you already happen to have the studies that you think are supportive of the device, be it. You can just submit under the -- under there.

So many have mentioned already the various activities from last year, so last September of 2016, we had draft guidance out. We received comments on it. I have some points about that. We also have the workshop and received some comments on that. But -- you don't need to read this slide. It's busy. But the idea is that you will see that there were pre-submissions from device companies, pre-submissions from drug companies asking us about how do you do this, how can we proceed more effective? And, in fact, there were results -- there's some that have resulted in a 510(K) clearance just recently.

So the system, we can say, is actually working, possibly, of course, can be improved, and we're happy to hear any thoughts on that.

So if you remember only one slide on coordinated development, this is it. If you look at the bottom half of the slide where -- I want you to focus on, the blue bar. The blue bar in the bottom -- and these are real data. So -- with a drug that was not, quote, coordinated. Let's

just maybe put it that way. And when the drug got approved, then perhaps the companies began doing the studies, et cetera, et cetera. So the word for FDA -- the pointer is not very well here. But the point where FDA/CDRH would be receiving that application would be at the end of that blue bar. So all that blue bar time is really device company interacting perhaps, of course, with the drug company, understanding the issues. Maybe there are issues with reference panels for that drug. I don't know. It could be variable.

But if you look at the top one now, this is an example where -- this is delafloxacin. No hidden data. So everybody knows which new drug just got approved. So the three devices (in 33 to 41 days after receipt) were cleared for the device... In 44 days after the drug was approved. So obviously, it takes all that collective effort for that to happen, right? We have taken the drug company, the device company, have worked together, and everybody has the data. Some of these devices came in with data to FDA looking at it prior, such

that on the day of, all they needed to do was just submit that data.

Now, what is the caveat to all of this for this timeline? I'll share with you the routine timelines for FDA. The caveat here is that the studies and the nature of the submission is such that it is really well organized, the data is nice, everything is laid out such that the reviewers can achieve this timeline. Please don't hold us for this timeline. This was just, I would say, exception, but we try to strive for that with better coordinated development.

This is the review timeline. And we strive to not do things in the maximum 90 days. We try to do it earlier for sure, but really, quality, quality, quality of the submission is very, very important.

A point that also comes across, especially for device panels that are on automated devices that have panels -- different panels that contain multiple mixtures in order to meet the formulary of that particular hospital or what have you. I

think some device companies probably have like upwards of 40 different panel combinations. In the AST special controls guidance, when it was first published -- this point is highlighted. This is not a boring point. That you submit for a drug and organism combinations that do the testing in the same manner. In other words, same media, same incubation conditions, et cetera, and you can submit that. That is drug organism combination together. Great. That is what you submit in a 510(K).

But what that allows is that it allows manufacturers to now put that drug that receives the 510(K) clearance on those multiple panels to meet the marketing that they need. That's a very important point.

So I'm focused four or five slides on broth microdilution variability. I'm trying to speed it up a little bit because many of the points have been mentioned. So I'll hit the highlights of it.

We all acknowledged that broth microdilution variability is an issue and can be more striking

for certain organism combinations. So reproducibility of the reference broth microdilution is addressed in CLSI M23. Assessment of the broth microdilution variability is an important aspect when planning for a new AST device. And consider replicate testing for the reference method. So that's already been discussed and also something that we -- I don't highlight it. I don't need to repeat it, that interactions between drug developers and device manufacturers is critical for this.

So I'm sharing now with you from our FDA data to look at -- this is only simply looking at broth microdilution test 1, broth microdilution test 2 for the various drug organism combinations that you see on the bottom, and you see the data points underneath that that make it up. So you can see that. When you look at -- exact means that I got -- test 1 gave me an MIC of 0.5 and test 2 gave me an MIC of 0.5.

So if you look at the upwards -- these two examples or three that come in close to even 95 or

93 data points where of those values, the value -- the first value is equal to the second value. And even if you look at the bottom where you get the distribution, they are really falling on the right and the left of it, almost distributed really nicely.

Now, the other aspect is this is the forefront for how we evaluate AST devices if we look at the essential agreement. Everybody understands what the essential agreement is. Plus or minus one dilution. And so when you look at this, in the last 34 cleared devices, we just simply were curious. We just asked ourselves, how often do we really get submissions that have a problem with the broth microdilution.

In other words, the point at which essential agreement requires a greater than or equal 89.9, and after that you get the clearance if you achieve that, plus many other conditions. So we're looking at this. We find the vast majority really achieving a very high concordance with essential agreement. It's really, really striking

the way that -- based on the submissions that we have received and looked at.

So repeat testing of reference broth microdilution of testing multiple replicates of the referenced broth microdilution can be used as part of a study plan. So (inaudible), you can define that. That's what you want to do. Great. Discordant analysis, in the understanding of what discordant analysis is, meaning that I'm only going to focus on where I get error or where I get not the value that I like or not the value that matches the device. It cannot be used to change original performance.

By the way, this is not actually something that is just specific to ASTs, this is -- or AST devices, I should say. This is something that we can have -- people can do discordant, but you can possibly either footnote it in the table, but original performance cannot be changed if you do think selectively.

So repeat testing may be appropriate in cases where there was evidence of technical error.

That's kind of like a no-brainer, right? So we can do that.

Now, this is the slide that I'm going to be looking at each of these bullet points and presenting a couple slides on each. So these are our review requirements and challenges that we all face, either we face it or the manufacturers face it, and solutions that we have come up with. I'm not going to read every one of them because the title of the next slides is going to show those.

So the species spectrum and number of devices is always something that comes up and there may be either confusion, even sometimes confusion on our part here, although we're not going to claim that. We don't make any of those errors. Maybe sometimes. But the idea is that all claimed species should be evaluated for an AST device. Isolates should predominately be from the -- you heard of the first list, second list. So I'm not going to explain it further than that.

But FDA allows inclusion of isolates representing species from the in vitro list or

from the second list, meaning, again, because as John had said, that those will be related to the -- those are -- maybe they were not enough isolates to be put on the first list, but they are -- for the indication of that drug, they are relevant organisms. So we allow that, as well, to be included.

And I'm -- one thing I failed to mention at the beginning. I think those of you may have seen -- I have this 21st Century Cures on some slides, and I forget to mention that when I put that on the slides, as you will see then perhaps there will be implications in 21st Century Cures Act that help out in that process. So that's why I have that 21st Century Cures on this slide.

Just a further dissection, further going down on the isolates and what we require and what we have modified. We actually have written to STMA and to various other -- various sponsors individually, as well, when they submit things in a Q-sub and a pre-submission asking us about, here is what I want to do. What can I do? What can I

not do? And what definition -- so this is really taken sort of from that. Only to say that we like to include and keep including what we call fresh isolates. And fresh in this case mean it's real world conditions. It's isolates that are done -- obtained in the lab, tested in the lab in that particular device. And in order to really obtain that experience.

And you can see that it's really limited, and this chart just shows how many other types of organisms that we do allow. And clearly, the FDA/CDC Isolate Bank is one. We know of several submissions that have already obtained the isolates from the bank and tested those in their devices. So that's -- that's important to include. Of course, this would be as either stock or as challenge.

So there is a reason for those requirements and in particular the fresh, I want to emphasize that. That is something we want to maintain in order to obtain real world experience.

It is very important to evaluate categorical

agreement, and this is a point that, of course, we are addressing some of the comments that came in to the docket, as Bill had mentioned, regarding some of the requirements for the special controls guidance. So one aspect of it would be -- this is kind of flipping it on its side. So why is categorical agreement important? I'm emphasizing this here because there were those requests that we only do evaluations using essential agreement and not do categorical agreement evaluation or evaluation of errors. So I want to emphasize this point, that evaluation of categorical agreement is implied in the regulations regarding AST devices. These are at least some of these two important regulations.

Results from AST tests are -- and this is the quote -- used to determine antimicrobial agent of choice to treat bacterial disease. Now, we might argue with or against this. Maybe using empirically, using it to change the antibiotic. But the point is that the S & I & R, which is the categorical agreement in this case, is important

and it is -- goes on the test report and test report must provide the interpretive criteria users should use for each antimicrobial agent. And the S, I and R is a component of device labeling that is provided in the patient's report. So that is important information I think we should keep.

This point was mentioned and this slide -- so this is a second slide that is -- if there is a slide you want to remember, you'd remember this one. This is an illustration of a case where you do not have an intermediate breakpoint. And we do understand that if you do not have intermediate breakpoint, then all your errors are going to be either major errors or very major errors. And those are defined, that if you do not meet this very major error, if you get something above that, you will not be cleared with some give, take. But we analyze things not just solid line. We evaluate things.

In this example we have looked at, yes, we do understand that if one thing just moves one way or

the other, the error is going to be very major or major. So we said, why not look at this box, the yellow and the yellow and the one surrounding that and see what the errors are and whether they are within essential agreement. And the example that I'm showing, you'll have -- the number of very major errors is 20. If you add 9 and 11. That comes at the rate of 6.3 percent, which would not be acceptable.

But in this example we looked at the 11 and said, those are within -- we would consider those within essential agreement. And this is the data that we now take and say, we're going to adjust the very major error and bring it down to nine.

I have a yellow light. Why do I have a yellow light?

All right. So I think the point gets across that when there is data, we look at it, and when there are scientific considerations, we take them into account.

A couple final slides. Examples of cleared devices with variable on scale results. I had to

change this slide. This is a many, many off-scale results, that would be a better title for this slide. We often receive data that will evaluate essential agreement. And let's say we're going to rely on essential agreement. If the device and/or the reference broth microdilution is such that all the results -- and I understand that this could be because of the spectrum of the drug organism combination, et cetera, but if all the values are less than or equal to four or all the values are greater than or equal to eight, then in principle essential agreement cannot really be truly evaluated because I don't know what the values are. So how would I dare plus or minus one if I only know that it's less than such number? So there are examples where the data, as you can see, very, very small number of data are, quote, evaluable. However, we still look at that data, and this may lead to either -- FDA either unable to determine EA, maybe you ask for more data points, or maybe just a notation or a footnote labeling saying that the vast majority, X number

or X percent, where -- of the on-scale results.

This problem is also highlighted in the quality control ranges -- sorry -- in the quality control strains that are used in support of that device. That's one of the requirements that we have and do -- manufacturers do that all the time. They have to have quality control strain run for certain periods of time during the clinical study. And we have devices that have used -- if a device used any one of these combination, that would be perfect. That's the device range at the bottom, and these strains would be fitting.

But we had applications that used only this E. coli, and this is below their range. So yes, the results will be less than the value. And perhaps one could say, yeah, I think he met the QC, but that's what CLSI does. CLSI takes quite an extensive effort in setting those ranges for those isolates. And where there is an isolate that fits your range, you use that.

Now, sometimes the problem can be exacerbated and you might need another isolate, and we have a

process for that. You can follow either M23 or other types of study in order to validate that strain for your use if you -- if you -- MIC training, and this was mentioned. And we -- we feel that some data speaks so strongly that we're able to say something about it. And most of the time the way we say it -- and we're open to discussions of how it's stated and what the values are and how it could be more helpful to ultimately be the end user. But that is simply added in this example as a footnote, and this is exact data.

So you have device compared to reference broth microdilution. This is one data to another data. Only about 30 percent or so are exact values. Upwards of 60 percent are above one MIC and if you (inaudible) percentage of the two. That to me and then people -- many people in the audience here are used to looking at CLSI bar charts and this kind of thing, and you'll be looking at this and say, yeah, I think this is an upward trend. I think I agree with that.

And breakpoint changes. Also, this is another

slide that I think will be important. And to highlight that there may be different scenarios for -- there will be breakpoint change, there will be an existing device, and what to do about it. And I'm not going to read everything on this slide. Only suffice it to say that we have done various of these scenarios where there was one drug, then there's another breakpoint and it changed, and the data was available. It was reanalyzed or the data was not available. There's a design change in the device that need to be made. In other words, your range simply does not cover it.

So just communicate with us. Whatever scenarios, we have a solution for that, or we think. And I think also maybe 21st Century Cures might have some aspects of that.

This is my last slide, future direction. There will be implications for AST submissions and reviews from 21 Century Cures. While addressing comments in the coordinated development guidance with the goal of finalizing that and were

interacting with STMA and other stakeholders. For example, planning a frequently asked questions guidance to address many of the comments and welcome any other suggestions for that.

And again, I'm sorry I took one or two minutes over time, but it is time now for a break, right? All right. So 15 minutes, and we'll be back.

(Applause.)

(Break.)

DR. GITTERMAN: Okay. At this point if everybody could stand up for one minute. Stand up. Everybody who can. If you're unable to stand up I accept it. Okay. Everybody who's standing, if you could take two steps to the left. Just two steps to the left toward the next seat next to you. Now take two steps back, okay? And sit down in your original seat. Good. And now everyone could say -- please sit down -- that you came to the FDA and you were moved by the FDA speakers.

(Laughter.)

Okay. Thank you.

Dr. Shawar, do you want to introduce Dr.

Metzger? My God. I'm not supposed to do this, but okay.

Dr. Metzger, probably everyone knows him, but having said that, you -- I'm not going to read his bio. It's on the -- it's not even in alphabetical order, but it's on the third to the last page. But we're very, very pleased.

And I just have to say something I forget this morning, which I apologize. The people at the table, plus Ribhi, he's not at the table. You know, really, Ms. Conville, you know, Ms. Benahmed, Mr. Brocious, Dr. Anderson, Dr. Shawar, and a bunch of other people, Dr. Scherf, really I think we all owe a great thanks for putting this together.

All the things you've seen, the food for those people who partook, every aspect of it. They were in here arranging seats before, cleaning off with those little brushes. Really for putting this together -- I know it's going to come up again. But I, you know, in my anxiety did not mention them before. So they're all at their desk and

please feel free to thank them yourself individually.

(Applause.)

Now -- I'm so sorry.

MR. METZGER: Thank you, Steve. Thank you, Ribhi, for the invitation to speak here today.

So as I was sitting through the information-packed morning, the thought occurred to me that we were focused exclusively on isolate-based challenges associated with AST. So we're going to shift gears here a little bit and talk about Accelerate's experience working directly from specimens and providing susceptibility test results. So if you thought things were complex with isolates, wait until you get to direct from specimen testing.

All right. So how do I advance this slide here? Oh, there we go. All right. So the talk is outlined into five various areas. I'll touch on each of these topics rather lightly. We could spend hours talking, I think, about many of these bullets here. So I'll start with general

recommendations. That starts with first and foremost forming a partnership with FDA. I think that's one of the keys to success in bringing a product to market. We've talked a lot about reference method challenges. There are some things that we can do to mitigate those challenges. So I'll provide some practical tips in terms of how Accelerate mitigated some of the risk there.

There are ways to drive efficiency in the review process, and I'll again provide some ideas in how manufacturers can help speed up the review process as that's certainly critical to industry.

Then, of course, meeting the performance criteria. I think there's some practical development tips that will help there. And lastly, I'll close with some report and interpretation issues to close out the talk.

So you have a new approach to developing AST results directly from specimens. You know, there are going to be lots of challenges, so my recommendation is to utilize this mechanism called

the pre-sub process. And I know this is review for many of you, but I just wanted to highlight again that it's a very useful mechanism to align on very important points, like what type of classification will your device have. You can discuss submission strategies and work through challenges associated with a large submission as we submit it to FDA.

Certainly there is an opportunity to align on some of the subtleties associated with performance requirements as Ribhi spoke to you earlier, and then it's a great opportunity to describe your technology. And the better -- I would say the better understood your technology, the better chances of success through the submission process. It will identify potential risk areas that you can work jointly with FDA on in terms of developing the right analytical studies to address those issues that may -- that may exist with your particular device.

When you utilize a pre-sub process, our experience is that it's directly correlated to the

amount of effort and energy that you put into the pre-sub. So you really want to be very thoughtful about the questions that you pose. The FDA has a tremendous amount of experience that you can leverage. But again, they're very busy, so I think we would all -- I think they would appreciate if we didn't waste their time with frivolous types of questions.

You can do your homework by digging into documents that are freely available. Obviously, there's the susceptibility guidance document, that's a primary tool for manufacturers. There's also a plethora of CLSI documents that are very related and relevant to analytical studies that you can leverage moving forward and really advance your submission and increase the likelihood for success, which is, I think, what we're all going for.

So I'm going to skip over the variability slide. I think it's been talked about ad nauseum this morning. I think there are some things that you can do to control the variability and make it

a little bit less risky moving into the trial.

So once you understand the root causes for why the method drifts, you can mitigate them. So in our experience we found that the process itself, not just making of the frozen panel, but the entire process starting with how the isolates are prepped, how the frozen panels are made, how they're shipped, how they're read. There's just a number of things where -- a number of areas where you can introduce variability. And so we looked very systematically at the entire process and really developed an approach to manufacturer high quality and high volume MICs, which is key for the reference method when you're comparing yourself against the standard.

There's certainly biological variability that exists as we've seen this morning. Again, replication is an approach that's an effective strategy to deal with biological variability. And then lastly, I'll speak a little bit about direct from specimen challenges where you have to think about studying representative populations. We'll

get more into that in later slides.

So in order to provide consistency from an MIC perspective, we really borrowed heavily from just basic manufacturing quality approaches. So there's something called the six M's, and it's basically a list of the variables that typically, you know, can go awry when you're producing and want to produce a high quality, high volume product. And so we looked at methodology associated with the BMD approach and really focused on training the operators such that they could consistently perform the BMD process day and day and over again.

We felt that a reference site model was the best approach to implement many of these controls, and so we utilized that in our trial and submission. We collected isolates from various clinical sites, shipped them to our reference laboratory and were able to implement these controls in one reference laboratory as opposed to many clinical labs simultaneously. And I think that really worked well for us.

When you think about machines, I mean, incubators. Something as simple as an incubator can be a critical piece of delivering a quality result. So there are other machines that are involved in the BMD process, as well, starting with maybe the filling equipment that Romney showed earlier this morning. When you look at a BMD filler, there's certainly -- that's an important machine in delivering a consistent frozen panel. So there's lots of controls that you can introduce there to reduce variability.

In terms of lab personnel, just a fewer hands on the BMD process is generally better. And so it's an additional benefit that we found with reference site model. And then getting into some of the more kind of, I guess, routine sorts of variables, like materials, dealing with MHB lots and making sure that you have consistency. Again, a very critical component of delivering a reproducible referenced result.

So there were additional items such as transcription tools that we use to detect when --

when an operator simply just misread a plate and recorded that result incorrectly. So it's another level of control that we introduced. And then, of course, with the reference lab, having a single site eliminated the variability due to environmental factors. So we found this approach to be very helpful in terms of not eliminating variability, but certainly controlling it. Controlling it to where it could become a manageable risk for a trial.

In terms of dealing with biological variability, we went with replicate BMDs. We ran triplicate BMDs for the trial and compared our result against the mode. And again, it's another tool that can be used to really handle and mitigate biological variability.

And then the last point with respect to the reference method is, it's going to take a little bit of background and background and contents. So what I'm showing here is essentially our view of microbiology. So this is what the Pheno system produces at a fundamental level. So on the Y axis

we have a measure of basically a clone growing into many cells mass. And then on the X axis we have time. And as you can see, not all clones behave the same way.

So after running thousands upon thousands of isolates and seeing this variability, we became very concerned about statistical sampling. Imagine pulling from a plate a relatively small number of colonies and then comparing that against a full, rich population direct from specimen. So you have to be very, very thoughtful about how you design your trial to control that particular issue and make sure that you -- the test device and the reference method study the same population. Obviously, if you study different populations, you'll get a different result. So that was another key to addressing variability associated with the MIC.

So this is a summary slide of the things that we did. We looked at manufacturing controls and utilized them to drive consistency with the MIC results. We also used replicate testing, and we

were very thoughtful about how we sampled direct from specimen to make sure that we were studying the same population test versus reference method.

So in terms of the review process, everybody from the industry side would certainly like to get through it -- I think everybody would like to get through it as quickly as possible. And so I think there's a lot of things that a manufacturer of a test device can do to really facilitate this review process. So, for example, with our FDA submission, we submitted really a syndromic solution to positive blood culture. So it comprised an integrated identification and susceptibility test result.

The trial was very large. We had over 1800 positive blood cultures run in various clinical labs, again, covering a number of different drugs and species. And so if you think about a gram negative/positive blood culture, let's say it's E. coli, you're not just getting, you know, one ID and one AST. You're getting, you know, a dozen AST results to go along with that ID result. So

the data that we generated was quite substantial, very substantial. And this was just for the clinical studies. The analytical studies were, in fact, larger by run than our clinical studies.

So the volume of data that was generated was significant, and we discussed this with FDA during the pre-sub process and aligned on the idea of providing tools to facilitate the review. And again, it was something that we could do, I think, compared to the overall resources required to run the trial was a minimal expense to take the next step of providing an Excel tool that enabled us to view the data and cut it by individual drugs. So you can see there's tabs of -- available for each and every drug, along with corresponding line listings, and really create a tool that can be used to explore the data and understand differences between, for example, fresh samples versus challenge or fresh versus fresh seeded or look at very specific organisms and their responses to various drugs.

Of course, we can also break the results down

by those results that were evaluable versus those results that were not on scale and evaluable. So this was a tool that, I think, worked very well overall in the partnership in terms of facilitating a rapid -- a rapid review and it's certainly something we'll look to do moving forward.

Just a quick little note on line listings. It's a fairly rudimentary task, but I can tell you with an extremely large data set, you're better served by getting it right the first time so that you don't have to continually recompile and regenerate results. So spending some time thinking about line listings and being very sensitive to, I think, requests from FDA is generally a good idea in terms of getting an efficient review.

So a couple ideas real quick in terms of how to go about performing or setting the table, if you will, for efficient review that I've just discussed.

Okay. So I'm going to move quickly now to,

you know, some other general -- general pointers. So first I'll talk about performance requirements and how to meet the goals that FDA has articulated. Certainly, you know, as Ribhi just described, fresh samples are a key component of the review process, and balancing the percent of fresh samples versus challenge isolates is a very important and critical factor during the review process. So you want to be very thoughtful about maintaining that fresh balance. It is a requirement, and it is something that can easily slip away if you're not monitoring it very quickly.

I would say that access to challenge isolates are a key, and I'm very excited to hear about the joint FDA-CDC effort to make challenge isolates more widely available. So I think having challenge isolates on hand is very important in the submission process. And also, I would say be prepared to convince with additional data.

So I think the results are king in the FDA review process, and so if you feel that -- perhaps

that you can -- you know, if you feel that your -- your performance is not representative, then I think additional repetitions of additional samples can help out there.

I'm not going to spend too much time on reports and interpretation issues. I will say that I'm very interested in hearing more about the 21st Century Cures Act as the website goes live in December. So I think that's something that all manufacturers should be aware of.

And then, of course, just a quick final note. When developing expert rules, again, I think a key point here is to make sure that they have significant scientific merit behind them. I think that's the best way to put it.

So that's it for the talk. I just wanted to thank again Ribhi and the team for giving me the opportunity to speak. It was a great first run, and we look forward to working with the team on future submissions. So thank you all.

DR. SHAWAR: Thank you, everyone. I think we now going to move to the panel discussion. I

think we're about maybe five minutes late. Are we? But we'll make it up. Just maybe break -- so if I could ask the panelists for the morning. You know who you are. But I'll be putting the names on the table, so if somebody forgets.

Can you hear me? All right. Great. Thanks. Share one microphone here, John and I.

All right. So everybody I hope enjoyed the presentations in the morning. This is sort of background information with various perspectives. And the team had put tremendous effort into trying to formulate questions that will lead into helpful discussion, and hopefully, as Steve mentioned in the morning, perhaps pass forward our recommendations that you, can as a reminder, go to the docket. And for those listening on the web, as well, this will be open for comments.

So this is the meat of this morning's session, this panel discussion. So I will start with the first question, and the first part of the question is really just sort of the introductory. So I will read it really, really quickly.

Essential agreement evaluates the concordance of the test method compared to the established reference method. The most important evaluation of essential agreement defined as plus or minus one broth microdilution requires on scale, i.e., evaluable MIC results. Typically when the device dilution range is truncated, fewer on scale MIC results are available for performance evaluation. Please comment on the following:

One, the importance of including on scale MIC results for clearance of new device, i.e., appropriate percentage of on-scale results, if you will.

Two, the value of evaluating essential agreement of MIC results that fall at the extreme ends of the dilution series, i.e., very susceptible or very resistant.

So how we're going to do this is we're going to try and cover -- we have, I think a total of six questions. And I already took two minutes already from this. We're going to take 15 minutes perhaps for each, and we will go maybe from right

to left. And if you could limit -- just try and address -- I think it will be good to address those two points, just to comment on the two points. And if you think that, well, somebody has already mentioned what you thought, you can concur or not or say thank you.

So -- so maybe we'll start with Steve, and then move across the table in 15 minutes.

MR. METZGER: Okay. All right. So I guess what I would say is that, yeah, I mean, it's very important to include on scale results. I think when you're looking at a full scale device versus perhaps an abbreviated or shorter scale device, the challenge associated with sourcing on scale isolates becomes more acute, and it's just due to the wild-type distribution of the particular isolates for certain bug drug combinations.

So when I mentioned in the previous talk that it's important to focus on challenge isolate acquisition, I think that's one of the main reasons why I mentioned that.

Ribhi, I think that's it.

MS. MILLER: So I certainly agree that including on scale MIC results is very important. In term of the appropriate percentage, I don't know that I could comment on that. Other than the slide that Ribhi showed, it seemed like the percentage was very low, too low. So it clearly needs to be higher than that, and maybe there's some sort of power calculation or something that you could do to determine what the appropriate percentage could be.

And in terms of looking at the extreme ends of the dilution series, I think Romney pointed this out quite well, that you really -- those -- it isn't really where the concern is. It's really right around the breakpoints that becomes more important. And while we certainly need to look at the extreme ends, that's not where the focus should be in terms of if we're going to look at essential agreement versus categorical agreement.

DR. HUMPHRIES: So I think that this question, it's a good one. But I think it really depends on where the wild-type is. And what do you mean by

very susceptible or extreme ends of the dilution series? And so, you know, breakpoints are a changing thing. I don't think that we're going have the same breakpoint for every drug bug combination, you know, ever again. And I think that if you're talking about isolates that are -- you know, if the wild-type is way, way low, way lower than is, you know, clinically relevant with PK/PD, then that's one question.

But if your extreme ends of the dilution series are right where your wild-type is, that's a different type of question. And so I think that it needs to be taken into the context of where the wild-type sits. But otherwise, yes, having on scale MIC results would be important. But I think we see this coming up with the newer drugs where the MICs are so, so low that you kind of start wondering, you know, how are you going to get those on scale MICs and still have clinically meaningful results.

DR. SHAWAR: Thank you.

MR. BRASSO: I think one of the -- one of the

keys here is where it says in the parentheses under 1.1 is the appropriate percentage of on scale results. I think in just talking, I do not pretend to be a statistician. But in speaking with some of the statisticians that work with the STMA group, we feel that -- that this can be lower than what is -- or the appropriate percentage should be a little bit lower than I think what everybody automatically thinks of should be.

When we're speaking of -- looking at the data as performance, statistically speaking, we all want to look and be able to see those MICs on scale for all the different groups. But that's very hard with all of the species to make sure that you get enough that are on scale. So if you only get a few on scale for one species, is that going to work against your submission or your clearance for that device?

DR. SHAWAR: Just to clarify then, if you -- your point is that it would not be necessarily for each species. Maybe you could say, I have this many evaluable results across many species. Maybe

for one I don't have, but for others I do.

MR. BRASSO: Yes. And then the second part that I was going to say is the value of evaluating the very susceptible and very resistant, we also feel that that's very important because the device must be able to detect -- resistance must be able to detect the susceptible. So the extremes are good, but as Romney pointed out, with some of these newer drugs, especially trying to get QC on the panel, especially for the FDA submission process, you're getting a very long, maybe 12 dilution set. And you're evaluating or wind up evaluating those dilutions way down there on the low end for every organism. And it's important that at least we have the availability to truncate some of those because some of those dilutions are so low, they're never going to go on our devices and things.

DR. SHAWAR: John, do you have --

DR. FARLEY: I pass.

MS. PATEL: So I'm going to echo some of the comments already. But I do agree that evaluating

essential agreement at the MICs that are at the extreme, at the very far ends from the breakpoints, has limited value and that the focus should be on isolates that are closer within a reasonable range of the breakpoints that are most likely to be tested in a clinical setting.

MR. THOMPSON: Well, a few thoughts I have that don't duplicate what others have said and some may even disagree with what others have said.

In terms of the first, it depends on what we're using the MIC test for. Are we using it as a breakpoint test? Do we just want to know if it's S, I or R or are we actually using it to find an MIC so that we can do some pharmacokinetic calculations that our pharmacists are doing more commonly these days?

So I think that it would make a big difference in deciding whether those low MICs have to be accurately predicted. I'm concerned that the low MICs are hard to test because the concentrations of drug are so low and you increase your error rates when the amount of drug is really low. So

we have sort of a double whammy here. We may need it. We may not need it. And when we do need it, I think that the accuracy of -- we have to come up with ways of improving our accuracy at those low concentrations.

I don't think it's as important to be able to differentiate the MICs of very resistant organisms, but for reasons I just mentioned, if you're using it to perform pharmacokinetic calculations, I think you do need to know some of the calculations at the lower concentrations if that's what your MIC is for.

So maybe in submission the trays could differentiate, you know, what type of result they're trying to portray. Are we just looking for an S, I, R result or are we actually offering a longer dilution scheme so that we can do some calculations?

DR. SHAWAR: I'm sorry. I failed to mention that for the recording and for those online, maybe if you mention your name before you speak. The person who was speaking was Ribhi Shawar right

now.

MS. MATHERS: Amy Mathers. And so as sort of the clinician, of course, this is going to be really important that we know that the susceptibility testing is accurate around the clinical breakpoints. And so when I think of on scale, what comes to my mind is the thing, you know, whether or not it's going be relevant. So it doesn't help us very much if all that went through the clinical trial was highly resistant or highly susceptible, and I know that's not ideal. And also, this topic is being taken up in the setting of a lot of other changes that are happening, you know. So I would put a higher priority to something like having on scale susceptibility testing over, you know, X number of fresh results. So how all of that math, and I know that's a different topic, but how all of that is doing is all probably feeding into each other, but I think this is a high priority.

And then also I think we can't be agnostic to the fact that we need to have -- there's going to

be more and more molecular data coming in on resistance and what those compare like potentially depending on what's sort of in the range and what kind of molecular data goes into some of this. And I know that, again, is also a different topic. But, you know, I think it's relevant in this realm of can you use -- do certain molecular mechanisms make it so that the on scale range is more variable?

And so that's probably going to be increasingly well known as people come with applications.

DR. SHAWAR: Thank you.

MS. ZIMMER: Barbara Zimmer, at the end -- I'm the last -- for those who are on the web, I'm the last one. So a lot of what I'm going -- what I'm thinking has been said before, but I want to talk about two practical aspects.

You know, on scale MICs are important, but sometimes from a practical method, they are very hard to get. And we -- I remember when the cephalous borne (phonetic) breakpoints were 816

Comment [FDA1]: cephalosporin

and 32, and then they started going down. And to try to find those for all species under fresh isolate so that you have the appropriate number of evaluable isolates online for EA is practically sometimes a little difficult, particularly for some new drugs.

And I'm going to make up a drug. This is going to be something of vancomycin equivalent, okay? And this equivalent is going to be used for testing enterococcus. So that's either resistant or it's not. And so at that point trying to find on scale MICs for some of those type of drugs is really difficult and is almost a little superfluous. So I think what we'd like to do is, depending upon the drug, depending upon the breakpoint, depending upon where things are going, really look at the number of what we need for those evaluable EAs, particularly under the fresh isolates, because from a practical standpoint, sometimes they're hard to find.

Certainly evaluating the EA MIC results that fall under the extreme ends of the dilution, it

just depends on what those extreme ends are for. EA is plus or minus one. If you don't have the other plus, it becomes a little more difficult. But from a practical aspect, we kind of use those all the time to say, okay, we have really met the appropriate criteria.

So certain mixed feelings just from being a little pragmatic about what is -- what you're able to do from a device manufacturer's viewpoint.

DR. SHAWAR: Thank you, everyone. That's really great. One thing, as you see with these questions, we try to come up with a question that's so general. Now, of course, there are other aspects that come into play, for example, if a device is on the qualitative test. Therefore, you're not necessarily looking at essential argument or on scale. And so there may be situations where, maybe in your vancomycin example might be sufficient for that.

How we doing on time? Two minutes left? Can we use them for the second question? Unless -- does anyone else have any -- on the panel. Maybe

somebody remembered a point or --

MR. BRASSO: I think one thing that Barb mentioned is -- and that will help with the co-development effort is that if we -- when we find these new drugs, if we can work together with the FDA and also the pharmaceutical manufacturer -- and I'm saying "we" meaning the device manufacturers -- to determine which species are going to be relevant early on and to determine which ones are going to need more evaluable data, things like that, or to try and find that ahead of time so that we know ahead of time and that all the device manufacturers are on the same level playing field, that we know we're looking for the same thing I think would be very helpful.

DR. SHAWAR: Thank you. That's great. All right.

Can we have the second question?

All right. Same thing, I'm going to read and ask for the comment. According to the Class 2 special controls guidance document for antimicrobial susceptibility test systems, testing

a minimum of 375 clinical and challenge isolates combined is required to establish performance for an AST device for non-fastidious organisms. Again, coming up with a broad -- as broad as possible example and then asking the questions. Using an example of a device with claims for testing, say, Enterobacteriaceae group, please comment on the importance of testing each claimed species and on the minimal number or proportion of each species that should be evaluated.

And I'm just going to caveat it a little bit with, what could be coming as the 21st Century Cures implementation comes along that perhaps be aspects that would be helpful. So keep that in mind for your comment.

So we'll start. Can we switch gears? So we're going to start with Barbara this time.

MS. ZIMMER: Okay. So using it as an example of device with claims for testing all Enterobacteriaceae for a drug that would have activity or breakpoints against all Enterobacteriaceae.

So I looked up in the manual of clinical micro how many members of the Enterobacteriaceae there are, and, of course, it depended on which volume you looked at because more were being described and broken out. But let's say they are, you know, a couple hundred or -- we'll use 150. It is probably unlikely that in an average clinical lab they will isolate all those 150 members of the Enterobacteriaceae. And so I think you need to concentrate and almost use that type of analysis if E. coli -- and I'm going to assume the drug is intended for all Enterobacteriaceae. It's not urinary tract or anything like that.

So if you just try to look at the proportion of isolates that you see and make a reasonable attempt to work your way down to the most common 20 or so, and if you get some of the others, that's nice. If there's some indication that the drug does not work for some member of the Enterobacteriaceae, that's good. But if you look at the different resistance patterns, you know, citrobacter freundii has different resistance

patterns and citrobacter koseri or those in the Enterobacter Serratia group or proteus providencia group, if you make a good effort to look at those that had similar resistance patterns without trying to find all members of the gene as proteus or all members of the gene as Serratia, then I think that should be what you strive for.

DR. SHAWAR: Thank you. Amy?

MS. MATHERS: So I think that I second what Barb just said in terms of it could be infinite, and that's putting the devices and the clinicians at a disadvantage. And so I think this need to be tackled. Because I'm representing IDSA here today, some of the ideas out of that work group that they wanted to bring here was could we emphasize and encourage use of isolates that were used in the clinical trials? Because I think it would be great if those could be widely shared. And I don't know -- I mean, I don't know if that's a possibility, but -- from the pharmaceutical industry, but if those could be widely shared so that we've got at least clinical data that could

then be inferred from those isolates. And you -- it's sort of more valuable, more rich data.

And then also I -- I think that if you smartly pick your isolates, you can really make a lot of inferences about the rest of the families and should have a requirement around that depending on sort of what the drug is, what kind of resistance mechanisms are going to arise and how that's done. So just do it thoughtfully with a written out approach by the manufacturers as to how they came up with their list of isolates that's then going to be able to cover all, say, the Enterobacteriaceae. So that was it.

DR. SHAWAR: Tom, before you go, so let me just clarify. Maybe it wasn't -- the focus here would be taking again Enterobacteriaceae as an example. We're not really talking about the last species that was included in Enterobacteria. But each claimed species, for example, going back either to what the microbiology information in the package insert is, the list 1, the list 2. So maybe just focus on that as a group and then just

qualify the question.

Tom?

MR. THOMPSON: So I'd like to answer this by combining two thoughts. One is using fresh isolates and the other is using a culture collection. My interpretation of the reason for using fresh isolates is so that you have the most recent resistance mechanisms that have appeared in our communities. And I think that -- I think that a way that we could address that is to take a group of Enterobacteriaceae and we look at the resistance mechanisms that the species have and make sure that we have a culture collection that has all of those resistance mechanisms.

So if we were to see a very unusual species in the laboratory, if it actually is resistant, it's probably going to be resistant by one of the mechanisms shared by other genera or other species, you know, within the family of organisms.

So I think that we should -- my suggestion is to migrate toward some sophisticated culture collections that all the different manufacturers

could use that would be representative of organism groups, like the Enterobacteriaceae or Pseudomonas aeruginosa or some other (inaudible). But use those groups, keep them up to date. Jean doesn't have anything to do these days. (Laughter.) Keep all of those culture collections up to date, add to them and certainly use some fresh isolates, but, you know, migrate toward collections.

DR. SHAWAR: Jean?

MS. PATEL: Yep. So, Jean Patel. I think the isolates that should be tested should be proportionately focused on the kind of isolates that are causing infection at -- for the given indication for the drug. The -- and using challenge sets to identify species for which the drug may not be active, or may have problems in activity.

DR. SHAWAR: And, Jean, would you comment on -- I think those were nice ideas laid out, shared by several about, you know, isolates that will be, you know, certain culture collections, of course building off of the FDA/CDC Isolate Bank, and I

know that we -- you know, we were approached with drug manufacturers that either already have isolates for that particular drug. They are the best source for that. How do you -- maybe -- maybe if you made a comment about how could we possibly enhance the collection with those -- how people can perhaps approach?

MS. PATEL: Yeah. So actually in a recent customer survey for the AR Isolate Bank we had some very specific suggestion for panels that should be added to the bank. That was very helpful for us. And so I think anywhere a new panel is needed for specific applications, we just need to, you know, talk to the groups that are asking for it and make sure that we can really deliver that panel, and that's going to be useful not only to them, but other groups as well. But I think we have lots of capability for making specific panels.

DR. SHAWAR: Thank you. All right. John?

DR. FARLEY: Yes. Just a couple of comments. So I agree with Jean that probably about a year

prior to marketing, we'll know in the Phase 3 trials what the isolates were, and that would certainly be a priority.

The other thing that we're noticing with unmet need development programs is that very often the organisms, for example, that produce a particular serum carbapenemese that you want to know the most about and that might be of interest to clinicians to include are not going to be isolated in the trial just because all you have to do is have a trial and the organism goes away.

(Laughter.)

But also there are some essential trial -- you know, there are some trial design mechanism -- you know, to streamline this process, we're often not going to have patients that actually have the resistance phenotype of interest in the trial because they may be, for example, resistant to the comparator.

So that's -- so I think it's going to be a combination of isolates, for example, that you guys have available with particular resistance

mechanisms as well as what's in the trial. But because it's so streamlined, it's really going to be about a year, I think, before developers are -- as they're preparing their NDA, that's kind of when that data becomes available. That's what I think. I'm looking at a few drug developers out there who at least aren't shaking their heads no at me, so that's good.

DR. SHAWAR: Bill?

MR. BRASSO: Bill Brasso. I think one of the things in this question that we need to be -- or that I'd like to be clear on is where it says with the -- example of a device with claims for testing the Enterobacteriaceae group, and comment on the importance of testing each claimed species. So the claimed species are the ones, as I said, to make sure what we're talking about, are the ones in the -- that are approved in the package insert.

UNKNOWN: That's correct.

MR. BRASSO: So in order to get those on your device, you have to show good performance with those. So I think what -- in the discussions that

we've had, we should focus -- the device manufacturer should focus on those. And I think that's for -- we can use guidance up front, especially hearing what John just said, that a lot of times that the FDA knows what resistance markers might be -- they might be looking for in a new drug as early as a year before the actual NDA. Things like that. If we can -- if that data can be somehow transferred, and I don't know how we do that, again, across the AST manufacturers, maybe through the STMA, to let us know you need to be looking for this, we're seeing this. Tell us a proportion that you're basically looking for so that we all hit that, you know, early on. Because if we don't, some of us might have ten of those organisms, some of us might only have one or two. It would be nice if we could have those same ones.

DR. SHAWAR: Okay. Thank you.

DR. HUMPHRIES: So I -- you know, from the clinical lab, I look at this a little bit differently. So I think, I mean, obviously, yes, you need to test the claimed species and make sure

that they work. And if there's -- you know, pharma in the development of their drug, knows there's some issue with a given species or genera in the Enterobacteriaceae, then it's good to know that up front. But the reality is in the clinical lab, yeah, we're going to mostly see E. colis, klebsiella and Enterobacter in the Enterobacteriaceae like we do. But then the tail of everything else that we see is very, very long.

And so, you know, we're kind of going back in this discussion to the List 1, List 2. And my hope is that we at some point get away from that a little bit, because at the end of the day as a clinical laboratorian, if I have a physician that's treating pseudo citrobacter that has an NDM-1 gene, being able to give them some kind of MIC data, even though it's maybe off label MIC data, is more valuable than being able to say, well, sorry that's not a claimed species, I have no ability to give you any data.

And so again, I think, yeah, obviously during the trial there needs to be some target focus that

you go after, but after the device is cleared, we don't want to shut things down to the point where you can't test anything that was not specifically evaluated in the trial because that's impossible to look at everything.

DR. SHAWAR: Thank you. That's good point.

MS. MILLER: Melissa Miller. Actually, I was going the say the same thing that Romney just said. From a clinical laboratory perspective, our hands become tied when we can't see the data. We are only focusing on the claimed species.

That being said, I also want to echo what Jean said in terms of focusing on known resistance mechanisms, known problems because the limitations are also very important to us. We need to know when to trust the results, when we need to have a backup method. Somebody mentioned this morning -- I can't remember who it was -- that once there's a limitation in the package insert, labs really have a hard time dealing with that. But we do need to know that we can trust the result. And as several people have said, having like an AST device panel

of well-characterized isolates that all the manufacturers could use is absolutely needed.

DR. SHAWAR: Steve.

MR. METZGER: Yeah. So I just want to echo from the device manufacturer's perspective the need. There really is an extreme need for some standardization of the challenge testing. A manufacturer faces a number of development challenges bringing a device to market. The last thing that a manufacturing -- a developer wants to do is go out on a global search, really, to find isolates that meet -- meet requirements. And so I think this idea of having a predefined challenge isolate could really be of great service to the community and very much would be embraced from my perspective.

DR. SHAWAR: All right. Thanks.

How we doing on time? We're three minutes over? We have three minutes?

Any more comments on this topic?

Barb.

MS. ZIMMER: Yes. I started out the

discussion, and it kind of went through with Melissa and Romney talking about all Enterobacteriaceae, and then we talked a little bit about claimed species. But from the clinical lab perspective and also, you know, from other perspectives, there are members of the Enterobacteriaceae other than those six that might be claimed.

So just as a kind of a plea for let's not -- let's remember all of the rest of those Enterobacteriaceae, as well, as we try to design our trials and try to say what we are reporting. There may not be S, I, and R criteria, but it may be important to have MICs. So just wanted to kind of tie into the other ends of that.

DR. SHAWAR: Thank you.

Just maybe I'll take a minute since we have time to sort of sum it up, the way I then understood the perspectives. Of course the idea of standardized challenges of organisms that -- just again to clarify, that for the evaluation -- this is just focusing on what we -- evaluate. So

the two buckets, one is what we evaluate and what species you are able to include, whether from fresh or stock. And then what the extension of that would be in allowances of the other organism that were not, quote, either studied or whatever.

So there's two buckets here, and I just want to then echo that we -- there was focus on, yes, to include the claimed species but also to perhaps not so much limit it in labeling. And I'm hoping that with the 21st Century Cures, be able to do some of that hopefully. It's not a promise, but I think it's doable.

Any other final thoughts?

UNIDENTIFIED SPEAKER: Just a quick thought on the claimed species. There's also been, at least in our experience -- clinicians like to be able to know -- to see an MIC result even for intrinsically resistant species because they actually use that data to make sure that the ID -- they put those back and forth -- the ID is correct, to see those. And if there's an organism that's intrinsically resistant, it probably is not

on the claimed species list.

So we should also at least think about some of those things and outside the box that clinicians do use that information.

DR. SHAWAR: Thank you.

All right. Can we move to Question 3, then? Okay. All right. So for a device that include a limited number of antimicrobial variations, the acceptable range for recommended FDA/CLSI QCR organisms may not be covered resulting in off scale QC results as in the one example that I said, I hope this will be straightforward one.

Please comment on the appropriate studies to validate the use of a new quality control organism with a suitable MIC range for use with such device.

So in other words, what if there is not -- if the CLSI, any of this that already have passed through the CLSI, just do not fit your device, whatever your device range is, please comment on the appropriate studies.

And we can start with you, Steve.

MR. METZGER: All right. Steve Metzger again. So I don't have any direct experience with developing new quality control organisms, but we did -- we did look at that approach, and I would say that the studies to validate the use of new quality control organisms are fairly substantial. And, you know, from -- when considering things like timelines and development timelines, sometimes these sorts of studies can get in the way. And so I understand that, you know, there are -- there are certain amounts or levels of work that need to be done to validate new QC organisms. It does pose an additional set of challenges for AST device makers.

And so I think perhaps we can look at ways of getting -- you know, alternative approaches. Maybe there could be an additional set of QC organisms that CLSI provides that might be, you know, alternatives to the standard isolates. Just kind of thinking live here, but these are my thoughts.

DR. SHAWAR: Okay. Melissa.

MS. MILLER: Melissa Miller again. From an end user perspective, this is critical, right, to have QC within a range that we can actually test. We also don't want to be testing five strains to be able to get the important parts of the range. So in terms of the studies that need to be done, I mean, I'm aware of the CLSI studies, not anything beyond that, but again, working closely with these organizations. Like Steve said, to come up with a new approach to this is critical. It needs to be simple for the end user.

DR. SHAWAR: Okay.

MS. MILLER: So I think we're starting to see this come up with CLSI and new QC bugs. And I think that this is something that can be done earlier on in drug development. If you know your breakpoint is going to be way off from where the typical QC bugs live, then that's something to look into earlier on as far as if there's an alternative, you know, QC organism that's already available. Because as Melissa said, we don't want to be in the lab having, you know, 18 bugs to test

for QC. And then, you know, we already have a process for setting QC ranges with CLSI. And I don't think there's any need to reinvent the wheel there, because again, we do want to make sure that those ranges are robust.

And then, you know, just as an aside in my lab, like I mentioned and described, we do reference broth microdilution, and this issue comes up actually quite a bit. And so we have our own set of QC organisms that we validated years and years ago that we still use. And sometimes there's new isolates that we need to bring in to account for new issues. For example, colistin, we have our own QC bugs for colistin because the ones that we have currently have such low MICs. And so I do think it is something valuable to have. But we do want to make sure that we don't have so many QC isolates that all a lab does is QC.

DR. SHAWAR: Thank you.

Bill, STMA perspective. I think is important to say your thoughts.

MR. BRASSO: Me speaking for the FDA, that's

dangerous. Bill Brasso, still with STMA. I think there's the rub. I think what Melissa, you, and Romney both said. As you say, you want the appropriate QC bugs, but you don't want a lot of them. I think that's what it is. I think device manufacturers, just like pharmaceutical companies, we can find new quality control bugs that are going to be around the breakpoints or more on scale. But that's going to be more quality control testing for you, because if -- and that's what I was going to ask Dr. Shawar, Ribhi, if we find quality control organisms that are on scale and do those studies when we're developing the AST, the drug for AST panels, is that a requirement to have that drug tested each time on our panels? Does the QC or the regular clinical laboratory have to test that every time or do we just get to provide that data to the FDA with our submission and then it sort of gets filed away?

DR. SHAWAR: I'm not going to be able to answer your question, Bill. But I think that sort of directs to what the question is asking

because -- and I'm going to in a minute turn on -- John, do you want to have any comments? Have any comments on this?

DR. FARLEY: At the very end.

DR. SHAWAR: Okay. Because I'm going to turn it to Jean to maybe a little bit explain how -- this is what we go with, and when we're asking this question, we're saying, well, somebody could bring to us an isolate, X, Y, Z, and they've tested it 20 times or 60 times. And I think that's the range. And because, as Jean now will say, what is the process for getting that? And so we recognize CLSI as a methodology, and we rely on that. So that's kind of like the gist of this question is, is there something else that we could use for, say, studying a new quality control?

MS. PATEL: Yeah. So Jean Patel. The quality -- the study requirements for obtaining quality control range from CLSI are robust. It's an eight-lab study. These studies are very costly, and yet, there is the a need for having an on scale QC during test development. So I would

encourage very strongly that there be an abbreviated version of a study that could be done to establish an on scale QC for drug development, for diagnostic test development, and it has to be much simpler than what's required currently for CLSI.

I think also that these on scale QC organisms are most important for developing the drug and for developing the test. And I don't think clinical laboratories need to be overburdened with a whole bunch of new QC strains.

DR. SHAWAR: Tom.

MR. THOMPSON: Yeah. I do think that on scale QC organisms are essential to the clinical laboratory. I wonder if going forward we can actually manufacturer our QC organisms. I mean, we can move genes around quite easily. Well, you take a nonpathogenic -- you laugh, but you take a nonpathogenic organism and you insert the appropriate gene to put that MIC on scale. And, you know, the pharmaceutical company can do this and distribute it, and we've got it.

DR. SHAWAR: Thank you. Thanks.

Any more thoughts?

MS. PATEL: I don't have anything to add except what's been said.

DR. SHAWAR: Yeah. You couldn't think of another engineering thing to do.

UNKNOWN SPEAKER: Yeah. From a -- again, a susceptibility test manufacturer's panel, your AST manufactures have on scale QC organisms that work for their device to ensure that the device is manufactured appropriately. It's part of our study, R&D study. It's part of that real long timeline that Bill showed. They're usually tested, you know, for robustness. Actually, one of those slides that I think Romney showed was at different turbidity levels, at different incubator levels. There's a whole robustness series that are done.

And I don't know that the end user needs or wants all of that. You know -- and I don't know that you all, the FDA, want or need all of that, as well. So I think there's a fine balance

between the two. You know, certainly what works for microscan panels may not work for BD Phoenix, you know, but they're our own to ensure that we manufacture things correctly.

DR. SHAWAR: Jean, you have another --

I'm sorry.

UNKNOWN SPEAKER: Actually, to add to what Tom said, not to design new things, but usually your susceptibility test manufacturers have biochemical tests to ensure the right amount of drug is in the well, also. So each PLC (inaudible), as well.

DR. SHAWAR: Jean, do you have another?

MS. PATEL: So quick comment. I also think that any requirements for QC that is establishing these on range QC organisms, there should be some flexibility in the data necessary to, you know, obtain a QC range so that we can take advantage of things that have already been established, like by a device manufacturer.

DR. SHAWAR: So I'm going to sort of, not summarize, but go over a few key points. I think maybe I'll turn it to -- I heard a couple

suggestions about perhaps an alternative or abbreviated approach and if either STMI -- STMA, or CLSI or others can think of what an abbreviated would be. Because again, that's the kind of thing that we're struggling with is we know what is required for qualifying a strain and establishing that range and the effort that goes into it. Members of FDA staff here sit also on CLSI QC evaluation group, and we understand the level and the depth that goes into that.

So what may be an alternative appropriate would be? Would be a, what, a four-lab study, a two-lab study, a seven-lab study? Just -- I think my advice is to think along those lines, and if there's any proposal or something that would be -- can be put in front of us, that would be helpful, I think.

Any additional thoughts? How are we doing on time? One minute?

All right. Question 4, please. Establish performance of an AST device. Current FDA recommendations include testing a minimum of 300

clinical isolates, of which at least 25 percent are fresh clinical isolates less than one week from isolation and tested at a clinical study. I had a slide on this.

Twenty-five percent of recent clinical isolates, i.e., less than one year from isolation, and no more than 50 percent are, quote, stock isolates, which would be including challenge or panels from the FDA/CDCI Bank or your own collection.

So please comment on the current recommendations described above, including the importance of testing fresh clinical isolates and the appropriate proportions of each isolate type, given that we just stated, what the current proportions are.

But where did we end? I think we're going to start at your end. Yes, sorry.

MS. MILLER: This is Melissa Miller. I just had a question. Where did the 300 number come from?

DR. SHAWAR: It's from the AST guidelines.

MS. MILLER: I understand that, but how is it determined that 300 was the number?

DR. SHAWAR: I was not born when that -- no. (Laughter.) No. The special controls guidance document was actually an effort between FDA and the susceptibility device manufacturers at the time. Prior to -- I forget the year -- those devices used to be submitted as Class 3 devices. And as a result of the down classifying of the whole devices, it wasn't like one manufacturer -- like, now we do this, for example, for a de novo submission. Something that does not have it used to be a PMA, now we down classify it.

As a result of that, you come with what we call special control -- controls so that the manufacturers of the future, ones that are coming, follow that. So it was done -- many perhaps people who are -- well, I was going to say older than me. No. There's nobody older than me.

MS. MILLER: I guess my question was, was there a mathematical or statistical --

MS. ZIMMER: I was born.

(Laughter.)

DR. SHAWAR: Sorry.

UNIDENTIFIED SPEAKER: No. What we did -- the down class was for rapid methods, those that gave us susceptibility test result in under 15 hours. That was the magic time frame. Those that were overnight before were still a 510(K). And so what we did was we took the number that was currently existing in the 510(K) number and just made it across the board. So there was no statistical evaluation or thought put into that. That's just the way it kind of happened.

DR. SHAWAR: Yeah. But it kind of -- let me just add one caveat, and that is we actually rarely get a submission that only has 300. I mean, we get a lot more. And perhaps if I were to guess, and people are going to correct me, that idea in this, for example, to have kind of a hundred -- because there's a clinical testing, there's clinical sites, and you have to have three sites. So approaching it, like, maybe 75 in one site and 25 challenging that same site, some

combination like that. But you're right. It may be a number out of the air.

But the group sitting at the table on the far end have perhaps better answers for me. So maybe at the break we can -- we can get more information on that. But is -- so is that -- okay. So we're going to start. I forgot which end.

MS. ZIMMER: I get to start. Okay. This is Barbara Zimmer. And the 300 clinical isolates -- and I would like to comment on the percentage that are fresh, recent, and stock. Fresh that are less than one week old, that's really hard to do for a clinical trial site. You can do that. I think it's important to see what's coming across the bench. With this caveat, what are you looking for? Are you looking for colistin resistance in E. coli? If so, it's unlikely that testing fresh isolates -- 250 fresh isolates that you're going to see that coming across the bench. And that's where you really rely upon the stock and challenge isolates.

I'd like to probably encourage that less than

one week of isolation to move out to less than one month, just from a practical aspect of setting up a clinical trial and having -- getting things moved over from, you know, what is being isolated in the lab to what is then being tested. So from a practical aspect the one week is a little hard. The 25 percent and 25 percent recent clinical isolates and 50 percent stock isolates, again it depends upon what you're looking for, and if you're looking to detect a particular type of resistance -- and I'll use colistin resistance. If you're looking to detect MCR-1 isolates, you're just going to have to rely on those stock isolates. And at that point the recent clinical and fresh become just additional nothing other than to see what's there. So --

MS. MATHERS: Amy Mathers. So a couple of things that I think are really important about this question. I think that as we're running out of drugs and as a clinician who has, you know, just come off service who sees multiple -- I mean, so let me back up.

So there have been multiple studies showing that the majority of antibiotic use is off label. And so we need to step back as we're losing drugs or fast tracking drugs so we can get them in the hands of patients who are facing multi-drug resistant infections that we have a way of doing susceptibility testing.

So although the 25 percent clinical isolates was important at some time to somebody, I think the idea may have been to accurately represent current contemporary isolates from a resistant standpoint.

And I think we just need to be thoughtful about the priorities and sort of just reprioritize why do we need AST manufacturers to meet some of these criteria. And I think the idea is that, you know, if there were similar, one of our suggestions was similar clinical trials, networks that set up and can test real-time clinical trials, isolates. And I know many people do that, but I think having those would be helpful for device manufactures so the same isolates are

available and contemporary.

Fast track drugs, it's already been said, but we need -- we need to be testing -- I think the priority is to test on the drugs that may not have gotten into the clinical trial, may not even be in that top category, but the places where they're being used. For example, there was a recent publication on the use of tigecycline. Eighty-one percent of it was off label. As a clinician it's indicated for skin and soft tissue infection, and I've never used it for that. Yet, I think it's a really, really important drug in the arsenal, and we use a lot for multi-drug resistant or carbapenem resistant acinetobacter. Yet, there's no approved susceptibility testing.

And so you're really stuck as a clinician with no interpretation, no -- which the interpretation is different, but you can't even get an accurate MIC. And if there's no problems around accuracy, it would just be nice if we could sort of reprioritize that as long as we know that the devices are accurate on the drug -- on the

organisms for which the drugs are going to be used.

And I think we can sort of see some of that for these orphan drugs that are coming through the fast track, and maybe those get treated slightly differently.

And I think that was -- that was about it. Just sort of a prioritization around these 25, 25, 50 and some of the restrictions that are creating barriers that, without tons of data behind why they were originally established, and maybe just rethinking that. So --

DR. SHAWAR: Thank you.

Tom.

MR. THOMPSON: Reflecting what I mentioned before, I don't know that there's a big difference between a fresh isolate that's one week old and a fresh isolate that's six months old or one year old. I would focus more on the resistance mechanisms. And I would really divide the strains into those that are wild-type and those that are not wild-type. And of those that are not wild-

type, then you define how many various resistance mechanisms you want from those non-wild-type strains. That will be more representative, I feel, than trying to get a strain that's less than one week old or trying to get a strain that's six months old.

And if we assign some responsibility to the device manufacturers or to the standards development committee, probably most likely, to come with some of these recommendations because they're looking at all this data, you know, frequently and they can say here's a representative population, you know, as of today that should be tested if you're looking at, you know, the Enterobacteriaceae, (inaudible).

DR. SHAWAR: Thank you.

Jean.

MS. PATEL: So I think I also agree that the definition of less than seven days for a fresh isolate is hard and not necessarily of value. So creating a longer timeline is better. I think Barb had a great suggestion of one month. I also

agree it could be six months. The -- and I think we all need to keep in mind that these isolates are being compared to the reference method. So we're still doing a comparison of the test method to the reference method.

The -- I do think the proportion of these that are needed could be flexible if there is a need to focus on more resistant isolates, and then you would turn more toward stock isolates as opposed to these clinical isolates.

I think the idea that you mentioned -- you know, the value of these that you mentioned maybe in your talk was that they earned the preselected. They're the all-comers. You know, I think that's a good concept, but I do think we need a little bit more flexibility here.

Comment [FDA2]: aren't?

DR. SHAWAR: Thank you. And one caveat alternative.

John, is that -- why is your name in front of me? I'm not John Farley.

That the -- I agree with the focus on resistant isolates. However, the whole idea of

this is, let's remember, the test is also testing for susceptibility. Yes, of course, we want to know absolutely how it does perform for detecting resistance or failing to detect resistance. But you're measuring susceptibility. And for the vast majority on this, we're dealing with drugs that have, you know, high resistance.

The vast majority of your results in real life is going to be susceptible. So we need a balance. That's just a commentary from me as the chair.

John.

DR. FARLEY: So CDER officially defers to CDRH on the answer to Question 4. But I -- but I do want to follow up on the -- I think the important point that our clinical colleague has raised, which is really kind of the elephant in the living room, right? So it's the use of drugs for which they were actually never developed and we don't really have breakpoints for. So we have a statutory pathway to recognize breakpoints for -- in that scenario. And the question is how we get there. And we really need to get there through

providing the data to do so.

So what I've gone through in the last few months is identified all of the breakpoints that standard development organizations have discussed publically in the last ten years, which FDA has never looked at. And so those are the most of the drug bug combinations that are important to clinicians. It's most of those that are important to clinicians that have breakpoints by an SDO have not been looked at in ten years. And so I focused -- we focused our efforts in CDER right now on the last ten years because we figure, well, that's -- we're most likely to have a scientific rationale available, and the science that was done is most likely to be reasonably contemporary and not outdated to set those breakpoints. But I don't want you all, particularly the clinical community, to be disappointed in January of 2018 because this is going to be an ongoing effort. But I kind of have a target audience, and I really want to challenge you guys to work on this and to recognize that we've tried to go through

systematically, but we recognize that that's a clinical need and this is the community that can help address that need.

But it's going -- we're going to have to base our decisions on scientific rational, and so we're going to need the data to support that, and we now have a statutory pathway to recognize that so devices could be developed to meet your needs.

So I know that's off track, but I wanted to get it off my chest.

DR. SHAWAR: Bill.

MR. Brasso: Bill Brasso. So I had mentioned in the presentation that I did opportunities for low hanging fruit, and I see several right here. I agree with the panelist to my left all of them that the fresh isolates I think we can carve that down and say six months or whatever. We can decide on that one but I think that's very important that will help us get our submission to you quicker.

DR. SHAWAR: The group to your left said one month.

(Inaudible.)

MS. ZIMMER: I said one month, but I'm okay with six.

(Laughter.)

DR. SHAWAR: Just for the record, Barbara Zimmer said one month.

MR. BRASSO: Just for the record, Jean Patel said six months, I believe. That's okay.

The second item for low hanging fruit is that I think the point that Tom made is incredibly important for us. If we would switch to these, especially the newer drugs and focus on wild-type population and a non-wild-type population covering the resistance markers, that would drop this number I think of 300 clinical isolates significantly. I think we could make a statistical argument to say if you have a certain number, and I won't say, but let's say a hundred and a hundred, a hundred wild-type, a hundred non-wild-type with specific resistance markers. That carves a hundred organism isolates down in what we would have to do. These are the type of things

that we're looking for to be able to reduce our burden.

Lastly, nobody has said yet so I'll say it. Is there any statistical reason why stock isolates should not be -- have to be less than three years from isolation. People who dig into their freezers to pull out the isolates to challenge our drugs, those are way in the back, way deep and many of you have come to ask for some of these isolates. So they're much older than three years. I think that's a hard thing to categorize, especially when you're asking clinical laboratories to do that. That they might not even know how old they are or they might just be pulling strains that they know have the resistance markers. So I'm wondering if we could revisit that one because that opens up a lot more strains to us.

DR. SHAWAR: Thank you.

MR. BRASSO: Thank you.

DR. SHAWAR: Romney?

DR. HUMPHRIES: This is Romney Humphries. So

I think that this is right. I think that it's not so much the age of the isolate but the resistance mechanism that we're concerned about. And we've done some work in my lab to try to address this issue. I mean, do isolates when tested fresh from the patient change after you've subbed them and after you've frozen them? And what we specifically looked at was vancomycin resistance and staph aureus. And I can tell you that we had -- you know, it was really hard to find visas (phonetic), but we found them, and even after, you know, 30 subcultures or a year in the freezer, they didn't change. And so, you know, that's a drug bug combo that we think changes a lot, and in that study it didn't. And so I think that, you know, while this is -- it's good to test fresh -- excuse me -- fresh isolates and it's good to test these resistance mechanisms, I don't know that this guidance really is getting at what we want.

The other thing I'll throw out there, and I'm kind of kicking myself for even bringing this up, but I do think it's important is, you know,

resistance is a moving target and bacteria develop new resistance mechanisms. And so at present, you know, once a device is cleared, we don't really have a mechanism other than those of us in the clinical lab who are looking for these things to assess if the test still works with the new resistance mechanism. And while that is added work, it is important if you look at what the end of the day goal, which is to make sure our patients are getting treated with the most, you know, reliable information available to the clinicians.

So I think that's another thing that this study design, while we're looking at these fresh clinical isolates, does not address.

DR. SHAWAR: Melissa.

MS. MILLER: Melissa Miller. I certainly echo what's been said, and I echo that the timing of the isolates is less important than the actual resistance mechanisms or lack thereof of the organisms. Just for the record, I would also support extending, even if we need to put a

timeline on it, six months at least for the clinical isolates.

In terms of Bill's proposal of lessening the number -- so you might have guessed, I'm not a fan of pulling numbers out of the air. There must be some sort of mathematical model that can be looked at in terms of how many are really needed to determine the accuracy of the device from an end user. And we deal with this with molecular tests now all the time where you look in the packet insert, there were four true positive samples. There's tons of negatives, so the sensitivity and specificity looks good, but the reality of it is there's a lot of false positives, for example, in that test.

What we don't want in the clinical laboratory is the number to get so small that we're not accurately determining the safety and the efficacy of the device. And I think all of us would agree on that, so I think there needs a balance between a less burdensome route for the manufacturers but still making sure that the consumer, the end user,

the clinicians are confident in the results coming out.

DR. SHAWAR: Thank you.

Steve.

MR. METZGER: Steve Metzger. So I guess what I would say is I would echo a lot of the statements that have already been made. I think that from my perspective I think making isolates available from a challenge perspective -- again, I'm going put a plug in for a defined challenge isolate set -- would be very helpful from a manufacturer's perspective. I do agree that fresh samples need to be run in a study. I share a similar view to Melissa in terms of having some concerns about the statistical relevance of the existing numbers. If we're trying to do a study of -- essentially a surveillance study across three -- minimally three but sometimes, you know, less than ten -- let's call it sites, I mean, guess I question how representative that is of the overall -- of the country as a whole.

So I guess what I would say is that I think

that's where challenge isolates can help. Clinical labs across the country are out looking for these new isolates that trip up existing test methods, and I think if we really want to challenge systems, the best way to do it is collect those isolates, consolidate them, develop a criteria for what success looks like with those isolates, and include them in the trialing process.

DR. SHAWAR: Thank you. So while everybody was talking, I kept thinking also about things that I even said about the AST guidance -- special controls guidance document. Document has tables, and there was a very talented statistician from the FDA side who participated in the preparation of that document. And if you look at the details of it, so maybe it wasn't a first statement to say either number out of air or what have you. Because there are tables -- for example, when you -- let's take a drug that there are resistance isolate, because if there is no -- there is no resistant isolates for the new drug, which is

great, that's why we're developing this new drug, then that is easily handled, say, for example, by the FDA AST labeling where we say knowledge about the ability of this device and the resistant is unknown. I mean, we don't have any isolates. Thank God that we don't. So it's okay.

But there are tables in that guidance document that sort of define that aspect of why, for example, you need to test how many resistant isolates so that you don't end up with a lot of errors.

In order to expedite things, being asked to move to Question 5, so we'll do that.

Data analysis is performed to assess systemic bias or trending towards a higher or lower MIC values between AST device and the CLSI reference method, and are included as footnotes to the performance table and device labeling.

And I'm going to just explain one second that footnotes are not necessarily -- they're not the same as a limitation. So this just explains what we observe. So please comment on the usefulness

of bias or MIC trending information for the end user as reported in the device labeling.

I'm going to ask perhaps more of our clinical colleagues -- clinical lab colleagues here to sort of focus on this question in interest of time. We're going to start --

It's okay, Steve. If you have a comment, go ahead.

MR. METZGER: No. I think you're correct in deferring to clinical colleagues.

DR. SHAWAR: So starting with Melissa, I guess.

MS. MILLER: I think footnotes are confusing. People in the lab don't know what to do with these. They're not a defined limitation. They're there. What are we supposed to do with these? I think if there's a systemic problem with a device, that's one thing. But, I mean, what are we supposed to do with the trending information? I think there's a lot of confusion there. And I would say 90 percent of laboratories aren't even -- don't even know if there's a trend in their

device or not. So I guess it depends on what you're trying to achieve by including this in device labeling.

DR. HUMPHRIES: So I look at it a little bit differently, I suppose. I would use that information in conversations I had with physicians if I had an isolate that had an MIC near the breakpoint. And so if I knew, for example, that the test had very good essential agreement, but it was consistently one dilution higher than broth microdilution and, you know, I was right at the breakpoint or I had an intermediate MIC, you know, I would use that in my considerations, especially when you're kind of between a rock and a hard place with some of these really resistant bugs. So I think it's helpful information. But again, I agree that most labs, to be honest, they don't even look at those and -- or the limitations, for that matter.

You know, most labs they just use it as is out of the box, and that's the way it goes. So I think that's some people probably use it, but it's

not widespread.

DR. SHAWAR: Bill.

MR. BRASSO: Bill Brasso. I think I mentioned this when we were -- when I did the presentation that we had actually notices of complaints from laboratories coming in saying that they had read the FDA approval for the drug but there was a statement about trending. What do we do? And that's very difficult. We don't know what to do. And as Melissa said, it can be very confusing. I think also there is no current criteria that's in the document for what is considered bias. Is it 20 percent below the median or is it 30 percent?

We have some -- some numbers that we're proposing in our talk with the FDA. But those would be very helpful to know when we're getting close. So maybe before when we're looking at our data, maybe we know that ahead of time because we really don't know when we're going to get a trending statement.

And last, if a trending statement is going to be added, maybe it could be -- maybe there could

be some clarification from the FDA to say, though there was or is trending in a certain direction with this, but that is still acceptable to we still approve this drug, something like that, so that folks like Romney can get that information, which I think is incredibly useful what you said, and be able to use it that way.

DR. SHAWAR: All right. John, do you have any thoughts on that?

Jean?

MS. PATEL: So I have concerns about the trending information. I think unless there is very clear indication on how the end user is supposed to use that information. I personally think every MIC or every AST method does have some trends, some bias, and that's why over interpretation of small MIC changes for a clinical use worries me very much. I think, you know, we have to be careful doing that because small changes in MIC can simply be technical variation or a bias in the testing device. So unless there's -- you know, if a device has already met

the essential agreement and the category agreement requirements, I think it's difficult to start reporting out trends without telling the end user exactly what to do with that.

DR. SHAWAR: Tom.

MR. THOMPSON: Yeah, I agree, and I don't have anything novel to say. It is important to recognize that there's a wide variety of laboratories out there, those that are very sophisticate and those that are very unsophisticated. And I think that the usual laboratory that uses devices is pretty unsophisticated. I think the penetration of this trending information is very poor into that user group in particular. And when something changes, you know, manufacturers recognize that there's an issue, they make changes, the issue is corrected, nobody really realizes that, you know, in many laboratories. So this is a major issue.

DR. SHAWAR: Amy.

MS. MATHERS: So as a clinical micro director, I can tell you that my staff or, like, the people

who work in the lab would hate it or hate this kind of information because it's not clear what to do with it. As a clinician I would completely want to use that information. But I think that the resolution to this is probably not from here. I think that we need to get clinicians more on board with the amount of variability that goes into this system so that they don't believe that the MIC is a final piece of data. And I just think we need to really reach out to our -- or my clinician colleagues stewardship and education Pharm.Ds and clinicians on the variability in microbiologic susceptibility testing because it is personalized medicine, and when you're right there at that breakpoint and you're trying to decide what to do, I can tell you that most average clinicians are not thinking, oh, well, the MIC is probably off by one or two dilutions. And so I think that -- well, hopefully not two or three. But anyway, they should. So that would be my comment.

DR. SHAWAR: Thank you.

Barbara.

MS. ZIMMER: I actually have nothing to add to everything that's been said. I think -- I can tell you the majority of Microscan users do not read the limitations. They probably don't give the information to anyone else. We're very clear about putting them there, but every so often our tech service people get a call saying, what does this mean? So I think further education of clinicians and other personnel is appropriate, and I agree with Amy. There's not the MIC.

DR. SHAWAR: Thank you. If we can -- I think the message was -- Question 6, and I think we have about -- we will finish on time. This is about variability. So let me not read the whole thing because we now know what we're talking about.

So please discuss when and by whom should the reference method be determined. And I'm going to actually take those -- well, I don't know if I have enough time for that. But I'm going to read all those three, and then perhaps if you can lump your comments in all them.

Possible alternative strategies for addressing reference method variability during device evaluation. Approaches to resolve results in cases unrelated to technical error. So maybe we would start now with Steve. And appreciate maybe a quick comments on this since we all know kind of what we're talking about.

MR. METZGER: Ribhi, did you want me to address all three points?

DR. SHAWAR: Yes.

MR. METZGER: Okay. So when --

DR. SHAWAR: And we will be here through lunch.

MR. METZGER: Yeah. I guess I think the CLSI spent considerable energy and time working on studying the, I guess, lack of reproducibility of the device. I think the data is compelling, and it's very clear. I don't think there's really any question that the BMD approach has inherent weaknesses because it's a manual method, which leads into 6.2.

You know, for our particular case, we didn't

have an alternative strategy, so we had to deal with the requirements that were in place. And so we looked at -- we took a risk mitigation approach to addressing the issue. And I think it was the right decision. It certainly added to the burden of running the trial itself, and I think that is a challenge for some device manufacturers. For us not so much, but I can see where that could be an issue for others.

So I guess what I would say is that, you know, it's probably -- the strategies that we employed were worth it from our perspective to get as close to the truth as we possibly could. And I think that's the best that can be done right now. Certainly I would, again, put in my plug for challenge isolates. You know, the idea behind the defined challenge isolates is that they are a known entity. There's no debate about what the resistance profile is with that set of isolates. So I think that's a nice tool that we can really look at adding to the overall process of registration.

In terms of resolving discordant results unrelated to technical error, I mean, I think you're going do have discordant results because the statistics say so, right, with the percent EA that you see. It creates challenges. It results in additional powering, and again, increases the burden on registration. But it does give you a clearer view of the reality of the performance, which is what I think we all want to get to and it helps with appropriate labeling.

So I guess what I would say is I think the process that we have in place works. It does create substantial burden on the manufacturers and to prove that it works, and anything that we can do to facilitate development, I think would be a great benefit to the overall community. I think it would increase the availability of new technologies to the marketplace. And so I think we ought to look at that very carefully.

DR. SHAWAR: Thank you. Let me just clarify one thing, especially for the first question. Think of a new drug. In other words, a new drug

company is developing a drug. It's in Phase I, Phase II. They're the ones that understand this best. So that's, I think, where this is sort of asking. But --

MR. METZGER: Yeah. That's an interesting question. I can't comment on that directly, but Melissa.

DR. SHAWAR: Melissa.

MS. MILLER: May not be able to add too much, but in terms of 6.1, I was thinking more back to the coordinated development workshop and coordinating, looking at BMD reproducibility with the drug manufacturers and the diagnostic device manufacturers. The earlier this reproducibility or lack therefore is determine, the better off, I think, the whole field is.

In terms of -- well, and I kind of lumped 6.2 and 6.3 together in terms of variability during device evaluation, discordant results. I think if discordant analysis is very clear in your talk, Ribhi, that this is not allowed. So in light of this and knowing the inherent variability of BMD,

I really liked the approach that Steve laid out in his talk where they use a reference lab model for BMD. That in and of itself is going to decrease some of the variability but also the replicate testing and using the mode of BMD I think could certainly aid in that. Although, I'm sensitive to saying all that, and Steve said the same thing. It puts a greater burden on device manufacturer, which we're trying to decrease here. So good luck with that.

But in light -- you know, and if all of these things can happen, I mean, discordant analysis is important even if it doesn't change the original BMD result. Those of us that are really looking in these package inserts are going to look at those data.

But again, back to my point, and others have said, 90 percent of laboratories aren't looking at this amount of detail in the device package insert.

DR. SHAWAR: Romney.

DR. HUMPHRIES: Romney Humphries. So I have a

lot of thought about this, but I'll be brief. So first off, I think that the reference broth microdilution method, it is a defined method, but there's variability within the definition. And so I think that early on in development of the drug, I think assessing which variables provide a more, you know, tight MIC for drug bugs would be important. So maybe testing at 35 degrees Celsius as opposed to 35.5 makes a difference for your given drug. Maybe using Manufacturer A as opposed to Manufacturer B makes a difference. And, I mean, those seem trivial, but we've seen time and time again that that type of thing can make a difference. And so going into the trial, then you know exactly what conditions to do the reference broth microdilution under to help make sure that you're getting as precise of MICs as possible.

There will be cases -- you know, I was kind of chuckling when Steve said, as close to the truth, but I think that honestly there are instance where there is no truth for some of these drug bug

combos, like there is no reproducible MIC for some of these strains. And so in that case I think discrepant resolution is really important. I think that the strategy that Accelerate used is good. But I also think that we need to open up the concept of doing repeat testing of both concordant and discordant results so that you're not totally biasing yourself to allow for resolution of these. Because the reality is while maybe you can put that in your package insert depending on the drug -- or the device manufacturer, they may or may not just block those results from the user if they don't get a claim, in which case those labs will never see them and we're not really any further ahead.

That all being said, you know, I think that, again, making sure that the trial that you're going into, you have the perfect conditions, that doesn't always translate to the real world. And so I view, you know, looking at a more manual methods like disks and strips a little differently than automated systems where it's a package deal

for the lab. Because again, as I pointed out in my talk, if there's differences in the Mueller Hinton agar performance by disk or strip, then that's something that's going to show up down the road after the lab has implemented the test. And we've seen this happen at the present with some of the new beta lactamase inhibitors where clinical labs just won't trust any of these tests any longer, and now we're in a situation where labs don't want to test the drug, and yet, the clinicians really want to use it, and you can't, you know, predict susceptibility. So in those cases adding a bit more variability into the trial may be helpful.

DR. SHAWAR: Bill.

MR. BRASSO: Bill Brasso. For 6.1 I think it would be very helpful if the pharmaceutical manufacturer would help to establish this. I know that they have enough to do, but that would be incredibly helpful for them to come and say, we've tested all of these organisms and we find it to only be 95 percent reproducible for us, and maybe

we can use that as our denominator and maybe work with the AST manufacturers to see if we get the same results.

Alternate strategies, from the slide that I showed of the data for the six Serratia species where there was spread even past a mode where there was actually a range for some of those. I think the importance of being able to use a range as the result for the -- for the reference method or a range or a mode would be very helpful for a lot of these species, if not for all.

And the approach to resolve the discordant results, the one thing I don't like that it always says is unrelated to technical error. And technical error seems to point to the technician for me, and I think we've shown enough data in the last two years that it's not really -- the technicians are pretty darn good at getting the reproducibility. It's really the inherent variability in the system. So unrelated to technical error.

Inherent variability, I still -- I feel

strongly for the STMA that we still have to say, we've got a long way to go. We have a great divide. We still would like to use the discrepancy resolution used in the ISO document. I know, Ribhi, you've said, you know, it's pretty much not going to happen, but we're going to be like persistent kids. We're going to keep tugging on your pant leg, and maybe one day we'll get to at least a middle ground.

THE COURT: And we'll be the parents.

John.

Jean.

MS. PATEL: This is Jean. I also think it would be very helpful if pharmaceutical companies could help us understand the variability of the reference method. I think this would be important information at the time of setting a breakpoint. I've said this at CLSI meetings -- well, everywhere I can that I think we're setting breakpoints too low. And sometimes we need to separate points -- a susceptible breakpoint at the upper limit of an MIC distribution, and Colistin

was an example of that. But for other drugs, that just isn't necessary. A good example of that is ceftaroline. I think that susceptible breakpoint is just too low. And understanding the variability of the test I think could help us avoid making mistakes like that.

I think that the -- you know, the ideas of comparing test result to a mode reference MIC is very helpful during device evaluation. I also think that repeat testing is helpful if it's done appropriately and the data are analyzed appropriately.

DR. SHAWAR: Thank you.

Tom.

MR. THOMPSON: Tom Thompson. Thanks, Ribhi. You know, we've been talking about plus or minus one dilution as an error with broth microdilution testing. When you look at the data that's submitted to CLSI and it comes from, you know, six or eight different laboratories, it's clearly much more than plus or minus one tube. One laboratory keeps it pretty tight, but when you look at six

different laboratories, the variation is quite broad. And this is concerning, and it makes this question really quite a challenge.

I do think that -- I don't have any great solutions to this, but I do think the idea of replicate testing is a good idea. I do think it would be useful to resolve some of these discrepancies. We need to see where these discrepancies are coming from and why they are there. But I also think that going forward we may be able to improve the broth microdilution test methodology. We need to maybe try some other dilution schemes at the lower concentration of drugs, maybe not use a too full dilution but have more frequent dilutions. Yet, maybe we need to deliver those low concentration of drug differently than making dilutions. We have finer ways of putting exact concentrations of drug into a well, and maybe we should try some of these to see if we can make the broth microdilution a better test.

DR. SHAWAR: Barbara.

MS. ZIMMER: Yes.

DR. SHAWAR: You have the last word.

MS. ZIMMER: This is Barbara Zimmer. And in the response that the susceptibility test manufacturers prepared and sent on the docket to the FDA, we had a very large section that was put together mainly by a statistician, that would be Michael Ullery (phonetic) at bioMeerieux who did an excellent job on options for study design, for paired options with both replicate reference testing, as well as potentially replicate test testing with lots of tables that indicates statistically how to come up with median agreements from a statistical basis. And I want to acknowledge that work that he did, all of which are consistent with the current guidelines using either single method approach or a paired method approach for either one.

In addition, it also went through the idea of the repeating discrepancies on both the test method, as well as the reference method for both discrepant isolates, as well as for those on

random selection of isolates that already had concordant results and with the statistic that went with those, as well.

So I think this is when the STMA would really like to continue working with FDA on because I think that that will help improve things. What Accelerate did was one version of that with a mode here. We'd also like to propose, if need be, a, mode even for the dry test, as well. So again, there's a fair bid of that information that's available.

I don't know that this is low hanging fruit, but we'd be happy to again work with you. And thank you for the opportunity.

DR. SHAWAR: Thank you. And also on that note, yes, the team is actively looking and has been actively looking at all of those, and that's one of the -- the discussions here are going to be very helpful and thank everybody for their thoughtful discussion. And so stay tuned. As Steve also said at the beginning, not going to come out here and say we solved everything.

So right now we're going to break for lunch.

DR. HUMPHRIES: (Inaudible) for questions?

DR. SHAWAR: There are no opportunities for questions. But you have a burning question?

DR. HUMPHRIES: I have a question.

DR. SHAWAR: For everybody who is going to be late for lunch, it's Romney.

DR. HUMPHRIES: I'm sorry. It's my fault. You don't have to listen to my question.

John, I had a question for you. When you were discussing the breakpoints that would go on this website, it seemed to me and a couple other people, and maybe I just misheard you or didn't understand correctly, that it was possible that there would be more than one breakpoint for a given drug bug combination listed on the website. Is that what will happen?

DR. SHAWAR: John, if you want to leave the room, you're welcome.

MR. FARLEY: No. I think that's confusing statutory language that I'm even having trouble understanding. I mean, I think what we're looking

at is, you know, there some urinary breakpoints versus non-urinary breakpoints, right? But that's the only situation that I could think that they might have been referring to, but I was equally confused.

DR. HUMPHRIES: If then when there's multiple breakpoints that are around for a given drug bug combination, it would be -- FDA would assess the data that went behind each of those and decide what data you best agreed with? Is that how it would work?

MR. FARLEY: Yeah. So we -- we continue to have a statutory responsibility, and we'll do a recognition, yeah.

DR. HUMPHRIES: Thank you.

DR. SHAWAR: All right. So thank you, everybody, for participating. We'll meet back at one o'clock.

(Lunch break taken.)

MR. ROTH: Okay. Thank you. It's 1:00, so I think we'll get started. As everyone kind of

takes their seats, I would like to remind panelists to speak directly into the microphone. We've had some issues, I guess, with the closed captioning and folks that are online have had difficulty understanding and hearing all of the comments. And indeed, that's what this meeting is for, so we can capture those comments from the community. So please do try to speak directly into the microphone. Fantastic.

So my name is Kris Roth, I'm a branch chief in the bacteriology 2 branch in the division of microbiology and I'm going to be introducing this session. You know, addressing challenges of diagnostic devices, I think this session is going to focus more on molecular devices and how we can improve the landscape -- I guess maybe push forward the landscape of molecular devices. Indeed, as Steve mentioned earlier – Dr. Gitterman mentioned earlier, Rome was not built in a day, but hey, let's try to get some bricks laid and this is a large group of people, this is a large effort organizing this meeting. And thank you to

the organizers and thank you to all the panelists that have come today; really without your input, this meeting is not possible. So, therefore, we want to make it as productive as possible.

I just want to highlight some progress in the area. These are cleared devices: Direct from specimen devices that are nucleic acid amplification tests – NAAT tests, and I think there's been some talk about baskets of fruit, low-hanging fruit and things like that. And we have, I guess, cleared some of those devices which maybe from sterile specimens, maybe for markers that are well accepted and have, you know, robust literature support. And here's just a brief mention of them, I think, you know, to go on into the future, I think what we're going to see is, you know, more complex use cases, more complex devices. Devices that can detect 10 or greater analytes, that have the capability of maybe detecting both common AMR genes and also newer resistance genes, for lack of a better term.

Again, sterile specimen analysis is something

that is going to be a challenge for us going into the future. For instance, when is it appropriate to report commensal organisms? I guess that is just maybe one question in a sea of questions that we're struggling with. A margin detection by PCR is a little more nuance in organism ID. I think we've got a good grasp on a one-to-one relationship between a nucleic acid from an organism and how that relates to maybe infection, whereas, I think, the phenotypic resistance of a bug is a little bit more nuanced to interpret when you have just a gene or segment of a gene from a PCR assay. And so I'm certain that we will discuss, hopefully, that and I think there are limitations, you know, small gene targets, is that gene being expressed, alternative AMR mechanisms. Are those actually conferring resistance outside of the gene?

We do want to talk about -- a little bit about labeling. We have, I think, a dual purpose on our label and we want to be transparent in the, I would say, clinical study data that was presented

to us, but also we want to make sure that users understand the value and limitations of these devices that rely on detection of AMR genes, solely. And so, hopefully we can get some input on that and, you know, this is a dual goal. We do want improve patient management, but also we need to have stewardship always in mind.

So immediate goals here in the last couple minutes: I think, better understand the issue and gather input from you is the scope of this meeting, the scope of these challenges; what information do comparator methods confer about patient status, and I think we've got both, direct from specimen, comparator methods, or comparator methods from the cultured isolate, molecular versus phenotypic and combinations of the two. Also, how to analyze and present data from multiple comparator methods. We've got both, phenotypic and genotypic comparator methods giving you different information. How do you combine those two into an answer that is, I guess, reflective of device performance and also of the,

you know, patient status.

And what information can we put in the label to help physicians make better decisions. Strict data analysis based on the agreement is one thing, but also kind of interpreting that. Is that something that could be improved to help these labels be more informative?

And another challenge is how to present data when there are multiple organisms and/or markers detected in one specimen, indeed for sterile – nonsterile specimens. You going to get multiple organism detections and you may not always know where your AMR gene, in fact, came from. So briefly, the agenda, you all have it in your handouts and we're very fortunate to have, you know, world experts to come here and speak and help us discuss these issues. And, I think, if I could just introduce our first speaker, Dr. Michael Dunne from bioMeerieux. I'm not going to -- you all have the biographies in your handout, so I'm not going to do any even short bios because it would do a disservice to all of

our panel members, but please help me in welcoming Dr. Dunne. Thank you.

DR. DUNNE: Good afternoon. I get the PPP group, the postprandial participants. (Laughter.) You know that you're getting old when you realize that you were in the eighth year of your academic career and the organizer -– one of the organizers of this meeting was one of your fellows. That goes back to, I think, 1991.

Anyhow, I'd like to talk a little bit about the theory of sequence-based antimicrobial susceptibility testing. This is my first disclosure slide, this is the group that gives me lunch money and these are my two academic affiliations. Now much of –- this is the second disclosure, much of what you're going to see -- or what I'm going to present was already presented as part of a Keystone Conference that was held this past February in, of all places, Keystone. And I co-organized the meeting with Julie Segre and Ramnik Xavier and it was an excellent meeting on the microbiome and health and disease.

The first day that I got to Keystone is what it looks like on your left, the second day was what it looks like on the right and there were 12 inches of snow to accompany that, so things change rapidly in Keystone and I guess we can say the same holds true for antimicrobial susceptibility testing going down the road.

I'm a firm believer that good acronyms equal good science. And so, I was kind of perplexed at what to call sequence-based antimicrobial susceptibility testing. You could call it GAST, genotypic antimicrobial susceptibility testing; SAST for surrogate; FAST for functional, but, of course, if you detect a gene, it doesn't mean it's expressed and so this would kind of be a half-fast approach; and finally, virtual antimicrobial susceptibility testing or VAST. That holds promise, but, as you know, virtual is probably the second most overused word in the English language, second only, to literally. So literally, I selected GARP, genotypic antimicrobial resistance prediction, because, in fact, this is what we're

trying to attain.

Currently, as you all know, most clinical laboratories rely on phenotypic or growth-based susceptibility testing or PAST, which is kind of a good acronym for that one. And there are a variety of manual and automated methods to accomplish this goal. But to be fair, there have been attempts to improve the performance of PAST over the past couple of years and they include the use of MALDI-TOF to evaluate antimicrobial modifying enzymes, flow cytometry to differentiate between live and dead microorganisms in the presence of an antimicrobial agent. The problem with flow is that this group of organisms here are neither live nor dead, so they're kind of like the zombie version of bacteria and we really don't know what directions they're headed back into the live population or into the dead population.

As Scott Manalis at MIT and a number of others have looked at cantilevers, vibrating cantilevers to actually assess weight gain by microorganisms in the presence of an antimicrobial agent. And if

it's increased relative to the surrounding medium they're growing and if it's decreased they're not. A number of groups have looked at micro calorimetry as a measure of metabolic function and bacteria where you actually see heat production when they're resistant to a micro -- to an antimicrobial agent and/or the lack thereof if they're susceptible.

We've also seen the development of nano broth microdilution where you, in fact, take the contents of each of the wells in a 96-well plate and scale it down to one picoliter or one femtoliter that contains growth medium, a single organism and a scalable range of antimicrobial agents, that's virtually unlimited. This way you can modify or absorb the growth of billions of microorganisms, all in a period of about two hours. So that's kind of intriguing. And then our own group looked at intrinsically fluorescing proteins and/or pigments in microorganisms as a judge of whether an organism was actively multiplying or not.

GARP can be used any number of ways. We can do direct sequencing of isolated organisms to examine a resistome-wide analysis or RWAS. We can do transcriptome analysis in the presence of antimicrobial agents. As was previously described by Kris, there are a number of assays that use heteroplex PCR for major resistance determinants. These can either be genes or mutations in regulatory functional promoters. Metagenomic analysis directly from clinical specimens offers its own challenge in that it's sometimes difficult to assign a resistance hit to a particular organism. And some people refer to that as phasing. You can also assign a resistance to major chloro groups and this would be resistance by association and you can use MLST, SNP typing, chloro cluster analysis, and you can skip down to the bottom, you can also use Kamer analysis to do this function. And I'll talk a little bit about that later on.

Another novel approach was to look at the expression of SOS signals by microorganisms after

they were exposed to an antibiotic to predict susceptibility. And this was really kind of a cool approach. I won't go through this laundry list of what GARP has to identify, but the more intriguing ones that will be difficult to discern by GARP will be gene anthrofication of antibiotic modified enzymes either in plasmid copy number or in tandem duplication of genes.

And the last one, the combinatorial effects, that is taking two distinct mechanisms that might not in themselves confer resistance, but when combined with each other would.

So some of the questions about GARP is the answer is the absence of a known resistant determinant equal to susceptibility. Can GARP replace PAST? Is metagenomic detection of a resistance marker directly from a sample useful in the absence of an organism ID? And does it work in real life? Well, in fact, here are a couple of examples of where it works well: ZYNE Colleagues in 2016 evaluated 114 clinical food or vet isolates of campylobacter cholera jejuni. They

looked at 18 resistance genes, two gene mutations and they ID'd 14 resistant phenotypes and 55 resistant genotypes. Of the 1026 PAST results they've collected there were only eight discrepancies. And so that gave about a 99.2 percent correlation with phenotypic susceptibility testing, which isn't too bad.

Again, it works well with Staphylococcus aureus. This was a study by Gordon and colleagues in 2014. They examined 12 antimicrobial agents and they looked for chromosomal and mobile elements and sequenced both of those. They developed an algorithm set using 501 unrelated strains, they performed PAST by Vitek or disc diffusion, then they put a validation set consisting of 491 individual strains through their algorithm and then they did PAST once again, but used a different method, which is kind of unusual.

Unfortunately, neither of the two groups were tested by broth microdilution. But, that said, the sensitivity and specificity of GARP to predict PAST was 97 percent and 99 percent, and the very

major error rate was about a half a percent and the major error rate was .7 percent. Not too bad.

So where does it work “kind of”? Well, kind of works for Pseudomondas aeruginosa, and this was a wonderful study in 2015 by Kos and colleagues. They looked at 388 clinical isolates for resistance to meropenem, levofloxacin, and amikacin and they did their whole genome sequencing reference to 15 NCBI genomes and that contained 5,507 ORFs from the PA01 strain. PAST in this case was determined by broth microdilution.

So, how did it go? Meropenem, it worked. If you combined OPR D mutations plus or minus a metallo-beta-lactamases, plus or minus a carbapenemases gene, it predicted about 88 percent of PAST non-susceptible isolates. Interestingly, 13 of the strains had greater than one of the above resistance markers, but were fully susceptible, 15 strains had no resistance markers, but were meropenem non-susceptible. In the end, the sensitivity and specificity for meropenem was

91 and 93 percent. Almost identical results for levofloxacin, but 17 resistant strains had no QRDR mutations detected. So some other function is at play with these strains.

And finally, amikacin, not so hot. 105 of the 388 strains were non-susceptible by PAST, they used GARP looking for aminoglycoside modifying enzymes, 16S ribosomal RNA methyltransferases, and/or efflux and that only accounted for 60 percent of non-susceptible strains. Thirty amikacin strains had resistance markers and so it indicates that there is some form of regulation that's required to express those resistance markers. And the overall sensitivity and specificity, in this case for amikacin, was 60 percent and almost 90 percent.

Now, we undertook a re-evaluation of 672 individual strains of Pseudomondas including 390 from the Kos collection, and 219 bioMeerieux strains and 63 strains from another collection. We developed an internal database of resistant determinants, 147 of them, and then using these

markers along with quality and quantity RWAS correctly identified the resistance mechanisms for meropenem, amikacin, levofloxacin, and cefepime, but we could not account for plasmid copy number.

Now, recent analysis of the same group of organisms using Kamer position and frequency seems to do a better job. And that's kind of interesting because Kamer analysis is non-biased. You don't have to know what the resistance determinant is ahead of time to predict resistance.

Here's where it gets sticky. Enterobacter cloacae, this was a study done in 2016 and this group tried to predict carbapenem resistance based on point mutations and/or Amp CB repression. They sequenced 24 strains, none had carba resist- -- none of the carba resistant strains had a carbapenemases, ESBLs, or plasmid-borne AMP C. They saw multiple sequence variants of AMP C, AMP R, OMP F, and OMP C, but most of these correlated with the sequence type and not with carbapenem resistance. There was no correlation between 21

SNPs that were located within the AMP C and carba resistance. There is no correlation between amino acid changes and AMP R and carba resistance. Amino acid changes in AMP R did correlate with a cephalous borne resistance and amino acid changes in OMP F were common to both carbapenem resistant and susceptible strains, so no use there.

End Ls and OMP C did seem to correlate with carbapenem resistance, so did increased expression of AMP C, but at a level of 10 to 27 times that of the carbapenem susceptible strains. An increased expression of OMP C or OMP F actually correlated with carbapenem susceptibility. So put all together, this is very –- a fuzzy picture in order to predict one particular resistance in Enterobacter cloacae.

Just recently, and this was a wonderful study that was done by Long and colleagues and this is done in Jim Musser’s lab in Houston. I don’t know how much of that is still intact, but I called him and he was still high and dry. They evaluated the genomes of 1777 ESBL klebsiella -- positive

klebsiella pneumoniae and they sequenced these over a three-and-a-half-year period in Houston. So quite a tour de force.

About 1437 had shiv (phonetic) LEN and OKP family enzymes, 1162 had BLA CTXM, 796 had TEM, and KPC -- 796 had TEM and KPC were 579. There were very few oxas in this group and they had 6 that produced NDM 1. So a nice collection. They applied a machine learning tool which is add-a-boost algorithms and analyzed 10 iterative rounds of a 15-base k-mers to generate classifiers to predict phenotypic resistance to 16 different antibiotics.

So again, this is a non-biased review of the whole genome of these klebsiella strains. And the three highest scores correlated to carbapenem resistance. So this is a busy slide, but what you see here is the ROC curve and area under the curve for the drugs that correlated well with Kamer analysis. Now, the ones that didn't were aztreonam, cefepime, fosfomycin, and tigecycline and the TZP didn't do well either. But if you

look at the correlation of the ones that looped very nicely with Kamer analysis, you get an area under the curve that exceeds 90 percent in many of the cases. And I think this would be a nice way to approach prediction of resistance in organisms that you're not entirely sure of all resistant mechanisms.

So where does GARP make the most sense? At least to me it would be with slowly growing or difficult to grow microorganisms, like mycobacteria. And why is this? I think it's obvious, the time, the cost, and the safety involved of doing phenotypic susceptibility testing of mycobacteria. Tuberculosis can be quite difficult. PAST can take weeks, it requires some degree of technical proficiency, you need reagents, you need a BSL 3 safety condition, and it is labor intensive and it's costly, especially for the equipment in many cases.

Further, rapid ID of MDR and XTRMTB is a major public health concern. If PAST is centralized, it means that you have to transport live organisms to

do the testing and there's poor correlation with phenotypic results in some of the secondary anti-tuberculous drugs. But if you could -- if you use or apply GARP in mycobacteria you come up with some pretty nice results. First of all, it can be used on DNA extracted from isolated colonies or directly from patient samples. The analytical sensitivity for detecting resistance mutations in TB is nearly 90 percent for INH, 98 percent for rifampin, 90 percent for fluoroquinolone, 85 percent for kanamycin, and a hundred percent for amikacin and capreomycin. And the specificity for all of these drugs was 100 percent in the study of Lynn and colleagues.

Phenotypic resistance prediction therefore achieved a level somewhere between 92 and 99 percent, and that's not bad.

You can also use metagenomic analysis because the analytical sensitivity of this approach is a hundred percent at one picogram per microliter of mycobacterial DNA. If you have smear-positive samples, you have enough DNA to perform that

analysis.

All right. So for isolated colonies or patient samples the correlation with PAST testing was nearly 94 percent for all drugs and the assay can be performed and centralized in about six hours. Other applications where GARP makes a whole lot of sense, viruses obviously, we're doing it already, fungi and parasites, especially plasmodium species. Drug susceptibility modifying SNPs have been identified in a number of loci that correlate for resistance to antifolates, piperaquin, quinine, and artemisinin derivatives. Sorry for the misspelling. And it's far more quicker than any of the current growth-based methods that are being used.

Here's that study I was telling you about transcriptome analysis, GARP requires a priori knowledge of many variables causing phenotypic resistance and it requires a curated database.

Byerzach and colleagues developed a probe set that recognized up-regulated transcripts produced by susceptible organisms when exposed to

antibiotics, a so-called SOS response. Some responses were universal, but many were specific to particular drug bug combinations. But here's the problem, hetero-resistance. If a susceptible organism is squealing and spilling the beans, the hetero-resistant ones aren't saying anything. So in conclusion, GARP is an attractive alternative to PAST for resistance detection, but is not quite ready for primetime. There is some database development that would be required for GARP and that'll be never-ending, but we should come to a point where accuracy is not an overriding issue. PAST will never outlive its usefulness, it's the primary way we'll detect novel resistance mechanisms. And GARP will likely be used first for difficult to culture organisms of great public health concern.

And I'm going to stop there. Thank you.

(Applause.)

MR. ROTH: Thank you. I think we'll hold questions until the end. Our next speaker is Dr. Dan Sahm from IHMA, Incorporated.

DR. SAHM: Thank you. Since I didn't get a nametag, I think I'm going to use Mike's. (Laughter.) I hope I won't embarrass you, Mike, too much, but...

My presentation's is going to have to do with public health implications of antimicrobial resistance. There's a little bit of a molecular bend to this, but I -- the way I tilted this presentation is talking about another resource that I believe you might want to consider to tap into to help coordinate efforts to bring products to the clinical labs in a much more timely manner.

Basically, from a central microbiology laboratory perspective is where I'm coming and that is how can we use the resources' capabilities indeed – thank you very much, where's the glitter? -- that's acquired through our resistance programs and how can these be used to expedite development of approval of new susceptibility testing. And that's not only to do with new drugs on current platforms. But also that can help expedite getting new platforms and technologies into the clinical

laboratory.

So I apologize for the first couple of slides being a little bit word dense, but basically a little bit about antimicrobial resistance surveillance for those in the know -- not in the know. It's an ongoing requirement of any drug sponsor to conduct this kind of research to keep track of how their drugs and comparators are doing out there in the real world. It maintains an ongoing update status of new agents against all the relatively relevant organisms for which we have interest and hence the clinical labs would have interest as well. This is often done in concert with phase 2 and phase 2 clinical trial focused on the clinical safety and efficacy of the same agents for which we're doing surveillance.

So based on this there's data and organisms are focused on these agents that are also in the diagnostic pipeline and need -- and in need of access to testing for clinical laboratories. Focuses -– focuses on some drug -- they focus on some drugs and clinically relevant organisms of

concern to the clinical microbiologists already and infectious disease specialists and medical environment overall.

The testing is performed centrally in a central microbiology laboratory using standard methodology such as those outlined by the CLSI. And organisms are stored and available for further analysis. And the resources generated by this surveillance could provide collateral support for industry needs for new drugs on current program -– platforms, excuse me, or new platforms altogether.

So overall, what do I mean by a central laboratory? Many of the robust antimicrobial resistance surveillance initiatives are conducted by a central microbiology laboratory. The capabilities in these labs is they have an ongoing production of current and robust data and a collection of target organisms. I heard a lot this morning about these study sets. Well, these surveillance programs are a huge catchment area for replenishing these organism sets year in and year out and keep a track of what a new -– what's

going on with known resistance mechanisms and what might be emerging.

I have regular interaction with clinical microbiology laboratories throughout the world, there's high through-put testing with susceptibility testing being between 500 and a thousand organisms a day. The sufficient high-volume molecular characterization and sequensing of strains of interest is ongoing, and I'll give you some data to show you that. And there's a strong scientific and clinical expertise in these laboratories in general on the most drugs that are in development. In general and those that are in development specifically. And the strong data management and project management and infrastructure support this data.

The other key factors are these labs have a strong business and collegial working relationship with almost anybody in the pharmaceutical industry that's developing a drug and also there's a good, strong working relationship with diagnostic manufacturers and the FDA as well.

So just get -- as an example from some of our experience to talk about what the kind of information and strains that we can accumulate, this is just data from one of our studies from 2013-16. We've accumulated 290,000 target organisms and collected them and susceptibility tested from all four regions of the world. And of these, over 36,000 had had their underlying resistance mechanism molecularly characterized vis-à-vis the beta lactamase content, porin mutations, efflux changes, et cetera. All the strains also are catalogued by demographics, resistance profiles, molecular mechanisms and can be made available to whoever for further analysis.

Here's some examples of the output of this kind of information. This one has to do with MCR and there's a couple of points I want to make on this slide, is that, first of all, there's a lot of important interest in MCR, but what this data showed in our analysis of 24,000 isolates of which 587 were colistin resistant phenotypically with an MIC greater than four. Very few of them or about

3.6 percent had the MCR gene, the MCR 1 and 2, this is very consistent with Mariana's publication where it was 4.9 percent. The point being, you can take a look here and see very quickly what is the –- what is the burden of MCR on overall colistin resistance and also the availability of such stains that could be used for developing diagnostic devices for new drugs.

Some other type of the data that I want to -- I don't want you to focus so much on the names of the drugs or what have you, but the fact that these kinds of strains with this background of information could be fed into systems for evaluating new drugs on old platforms or new platforms altogether. This simply looks at the proportion of beta-lactamase positive Enterobacteriaceae collected from 2012 to 2015 available by each region and by year, so imagine if you will, here's the percentage of the enterics that have those mechanisms and just again, imagine that they could be available or applied to new device development.

Here's -– the next couple slides come from a poster presented at ATMA (phonetic) 2017 by Christina Kazmierczak with our organization. Basically, this is -- as an example, Ceftazidime-avibactam MIC distributions against KPC positives CRE, from patients with respiratory tract infections, and you can see there's a wide spread of MICs, although they're all KPC positive from different regions of the world. You can see that that would present a robust selection of organisms based on which MIC you might want to test in your system.

Similarly, using ceftazidime avibactam again, MIC distributions against Oxa 4D8-like strains, you can see the MIC distribution that they're all not clustered around one MIC, so there could be a selection of MIC range for strains that are Oxa contained -- Oxa 4D8-like containing. And also, even with ceftazidime MIC distribution beta-lactamase producers, there's only 45 of these strains, but you can see that some of them have relatively low MIC's given the fact that they

contain MBL. So the bottom line here that I wanted to just point out is that these strains can be made available to regenerate or rejuvenate study sets or it could be used specifically for new device development.

So the way this could work, I just propose on the next couple of slides, and this slide is the potential collaborative structure to expedite development and deployment of AST systems capabilities for new drugs. First, I want to emphasize that this would have to be initiated in close collaboration with the sponsors of the drug in question because nothing that we do would be done without their interest.

So in the central microbiology laboratory, we have the data, the MIC, the molecular, the demographic, the geographic data. We have the strains and we can provide testing services, and I'll focus on that in a few minutes on the next slide.

Then that data could be sent to any government or designated regulatory agency to help evaluate

what might be going on with a particular system.

Similarly, the same set of data could be provided to the diagnostic industry just directly and that kind of information could be shared between the government and the regulatory agents in the diagnostic industry for analysis of data information to support evaluations of new drugs and platforms.

So if we talk a little bit about what we mean by testing services. What goes on in these central laboratories is that in addition to the surveillance where we're getting tens of thousands of strains in for characterization year over year, at the same time many of us are also running human phase 1 and phase 2 clinical trials where we're getting organisms in for identification, susceptibility tested and molecular characterization. I think it's a strategically positioned opportunity that if there was a new device or new platform that's being developed that this could be used and test -- and incorporated here and tested simultaneously while the clinical

trial and surveillance isolates are coming through so that some set of this -– some subset of this could be used to evaluate new technologies or platforms or new drugs on older platforms in support of any kind of regulatory submission.

So basically I just wanted to get this out there as food for thought that a central microbiology laboratory is a vast resource that I think that’s been primarily under tapped to help coordinate the initiation of getting new drugs to market or new platforms to market.

Again, just to summarize, the application of these resources could be leveraged to expedite deployment of critical susceptibility capabilities to clinical laboratories. And the underlying thing here is the clinical laboratories are our really front -- no matter what kind of surveillance we do, clinical laboratories are our frontline for detecting and monitoring resistance trends and if we don’t get these devices and capabilities in their hands sooner rather than later, then we’re really losing a critical

opportunity to have a frontline monitoring system for resistance.

The other point I want to make is that a working relationship already exists between the central microbiology laboratories, the FDA, drug sponsors, and diagnostic manufacturers and the clinical laboratories. So, it's not that these groups are unfamiliar with each other, it's a matter of codifying the relationships and what could be leveraged to help things be employed more effectively.

So essentially this community is really well positioned to take the next steps so these relationships can be optimally leveraged to most successfully and effectively ensure critical testing capabilities reach our clinical labs in a more timely and reliable fashion. And I know there was a number of things discussed this morning about the number of organisms tested, what the characteristics of the testing should be, how many organisms, what type, et cetera. I think that if you look at the databases and the

organisms that are available on clinical laboratory –- clinical central laboratories, microbiology laboratories, is that essentially the world's your oyster to pick from for doing that kind of testing and it's –- I think it's time to start bringing that facility or those capabilities into this discussion.

Thank you very much.

(Applause.)

MR. ROTH: Thank you. Our next talk will be Dr. Trish Simner from Johns Hopkins Hospital talking about clinical laboratory experience with interpretation and reporting of resistance markers.

DR. SIMNER: Okay. Good afternoon, everyone.

So here's my disclosures. So today I'm going to talk about the use of detection in the antimicrobial resistance gene for antimicrobial stewardship and for infection control purposes that we currently have applied in the clinical lab; and secondarily some -- some research stuff that I'm doing that will be of value to our

discussions this afternoon.

So as a clinical microbiologist, it's really exciting right now, we're seeing more and more new techniques coming into the lab, most of which are molecular. And we see everything from, you know, our first point a care molecular test to sample to answer-based molecular platforms from single targets to multiplex panels, to now the introduction of whole genome sequencing. And my little disclosure at the bottom, not all are FDA cleared platforms.

And so, what most of these new molecular methods that are coming our way do provide is the rapid identification of the most common pathogens, and so what we're seeing now in the current clinical paradigm where we get collections of specimen usually day one, after incubation, you look at a MALDI-TOF ID and most labs that have MALDI, day two, you look at your standard AST profiles and if you need additional ASTs, that will be on day three. But now what we're seeing is some of these novel methods, such as point-of-

care tests, molecular panels, NGS and total lab automation, that are being introduced, that are helping us more rapidly perhaps narrow and perhaps more rapidly narrow and provide perhaps targeted treatment.

So does the ID only matter? So this is randomized control trial from the Mayo Clinic; many of you in this room have heard about it multiple times, it's been presented at many conferences. And so what they've shown is their control group –- this is not using a rapid molecular diagnostic from plasma blood cultures such as standard culture and AST. And they had two separate intervention arms: One, using the biofire rapid molecular diagnostic on its own and the second arm -- intervention arm was with stewardship intervention. So stewardship would then act upon these results, call the clinicians and suggest what to do for management of these patients. And what they found was that with intervention arms they found reduced treatment of contaminants and reduced broad spectrum antibiotic

use. But what the -– what they really need -- what they really showed was that for their -– the physicians are happy to escalate based off of rapid results, molecular results, but they’re very hesitant to de-escalate and it was only in the arm with stewardship that did see the significance in de-escalation of antibiotics. And also, they didn’t find any mortal- -- reduction in mortality, length of stay, or outcomes. But that’s because the study wasn’t powered to do so.

So what we find ourselves in a situation now is that the gap between ID and the AST continues to grow, and so blood culture diagnostics is the best example where, you know, we’re waiting for day 3, our traditional methods when we used to use biochemical based IDs and AST, we'd be at day 3 to get an ID in AST. Now we’re getting a MALDI ID at day 2, we’re getting -- we can get direct from positive blood culture, molecular based assays where we’re getting an ID at –- after the blood culture signals positive and this is getting even larger now with these direct from whole blood

diagnostics.

So what most of these molecular panels don't provide is a comprehensive AST panel and some of these panels do target specific or common resistance mechanisms such as VanA, VanB, and VRE, MEK A and MRSA and then your common ESPL and carbapenemase genes.

So what is the advantages and disadvantages of resistance marker detection for AST currently? So from a phenotypic standpoint we have standardized methods that we've used for a long time in the clinical lab. In general, we call these slower comparatives, some of the molecular methods, because we require overnight, it's growth dependent, so overnight. For the most -- most methods, it provides an MIC. We have clinically interpretable break points for these MICs. It's independent of resistance mechanisms and then physicians, this is a key point, where physicians are more experienced, confident, and reliant on the AST profiles. Or I've seen sometimes where we try to implement some novel methods to try to get

them a resistance mechanism up front and they might not be as confident to act upon those.

From a genotypic method, this is a growing field, we get fast either direct from specimen or cultured isolate detection of resistance genes. The problem is it only detects the specific resistance genes that are in that panel or by whole genome sequencing it's only as good as your database that you're using. If it's present, you assume it's resistant and it's less than ideal for accurate detection -- or sensitivity and specificity for predicting both susceptibility and resistance. And so what some recent studies and UCASTs have shown is that perhaps not the breakpoints aren't what we should be comparing these too, but more the ECBs, so the epidemiologic cutoff values.

Physicians are likely to escalate treatment if we find a resistant gene, but physicians don't always understand, or clinicians, what the error genes, what these antimicrobial genes mean -- resistance genes mean. Heck, I look at some of

these reports that I'm getting from whole genome sequencing and I need to look at what some of these resistance genes are. So how do we expect our clinicians to know all of these? And I study antimicrobial resistance. And so, again, physicians are hesitant to de-escalate without AST profile, especially without antimicrobial stewardship intervention.

And so what we've -- so for an example of implementing some of these AR detections from clinical specimens in helping stewardship and clinical outcomes, we've implemented the verigene gram positive panel from positive blood cultures that are single positive by gram stain with a gram-positive organism. And so what we've shown with our stewardship group is a little bit of a different study from Mayo Clinic, this is just more of an observational study afterwards where at baseline this is traditional culture in AST methods. An intervention group, this is when we put -- we went live with the verigene gram positive panel, we had stewardship actively

calling on these results right away. So it was more of an education campaign up front.

And then the third arm was after we removed the stewardship involvement, did that -- did this continuous improvement in treatment in optimal therapy still be maintained without stewardship intervention? And we found with seven months of robust stewardship involvement and education, that we can see sustained impact of implementing this meth -- the rapid blood culture methodology despite the interventions from stewardship being removed.

And so -- and then lastly, there was no decrease in time to effective therapy in the study that we observed as most were on (inaudible) therapy and no difference in length of stay or mortality. Again, this is just because it wasn't powered to do so.

But what we do encounter sometimes with bringing in a molecular technique is the following: So blood cultures signals positive, we do our gram stain, it's positive for gram positive

cocci in pairs or short chains and then we run or verigene panel, which we try to get out and released by four hours of a positive blood culture and this says a VRE was detected VanA, enterococcus faecium detected.

The following day we confirmed the growth of enterococcus faecium and then on day 3 we got a vancomycin susceptible result. So we get this discordant analysis between the genotypic method and the phenotypic method. And so as mentioned a little bit already, but the detection of the gene doesn't always result in expression. And not only expression, it's low level expression can be occurring as well, just not bringing it to a level to where it's crossing that clinical breakpoint as being resistant. So it's -- it can become tricky, so how do we resolve some of these discordant analyses? Well, the CLSI molecular working group did a really good job and put together three tables on -- for labs to use on how to resolve these discrepancies, or how to handle them. And so in our scenario that I presented it was VanA

positive, vancomycin susceptible, so you want to confirm the ID, repeat ASTs and if the discrepancy does not resolve, then you should report out the vancomycin resistant, vancomycin MIC is resistant. And so that's the conservative approach, the approach we use. We don't see these very often in our clinical setting, it happens maybe once every two to three months with VREs specifically, and so we just add the following comment, just so that both infection control are aware of us detecting a VanA positive enterococcus and then so our clinicians and team can understand that, what the discordant analysis was. And I usually field phone calls from these results, so...

And so again, that would be in the setting with the more conservative approaches when you don't have the, you know, active microbiology directors available, a big stewardship program available to help them with treatments so, again, we're very fortunate in our setting.

So what gets even more complicated is when we start to talk about the gram negatives. So the

gram positives are pretty straight forward in that they have a single mechanism mediating resistance, so methicillin resistant, staph aureus are mediated by MecA and vancomycin resistant by VanA, VanB. But it becomes a real alphabet soup when you start to think about the gram negatives. And so they have this heterogeneous resistance mechanisms that can provide different -- that can provide the same phenotypic AST profiles, and so the absence of a gene does not mean it's susceptible like we kind of apply in the gram positive side. And so, for example if you're trying to predict third generation cephalosporin resistance, most of the tests out there right now detect either CTX-M only or CTX-M-10 (inaudible) variance. But there are many other ESBLs, there's AmpC that can be either chromosomal or plasma mediated, there's carbapenemase genes that could also provide cephalosporin resistance and then there's these non-inquired mechanisms such as porin and efflux that can contribute to cephalosporin resistance. So it gets a lot more

complicated from the gram negative side.

But nonetheless, here's an example from cultured isolates of how we've implemented a molecular based technique in the clinical lab to help out with both infection control and stewardship. And so from an infections control standpoint, they wanted to know, not only are we detecting -- what are -- how many of our CRE's or carbapenem resistant Enterobacteriaceae are carbapenemase producers? And then the stewardship side is asking, well, what type of CPE – what type of carbapenemase producers are these? and this was right when ceftazidime avibactam came out where they're not active against metallo beta lactamases and so they –- and the devices weren't readily available to clinical labs and so we could kind of use some of this information to help us in terms of treatment.

And so ceftazidime is a new beta-lactamase, beta-lactamase inhibitor, I just mentioned it has activities against carbapenem resistant organisms, including searing carbapenemase, but not metallo

beta lactamase producers. We just did a quick study in our -- set all of our -- we tested all of our CRE. I just want to draw attention that most of the resistance was due to NDM producers, but we also did encounter some SHIV ESBL's that were resistant to ceftazidime. So just because it's not a metallo beta lactamase producer doesn't mean it's going to have activity, and so testing -- EST testing should be performed.

But here's a clinical scenario where reporting the clinical markers helped us out, so we had this highly resistant klebsiella pneumoniae, the only thing it was susceptible to is amikacin. We set up the phenotypic modified carbapenem activation method in our lab to detect carbapenemase producers among CRE and this was positive for a carbapenemase producer. And then can we detect quickly and rapidly whether ceftazidime could be a potential for treatment in this patient and so we ran the carba R assay and it was NDM producer and so it effectively, essentially ruled out the use of ceftazidime. So it could be helpful for ruling

out its use, but not ruling it in. So AST still needs to be performed in those cases.

So those were two examples of clinical detection of resistance mechanisms where we currently apply them clinically in the lab for stewardship and infection control reasons.

But I want to talk a little bit about the applications of next gen sequencing both from direct from specimen and clinical isolates.

So direct from specimen, here's an example of metagenomics next gen sequencing, meaning that we're not -- we're unbiased, we're chopping up all the DNA present and sequencing it. And so our comparator to our results were our vancomycin screen. This is a rectal specimen, so we detected VRE and then we detected by chromID carba and the direct MacConkey plate method, both a carbapenem resistant klebsiella pneumoniae which was confirmed to be a KPC producer, and then we performed a research use only direct from swab, detection of resistance genes and confirmed the KPC. And of note, it's a high-level positive;

there's a lot of KPC present.

We then took the remainder of that rectal swab and were able to essentially replicate our culture based results by studying the metagenome, so the microbiome of the isolates, so we could detect that the majority of the gram negative present was klebsiella pneumoniae, which correlated very well with what we were seeing on the -- on our culture plates. And also we could detect enterococcus if we dived down further into these smaller areas on our chronoplot. And we also compared illumina short -- short read sequencing to nanopore long read sequencing and we saw very good correlation between the two different sequencing based methods.

And so the cool part was is that with the nanopore sequencing, which is called the menION, and having two kids at home, I always think of minions, when I look at this. And so what we could do is, that KPC gene was detected within 2.3 minutes of starting the sequencing run. So we get real-time resistance gene analysis using this.

So thinking about it, so this could be applied from rectal swabs to help us with surveillance, and the thing with surveillance now is we have VRE, we have CRE surveillance from rectal swabs, you know, we might have colistin resistance from rectal swabs. So this is nice catch-all for the resistant mechanisms.

We've also applied metagenome sequencing from CSF specimens and had a shunt infection with an MRSA. We were both able to detect staph aureus and MacA that correlated with the MRSA infection or that we grew in culture.

So this is the other end of applying next gen sequencing from clinical cultured isolates. And so I'm going to present this as a case. So this was a CRE isolate that we performed whole genome sequencing and this is a retrospective analysis. So we did the sequencing afterwards, but now we're correlating it to what happens in clinical care with our results that we had after analysis. So this was a clinical case of a 64-year-old female, post -- status post-liver transplant, presenting

sepsis, she was empirically initiated on vancomycin and meropenem, blood cultures grew and the AST results were available about 48 hours. An isolate was found to be meropenem resistant. Additional testing for colistin, tigecycline, and imipenem were performed and were resulted 72 hours, and ceftazidime avibactam at that time was not available due to a backorder of the device that we were using. And so amikacin and colistin were added to the regimen at 48 hours.

And so this is just showing that we, with our real-time whole genome sequencing analysis we can prepare libraries and extraction on libraries in four hours, and within ten minutes of starting our sequencing run we could detect the -- most of the required resistance genes from this clinical cultured isolate.

The problem is with nanopore which correlated really well with the susceptibility. This is an N of 1 right now. We have a larger study going on, but his is like hot off the press, so...

But -– and the other thing I should say is

that colistin should be wild-type and not susceptible written in there. I noticed that afterwards, but…

But the other thing is that we're –- nanopore has a high error rate and so we're having a little bit more trouble in terms of detecting chromosomal mutations associated resistance at this point, but we're trying to find some work-arounds with that.

So this is what just occurred. So the patient was started on meropenem and colistin and amikacin was added at –- it was more around 48 hours. And so what we found is that with our methods and what we applied we could have potentially allowed for real-time gene detection at about 28 hours and ruled out the use of ceftazidime because again, this was an NDM producer and then there was no known mutation or colistin amikacin resistance that we found in there and potentially could have -- that made that decision to broaden therapy and add on these additional agents with that resistance profile quicker than what we did -- would provide with standard AST results.

So UCAST had done a study recently, or a guidance document on applying whole genome sequencing for predicting AST results, and so their conclusions were that the availability of evidence right now is poor, does not -– and it does not support clinical decision making at the point when they did the review and was published in 2016.

The primary comparator that they suggest is ECV and I agree, if you think about it, you're detecting wild-type versus non-wild-type. So you're detecting a resistance mechanisms and we don't know how those correlate to clinical outcomes. So that would be a more appropriate comparator. There is a need for advancing bio (inaudible) tools in terms of quality controlling, QC'ing them as well as creating a standardized database because your results are only going to be as good as your database, and we found differences in using different databases for analyses. And the technology might not be there yet, so some of the methods are still very costly, the speed might

not be there and can be very labor intensive.

So in conclusion, the use of antimicrobial resistance genes for predicting -- for use in the clinical lab for stewardship, we've shown some successful applications for resistance marker detection. However, it's most beneficial from the gram positive organism side. It's a growing field right now, especially in terms of applying next gen sequencing, applications for AST where there is no to little data on clinical correlation. And again, just reiterating that we need some standard databases and ECBs are probably a more accurate comparator.

And lastly, just, it might be that we should be studying not just the detection of the deem (phonetic), but the transcription, so studying the transcriptome.

(Applause.)

MR. ROTH: Thank you. Our next speaker is Dr. Kim Anderson from FDA. She'll be speaking about the FDA perspective on scientific review of novel technologies for the detection of

resistance.

Kim?

DR. ANDERSON: Good afternoon, everyone. I'll be speaking briefly about FDA's perspective on the scientific review of technologies for the detection of resistance, which will be limited to molecular devices in the interest of time. I really have nothing to disclose.

During this presentation, I will speak briefly about the common devices for the detection of antimicrobial resistance, nor molecular technologies as well as the regulatory framework for the review of AST devices. I'll also speak about the advances in diagnostic devices and how this has led to new regulatory and scientific challenges throughout the review process, and finally, a few key resources available to aid in evaluating new devices.

As you can see from this abbreviated timeline, FDA has had an extensive history with AR test clearances, dating back to culture media in the 1970s to the first clearance of a nucleic acid

amplification test for -- oh, sorry, back -- to identify MRSA from direct specimen. And less than a decade later we had the introduction of multiplex instruments targeting large panels of organisms in conjunction with the detection of resistance markers. And these resistance markers have been identified by a number of sources really starting with colonies and going to positive blood culture and now to other direct specimen.

In terms of regulations, FDA has created a regulatory framework to support the evaluation of new devices that detect antimicrobial resistance as shown here in blue, as well as future regulations related to new organism resistance mechanism combinations.

If we look at the number of AST device clearances of a five-year period from 2011 to 2016, nearly 20 percent of the AST devices cleared have been molecular in nature. Please note that this slide doesn't include the number of devices reviewed through the pre-submission pathway.

Due to advances in diagnostic devices we've

se -- there's -- which has spurred the development of rapid molecular and phenotypic devices, panel-based devices, combination devices which include devices of combined function as well as devices of new technology. We're starting to see a shift -- that this shift in technology is having a dual effect, depending on your point of view. So from the viewpoint of the operator the instrument system, which includes the instrument, assay and software it's becoming simpler in that they're may be little to no sample manipulation, limited training to run the device, a reduced workload because now the operator has fewer instrument to interact with, the ability to generate rapid results. And not only that, the software is actually doing the results interpretation and also less time spent on maintenance and calibration. However, if you look at this from the viewpoint of the reviewer, the instrument may be quite complex, in that one would have to look at the new technology, the interdependence of the device functions, the processing of different specimen

types, the detection of multiple targets, the testing of multiple drugs, and its compatibility with other instruments.

FDA relies on the review of valid scientific evidence to support device performance. With this in mind, we come to one of the challenges of evaluating molecular devices that detect resistance markers in that the level of evidence to support claims for say, a device that detects one resistance marker in a single species is much less that what you would expect for a device that detects multiple resistance targets and multiple species. If, for example, we take a device that detects resistance markers associated with carbapenem resistance, what we would consider during our review would be as listed here: The intended use, how broad and narrow are the claims, are we talking about a CP CRE or CRE; do certain variants need to be included in the intended use; of the types of the specimens to be tested, are we talking about colonies versus direct; and if the target is not detected, is that an issue due to

prevalence or the fact that that specimen type is not appropriate for detecting the target. Also, the types and number of species, the genes and gene variants targeted by the device, whether different resistance mechanisms were evaluated, a suitable comparator method, talking about a culture method, molecular, other phenotypic tests, or a composite reference method. If a new comparative method is chosen what's the level of validation. Also, how is the data presented as well as the results interpretation and labeling?

So, we not only want a safe and effective device, but we also want one that provides meaningful information to the end-user. We have encountered several issues during our review of molecular submissions which will be discussed later in the afternoon panel and I have here listed a few, which I'll describe: Such as determining an appropriate reference method for molecular investigational device, assessing organism resistance marker identification in the context of specimen types with known bacterial

floor, a colonizer versus infection, reporting of resistance markers without organism identification and what to communicate to end-users. And presenting the detection of gene variants given the dynamic nature of antimicrobial resistance, prevalence, and new variants identified.

So, we have -- we are continuing to meet the challenges posed by new diagnostic devices in a number of ways. Given the fact that some of these new devices have the capacity to generate large quantities of data, we have organized review teams to analyze data sets from the submissions. So instead of a one-to-one relationship of the submission to review, we now have submissions being reviewed teams of individuals. And these reviewers work collaboratively from the earliest stages which can include informational meetings, pre-submissions to the official review – official submission review, and final agency determination or recommendation for the device. All of which increases the efficiency of review. And this approach was used successfully with Accelerated

submission which you heard earlier in the morning session.

There are several resources to evaluate new devices, which include pre-submissions which allow reviewers and device manufacturers the opportunity to discuss important elements of the clinical and analytical study design, result interpretation, data presentation, and official submission timeline. The novel pathway can be used to assess devices of a new technology and new intended use. Once granted these devices can serve as predicates for other -- for future devices through the 5-10K pathway. We encourage collaborations with subject matter experts within CDRH, other FDA centers, sister agencies, academic institutions and scientific organizations, workshops such as this one, serve as a forum to discuss important issues related to study design and performance characteristics of real literature and real-world evidence. It may be possible to use real-world evidence to look at the regulatory decision making for medical devices and the new guidance document

concerning that was just issued August 31st, I think.

Finally, a little bit of creativity in the design which I'll show in the next slide. Because a well-established reference method may not always be available, we've development these composite reference methods to use to compare to the investigational device.

So, here we have Approach A and Approach B, which are two hypothetical composite reference methods which the combination of tests is used to define the patient population status. Approach -- these approaches are not static and they can be changed or modified depending on the device's claims and the technology.

So, in summary, the number and the scope of diagnostic devices for the detection of AR markers continue to increase. Current technologies identifying AR markers have introduced new regulatory and scientific challenges prompting a dialogue of stakeholders and we will continue to discuss issues pertaining detecting, reporting,

and interpreting AR markers later in the afternoon panel. So, thank you.

MR. ROTH: Thank you, Kim. Our next presentation is by Dr. Robert Bonomo and Dr. Scott Evans challenges of the clinical use and interpretation of genotypic versus phenotypic drug resistance testing. Who's going to go first?

DR. BONOMO: Good afternoon, I'm Robert and I'll be speaking first, and Dr. Evans will be following.

So I would like to start with my acknowledgements and funding. And appreciate the invitation by the reviewers to be here today, it's a real honor to hear what's going on.

So, I come to this as a strict clinician. I made the observation during the first couple of presentations is that I am probably the only person in here that has not been trained in clinical microbiology or have a PhD behind my name. So, maybe there's one or two other people, but that's -- we're not of the majority in this room.

So, but I – let me tell you how I came to this issue. Can a rapid molecular diagnostic test improve empiric antibiotic choices and affect clinical outcomes? Very simple question, I mean you could frame that very easily, the problem is you have host response, you have phenotype, genotype and you have proteomics and expression. And you have pathogens that can elude some of our best defenses. So this is not an easy clinical problem, it's actually one that is exceptionally challenging. So, what it -- what did we do, you know, as part of this to try to solve this problem? I think today one of the real elegant aspects of this conference is you've heard so many people talk about some amazing things, that, you know, I -- I just have to congratulate some of the speakers as to what they did today. But what we did in our consortium is that -- well let's see how we can approach this from the clinical standpoint marrying this to a microbiologic and genetic standpoint. And also, marrying this to a statistical analysis. So, a series of studies was

started called primers, primers 1, 2 was the – was basically – and primer stands for platforms for rapid identification of multi-drug resisting gram-negative bacteria and the evaluation of resistance studies. So, primers 1, 2 was our first foray, focused mostly on E. coli and klebsiella; primers 3 was a challenge because we decided to go into acinetobacter and ask the same questions in an organism that is very difficult to characterize, grow, and microbiologically figure out; and primers 4 we had the idea and this is totally out-of-the-box thinking, you know, can we mimic a clinically registration trial, if you put this in, if you put this organism against this antibiotic in a trial can I use a rapid molecular diagnostic to test whether that organism will be susceptible or resistant to that? And lastly, I'll finish with, can primers assist with stewardship? Well, could studies like this assist with stewardship? In primers 1, we used 4 molecular diagnostic platforms and I think it's important to keep in mind that it doesn't matter what the platform was,

that was not important. What was important was the phenotype -- genotype and phenotype that we tried to focus on. Because of my previous interest as an ID physician we focused on beta lactam resistance mediated by beta lactamases. In hindsight, if we would have done this with fluoroquinolone resistant it would have been a snap, it would have been easier. Because you don't have the same genetic complexity, the conveying that resistant phenotype as you had in beta lactam as you have with beta lactamases.

So, in primers 1, we took 72 strains of highly drug resistant E. coli and klebsiella, we applied nucleic acid amplification technologies of which they are listed on the slide as well as whole genome sequencing. And then how did we do this? Well, it's interesting there, cause -- since you're not a clinical microbiologist you don't really know all the databases that are out there and you decide to look in the literature and you go on your own ahead. So, we decided that we going to put together a series of genes and what

was really interesting in retrospect is that when you look at some of these genes and the phenotypes that they give, you have so much overlap in the beta lactamase field that it's almost mind boggling. And you're not even considering the opportunity for a single CTX-M or CMY or an AmpC to have a point mutation that's going to take you from a regular cephalosporinase to an expanded spectrum cephalosporinase that's going to take out ceftolozane tazobactam or ceftazidime avibactam.

So, having this complex challenge is really very difficult. So, we had to come up with a series of susceptibility gradients, if you will. The number of genes that can give you a resistance to ampicillin is huge, you know. Almost every gene that's on the list as you go down the list, it gets infinitely easier to predict in most cases carbapenem resistance then it is to predict resistance to cephalosporins.

How did we put this together? Well, we did susceptibility testing on all these and the way we represented the susceptibility testing was that in

primers 1, we took 72 isolates that was resistant to cephalos- -- and 37 that was resistant to all carbapenem and cephalosporins; in primers 2, we took a clinical mixture that was blinded, 73 of these isolates were susceptible to all of them and we started the frame the question. In the first one, how good are the tests; and in primers 2, we asked well, if you were a clinical microbiology laboratory and you got some that were resistant, some that were negative, how well could you discriminate? And Dr. Evans will be talking about that. In primers 3, we looked acinetobacter and the questions that was asked with acinetobacter, if you have an isolate and it's resistant or susceptible, can you come up with a better therapy? Can your genetic tools come up with a better clue as to what you have? And the issue with acinetobacter is that although you have a very complex organism, the number of carbapenemase genes expressed in acinetobacter are a lot smaller than the number of cephalosporinase genes that are expressed in E. coli and klebsiella.

Nevertheless, it was a challenge, as you'll see when Dr. Evans presents it.

And in primers 4, we took isolates of Pseudomondas aeruginosa and we asked the very simple microbiologic test, if you're resistant or susceptible to tazavi or ceftolazane tazo, if I use a rapid molecular diagnostic test and the three platforms we looked at were nanosphere, another nucleic acid based test in molecular beacons, can you actually predict this? Well, Scott will talk about the data, but what we decided finally to do in the primer studies is what are we doing right now is asking the question using the primers database from the isolates that were studied, 200 acinetos, 200 pseudomondas, 200 E. coli, how well could a clinician pick empiric therapy in the case of either E. coli or klebsiella in a bloodstream database model, and we're going to compare molecular diagnostics did to real data is how physicians practicing in the VA system treating 10,000 E. coli and 10,000 klebsiella isolates, how well did docs pick

empiric therapy versus how well do -- molecular diagnostics platforms can tell you what the right drug is and we hope that if you can put a rapid molec -- if you can show -- and this clinical trial will probably never be done -- but if you can show that once you have a positive blood culture and you apply a rapid molecular diagnostic test and you give the doc choices, either I keep him on the drug, I add a drug, or I take away the drug, or I totally mess up and I pick vancomycin, how well do I clinically perform versus how well does the doc in real life perform.

So that's sort of the algorithm that we're trying to do. I think Dr. Evans will be explaining some of the statistical analyses that support how we're going to try to get the best clinician thinking.

DR. EVANS: Good afternoon, everyone. Thank you very much for the opportunity to talk with you today. A few years ago, my friend, Dr. Bonomo, he said, Scott, you have a lot of problems. I'm going to try to help you out with some of them.

I've written you two prescriptions and he said, but I can only give you one because they interact and – but so you get to choose. So, the first prescription, it has an efficacy, it'll increase your intelligence, that's the efficacy. But it has a toxicity, it will decrease your good looks. He said, but the other -- the other one does the opposite, it'll increase your good looks but it will decrease your intelligence. Which one do you want? So, who wants the good looks?

Intelligence? In statistics we call that a missing data problem. So, I thought for a minute, and I said well, you know, I really don't have much to lose in either dimension, but I realize I'm a researcher and maybe I need all the help I can get, so I'll go with the intelligence. That's the best answer I could come up with. That's how I'm …

About a month later I get back the course evaluations from the course I was teaching that semester and I read them, and the first one said, I really enjoyed this class, Dr. Evans is an

excellent instructor, he's well-prepared, he explains things very well, and I really learned a lot. And I felt very happy that I was able to give this student a positive experience. Then I read the next one, and the next one said, I really, really like this class and besides Dr. Evans is hot, in capital letters. And I realized I was much happier about the second one.

So I went back to my friend, Dr. Bonomo, and I said -- I told him what happened, I said, you know, I'd really rather have the good looks and he said, first of all, Scott, you're a very shallow person and I really don't want to work with you anymore. And second of all, you're a statistician and you should know better. You had 40 students in that class and if only one of them said you're hot, it's probably false positive error.

So now Robert's very happy these days, the Cleveland Indians have won 20 straight games. I remind him that the Cleveland Browns haven't won since the world was flat.

Okay. So I wanted to describe our vision and

our strategy for the design analysis of the studies that Robert talked about. And the focus here is not so much on the results per se, that there might be some interest in that or on the methodologies, how we thought about this problem in trying to design and analyze it.

So I want to motivate this with primers 3, which was the acinetobacter study. And we looked at 200 strains, about half of them were susceptible to carbapenems. We were trying to evaluate whether we could predict resistance or discriminate between resistance and susceptibility to carbapenems. And the results were going to be based on the presence or absence of seven genetic targets and you see them there, Oxa 23, 40, 58, NDM, KPC, THM and IMP. The reference standard was MICs. Now, here's actually the data for imipenem and we -- I show you the data from two different platforms, that's a PCR on the left and molecular beacons on the right. And on the horizontal axis are the MICs. And so the idea is if the MICs are indicating resistance, which would be in the red-

shaded region, that hopefully you would be finding targets that would indicate resistance. But when you get to the susceptible, as determined by MICs on the left part of that graph, you would hopefully not be finding those targets, which then would be a good discriminator between susceptibility, resistance. So the coloring in the upper left, these would be sort of false resistance, down here we'll see, on the lower right, those would be false susceptibles. And you see there's a few more, again, PCR on the left and molecular beacons on the right. So, that's just to give you an idea about what the data look like. Now, our goal is really pragmatic, we were trying to think about clinical utility of using this sort of information. We're trying to help clinicians make better decisions, get better therapy for patients. There are lots of targets that get better with resistance, individual target analysis may be helpful, may be suboptimal, if there are way in which you can evaluate this in totality. So we were looking at the group of targets

together to try to figure out whether this could help us guide therapy. So, we came out with a couple of –- some terminology, susceptibility sensitivity, which is the probability the test result would give you a susceptible result when the reference standard is susceptible and resistant sensitivity. So, this is similar to your major errors vary and so forth. But we incorporate indeterminates into -- we sort of equate them with resistance, clinicians are going to avoid treatment if it's indeterminate.

And so if you think of things this way, this is sort of an analog to sensitivity and specificity in a traditional diagnostic setting. And once I have this analogous, I didn't know which to call sensitivity and which to call specificity, so I called it resistance sensitivity and susceptibility sensitivity. But it has an analog to sensitivity and specificity. And so, once we have that, I can summarize, on the left you see susceptibility sensitivity, on the right you see resistance sensitivities for the two

platforms, PCR and molecular beacons and for three different carbapenems. And so, you can see what the susceptibility sensitivities are when we start looking for these genes, what the resistance sensitivities are when we look for these genes. Now once we have sensitivity and specificity, we can also do things like predictive values and these are susceptibility and resistance predictive values. And I like to plot the predictive values as of function of prevalence because prevalence varies on the east coast and the west coast, and it will be different this year than next year and in order for you to really apply it, you need to know what's happening across a range of prevalence.

So the point here is not about what the result is, but the way we were sort of characterizing the problem. Now, how do we actually synthesize this information to try to figure out if we've got any clinical utility? And so we've been thinking about this problem about how do we – how do you synthesize this information in order to figure out

the true value of the test and suppose you take a very practical question, suppose there's two choices, suppose I'm choosing between molecular beacons and PCR, one has a higher susceptibility sensitivity, the other has a higher resistance sensitivity, which one do I pick? It's all the benefit/risk problem. So, we thought about how we would put some structure around this problem and try to analyze it. Now the key factors in this are, of course the magnitudes of the susceptibility resistance sensitivities, how big are they, what is the prevalence of resistance or susceptibility and realizing, acknowledging that this can vary place to place, it can vary time to time, it can vary over subgroups. And then, of course we have the relative importance of a false resistant result versus a false susceptibility result. What are the consequences of making those errors and is one more important than the other and if so, we would like to figure out a structured way to evaluate and -- diagnostics and incorporating that information. Now for many of

you, you're familiar with the term accuracy statistic that's basically the percent that you correctly classify and it's a nice statistic, ranges from zero to a hundred, higher score is a better accuracy. But it has two issues that we wanted to deal with, the first issue is that accuracy treats all errors as if they're equally important and they're not, not necessarily anyway. Ans so we wanted to build in a factor for differential importance of errors. The second thing is accuracy depends on prevalence and therefore it's not directly comparable between studies. If you go to ID week in a month from now and you see two posters, I've got a 90 percent accuracy and you've got and 80 percent accuracy, I beat you. Well maybe not, it may be we are comparing apples and rocking chairs because we have different prevalence, somehow we've got to -- if we're going to use that as a statistic to make comparisons we're going to have to level that off -- level the playing field. And we wanted to do that. So, we had written a paper last year called

bedframe which was benefit/risk evaluation for diagnostics and a framework for trying to evaluate this. And it took a very pragmatic view of things, trying to evaluate sort of global clinical utility of a diagnostic. We introduced this term, diagnostic yield, if you throw a diagnostic out into the world, what's going to happen? You're going to get some true positives, you're going to get some true negatives, true susceptibles, true resistance, but you're also going to get some false ones. And what's going to happen? And to try to evaluate the diagnostics based on that sort of idea. We show a lot of graphical ways of communicating the clinical impact of a particular diagnostic using this idea.

So, one thing we did in that paper was we introduced something called weighted accuracy and it was to try to deal with the two limitations of accuracy that I just mentioned. And conceptually the way you can think about is, it is accuracy but it adjusts for the relative importance of diagnostic errors. So instead of assuming they're

the same and clumping them together we're going to try to adjust for the relative importance of those errors. And still ranges from zero to a hundred percent, higher percentages indicating better accuracy. And I'm going to show you how it works. But in order to calculate it you've got to have different components and I'd like to just outline them and say a few words about each.

The first component is the resistance and susceptibility sensitivities. And you're going to get that from your study, you're going to estimate a susceptibility sensitivity, you're going to estimate a resistance sensitivity, you're going to get good estimates of that and that's going to factor in. Then I have to factor in what's relevant range, the resistant rate or susceptibility rate? And this could vary a little bit from pathogen to pathogen and again, over time and in different places. But if I can get a relevant range, you know, somewhere between 10 and 20, 20 to 30, whatever it might be, that would be helpful. Then we focus the weighted accuracy

around the relevant range. Then we're going to think about the relative importance of a false resistant result relative to a false susceptible result. I'll make a couple of comments about that. And then the goal is, so I calculate this weighted accuracy and give you a number, confidence interval. Is that a good number or is that a bad number? And so, we need to develop and idea about how I tell what's a good number and what's a bad number. So were going to rigorously evaluate each of those. So, the relative importance is an interesting and important thing to be thinking about. If we fail to identify resistance, that might be a more important error than failing to identify susceptibility, so in the case of Acinetobacter for example, if you fail to identify susceptibility, that implies that you may end up treating with something like colistin, which when something like imipenem could have been used. And that not necessarily optimal. Failing to identify resistance means maybe your treat with an ineffective imipenem when you could have gone

to something else. There may be some questions about how well colistin could have worked, but those are what you're facing. Now, ideally you would have some sort of contrast of, you know, what would happen or at least and idea of what would happen if I fail to identify susceptibility and what would happen if I fail to identify resistance and how important are those consequences in a relative sense?

Now, you may -- clinical data to sort of measure that is hard to come by, you may be able to get at it in some ways. But an alternative that we've been thinking about is we could survey experts about how important is a false resistant relative to a false susceptibility call in a particular disease area. An answer of a hundred percent would imply the two errors are equivalent, there's not any relative -- it's really not that different, but if you say 50 percent then that implies a false resistant call is half as important as a false susceptibility call. And that gives us some idea about how do we weigh the

relative importance of the types of errors that could be made.

So, how about, what is the goal? Well, in this world we have our problem where we treat today and we diagnose tomorrow, which is as a mathematician I can -- is not the right order. It's not the ideal order. Now, one thing to realize is the rapid molecular diagnostics, not necessarily meant to replace antimicrobial susceptibility testing. It's an add-on, it's to try to get, you know, can I get it to you two or three days earlier? You can still do your AST testing, I'm not necessarily going to replace it. The goals that we've been thinking about are can we evaluate whether our average weighted accuracy for a new test is better than a weighted accuracy, for say, what is the best random test. And there is a lot of different -- random test, flip a coin. Could be 50/50, could be 75/25, another random test is I assume everybody is resistant, another random test is I assume everybody is susceptible, or anything in between. And can I beat the best

random test, can I beat, essentially something that isn't providing me information? Or if there are diagnostic alternatives, can I beat that?

So, let me show you how this worked in primers 4, which was the Pseudomondas study. We had 197 strains of pseudomondas, we evaluated susceptibility resistance to ceftazidime, avibactam, or tol/tazo, and these were based on the presence or absence of genetic targets. You see there NDM, VIM, and IMP, KPCL, cefetol (phonetic), tol/tazo. And again, the reference standard of MICs.

Now, here's the data, you don't have to worry too much about molecular -- we looked at four different platforms so you see the four platforms here. So, what you see on the left side here is we're not identifying any of the targets so that means when the MIC is actually susceptible we're not finding any targets and so that's good. But when things are resistant, we do find targets for some but we miss a few. Alright, so we're missing something, we seem to be missing something in

pseudomondas. And in the other drug similar things are happening. Again, we're not finding targets when you're susceptible, that's good. We find some of the targets when you're resistant but there are cases where we are not finding some. We seem to be missing something, whether this is porins or something else.

Now, what that means is that if I calculate a resistance sensitivity and a susceptibility sensitivity you see -- so, susceptibility sensitivity is very high, we were getting everything right. Resistance sensitivity is a bit lower. Now is this good or bad? Well I can calculate – let's suppose just for a moment as an example that susceptibility sensitivity is half as important as resistance sensitivity, let's suppose it is half as important. And the prevalence of resistance is somewhere in a relevant range of 5 to 20 percent. I got that from the CDC report. Then the average weighted accuracy of the best random test is .78. So, the question is well, how do we do with this? Well, it turns the average

weighted accuracies are 90 or so here and 80 percent or so there, here are the confidence intervals. And I can calculate the P values of a test whether I beat the best random test, and so, that's what I get here.

So, out -- in there, basically, you know, the way we've been looking at it, is its sensitivity in resistance sensitivity sort of form the basis of evaluation of the building blocks. And we started to use this term average weighted accuracy, which provides a sort of synthesized and structured analysis that may provide the best overall measure of clinical utility and so we began to focus on that. And I'll stop there. Thank you.

MR. ROTH: Okay, thank you. Our last speaker before the public comment section, is Dr. Jean Patel, from the CDC. She'll be talking about efforts and resources for addressing antimicrobial resistance. Thank you.

DR. PATEL: Thank you. And specifically, I will talk about some of the CDC investments in

building laboratory capacity to detect antimicrobial resistance.

So, in the past year, we have been working with public health laboratories to build the antibiotic resistance laboratory network or the ARLN. This is a network of public laboratories that have enhanced capacity for detecting antimicrobial resistant pathogens and generating data necessary for our public health response to antibiotic resistance.

I'll describe the specific types of testing that we do in these laboratories, but basically the testing is done to fill the gap between the kind of testing done in a hospital to make a patient better to improve patient management. And the kinds of data we need to mount a public health response to resistance problem.

There is funding that goes from CDC to all 50 states and also to seven large cities for antimicrobial susceptibility testing. But, then more funding that goes to seven regional laboratories. These are laboratories that have

comprehensive testing, they serve all of the state within their region. So, those regional laboratories are: Wisconsin, Washington, the Minnesota Public Health Department, Texas Public Health Department, Tennessee, Maryland, and in New York, the Wadsworth Center.

We also, in this most recent round of funding that we just completed, awarded funding to the Michigan Public Health Department and this will serve as the National Tuberculosis Surveillance Center. In these laboratories, we provide testing for all of the antimicrobial resistant threats that are categorized as either serious of urgent. For resistant gram-negative bacteria, this includes characterizing resistance mechanisms for carbapenem resistant gram-negative bacteria. This is – Enterobacteria, ACA, Pseudomondas aeruginosa, and Acinetobacter. Much of this testing is meant to identify carbapenemase producing isolates and identify the mechanism. The carbapenemase gene in these isolates. It's also being used to scan for MCR-1 and the presence of that resistance

mechanism in the population of pathogens.

In all 50 states, we have the ability to do whole genome sequencing of salmonella isolates. These data are used to detect resistance in that pathogen and also perfor- -- generate molecular epidemiology data to identify outbreaks.

In four of our regional laboratories we perform reference antimicrobial susceptibility testing of neisseria gonorrhoeae isolates. The primary use of these data, are to generate treatment guidelines for Neisseria gonorrhoeae. This is a pathogen where all of the treatment decisions are based upon and empiric decisions. There isn't patient level susceptibility testing performed so these surveillance data a really necessary for guiding treatment.

We've also asked these laboratories to perform whole genome sequencing of up to 1,500 isolates per year. Right now, we're collecting these data as a way to correlate molecular resistance detection with phenotypic resistance and identify better tools for detecting resistance moving

forward.

Candida auris is a pathogen that has emerged in the process of standing up the ARLN. We've been focusing on how to best use this lab capacity to respond to Candida auris. These laboratories are asked to confirm Candida auris identification. This is a place where some of the routine methods used in hospital laboratories don't accurately identify the pathogen, so these public health laboratories can confirm identification, they can perform colonization testing, so identify patients who might be colonized and need enhanced infection control precautions or decolonization efforts in order to prevent transmission in a health care facility.

And these laboratories can now perform antimicrobial susceptibility testing of Candida special to identify when resistance emerges.

Mycobacterium tuberculosis we are using this laboratory to perform whole genome sequencing of a hundred percent of the isolates that occur in the United States. This is about 9,000 isolates per

year. These data will be used for rapid detection of resistance and also for understanding transmission dynamics.

We test streptococcus pneumoniae isolates in two of the laboratories. This testing is meant to identify vaccine escape strains. It is focused on detection of multidrug resistant streptococcus pneumoniae, this is way of -- it is suspected that vaccine escape strains will be resistant to multiple drugs and that this will be faster way to identify these escape strains.

We have one laboratory that is testing clostridium difficile isolates so it -- so this laboratory can perform culture, recover clostridium difficile and type these isolates using whole genome sequencing technology, we hope to use this help identify transmission dynamics for clostridium difficile and hidden reservoirs that could help with prevention efforts.

So, this new laboratory capacity is really focused on detecting new types of antimicrobial resistance, delivering data for preventing

infections, and delivering data for better treatment of infections. I wanted to give you a few examples: So, since standing up the ARLM we have seen an increased detection of VIM producing Pseudomondas aeruginosa. Carbape- -- Pseudomondas aeruginosa is a pathogen that can become resistant to carbapenems through multiple mechanisms but we want to know when a carbapenemase is present. Before we had the ARLM in place, there were few cases of VIM producing Pseudomondas aeruginosa, but since then we have identified an outbreak in a Florida long-term care facility. We've leveraged this laboratory capacity to support outbreaks in both Illinois and Florida, and that means identifying patients who are colonized with these pathogens and using this information to implement prevention measure to prevent transmission. And we've also identified isolated cases in Nevada, Texas, California, and Oregon. Two of the cases are associated with health care abroad. But no ongoing transmission from these cases. I should say that this example is an example that

illustrates how we combine these laboratory data with prevention efforts so in each one of the state we have also funded epidemiologists to focus on antimicrobial resistance and their job is to make sure these data are translated into prevention efforts within a hospital.

For neisseria gonorrhoeae this is a pathogen where the bulk of the susceptibility testing of the pathogen in the public health sector. And as I mentioned this is used to develop treatment guidelines. In 2015 the treatment recommendations were focused on providing combination therapy, ceftriaxone with azithromycin. Since we've implemented testing in the public health laboratories, previously it was really done in academic laboratories and it was kind of done on an annual basis, the results were accumulated at the end of the year and folks looked for any trends or any need to change resistance. Now that we've implement this in the public health laboratories, we've increased our number of isolates so we used to test 6,000 a year we are

going to test 20,000 isolates a year. In the test -- and we also improved our turnaround time, this is a dedicated level of activity that occurs. We're seeing an increase in azithromycin resistance since this treatment recommendation has been put into place, we are closely monitoring the increase in resistance that's occurring, the data from these laboratories are being monitored on a month by month basis. And there is a consideration in doing an early change in treatment guidelines based on the data that we get.

And as I mentioned earlier Candida auris is a pathogen that is causing health care associated infections. These are outbreaks that are very hard to control, the pathogen can colonize both the patient and the hospital environment and both of those reservoirs are sources for transmission within the health care facility. We've seen a number of outbreaks in New York and now this is spreading to New Jersey as well. This laboratory capacity is pretty new but the New York laboratory

was ready to stand up and start supporting detection and outbreak response for this pathogen. So, they're focused on supporting the outbreaks that are occurring in New York. Right now, the CDC laboratory is supporting all the testing that is occurring from New Jersey, but in this last year of funding we ask for all of our regional laboratories to stand up Candida auris testing because we anticipate this will be a significant need moving forward.

I also wanted to tell you about a pilot program that we want to implement in this lab network. And this is antimicrobial susceptibility testing of new antibiotics. This is a program that was meant to address a need and this is the gap between the approval of a new drug and the availability of testing methods in hospital laboratories. The immediate method we can use for antimicrobial susceptibility testing when a drug is approved is reference broth microdilution testing. But it's hard to implement reference broth microdilution testing in multiple

laboratories, we feel this is a necessity, we need to fill this gap because this lack of testing can result in underuse of a new antibiotic; it can also result in overuse of a new antibiotic and this kind of testing should improve stewardship so, that the patients who really need these drugs can get them. The testing will focus on the most important bacteria for us which are the pan resistant or nearly pan resistant bacteria and we feel like we can adequately leverage this laboratory capacity for this reference broth microdilution testing and also infrastructure that we put in place for electronic test order and reporting.

One of the types of testing that I didn't mention was the CRE colonization testing, this is being done to support outbreak detection. For this kind of testing to work well, we need a rapid test order and reporting system in the hospital laboratories and so we're using e-tor or a cloud-based system so that any hospital facility can order this test and then the public health

laboratory can report the results back to the submitting hospital, it doesn't really matter that these are in different states. In fact, the local state -- health department gets the result at the same time, that way we keep everybody in the loop, no one feels like they're being left out.

So, this whole system of reporting is being put in place, but if we're going to do susceptibility testing of new drugs, we need a similar method for rapidly ordering and test and delivering a result to the health care facility because this testing is meant to change patient care.

And again, we want to focus this testing on the most resistant bacteria. This is a case that was reporting in the MMWR, it's a case of 70-year-old female who was hospitalized for an infection in her hip. This patient had received health care in India prior to this admission in the U.S. The infecting isolate turned out to be an NDM producing klebsiella pneumoniae, it was pan-resistant. The patient developed septic shock and

succumbed to this infection. There were no antibiotics that were effective against this isolate.

We expect that cases like this will continue to emerge.

But delivering reference broth microdilution testing to a bunch of public health laboratories that are pretty new to broth microdilution testing is a challenge. We think that this technology that has been described by James Kirby for antimicrobial susceptibility testing can help us. This is a method, a digital dispensing platform for Atwell broth microdilution testing, it turns out digital dispensing platform are fancy words for a Hewlett Packard inkjet printer. But this is a way of dispensing drugs into an MIC panel. A very precise dispensing of drugs. So, to make an MIC panel essentially a technologist needs to thaw a suspension of the drug deliver it to a cartridge that can (Indiscernible, 3:53:13) drop it into MIC panel. You've now created a reference broth microdilution panel for susceptibility testing and

Dr. Kirby compared these panels to frozen panels that are made in the more traditional way and he found great correlation.

So, we're calling these on-demand MIC panels. This is a technology that we can use at CDC to develop a panel and then actually roll this out to the public laboratories just deliver them with a file on how to print these panels in-house. This overcomes a lot of our technical hurdles with placing reference broth microdilution testing in these laboratories, it's hard to ship a frozen panel. These have to be shipped on wet ice because dry ice changes the pH and then you have altered drug susceptibility results when the panel gets there. I should say, at CDC we make our own frozen broth microdilution panels and we considered this idea of just making them there and shipping them out to the public health laboratories but this wet-ice issue is a big problem. This way we really just have to make sure that these laboratories have the drug powder and with a protocol and that drug powder they can

essentially make an MIC panel without much technical expertise. We can link this up with a biomic reader which will read the MIC endpoints and this really automates a lot of the reference broth microdilution testing for these laboratories.

So, we think this is an important application for testing pan-resistant pathogens. It's also a way of collecting a lot of important data for break point decisions. AT CLSI, when we make break point decisions it's based upon the reference susceptibility testing results and so this will be a rich source of data for those. And again, we can leverage our infrastructure for test order and reporting so that the turnaround times are quickly as possible. Essentially the laboratory can receive an isolate on one day, test it the next day, and send out a report that same day to the hospitals.

So, to sum up the ARLN, these are our regional laboratories – or the bulk of the testing is done in regional laboratories with comprehensive

phenotypic and genotypic testing capacity for urgent and serious pathogens.

The goal of testing is to detect new antimicrobial resistance to prevent infections and to improve treatment of infections. The testing menu is flexible and it can be adapted in response to changing AR threats.

And this has been mentioned previously at this meeting, there is a CDC/FDA antibiotic resistant isolate bank. This is a bank of curated panels, we have 14 panels and these panels consist of isolates that CDC collects through surveillance programs through the ARLN, through their reference testing programs at CDC, we have a rich source of isolates, we put these into panels that are meant to challenge a specific diagnostic question such as carbapenemase production, implementing carbapenem break points on a device. We've worked with several companies to have panels for implementing new break points for new drugs. In the AR bank, these have been some of our most popular panels. We -- this bank is relatively

new, I think, it's two years old, we've had 637 orders that have been processed, 571 customers. We just completed a customer survey, we had a lot of great ideas on how to improve on this AR bank, some of those were already in process. In December, we're going to launch a new website that should be much easier to use, we're always looking at our ordering process and making sure our turnaround times are on track and that it's as simple to use as possible.

We have some limitations, one of them being, it's hard for us to ship these overseas. We have a robust process for identifying whether a recipient laboratory can use these isolates safely. That's a huge issue for CDC, it's hard enough for to do that for the U.S. but then for the whole world it becomes very hard to do. When we look to ship these overseas, we are really looking for a partner who can – who can do that assessment for us and identify whether a recipient laboratory is appropriately -- is an appropriate recipient and really take over the risk of sending

these to a laboratory that cannot use these appropriately, so we can do special contracts that would transfer that risk to another group such as the minister of health within a country and they could disseminate isolates within their country, if that's appropriate.

So, a little bit more about our customer service. Survey results, we found that these isolates are used equally by clinical laboratories and commercial laboratories. Commercial laboratories here mean patient care laboratories as well as researchers and developers of products. So, it's almost a 50/50 split between these two groups. Folks like the resource that we're providing; we want to make sure the panels we're put in this are the most important panels and are the panels that the customers really need, so we're looking for that kind of input.

And I'll wrap up by referring you to a website where we describe other CDC investments in antibiotic resistance. This is a website where you can hover over every state and see exactly

what CDC is funding for antibiotic resistance in that state. The activities here include not only state based detection and prevention efforts such as I've described, but also research for developing new ways to detect and prevent antimicrobial resistant infections. Thank you for your time.

MR. ROTH: Thank you, Dr. Patel. I think now we're going to have the public comment which will be moderated by Patricia Conville.

MS. CONVILLE: Hi everyone, I have the pleasure today of introducing several attendees who indicated they would like to speak during the public comments section. First, we'll have Dr. Roger Echols, he's a consultant for Shionogi and his role as infectious disease drug development consulting and he's going to talk to us today about the use of rapid diagnostic devices for pathogen target clinical trials.

DR. ECHOLS: Thank you very much.

This most recent talks have been both fascinating and very pertinent to some of the

comments that I have, so you're all warmed up. But anyway, thank you, my name is Roger Echols, I've been conducting anti-infective clinical trials for over 30 years either as an investigator with pharma and now, as a consultant. Most recently the focus has been on the development of antibiotics for treatment of multidrug or extended drug resistant gram-negative infections.

We find ourselves conducting off-target clinical studies, in order to meet rigorous evidence of efficacy. By design these studies often exclude the very type of resistant infections for which the drug is intended to be used. Alternatively, so called pathogen focus studies where infections are caused by MDR/XDR pathogens are notably difficult to enroll and are highly confounded. The irony is the patients are out there and the tools for highly specific patient selection are available. I'm speaking of rapid diagnostics both molecular and biochemical, devices which have been developed primarily for the identification of resistance mechanisms for

infection control purposes. Some include direct patient sampling from lower respiratory tract or urine sources or directly from positive blood cultures. Many of these devices are low tech while others require affordable machines which are suitable for clinical trials. I know this because I've conducted clinical trials where PCR device provided evidence of staph aurias wound infection. The results enabled the study to enroll more than 90 percent of the patients who had ultimately positive cultures for the target pathogen.

It's important to note, however, that the device did have FDA clearance for this purpose and was not considered investigational. Identifying carbapenem resistance in gram-negative infections when mediated by carbapenemase hydrolosis is highly sensitive and predictive of phenotypic carbapenem resistance. However, the same devices that are cleared for infection control purposes are considered investigational when treatment decisions or enrollment in clinical trials are involved. And while CDR and CDRH have been very

cooperative in reviewing devices integrated into clinical trials. There remains a major obstacle, the require of patient informed consent before the diagnostic device can be used for patient screening.

The regulatory argument put forth is the use of rapid diagnostic devices, off label, may result in a patient receiving a treatment that might be more toxic than what otherwise be used, for example: the treatment may involve a polymyxin if carbapenem resistance is detected. Now a negative result due to mechanisms of resistance not related to carbapenemases might result in inappropriate treatment.

The counter-argument is, that a negative results is not a declaration of carbapenem susceptibility, it only results in the patient not being related to the study. They would still be treated with standard of care, the potential benefit they could receive more appropriate treatment from specific available days before otherwise known. So, when used in the context of

a clinical trial when both treatment arms are optimized to treat resistant pathogens, a positive test would allow the patient to be considered for the study when negative test results which would not impact what would be, the usual treatment.

The key is to allow a waiver for the use of commercially available diagnostic devices, to authorize such that written and from consent is not required prior to screening. This would greatly enhance the ability to enroll the appropriate patients, these tests would involve clinical specimens already being collected as part of usual care, and if the screening results were consistent with protocol eligibility there would still be a need for informed consent before randomization of treatment was initiated. But the screening failure rate which is expected to be very high would not be so onerous. Frankly speaking the requirement for informed consent for screening for a study requiring randomization within 24 hours is an enrollment killer.

If we want to know how are new antibiotics

work against MDR/XDR pathogens, we need to enrich our patient studies in an ethnically consistent manner. The delay in phenotypic susceptibility testing means patients will be treated with days of possibly effective antibiotics thus making them ineligible. And the consequence, we only enroll treatment failure patients. There are many reasons why this is not desirable, only by incorporated in rapid diagnostics devices will we be able to rigorously and efficacy and safety of new agents. Thank you.

MS. CONVILLE: Thanks Dr. Echols. Next, we have Dr. Damon Getman, he's the director of research and development at Hologic and he's going to talk to us today about gonorrhea screening and antibiotic susceptibility testing, strategies for surveillance reporting and test algorithms.

DR. GETMAN: Thanks very much, it's really nice to be here this afternoon.

What I want to share with you some thinking we've been doing for resistance testing for gonorrhea and screening. As opposed to testing

for resistance on the individual patient screening presents screening unique challenges because any small deficit and device performance leads to huge gaps or deficits in clinical accuracy. So, if you realize it's a whole different ballgame and when you're talking about gonorrhea screening in the United States there about 37 million patients screened ever year. The prevalence, of course, is less than percent. And so, you run into problems associated with device performance and the real key is how do we detect gonorrhea infections that have evolving resistance profiles when there's such an exceedingly low prevalence in the population and at the same time using the same tests that have had appropriate safety and efficacy review. So, Hologic, we've been involved in the screening gonorrhea for almost 20 years, we do about 85 percent of the gonorrhea screening in the United States which is about 31 million patients each year. So, as we think about this, especially resistance testing, people tend to get a little week in the knees and need to sit down

because of the challenges involved and one of these challenges is again, how did we do accurate detection of resistance phenotype and in a screening population? And the problem you run into is the resistance phenotype prevalence is extremely low .01 percent .1 percent of the population. So even for a test that has 99 percent specificity, you can end up with a positive predicted value of 9 percent. So, that's one true positive every eleven test positives. So that's clearly not adequate in terms of clinical accuracy. Second problem we run into: How do we deal with this continuing, evolving resistance mechanism for a niciera we know this is going to happened niciera is very good at this and the problem with this or this evolution of resistance, could occur faster than the normal development cycle of these diagnostic tests. A development and review. So, we need to find a way to accommodate both these challenges. So, we think the best way of doing this is having existing cleared screening test and then a reflex test for

the resistance testing. And this resolves both of these constraints, we think. You can vastly improve the positive predictive eye if you're only testing the screening positives. There's certainly issues about reproduce-ability that creep in but that's certainly better than using a resistance modality in a screening mode. And a reflex test. And a reflex test can also be developed and validated much more quickly and much more cheaply too. Which is a key factor for industry.

So how -- what would be the best way to implement a screening test, reflex test, algorithm? Well, certainly when you thinking of the component of this is to have some kind real time reporting or resistance results by a laboratory to the CDC and that's also shared with those of us in industry. We need to keep track of this on a national basis, preferably in real time so we can adapt and develop new tests without significant delay.

We need to have centralized laboratories

involved in this reflex testing, I've listed the sites here, but as Dr. Patel just mentioned I think the ARLN network would be a good candidate for this because we need to correlate molecular test results with culture MICS values and sequencing results. We cannot divorce these molecular tests from those other methodologies. And we need to have predetermined thresholds of what constitutes failure of these reflex tests. WE can't decide after the fact, oh, things are starting to look bad, what does this mean? I think we need to decide up front, when we reach this point of escape units -- mutants where these tests are not detecting, that it's for manufacturers to revise these new tests and revalidate them.

So, with this background what kind of data could be included for premarket review. Well, certainly a perspective clinical study as we're used to doing is – be enormously large and huge take a long time. So, the alternative would be to use and established panels and look at analytical

performance with some understanding that there could be some risk for false negative results and clinical testing.

Post-market surveillance, we think is going to be an important component of this and our suggestion is the foundation of this should be special controls regarding annual testing, perhaps even emergency analytical testing with specialized panels, we need to follow the performance of these tests on a regular basis and one model might what's done for influenza testing, for rapid antigen tests, and for molecular tests where CDC provides characterized strains and these are looked at in terms of clinical performance for the devices on a regular basis. If there is poor performance of a particular strain then these could be covered by a special typed in (inaudible) to revise the labeling. Thanks for your attention.

MS. CONVILLE: Thank you very much. Next, we have Dr. David Perlin, he's the executive director and professor, public health research institute,

New Jersey Medical School, Rutgers dical and Health Sciences. And he'll talk about the molecular profiling of antifungal drug resistance.

DR. PERLIN: Thank you. Okay, the overall message I want to deliver is about unmet medical need with respect to antifungal testing. Of course, without getting into all the details of why we need to do this. Very high global mortality, and the reality is we have to treat, we have to treat these infections and to treat them we have to diagnose them. And of course, candida infections being one of the major bloodstream pathogens with very high mortality and like bacterial infections, the faster you can diagnose the faster you can implement antifungal therapy the better your clinical outcome. And that's the bottom line here is we have to push things closer into this realm to be able to do this sort of testing. The big problem with antifungals is that we have very few antifungal classes. So, if you lose a single class you're in trouble, if you lose 2 classes you're really in trouble. And in many

cases we've lost all three -- we've lost all three of the main classes of the systemic antifungals that we need.

Now you say if you look at the landscape of antifungal resistance, you say 1 or 3 percent these are surveillance this is for echinocandins, this is population based studies 1 to 3 percent, not such a big deal. But if you got to individual centers, high-risk centers, transplant centers what you'll see is that resistance can be as high as 10 percent, 12 percent, 15 percent in some cases, in some cases higher. And then if you factor on top of that in many of these center, not only to we have very high resistance for some of the azoles but – as well as the echinocandins now we have multidrug resistance including the polyenes and you have in this case for this very large center 7 percent of their islets. Which are completely drug resistant effectively untreatable. This is really unacceptable and we don't – the problem is in most places we're not even doing susceptibility testing. So, we're treating

empirically and, you know, we're making the best guess. We don't need to do that, we have, in fact, a tremendous amount of data which links specific mechanisms -- molecular mechanisms to resistance. So, here's the case of the echinocandins, we have two hotspot mutations, this has been known for a number of years, these confer resistance if you look at -- and we've been running now an echinocandin reference center for the last 10 years for and I will tell you we get a thousand islets in, they get referred to us from chemical laboratories, they say their resistant, 25 percent are resistant of the ones that get referred to us. So, there's a big problem in terms of susceptibility testing even from very, very qualified labs. But what you can see is that 90 percent of our – 90 percent of the resistant mutations actually occur within very, very few alios, so we can do profiling of this very easy. This is for candida. Albicans this is candida, glabrata which is a more significant problem with respect to the echinocandins but again the number

of mutations are really rather limited and the cluster, so you could easily account for 75 or 80 percent of it with just a few alios. In each case, we know, and has been demonstrated in a number of clinical studies, that this mechanism is a better predictor of clinical outcome than the susceptibility, than the MIC testing. Largely because break points have been pushed so low and many laboratories just can't adequately perform the susceptibility testing. And then from a molecular profiling standpoint this is an absolute joy, these are the that you have to be able to detect from the sequence. It's very limited, the amount of sequence you have to build into a platform. And you can easily dist- -- this is just a real-time melt curve. But you can easily distinguish these profiles. So, where you have a single mechanism of action and its very tightly linked resistance, this is really -- this is what you want to be able to do. And the case of the echinocandins this FKS mechanism is very easy to detect and it's very, very good in error, minor

errors and major errors for MIC testing based on whether there's a genotypic presence of an FKS mutation, so why not profile it directly.

Okay, thirty seconds I'll give you Aspergillus another major problem, global problem, we have acute disease, we have chronic diseases, CPA and allergic diseases. In many cases and certainly for the first two, we're treating with antifungal drugs. It turns out that for resistance, this mechanization their due to the use of environmental azoles, initially in Europe but now spreading now worldwide, I'll show you in a minute. If we can detect these we account for 90 percent of the resistance, certainly in most of Europe and now into Asia, and you can see it here as this mechanism.

Profiling, Molecular profiling for easel resistance. And these are now first line drugs voriconazole, posaconazole, that's what we need to do to provide rapid information from the clinical labs. And I'll just stop, thank you very much.

MS. CONVILLE: Okay. Last we have Dr. John

Rex. Gosh, he has a lot of hats that he wears. He's the chief medical officer for F2G Limited, chief strategy officer for Carbex, expert in residence for the welcome trust and operating partner for Advent Life Sciences. And he's going to talk about the challenges of new drugs and AST devices in a fast changing world.

DR. REX: So many thanks to the organizers for the opportunity to talk. By way of context, I'm an ID trained internist and my -- with about 30 years of drug development experience. And everything I do professionally is really focused on the twin problems of bringing new drugs into existence and ensuring that we have the tools that we need to use them and sustain them in the clinic.

So I want to extend today's conversation by speaking briefly on three themes. First, the future of antibiotic development points to the central nature of the measured MIC rather than the interpretive category. From my perspective, I see a number of new drugs coming forward. There are

various pipeline reviews if you want to look at them.

None of these drugs will be perfect and we're going to require tools to help us choose among them. Importantly, these new drugs will often be approved using smaller clinical development program in which preclinical PK/PD has been a key in the approval of the drug.

And this reliance on PK/PD increases our reliance on the measured MIC denominator that runs through the whole program. Actually, Amy Mathers pointed at this before lunch when she noted that she would want to know an MIC so that she could decide on the drug or the drug dosing regimen. I agree with you.

This is my one technical comment to those who are making choices about how to fine tune our approach to past GARP and whatever other acronym you, is that you really should focus steadily on the critical nature of the essential agreement of the MIC. We're going to continue to struggle with the fact that BMD can't demonstrate category

agreement with BMD. So let's actually focus on the marvelous way we can actually make essential agreement work.

And this is also a message to past and GARP developers. Going forward, there will be a continued and probably growing desire to have a numerical MIC that links back to the MIC used to decide a PD driver for the drug. So just think about that.

My second big theme is that we as a community need to do a better job of talking about the value of AST testing. Money isn't everything, but reimbursement and lack of reimbursement does drive behavior. And by way of context, let me point at the way that with antibiotics we have been thinking about this through a group called Drive AB and other activities, we now have a new language for thinking about antibiotics. And specifically, we often talk of antibiotics as being the fire extinguishers of medicine. And this is an analogy that works well in a number of levels. Fires and infections move quickly. You

need the fire extinguisher or the antibiotic on hand, and if you've got that fire extinguisher, you put on the grease fire in your kitchen and you order takeout. Without the antibiotic, you may die.

So now let's consider two questions. First is how often should you pay the firemen? Is it per fire? No.

The second question is, how often have you personally used a fire extinguisher? I want you to think carefully about that one. Because your initial answer, you'll probably say, well, actually never other than in fire safety training. The actual answer is you've used it every day. You're using one right now because are you in a building with other people that you hope doesn't burn down? So you're using -- you're relying a fire extinguisher every hour of every day. And this fire extinguisher analogy shows us that antibiotics have a value in existence that is not captured by the way that we buy them. In economic terms, antibiotics play off what's called a

positive externality. Merely by existing or the fact that if I use an antibiotic to treat my infection and you don't get sick with my resistant bacteria, actually you've gained something by way of the thing that I purchased.

So where does this take us for AST and diagnostics? Well, they key analogy here to develop is that these tests that we've been talking about are kind of like the fire chief who decides how to fight the fire. As Jean Patel just noted, lack of access to susceptibility data may lead to both underuse and overuse of new agents and old agents.

Hence, we see that AST development actually has a positive externality just like antibiotics, and the cost of the test that enables us to use the right antibiotic needs to capture that.

So today's discussion really makes it clear to me we need to spend more time on this in public, and I'm not sure of all the ways to move this forward, but I can say we are engaging with this conversation. Tomorrow's Pat Carr report will

point at this as will the value DX project that Mark Miller of bioMeerieux is leading. And if you don't know Mark and you don't know about value DX, find him at the break, or I'll point you at him.

Stay tuned on this and contact me if you've got some good ideas here.

Finally, my third and final theme is that I'd like to thank our agency colleagues for their steady efforts to lay the foundation brick by brick - I love that analogy - that will allow us to improve our approach to this area. AST testing is critical and it must be available to support the practical choices that balance how we use drugs and we have to find a way between the perfect and the merely good. And I'm grateful for the discussion and for the steps we've taken today. Thank you very much.

(Applause.)

MR. MILLER: I'm sorry, but we had arranged for some time in public session and I guess there was a snafu.

So my name is Mark Miller and I'm the chief

medical officer at bioMeerieux. And first I'm going to apologize, I have no slides, so you actually have to listen to me as you did to John Rex, who didn't have any slides either. So thank you, John.

So I would like to thank the FDA for the opportunity to address the agency and the attendees today.

BioMeerieux is a global company that supplies a large part of the world's AST testing platforms and assays. As such, we have a tremendous ongoing interest in diagnostics and specifically the use of AST methods for measuring, preventing and controlling AMR around the world. A significant portion of our revenue is invested annually back into AST research and development. This R&D money is used for two major objectives. One is to improve the AST methods that we already have available in our current offer, and then the other part of our R&D efforts is to innovate and create new methods for reliable AST determination.

So I'd like to make some key comments on these

two objectives because putting money back into modification of our current offer and all of us in manufacturing in the IBD business, putting money back, it may not be the sexy stuff that you've seen on the screen, but it's the bread and butter of what goes on every day and it's the majority of our R&D investment is into tweaking and improving the current offer that we have for AST testing.

There is a small part, and another part of R&D that goes into innovation, the sexy stuff, though it's stuff that you hear about it, the molecular, the sequence-based, all of the ARPs that you heard about. But essentially tweaking what we have already have is faster, it's better, it's a better way to get the useful information to the clinicians and to the patients.

But in both instances, we're trying to improve the speed and accuracy of AST. The continuous emergence of new resistant pathogens which you've heard about, novel resistance mechanisms which will continue to appear, new antibiotics, and you've seen the acceleration, regulatory

constraints, which are impressive. I know that this is a U.S. centric meeting today, but a global company has to deal with China FDA, we have to deal with CE marking, we have to deal with new regulatory agencies popping up in Africa and in parts of Asia. So we have to deal with all of that in order to get AST results around the world available to clinicians and to patients.

So keeping in mind our constant attention to patient safety, this is quite an onus and quite an objective.

We'd like to -- we'd like the FDA to consider timely and effective implementation of the 21st Century Cures provision - you've heard about this - as they relate to AST assays, especially as they relate to breakthrough devices provisions, the recognition of standards provisions and lease burdensome device review provisions. We also encourage provisions which allow the FDA to update breakpoint data in a more timely fashion, thus reducing inappropriate antibiotic use. And you heard about all this this morning.

We'd also like the FDA to consider the application of the agency's replacement reagent and instrument family policy, the so-called RR policy, as it relates to AST devices.

Alternatively, consider to develop specific AST policies that are similar in spirit. This would facilitate and speed up the continual addition of new antibiotics, changes in breakpoints and instrument family extensions to existing established instrument families that we have.

In terms of industry FDA interaction, we would ask for earlier and increased interaction. And you've heard about this this morning as well, with the agency to develop new or significantly revised technology assessment. There's a precedent for establishment already of industry FDA working groups to develop or modify significant FDA guidance documents and to work with the trade organizations, of course.

All of this would allow manufacturers to more quickly accommodate newly approved antibiotics and

to adjust breakpoint changes.

We would also request that the FDA align their AST acceptance criteria with SDOs, as you've heard about. And there are multiple SDOs such as ISO, UCAST, CLSI, USCAST. And to deal with the issue of what happens when these SDOs have different guidelines and different breakpoints.

So more importantly, we would like to see some accepted pathway when SDOs do not agree with each other. Global companies like us, with global clients, have to please everyone and we wind up pleasing no one.

A special mention should be made of newer innovative technologies for AST. New technologies have appeared that allow the use of novel methods, as you've heard, and novel ways of determining AST. They often require significant investment, and we'd like to propose more collaboration between the FDA and industry, those of us who manufacture, the CLSI, UCAST, et cetera.

Currently we are operating with limited understanding of what the agency wants us to prove

in terms of equivalency between existing methods and the new technologies, which in many cases discourages many of us from investments in this field.

A starting point would be to pilot some new technologies with FDA and to interact very closely with them. And as a final related point, we believe that there are increased opportunities and funding for FDA staff to participate with industry in order to provide training to FDA staff, particularly with respect to new technologies. Examples would be successful initiatives such as the FDA vendor days and the experimental learning program, or ELP.

So we hope that these comments have been constructive and they've been thoughtfully constructed to aid in a joint collaboration between the two of us.

And thank you very much.

(Applause.)

MR. ROTH: I know we're a little bit behind schedule, but I think it is worth it to take maybe

just a ten-minute break. So we'll see you all back here at 3:40, please.

(Break.)

DR. GITTERMAN: On the telephone we have Karen Bush and Shawn Lockhart; is that right?

MS. BUSH: Correct.

DR. LOCKHART: Yes.

DR. GITTERMAN: Good. Anybody else on the phone? Good. That's good.

And why don't we go very quickly, our time is limited. We are going to finish at 5:00 despite the fact that takes some time off the clock. But maybe we could go from the far right, or my far right here and just introduce yourself very briefly.

MR. KIRN: Tom Kirn, Rutgers University.

MS. CASTANHEIRA: Mariana Castanheira, JMI Labs.

DR. DUNNE: Mike Dunne, bioMeerieux.

MR. BONOMO: Robert Bonomo, Cleveland VA.

DR. LAU: Anna Lau, NIH.

MS. SHARP: Susan Sharp, Kaiser Permanente.

MR. PERLIN: David Perlin, Rutgers New Jersey Medical School.

MS. SIMNER: Trish Simner, Johns Hopkins.

DR. GITTERMAN: Okay. We are four questions to discuss, and we're going to hopefully go through them relatively quickly, but these aren't multiple choice answers, so they may take a little while.

And I do just want to make a comment. I'm an impatient person. I've waited my whole life for air cars and they're not here yet. And I'm more impatient now. I look at these things and say why aren't they solved, and I'm with a bunch of impatient people because industry has to be impatient. They have to get things out or they don't have jobs, or, you know, the company loses money. So we have to come up with answers, and we have to be able to move forward. But, in fact, the paradigm, and we should all be thinking about how the paradigm has to change. Because we clear a device, then we say it works or it doesn't work, but we all know that's not a hundred percent. And

we all know the day that that device is cleared or approved, there's going to be a ton of data that comes out from -- you know, for the rest of time that's going to significantly impact the use and the value of that device. Again, a device that has a hundred percent sensitivity and specificity may change dramatically overnight, a molecular device, if a new mechanism of resistance comes out.

So we need some ways -- again, the discussion earlier this morning, 300, these many fresh, these many stock, but the minute a device is sold, there's going to be more fresh than you could shake a stick at. If we had different models, perhaps, of the evidence and how we acquire it.

The word we always use at the agency is total product lifecycle. How we could move these and integrate the kind of information Dr. Patel is getting in the different laboratories in the ARLG. We could do amazing stuff rather than the way -- the static way we look at it now. And we're going to get to that question 4, I hope.

But question 1, the identification of MDR organisms directly from clinical specimens may be critical for appropriate patient care. However, relationship, as we've heard quite well, between the presence of genetic resistance markers and the phenotypic expression of resistance is fairly complex for certain drug organism combinations.

So -- now there's a -- there's a method to our madness. And to move quickly, I'm not going to explain the context of the question, but feel free if the panel has any questions why we're asking this, and it's not obvious, please stop me. But can the panelists please comment on the appropriate reference method to assess performance of molecular investigational device. And we saw that this morning. Is it another molecular detection? Is it a phenotypic AST? Is it the epidemiological cutoff? A lot of things to think about.

Additional considerations related to polymicrobial specimens. What do we do about a complex -- stool is complex while we're picking

out a pathogen. What about sputum? Very different. Skin? Not so difficult, but also perhaps polymicrobial.

And the third one is what about the need to quantify bacterial load in a clinical specimen? And, again, sputum is the perfect example of that. Right now all our processes are dependent on the microbiologist. He or she looks at a place -- excuse me -- looks at a plate and says, you know, we'll report those three, but the rest of it is not worthwhile. Well, that's normal flora. We don't have a microbiologist to look at the molecular plate. There is no molecular plate. So now it's a completely different paradigm. It's very diff -- or it's a different phase of quantifying bacterial load, especially in polymicrobial specimens.

So why don't we start at the far end, and please.

MR. KIRN: Sure. I was a little nervous about sitting all the way here at the end because I knew this was going to happen. But, you know, there's

a lot of questions here and this can go in a variety of different ways, I think.

I'm going to keep my comments relatively short to leave some meat for everyone else to talk about. But I'll first address the first question, the appropriate reference method. And I guess you could expand this to consider whether you're talking about, you know, a diagnostic device that's going to detect a pathogen versus a device that's designed to predict susceptibility and resistance. And if we go with the latter, which I'll focus on, I think -- I think there's a few things that we have to consider. And one that we really haven't talked about too much today that I'll put out there for consideration is the idea that, you know, while we have lots of information about using MICs to decide on appropriate antibiotics for infections, I think we're starting to learn more and more about specific resistance mechanisms and how, even though, you know, the MICs may suggest a good outcome, the resistance mechanism may play, you know, an additional role

that we have to consider.

So it may not be enough just to know a correlation with MIC, it may be that we need to know both MIC correlation as well as the, you know, presence or absence of molecular mechanisms. And so that may drive the way that we decide to develop these assays. You know, for example, using kamers, which really don't define resistance mechanisms versus platforms that actually identify resistant mechanisms like in the primer trial that we heard about earlier today.

So just -- that's my thoughts about that. I mean I think that right now what we're driving for as far as a reference method for -- to assess performance for molecular susceptibility prediction is -- or resistance prediction is really the MIC and broth microdilution, but I think as we learn more about the relative contribution of specific mechanisms to outcomes, we may -- we may expand that and it may be multifactorial.

And then just a couple brief comments on

polymicrobial specimens. I think you've already alluded to the idea, and I think this is related more to the detection of pathogens, you know, that I think it is going to be important in that context to have quantification associated with detection and relative quantification in many cases, especially in sputum specimens, for example, as you've already pointed out.

And I think that -- I think I'll stop there and I'll ask the other panelists to fill in the gaps, because there's a lot, there's a lot here to talk about.

MS. CASTANHEIRA: Mariana Castanheira from JMI Labs. So I agree with Tom that we need a multi-result approach. Like you have to have the genetic detection off of that gene, plus the phenotypic information because the gene can be there and not be expressed. So you need both of them.

And Kimberly, in her presentation, talked about that method that is like a composite method to prove how you can have multiple results for

different methods, then come up with a conclusion of those methodologies. I thought that was very interesting.

So about poly -- my answer is pretty much the same for the two last questions. If you have an organism colonizing or a load, you need to -- you need to think about the -- what's the impact if you -- the organism is not causing the infection, and you use an antimicrobial agent and that organism is the one being selected, that might be your next problem, that you were -- instead of a colonizer, now you have an organism causing infection.

So that -- the CLSI methods they say the table that they construct about how to select the correct answer. It's like the conservative ends choose resistance because if the gene is there, you might have transferred to other organisms or you might select for that bug.

MR. BONOMO: I'll make a comment from the clinical side on the consideration of polymicrobial specimens.

In some of the platforms that I've had opportunity to work with some experts, at first, you know, the consideration colonizer or infector is still there. And with time, I've decided to think outside the box in this particular issue. I'm not really sure I understand what a colonizer really is after a while. And I think that what I would like to challenge the diagnostic companies, help us understand what those polymicrobial infections really mean.

As we began to learn that there's significant cross-talk between certain bacteria and candida species in the lung. There's significant communication between one pathogen and another. In abdominal infections it's very clear that more than one pathogen is expected and sometimes those organisms are synergistic in their virulence.

So what -- instead of looking at this as a problem in microbial detection, I think it should be an opportunity for us to think, you know, let's try to understand why these organisms are all here. And I think the advent of nucleic acid

testing in this area, you'll find genetic evidence of things that are not grown in the laboratory. And maybe it's because those organisms are there, very difficult to detect by conventional mechanisms, but present by molecular techniques, maybe they'll give us the reason why no matter what we do, we can't improve the outcome of infections of pneumonia even with our best antibiotics and helping the host.

DR. DUNNE: That was Dr. Bonomo, whom I'm going to ask for a prescription for intelligence at this point.

(Laughter.)

DR. DUNNE: No, I think when we're -- pardon? Mike Dunne.

When we're assessing reference methods, for the time being I think we're kind of chained to broth microdilution. Then again, that assumes that we're dealing with an isolated organism and not just the detection of a resistance determinant. If we're looking specifically for resistance determinants, and they're not

associated with a particular microorganism, that brings up a whole new bag of worms. Do you treat on the basis of a res -- or avoid treatment based on the detection of a resistance determinant? Or do you associate it only when you have that determinant with a particular organism?

I think going down to -- I'll skip the middle one for the moment because I don't know if molecular methods will be able to be used to distinguish infection versus colonization, at least not -- not early on.

But in the last question, yeah, bacteria load is going to be significant in certain specimen types, but we're going to be burdened with the quality of specimen types just like we are with culture right now. So crappy specimens are going to give you crappy results. Endotracheal aspirates versus BALs; sputum versus BALs.

If we get good, clean bronchial lavage samples and can do quantitative analysis for genes associated with particular organisms of interest or can survey for the presence of any organism and

then do quantitation based on the amount of DNA for a particular organism, that'll be helpful, but I'm afraid that's going to be way far off in the future.

DR. LAU: Anna Lao, NIH. So I agree with the comments made by the previous speakers.

In regards to the appropriate reference method for molecular investigational devices, I guess, I've broken this down into two elements, the primary element being culture and isolation of the organism and then proving the presence of the resistance gene within that isolated organism with paired phenotypic susceptibility testing using frozen broth microdilution.

Of course, we then run into the particular problems in terms of difference and limit of detections between different assays. So now we're talking culture and isolation of an organism versus a molecular assay that is detecting a resistance gene target.

So in those cases where there is culture negative, but gene direct -- specimen gene

positive scenarios, then I would suggest an independent molecular assay that is targeting a different area of that resistance gene in lieu of sequencing of the primary specimen, deep sequencing of the primary specimen to try and find that resistance gene for correlation of the original result from the investigational device.

In regards to polymicrobial specimens, an infection versus colonization, I think this is really dependent on the type of organism that we're talking about and the source of the specimen. So if we're talking about sputum and mycobacterial tuberculous and RPOB, it doesn't really matter that it's polymicrobial. I think the detection of MTB and RPOB is a given and it's clinically significant.

However, if it's detection of KPC from a perirectal swab or from a stool sample, and the culture is negative, for which we have seen published studies of such, the clinical relevance of that comes into question. So this is more of a question now for infection control and whether the

organism is at a burden that is enough to require patient isolation and infection control precautions knowing that there are other elements that come into play such as costs and hospital isolation, et cetera.

I have another comment regarding the polymicrobial specimens. So if this is a stool specimen or a rectal swab and we're looking for VanA for vancomycin resistance VRE, we know that VanA is carried by clomensofluro (phonetic) and so just data from our laboratory alone, we do a VanA PCI direct from perirectal swabs, but we reflex all of those positives to culture. And for 40 percent of them we cannot recover an ABRI isolate.

MS. SHARP: Susan Sharp. I agree with what's said about the appropriate reference methods. I think we probably, with these new moleculars coming out, especially when we're talking about susceptibility testing, we probably have to compare them both to a broth microdilution method for accuracy and also expression of the marker, and then probably also test for the marker by an

alternative molecular method to make sure that we're making sure that the molecular target is present.

I agree with what Mike said about the polymicrobial infections and looking at difference relevance of organisms and clinical samples. Speaking as a clinical microbiologist, I can't even begin to think about how to work up a sputum without seeing the gram stain. Without seeing the gram stain to see, as Mike said, the quality of the specimen, I don't know how you could begin to determine what might be pathogenic and what might be a colonizer or a contaminant in that issue. So I think we've got some additional things to think about when we look at those kind of specimens that contain a lot of normal flora, if you will, those non-sterile type sources.

With sterile sources, it's a little bit easier. You don't expect a high number of different types of organisms in what we would normally consider sterile sources, but then -- so it might be a little easier doing the moleculars

on those, but then again, we have those sterile sources that might detect low numbers of things that are usually considered contaminants. So at that point they can be clinically significant. They can still be contaminants. How do we make that determination?

So I think in answering these three questions, we probably raised a lot more questions to answer.

MR. PERLIN: David Perlin of Rutgers New Jersey Medical School.

So I agree with my panel members with respect to broth microdilution testing as a comparator for molecular methods. However, there's a caveat and the caveat is that, especially as we push breakpoints down, you have to really remember that when we're talking about resistance, resistance is the failure of a pharmacodynamic response in patients, which we simulate in animals, which we then use MIC testing as a surrogate for whether, in fact, we're having that pharmacodynamic response. And if you look at a number of animal studies where you see MICs which are at the break

point, sometimes above, which respond pharmcodynamically, you say, well, are they resistant or are they not, and if that's the measure we're going to use to compare for direct detection of specific markers, we have to be careful about how we qualify that. So, in general, I agree with it. It will depend on the specific test, how good that particular marker then correlates with resistance. The example of MTB and gravampicyn (phonetic) as a multi-drug resistance marker, it's very good. For other things, not so good.

With respect to infection versus colonization, if you look at cystic fibrosis patients and start looking at molecular markers, almost every patient has resistance markers because they're built up over time, the nucleic acid is resonate, it's not turned over so readily, and so the question is what is the value in that sort of non-sterile bronchial wash of looking at a resistance marker.

I think there is significance there. I think you need to report that and it needs to go -- it

becomes sort of a clinical parameter that needs to be evaluated, but we have to be careful about necessarily calling a flare-up of Pseudomondas necessarily resistant certainly in that patient population. You've already heard about stools, how complex that can be.

And the last point is one that actually I'm a strong believer in. All the molecular assays that we develop are quantitative and we want them to be quantitative because we do believe in looking at both. Not only the number of organisms that we're looking at, but specific markers. How many -- how many gene targets are we detecting and is it relevant to whether we have infection or colonization. And that helps make certain clinical decisions.

MS. SIMNER: Trish Simner. So I agree with everyone so far. I just have a little bit of tidbits to add to each one.

So the appropriate reference method, I agree that we should -- for something that where you're trying to predict clinical therapy, we should be

using both broth microdilution as the reference method and some sort of resistance marker, but I want to add that it will be very difficult, as I mentioned in my presentation, to -- without having any really good clinical outcome studies, to be able to correlate resistance detection absence without knowing what these clinical -- what that means clinically. And so I'd be really scared to be comparing it to broth -- to breakpoints in the end because I feel like we're -- that correlation, you're not going to have that high of a correlation. And so the ECVs, as I mentioned, is separating your populations into wild-type and non-wild-type, and by definition, the non-wild-type are those with mutational or acquired resistance, which is what we're detecting in the resistance marker detection. So that was just a thought on that.

In terms -- I don't know how to correlate that in turn to clinical outcomes, but I think that with time, as we get more experience with these, is something that we could potentially do.

From the polymicrobial specimens, I ironically have an opposite experience with sequencing rectal specimens being a lot easier. There's less host present. It really reflects what we're seeing in culture as opposed to CSF. And CSF, although I say sterile in quotations, when we do metagenomic next gen sequencing, we see a whole lot of junk in there from -- from the people processing it, from it the reagents, et cetera. So even though it's a sterile source, it really is not easy to interpret a negative result. It's easy when there's a real pathogen present. That is super easy, and that's what we're seeing out there in the literature. The hard part is determining what a true negative is because you'll find E. coli in there, you'll find P acnes, you'll find staph aureus. And so at what point does it become relevant, even in a sterile source? So that was another point that I wanted to come.

And then the polymicrobial. What we've been doing is both DNA and RNA seq of some of our specimens, and using the transcriptomics to look

for transcriptional relevance to what we're detecting and finding that that could potentially help you distinguish between infection and colonization. Again, just prelim studies, nothing really concrete, but that was about it. I think when -- the need to quantify bacterial load in a clinical specimen, again, it'll be in these sources that we see normal flora.

I do think that with time we will be able to, like we do with our culture plates and our gram stain right now, is see some sort of clinical relevance, just looking at the plate and with time, with experience with these methods, we might be able to do the same. But right now it's so prelim that we don't know what a good -- what is significant or not, and so we could do that with some sort of quantitative controls perhaps (inaudible).

DR. GITTERMAN: Dr. Bush?

DR. BUSH: There are only a few more things I'd like to add that haven't already been touched upon. One of them is the concern about PCR-

related devices. And when you talk about an appropriate reference method, I would say for something like that, whole genome sequencing or next gen sequencing would be your appropriate reference method. The questions I have, though, about any kind of sequencing is that our databases are not annotated as accurately as they should be. A lot of the annotations that come back are inaccurate or are incomplete. And I think this is one of the limitations that we have with anything that relies upon sequencing of resistance genes.

Another issues that hasn't been mentioned since I follow beta-lactamases pretty closely, the level of production is not accounted for in a lot of the molecular methods. In fact, probably in none of them. And so we don't know, if you see an AMP C if it's basal level or de-repressed. We don’t know if there are induction methods or induction processes that may be going on that are not accounted for in any of our molecular analyses. I like functional testing, but it's hard to test each resistance gene for its

functionality.

In terms of polymicrobrial specimens, I think it's important to look for resistance genes and determine whether -- whether they're there regardless of what organism they're in. It was mentioned about VanA with a gram positive. With many of the plasmid encoded beta-lactamases, I think it's important to know if there's a gene for KPC or a gene for NDM that's sitting there in your gut. In places like acute care facilities, this would be something that would be important for them to know and to realize that they might have issues at some point if that person becomes infected with another organism.

And in terms of quantifying bacterial load, I think that's a very important issue. When we test MICs, we're testing at a fixed inoculum of ten to the fifth, ten to the sixth bacteria. If you've got an abscess that has ten to the ninth or ten to the tenth bacteria, even something that tests susceptible with an MIC will not be a very effective drug if it shows an inoculum effect.

So I'll stop here.

DR. GITTERMAN: Dr. Lockhart?

DR. LOCKHART: Yes. I agree with most of everything that's been said, but especially with what Dr. Bush just said about, you know, maybe broth microdilution isn't the best gold standard. And -- and I think what we may end up eventually considering is not necessarily whole genome sequencing, but in the context of -- of metagenomics and looking at the whole population of what's there. But you know I -- I'm a fungal person, so I think of everything in terms of fungal loads. And you know when you think about what Dr. Perlin said about FKS and you're -- you're comparing it to broth microdilution. Well if you say, "Plus or minus two delusions for fungi are in essential agreement," and you have something that's you know two delusions away and susceptible, but you have an FKS mutation, you've now got a test that's more sensitive than your gold standard. You end up with a number of false positives, at least when you're doing your initial

assessment of the test. And -- and these are false positives that probably really aren't false positives. So we have to very carefully choose what will be considered the gold standard and in how effective it is. As far as polymicrobial specimens go, yeah. That -- that's a big one because just in -- in terms of fungi again, you think of vaginal infections. We -- we all have women that'll have a -- a horrible vaginal infection with you know only a few yeast present, and then we'll have women with thousands of yeast present and they've never had an infection in their life. So you know, how do you -- how do you interpret these two? And then as far as the last one goes, the quantitation, I think back to when we first got our molecular test for pertussis. And you know we had all these people that were carriers of pertussis that were testing positive, that never had it, or never had any symptoms. And we had to figure out, "My gosh, what are we going to do with all these?" so that's going to be another consideration that comes to play,

especially when you think about how much is there, and what's the relevance of a positive in that context.

DR. GITTERMAN: That's the next question. Okay. Well it's -- it's good to see the answer's clear. But just -- just to put my own spot on it, you know, the responses were -- were very interesting. But they're very broad to some extent. But we could separate these out into scientific questions and regulatory questions. The question of the association in sputum would say where stool between a particular organism and disease is going to be a scientific question. The regulatory question therefore is: How well does your device detect that gene and the variance of that gene? We cannot expect every company, by any stretch, to answer every question. And it's going to be very difficult acting individually. I would challenge everyone in the room if we have time -- would be nice to get everybody up here to the mic, but that -- that might take a little while. But people should go back -- you know, people here

representing the idea say, "That means look up. Thank you. Thank you." Or ASM should go back and -- I would hope people and especially the ST Main other groups can go back and say, "What are the biological questions that go beyond any single manufacturer, or any single -- single company," and, "How could we answer them," and then, "What are the regulatory issues how we do that?" because again, if you could mix some of these biological relationships, then perhaps you won't have to do as much phenotypic work. These are -- as we just heard, these are very complex answers. And I'm going to need to do a lot of thinking by a lot of groups, and all cooperate to move forward. It's not something I suspect -- I don't think FDA could answer it. I'm not sure any single manufacturer could answer it. I'm not sure a symposium at IDSA's going to answer it. So I would really challenge people to go back and conceptualize it into, "What are the questions," and, "How do we answer that," and, "What do we do in the meantime?" But on that happy note, we save

the more complex questions, subsequently. This is a real question. This is one we face now. "For direct specimen testing, what do you do with scenarios where you can find a resistance gene, but you don't have a direct organism?" For -- just very quickly, I could sequence, for lack of a better word, sputum, or I could do molecular detection, find mecAs. It's a bad example, but mecAs there. But I don't find staph -- any type of staph, or you know for gram negatives. It becomes horrendous. What do we do in that situation? I'm going to be a little different. I'll save you. Let's go back to the end because you know, you've had all this time to be thinking.

(Inaudible-multiple speakers).

DR. GITTERMAN: What? I'm sorry?

(Inaudible)

DR. GITTERMAN: Okay. We have a -- there's a vote for people on the phone, first. So Dr. Lockhart, please.

DR. LOCKHART: So it -- we're on B. Is that the direct specimen testing con -- scenario is

acceptable? That's what --

DR. GITTERMAN: Right.

DR. LOCKHART: Yeah. So again, I -- I -- I come at this from -- from two perspectives: The fungal perspective and the public health's perspective. And I -- I think if I put on my public health hat, I'm more concerned about identification of these genes, in terms of infection control. And that's when they become portent, when -- when you're -- you're more worried about it spreading to other people than you were necessarily about in a patient. Even if it's not causing disease in the patient, it has the ability to be spread elsewhere in your hospital. And I think in that case, it -- it -- it's a result you have to be concerned with. As far as fungi go, there really are only a few tests, or -- or a few targets that would allow you to determine whether or not you're -- you're definitely going to be resistant. And I think if I -- if I identified any of those targets, certainly from a sterile site, then I would have

to act upon them, such as an FKS gene, or a -- a spp 51 TR Target in a -- an aspergillus.

DR. GITTERMAN: Okay. Dr. Bush?

DR. BUSH: So I -- I think I mentioned one of the scenarios where I think reporting the resistance gene is important for the medical record and for the institution, but perhaps not something that would trigger treatment. That would be in rectal swabs, surveillance swabs, perhaps places where you would find metallo beta lactamases, MCR 1, perhaps amino glycoside modifying enzymes. Some of these things that are on mobile elements, transferrable genes that you don't really have to know what organism it's in, because it can go to almost anyone that's there. And I'll stop at that point.

DR. GITTERMAN: Okay. Is anyone in the audience from infection control -- infection control nurse? Is your blood pressure rising very, very dramatically? Just -- just curious. But please, we'll go onto there now.

MR. KIRN: Yeah. I was going to make that

comment. So we're going to -- we're going to really shake up the infection control folks with this, because you know, they're going to have to establish guidelines and kind of protocols about what they're going to do with this information when they get it. And you know already it's -- you know there's dispute about, "Do you isolate patients that have you know CREs? Do you isolate just patients with CPCREs," and et cetera, et cetera, et cetera. And so if you're reporting genes detected, then there's going be have to whole -- have to be a whole set of you know protocols associated with that. That's not a regulatory problem. That's a scientific problem, I guess, or a process problem in the hospital. But I -- but I think that that would be a reasonable time if those protocols were established to report the detection of a resistant gene. But on the other hand, we already do this you know pretty routinely, right? So our blood culture panels right now detect mecA, and they detect staph, and we don’t know if they're -- you

know if there's two staphs, we don't know which one it's linked to. So we already do this in practice. And I think that in a -- you know a sterile specimen, if you detect a gene that's not necessarily linked to an organism, that's would be a case where you might report that detection of that gene, and then you're waiting for the, you know, the final results to kind of come up with the ground truth. So I think there are many applications for reporting the -- the detection of a resistance gene without necessarily a direct link to the organism. Now when the organism's not detectable, that's a whole separate issue in those sterile specimens. But you know that's my -- they're my thoughts.

DR. GITTERMAN: So just to make sure, you distinguish clearly sterile versus polymicrobial specimens.

MR. KIRN: Yeah. I mean, I just think it's -- it's so much more complicated in a polymicrobial specimen. And I think that you know and -- if it's a polymicrobe -- you know wound culture or

something of that, or a dirty specimen that may have multiple organisms that may carry those genes that aren't the target organism, that makes it more complicated. I think that those results may not be as actionable as when you get a -- a resistance gene from a sterile specimen. So I think there's some of the considerations.

DR. GITTERMAN: Okay. Please.

MS. CASTANHEIRA: Mariana Castanheira. I agree with Karen, I think because I seen as much -- as many whole genome sequencing results as she did, that I want to know if I'm carrying an isolate, even if it's a colonizer that's carrying KPC, or VIMS or -- so I agree with her. I think it's important information for infection control practice, and even we don't know when you use a drug that selects those organisms, how the patient's going to behave. And I worry that you might develop an infection with your colonizer.

DR. DUNNE: Mike Dunne, still wishing for that intelligence prescription. I want to make a point that in the first question, we're kind of mixing

metagenomics and whole genome analysis. And they should be two distinct things. And we have a lot more to do with the latter before we can jump into the former. And that means having accurate databases that tell us when to expect an association where resistancy determinate with the species, and how tight is that, and does it confer resistance in in-vitro susceptibility testing? Only then can we go back to metagenomic analysis and say, "Okay. We're going to have a stop light of resistance determinants that help us decide whether or not we're going to report it or not." So you have green for go, yellow for -- or red for stop, and yellow for -- well, if you remember Starman, yellow was go faster. But for the red stop sign, you would think about things like KPC, MDM1, VIMS and IMPS with yellow VanA, because you can't necessarily associate it with -- with enterococcus, or staph aureus, or CTXM. And green TEM1, what are we going to do with it -- a TEM1, although gene amplification of TEM1 will give us in-vitro false resistance to things like TZP. So

you know let's -- let's learn to walk before we run. We're going to have to develop very sophisticated whole genome sequence databases. And then we'll know a little bit better on how tightly these things are linked, and when we can report them without the identification of an organism when it's done directly from sample.

DR. LAU: Anna Lau, NIH. I think I'll come back to what I said at -- you know answer actually to the first question, where I think this is really dependent on this source of the bug, and the bug itself. So again, direct specimen testing and resistance to testing of (inaudible) resistance for TB. That's a no-brainer. That is definitely reported from direct specimen. I think from sterile sources and detection of mecA or VanA, or a KPC would be acceptable to report, again directly from the specimen. When we're talking about the more complex source types, like stool, and detection of potentially a KPC that is culture negative, again, we run into the whole point of whether it's epidemiologically

significant, and this is where I think hospitals and industry, whoever needs to play a role in this, needs to take into account the patient population and in which this testing is being performed, and the risk base analysis, and who's at risk, such as long-term care facilities or ICUs. And also I guess the prevalence of carbapanemases in that population. So you may already be in an area that is highly endemic for that, for which testing of a positive directly from a specimen is okay. I'll have a -- however, if you find it in a low prevalence scenario, then perhaps further investigation is required.

MS. SHARP: Susan Sharp. I agree and disagree with part of what's been said on the panel so far. And just -- just briefly, I -- certainly there are situations where you're going to want to use this for epidemiology and infection control, like stool screening, et cetera. That's -- that perfectly acceptable and understandable. Yes, there are as Tom said, some situations where we have blood cultures. We may have coag-negative staph

contaminant lung with a staph aureus. You get a mecA hit. You don't know which one it belongs to. I would never report that out without it being associated with one of those two organisms. Because again, clinically it may be important for the staph aureus. It may not be important for the -- the coag-negative staph, which a majority of our coag-negative staph have mecA anyway. So -- and I can't see our physicians -- they have a hard enough time without a lot of help from us, and -- and a microbial stewardship, interpreting the molecular test that we do now that are associated with organisms. I don't know what they would do with a molecular test for resistance gene that didn't have anything else associated with it. So I think we're -- we're a little ways away from that. But I -- I think we will get there using some of the techniques that -- that Mike has outlined as well. I think we'll get there, but at this point I think I'd feel very uncomfortable reporting something out like the scenario I just gave without it being linked to an organism,

without doing EPI or infection control.

MR. PERLIN: David Perlin. I -- I -- I agree with Susan. I think that if -- if we're -- if we're detecting a resistance mechanism, a marker unlinked to an organism, then it's a -- a risk factor. It's a -- an infection control issue. It's a potential issue downstream for that particular patient. But I don't think it's actionable in the absence of that organism. Now there are some organisms that are difficult to culture, for example from blood. And there you have to make a determination. So in -- in -- in my view, and as we've worked with a lot of clinical labs in this, it -- it gets reported as it's present, it's a risk factor, but it's not necessarily actionable from -- from a therapeutic standpoint in that individual patient. But it certainly goes -- it goes into the chart and it's something that's -- that's part of the -- the patient record.

DR. SIMNER: And then I just go back to intended use. Again, if you're looking for

colonization of MDR -- M -- some sort of antimicrobial resistant organism, then like the specific carbapenamase genes from rectal swabs -- and I think it might be okay. But then if you go back to the scenario you described with sputum, I would be very hesitant to report out a resistance marker without any organism from a sputum sample. I know that for sure I would confuse the heck out of the practitioners on other end, on what's going on, and I would definitely be fielding a lot of calls if I would be reporting that out. So if you look at it from a regulatory standpoint, in terms of clinical impact, it would cause more confusion that good I would think.

DR. GITTERMAN: Okay. How many people think they should be reported? Hands up. We have no clickers?

UNIDENTIFIED SPEAKER: It's not at all or none.

DR. GITTERMAN: Okay. It depends. Classic ID consult. But having said that again -- first of all, one is these are really important issues.

It's very difficult. We heard some clear distinction between different uses, infection control versus patient care right off the bat. When we think of things in FDA, a lot of times we think of how it's mitigated. We have a tough time saying you can't report it in this situation. You can't report in this station. We're looking at the greatest common good. And we look at the fact that there could be very negative implications. But taking an example back from HIV, it's not a perfect analogy. But you know people struggled all the time with TAMS and what to do with HIV, and you know again, there's sort of all gust (phonetic) bodies. It's probably the wrong word, but there's groups like the IAS USA where people come out with guides for clinicians, advice, and help because a lot of the HIV care which has now become primary care -- a lot of the clinicians don't know how to deal with interactions. They don't get a virtual phenotype anymore. So again, I look back to ASM and IDSA and other bodies who can start tackling these things. These are --

these are not regulatory questions. No matter what we do as FDA, it will be the wrong decision. And those are the only people who can write us because all the people who are happy with it are not going to write us back. These are very difficult things and have direct impact on patients and direct impact on hospital care. So we would welcome -- and I'll -- I'll use the word correctly (inaudible), but groups to come back and start thinking about how, "If we did it, what are the implications, and how do we do it?" These are very sophisticated questions. And we are looking for help. This is a partnership. It's also -- if Dr. Miller is still here, this is the way companies get reimbursed. They're not going to develop device to give you this information if they're not reimbursed for it. So there's a lot of -- these are very interesting. And the last time I've seen before -- they're evolving issues. You're not going to have all the answers now. So -- but we have an easier question coming up, now. So how do we tell this? The -- the -- if we're

giving this information to clinicians -- did I miss one? I'm not touching anything, honestly. Here's my hands. Okay. What's the best way to give this to the end-user? And who is the end-user? I will just give you an example. At the hospital I work at, they have one screen for ID specialists and another screen for everybody else. Now that's great for ID because you come and say, "Ah, it's -- we could use blank," even though you didn't know it. It's -- it's job security. But the fact is they -- as a mitigating factor for ordering medications, that's one very potent way of antibiotic stewardship. So even who is the end-user? Do we need shade to come up with guidelines that the FDA should distribute this to these people, but the company has to have software provisions to make different reports available or whatever. This is a difficult question. We're going to go to the phone last on this one, so let's start at the end and -- I want answers this time.

MR. KIRN: Well, I -- I'm going to -- I'm

going to more frame the issue a little bit more and -- and so -- and lets the other folks give you the answers. But you know I mean this is a huge problem right now, even for the molecular tests that we have that are FDA cleared. And there's tremendous heterogeneity in the way that individual hospitals have decided to report results from those molecular tests. You know we heard from Trish earlier about their antimicrobial stewardship team intervention and how it was durable for a period of time. I think that you know many hospitals have adopted that approach and so really there's a -- a lot of handholding associated with delivering the results to the physicians, at least for a period of time. And others have demonstrated that without that handholding, the expected outcomes are not achieved. So you know I don't know if there's -- I -- I -- I'm not sure that there's a -- necessarily a universally effective way to develop -- to deliver the information to the end-user if the end-user is the clinician. I think that you

know we're going to have to rely on that infrastructure being supplied by the individual testing sites and -- and as a service to their clinicians. And it may be that you know after a learning curve, there may be some durable transition in behavior. But I think at the early -- in the early stages, there's going to be -- have to be a lot of education and intervention as these results are reported, especially as they become more and more complicated.

DR. GITTERMAN: So you favor an AASLD type structure where you put up guidelines and every time the FDA approves the new drug they change all the guidelines. And it's happening so quick you always have to look it up. Is -- did I interpret that correctly?

MR. KIRN: No. Well not exactly that. I favor a -- you know, I think I -- what I favor is, and what I think will happen, is a -- you know programs to support the utilization, implementation, and dissemination of results at each of the testing centers for when these tests

come in.

DR. GITTERMAN: It's going to be a lot of work at every test center on some --

MR. KIRN: It will be. Yes. And it has been.

DR. GITTERMAN: Okay.

MS. CASTANHEIRA: My experience is very different from Tom's because I work in a reference lab that does a lot -- I just do recovered isolates. We don’t do primary specimens. But in a way it's very similar as well, because I think even when I talk to our clients that are pharmaceutical companies, I have to do a lot of handholding to -- to talk -- to discuss molecular data. So we still have to explain and there is a lot of questions in how the test was done, and what was used. With whole genome sequence it added another level of complication because people have a lot of questions about that. So I think the education is a key point. I think educating our -- our clinical microbiologists and the clinicians -- it will be the hugest task for molecular devices, to be honest.

DR. DUNNE: Mike Dunne -- I've actually come up with a report. And it goes, "Detection of resistance factor Y associated with organism X correlates with in-vitro resistance to drug Z. Alternative approaches to primary therapy should be considered until resistance is confirmed by standard AST methods to follow."

DR. GITTERMAN: Okay. Let's take a vote.

DR. DUNNE: Now you can -- you can make several iterations of that. Detection of resistance factor Y associated with gram negative rods. You can say detection of resistance factor Y without any association due organisms is meaningless. You know, you can -- you can do any number of iterations of that. But you have to figure out what's significant and you have to try and avoid a potential train crash if that's a possibility. But it's not -- you know…

DR. GITTERMAN: Okay. Well if you want to step to the table they can type this on the slide and we'll vote on it later. So let's…DR. DUNNE: Seriously?

DR. GITTERMAN: No. No.

DR. DUNNE: Good.

DR. LAU: So I agree with Mike and the previous panelist. So I think education is going to be the biggest point here for our clinical colleagues. And of course we're obligated from a clinical lab standpoint to report the presence of a resistance gene with a phrasing of suggestive of resistance to a certain population of that kind of drug. It'll be nice if we could define that level of percentage or the probability of resistance. And I don’t know if that could be done on an individualized hospital level, or in a regional level, or on a national level to say, "X percentage, finding of KPC has -- is suggestive of 90 percent resistance to capbapenamens," because we know that the presence of KPC doesn't necessarily convey resistance.

MS. SHARP: Susan Sharp, and I guess for an example how this might be utilized clinically is we were -- and I think from the clinical microbiology standpoint, if we're going to bring

on these more expensive molecular technologies that we use, we need to make sure that the information's going to be utilized appropriately downstream. Because we can send out expensive results all day long. If no one's going to act on it, it's not going to help patient care. And that's what we're trying to accomplish by doing -- doing these faster methods. With our blood culture -- blood culturing, we actually put out a report in our patient reports that says that this was the organisms that was identified. We indicate whether there are any resistant markers present or not, and then there is a link that they can click on that will take them to treatment guidelines. Based on what the organism is, based on what resistant markers you have, this is your first line therapy. This is your second line therapy. If you have any questions, call the infectious disease consult. We have one of those for gram negatives and one of those for gram positive. So that, we -- we rolled that out and we educated our physicians before we started doing

the testing that this is the results they're going to get. This is what the reports are going to look like. Here is the link. It'll take -- it'll take you to our empiric therapy guidelines so that you'll know how to interpret the molecular tests that were reported out. And that is based on -- in Portland, Oregon, our very low presence of carbapenamase producing introbacteriacy and based on our antibiograms. So those recommendations were put together by our ID and our ID pharmacy people. And we've had very good luck with that. It's worked very well. The education was important upfront to our clinicians. We do have stewardship following-up on all of these and someone else mentioned earlier -- Trish, maybe it was you -- that once this is established and people are educated about it, that the -- the level of acceptance does stay high. And we have found that to be true in our center as well. And I would say too for device labeling that certainly with device labeling if -- if guidelines want to be incorporated on how these -- how these results

may be reported or utilized, I would -- guidelines would certainly be acceptable. I think mandates will not be acceptable to the end-users. And I think we also have to look to our agreed -- our IDSA, or ASMs, our CLSIs, et cetera, for helping to put out recommendations for how to interpret some of these results, and then let the institutions make -- make their own decisions. Give them some guidelines. Give them some recommendations for the hey -- how they may go about doing this. But I don't think we can mandate that every institution must do things the same way.

MR. PERLIN: Our experience with clinical laboratories and in many -- many cases, very experienced clinical laboratories were in the New York Metropolitan area. And most of the hospitals that we support are in New York City. And what's interesting is that if we're -- if we're reporting on a molecular mechanism for example for gram positive, no problem. You know, methicillin resistance, vancomycin resistance, no problem.

They get it, easy. If it's fungi, if we're reporting an FKS mutation, they sort of get it. Although the question that always comes back to us is: Is that going to mean it's above the -- the breakpoint, or below exactly? They understand break points but they don't understand the molecular targets. And on the gram negative side it's -- it's -- it's somewhat of a wild west. They understand some targets. Most they don't. they don't understand the correlations and what they should do. And invariably, you'll -- you'll give them the analysis of what you've come up with, and they'll say, "Well what should we do about that?" It's not so clear-cut and I -- there's no question that we have to provide better guidance of -- of getting them to understand what these molecular targets are, how they relate to resistance, and the probability for therapeutic failure, therapeutic success. And based on that, that's all we can do. And as I said, some groups are more experienced than others. But I would say it's surprising that a -- they either -- that many

of the labs either don't have the patients for it, or they're just -- it's a cultural issue that we just have to overcome this barrier and we have to -- we have to educate people about how to interpret what these markers really mean.

DR. SIMNER: I agree with all the panelists. I was doing a lot of head nodding. I think the last thing that just to suggest and everything else, in terms of education and linking to the antibiotic guide is templated comments that you can put directly into the reporting that you've worked with your infection -- infectious diseases colleagues and your stewardship colleagues of putting some suggestions in what they might treat based off of those results. That was the only additional thing. Everything else was -- I agree with.

DR. GITTERMAN: Dr. Lockhart?

DR. LOCKHART: Yes. So I -- I like -- I like Mike Dunne's -- his comment. But -- but what I think I would add to that would be something about infection control concerns. Infection control's

not something you want to wait until you prove the positive on. It's something I -- I'd rather enforce now and be wrong than to -- to wait and -- and have something get out. So I -- I think in terms of infection control, I might want to have a trigger based on a molecular result saying, "Hey, you know, think about maybe putting this person in -- in contact precautions, or -- or whatever the case may be," and it -- as far as education goes, I mean we -- we went through this just recently with the CLSI when we were writing comments for ECVs. This is -- this is perhaps how you should approach putting a comment in. And -- and we went around and around, and we spent two hours writing a short comment. And then it got published and you know we thought it was clear as day, and I've seen a lot of people who think it's clear as mud. So as much transparency as we think we're providing, it never seems to be enough.

DR. GITTERMAN: Dr. Bush?

DR. BUSH: I think that a lot of these comments are on target, that if you find a

resistance gene, you know it's associated with a specific resistance to a known drug, that there should be some kind of comment. But I would say that it may be associated with resistance because we know that not every time you see a resistance -- we know that every time you see a KPC you don't always see carbapenam resistance, and certainly not carbapenam resistance to every carbapenam. So I -- I think that the -- the warnings should be somewhat tempered until you get the MIC data back. And then I was also thinking about the comment that Dr. Simner made when she was talking about phenotypes that don't agree with genotypes, and that at that point there should be an ID consult. I fully approve of that kind of statement for some of these discrepancies.

DR. GITTERMAN: Okay. If this were the GRA, I'd give you-all three for your answers. That on a scale of six. Because only Dr. Dunne really answered the question. And we as FDA don't want to be accused of giving people the rope to hang themselves. But the labels can only be so long.

They're impossible to read as it stands. They're not updated regularly. And I don't think -- and is there any clinician in the room who's ever read an AST label -- a device label? Please, no. And they go to the microbiology laboratory. Oh, did you read one?

UNIDENTIFIED SPEAKER: No, I'm very -- I'm not very (inaudible).

DR. GITTERMAN: Oh, well that's different. You know that's -- that's -- I mean, most clinicians don't know what -- what SIR means, much less an MIC, much less -- these are incredibly sophisticated issues. And the fundamental question of, "What do we even --" I mean, Dr. Dunne, and we appreciate his -- his thoughts, said is what to warn people about. But what do you put in the label? What do you give the information? Which we all know is based on a limited clinical trial, anyway. In there, that conveys to a clinical microbiology laboratorium enough that they could take this out and people would understand how to use this device. That is an

unbelievably challenging question. And I'm going to take my prerogative as chair. Dr. Lau has agreed to chair the new committee that'll be writing these guidelines and everybody else who's nominated is -- whose volunteering --

UNIDENTIFED SPEAKER: Please wait.

DR. GITTERMAN: No. But the point is whatever we do as FDA is going to be too much or too little. We'll have asked too much from the companies. It's not going to be clear. I have trouble understanding -- you know, when we read the submissions to -- you know these are often very large submissions to translate all the information that's relevant into a package insert so that somebody could extract it, use it correctly, and understand it -- I -- really, if you look at those people there it's unbelievable anything gets out of there. And we have to do it sometimes in 30 days. We need your help. I notice some people looking down you know all the time when I'm looking at the people's -- but this is -- you know I would say it takes a village, but

we don’t use that anymore. That's not -- you know, how about resistance, sad, or something with -- people, the companies, the -- you know governmental, the, you know the institutions, John, others really need to come together as a group. How are we going to collect all the more data? How are we going to distribute this? Because when we put these things out, everybody in the audience is going to be the first one to complain. And you're going to be on the phone saying, "Now, that doesn’t" -- and if we don’t put it out, well, no one's going to buy it. So we have to solve these problems for everyone. It's the only way we're going to move forward. But we have exactly 20 minutes and 11 seconds -- oh. Okay. Did you advance the slide for me? Thank you. That's a hint. Okay. In addition, now Michael Dunne already answered this question: Please discuss limitations, winning, other statements that may be informative. If you don’t mind, I'm going to move to question four because this -- we've already tackled most of question

three. I'm going to take my prerogative. Because this is another direct question we need answers now. For low prevalence resistance markers, any device manufacturer in any clinical trial -- and I think what Dr. Farley mentioned this earlier. The minute you do a clinical trial, resistance disappears. It does not exist. What is the value of post marketing studies to address low prevalence resistance markers? And I really like this question. It's sort of looking at a total product lifestyle -- lifecycle, excuse me. Is: What can we start doing and acquiring information to move the approval process faster, yet actually have a process that gives more information for the clinicians over time? I'm not starting with the phone first, please.

MR. KIRN: Okay. So you know I mean I think the obvious answer is valuable. I think you know given the fact that we see emergence of new resistance mechanisms, mutations within currently detected resistance genes and -- and other issues around these studies, I think you have to do some

kind of post market surveillance the same way we do with -- for other diagnostic tests. I think someone had talked about influenza earlier. And I think that you know we will continue to get additional information going forward. I don't -- that --

DR. GITTERMAN: So --

MR. KIRN: -- don't have much more else to say about it than that.

DR. GITTERMAN: Okay. Could I rephrase the question?

MR. KIRN: Yes. Sure.

DR. GITTERMAN: Would you go ahead and -- a lot of people spoke this morning, I thought very eloquently about -- let's say we had really good analytical studies. We bioengineered you know certain bugs --

MR. KIRN: Uh-huh.

DR. GITTERMAN: But we did really -- so we had a very, very good Bayesian prior to say this is -- this will work. Would you allow companies to market that so to speak, on really strong

analytical studies, and then acquire more of the clinical data post marketing?

MR. KIRN: Yes. I think that's reasonable.

DR. GITTERMAN: You think it's reasonable?

MR. KIRN: I agree.

DR. GITTERMAN: You complained about the four -- somebody -- you don’t have to own up to it, but somebody got up here and say, "You know they cleared advice only four cases," and that's what's going to happen here. So you're -- okay. I'll put you on the spot afterwards, please.

MS. CASTANHEIRA: I think that for first, we should have a minimal number for you to not have like four cases. Maybe have a minimal number of isolates in the --

DR. GITTERMAN: Okay.

MS. CASTANHEIRA: -- analytical phase with that resistance marker.

DR. GITTERMAN: Analytic -- but how many clinical?

MS. CASTANHEIRA: That will depend on how you're look -- running your clinical trials. And

it's what we discuss about the clinical trials. If you require fresh isolates that are collect a week -- in a week -- in the past week, you're not going to pick up the low -- the low currents ones.

DR. GITTERMAN: So --

MS. CASTANHEIRA: So you're going to have to go to stock collections.

DR. GITTERMAN: We can stock your ability and we should all be pushing Jean to expand the antimicrobial resistance bank so we catch everything we want. And who was the person who was going to bioengineer these? Tom Gursey (phonetic).

DR. LAU: He's gone.

DR. GITTERMAN: Okay. We'll send him a wish list.

UNIDENTIFIED SPEAKER: He's working on it.

DR. LAU: I think -- I think what we could do as well, it's to try to come up with guidelines for a spiked samples that the clinical labs can contest during the clinical -- clinical part of the study. But they are not collected in the

clinical like bench.

DR. GITTERMAN: Michael?

DR. DUNNE: Well, there was a bit of discussion about challenge panels. So if -- if you have low prevalence you can enrich in several ways. You can place more isolates that have that representative resistance marker in a challenge set to ensure that -- that you're picking it up. You can post market go to areas where a particular resistance factor is part of a -- is -- is part of an outbreak. So you do satellite outbreak analysis. Or you go around and infect patients and see what happens. But no I -- you -- you can enrich post -- post market release by -- by going to areas where you can sporadic outbreaks of organisms associated with that resistance mechanism.

DR. GITTERMAN: So you're volunteering?

UNIDENTIFIED SPEAKER: Uh-huh.

DR. GITTERMAN: Are you volunteering Dr. Dunne? Oh, I'm sorry. Please.

(Inaudible).

UNIDENTIFIED SPEAKER: Let me clarify that this question is mostly aiming at -- from direct -- something that's direct from specimen. So clearly if when you're considering it, challenge isolates, that you would be then considering the dose would be either spiked into a sample or whatever, versus I think the question talks about the study that was done and it's direct from specimen. And you only found one, two, three organisms with that particular resistance marker. So the level of evidence isn't quite like as robust if you will. And then what do you do in post-market? And perhaps what Mike was saying, that you'd like to go to a hot bed area of where those clinical specimens might be available. So this is really more talking about the clinical -- I'm sorry, Steve, for --

DR. GITTERMAN: No. That -- that's okay.

UNIDENTIFIED SPEAKER: -- interjecting.

DR. GITTERMAN: I -- I don't -- I'm not quite sure I see the distinction, but I appreciate it (inaudible). But, you know, we always say that.

We say, "They're out there." You know? You just -- the company's just going to pick up. Put a reference method, get a study in place, get -- you know? Get IRB approval. Get all these things. It's pretty -- you know in a perfect world, we'd have a system to collect these that could then be distributed. You know some direct specimens are very difficult to freeze. You know depending on the genetic markers you look at, but we always say that. Just go out to an outbreak. I like the idea of you know volunteer studies myself. I -- did you ever read that -- everybody here's read that BMJ paper on parachutes? Everybody -- everybody know what I'm talking about? You know, people survive their parachute not opening, so maybe we'd need to do a clinical study to see. Nobody's seen that paper? It's a classic. Okay. Send me your e-mail address all of you and I will -- I will forward it to you.

But so I apologize with the caveat that -- that Dr. Shawar said, which is really an important one for direct specimens, perhaps. Does that

change your opinion, Dr. Lau?

DR. LAU: I hadn't voiced my opinion yet, so no, it hasn't changed my opinion. So I think release of a resistance detection marker on a device in a low prevalence setting is really based on risk and what is carried, and the clinical urgency of having a testing method available for clinical labs and reporting to our clinical colleagues. I think in silico studies prior to release are fine, but I do agree that an isolate bank for challenging the device likely six months to a year after release is necessary.

MS. SHARP: Susan Sharp, and I guess I'll just answer briefly that there are going to be situations where we're going to have low prevalence of these positive resistance markers, and they're not going to be detectors. There are always going to be a few isolates you don't want to hold up new devices that can help patient care by holding them up because there wasn't a -- a robust enough population of resistant organs which in fact -- when there's just a posity of them out

there. So I think we need organizations like our guideline city and organizations like the CLSI have been very good in saying, "This is an unusual resistant pattern for this organism. When you see this combination, check your ID, you know test it again. If it doesn't fit, then let them know through guidance you know what is unusual and then what they should do with it." And perhaps the -- the ARLN will have some kind of a -- a mechanism for handling those organisms and -- and doing post market after that.

MR. PERLIN: And we've been involved in some of these studies and I -- I completely agree. When you have the -- a low prevalence of resistance in these markers, you have to enrich. You have to enrich those populations and they -- you -- you need to be able to help the manufacturers. So we -- we do a combination of things. I mean we try. I mean, in our area people come to us because we have in some cases high -- yeah, higher prevalence of resistance you know first -- for your -- for certain diseases and

so it is a little easier but you know in the case for example where we were looking at the -- the (inaudible) whereas low incidence. Initially it was very, very difficult to find resistant organisms, so you have to be able to enrich. Now we're not talking about devices back then. But we were -- we were talking about molecular so you know I think that -- I think that's part of the process. I you know I -- I -- I agree with Susan on this.

DR. SIMNER: So it's to my understanding that the -- the investigational devices need to do -- if they don't get enough positives they have to do spike in studies. And so you're already doing that. It's a -- so what we're discussing is building these -- you know, these banks of isolates which are great that we could use for the spike in studies. But I feel like the companies are already doing what we're kind of describing and challenging it with banked isolates. It's already a requirement of them so what I'm scared is is that now we're making into everything they

need to already and then they're -- are they going to be responsible for this post market analysis in and above? So it's -- to me you're not making it any easier. You're actually making it harder on them. And they already have to go through I think 1500 specimens before to just -- through some studies I've done, through multiple sites before they can even start to run spike ins. So you know the specificity of the assay is really, really good. You're not getting a lot -- any false positives. And so -- and then you challenge it with your spike in. So I think that this -- right now the amount that the manufacturers do is actually sufficient. I mean, from a scientific point of view, I would love to do the post market analysis and with a -- in higher prevalence settings, but I think they already do a lot of what's described already in a pre-five-time K pre-submission.

DR. GITTERMAN: Can I put you on the spot for a second --

DR. SIMNER: Yeah.

DR. GITTERMAN: -- before we go to Dr. Bush and Dr. Lockhart?

DR. SIMNER: Yeah.

DR. GITTERMAN: So you have a very good device. This example came up this morning -- 99 percent specificity. You have something which may be one in 100,000.

DR. SIMNER: Yeah.

DR. GITTERMAN: So your PPV is horrible.

DR. SIMNER: Right.

DR. GITTERMAN: Now the Oedipus we're building is antibiotic stewardship and you just killed it.

DR. SIMNER: Yeah.

DR. GITTERMAN: So how do you address that?

DR. SIMNER: Yeah. I guess so from --

DR. GITTERMAN: You just knocked it down.

DR. SIMNER: From that standpoint, but so I guess I see your point there.

DR. GITTERMAN: I'm just --

Patricia Gitterman: But if we're doing it for infection control purposes, which in this case this -- just thinking of some of the examples, and

I feel like you're already pushing the -- the clinical -- the invest the companies to do these spike in studies at near their LOD. They've already determined their LOD and so they've done some of the due diligence already. Like I said, I do see the value of a post market study. Don't get me wrong. I would love to see all of them. But I think it's a lot to ask, over and above what you're already -- unless you're cutting down somewhat the upfront. You know is there some sort of compromise?

DR. GITTERMAN: And there is. I won't make fun of you as an industry sympathizer.

DR. SIMNER: Yeah.

DR. GITTERMAN: No. But you're --

DR. SIMNER: I just worked at the museum also.

DR. GITTERMAN: It's all right.

DR. SIMNER: I just know what we have to go through, like as in --

DR. GITTERMAN: I only meet them at parties. I don't know.

DR. SIMNER: A trial site, so --

DR. GITTERMAN: An IT week I've seen at the free dinners.

DR. SIMNER: I've never been called that before, so --

UNIDENTIFIED SPEAKER: You're labeled.

DR. SIMNER: Yeah.

DR. GITTERMAN: No. On a -- on a serious note though, what we have highlighted is really -- the point I think is -- is we as FDA can't regulate it. And it's beyond the scope of any -- any company.

DR. SIMNER: Right.

DR. GITTERMAN: We need an infrastructure that prevents FDA and the companies from giving everybody the rope to hang them, and you're 100 percent right. How do we communicate? Is it going to be that when you get this in the lab you're going to send up a note to say how seriously do you think this person may advocate BC or how likely it is, or can the wait? It's -- it's -- this is something that has to be addressed.

DR. SIMNER: Right.

DR. GITTERMAN: Very -- and as colonization becomes more common, and it'll -- it'll become a nightmare. Then we'll be putting everybody in prophylactic colista. It's just problems and again we can't solve them as FDA. We can just put Mike Dunne's paragraph in the label to say --

DR. SIMNER: Sounds very great.

DR. GITTERMAN: -- think about it before you prescribe a drug. It's very -- but, Dr. Bush, I -- I didn't mean to ignore you.

DR. BUSH: Okay. I was -- I was simply going to say that post marketing surveillance is something that a number of drug companies do when they release a new drug. And they ask anybody who finds a resistant pathogen to send it to the company and then it will be verified and examined probably for resistance mechanism. If you're talking about low prevalence markers, you may be talking about 10 or 12 during a year. I would think that the companies would be very interested in having those sent to them so that they can

verify that their device is working properly.

DR. GITTERMAN: Dr. Lockhart?

DR. LOCKHART: Yeah. I -- I don't really have much to add except to say, you know, for as far as fungi go, this is the story of our life. I mean, this is why so few drugs are actually approved, because there just are enough bugs out there. And post-marketing studies are what really drives the field and -- and allows these things to be -- to be used at all.

DR. GITTERMAN: Okay. I just have one last comment before I thank the panelists profusely. But, Ribhi, did this get to the issues you had wanted to get to? You're okay?

I just want to talk about one FDA initiative that we're very proud of. Is Dr. Waters here? Boy, everybody's escaped. It must be too late. No, but FDA is actually -- you know, our resources are very limited, in some cases may have to spend the taxpayers' dollars very wisely. But we were able to put forth a grant/contract with Regenstrief Institute to work on semantic

intraoperative microbiology tests. We're very excited about this because this is the concept that tests at least will be coded similarly using one consumer and clinical laboratories without trying to make more work such that we can actually do passive microbial surveillance that actually is the equivalent of active surveillance. And some people may be dragged into that project or asked to do it, but we're very excited about it because we really believe, like the hyperlink revolution that occurred this morning, we're really hoping that we can actually do some things with interoperability which will be game changers in this regard. So were very hopeful for that. But again, let me go back.

I want to thank everybody by name. But and I -- if I embarrassed anybody, that was certainly not my intention. But it was really my intention to highlight that we need help and need to work together, the manufacturers, the clinical community, the FDA. We have to make this work. It's beyond the only model where a company does

something, FDA pronounces it good, and it's out there for you to worry about. That -- you know, it's getting difficult now. We all have consciouses, counsciouses, consciousness, whatever. But we all want to do the right thing.

Dr. Scherf, you were going to make some closing remarks? You've done a fantastic job with that.

MR. SCHERF: Yeah. I'd like --

DR. GITTERMAN: I mean really.

MR. SCHERF: Yeah. Thank you for staying all the way through the workshop. My name is Uwe Scherf. I'm the division director in the division of microbiology and I just wanted to finish up with some kind of notes and perspective on the -- on the review division, on this area here.

It's very clear that we are in an extremely exciting time. And you heard this. And I think it's exciting because it is helping us to move things faster, but as Dr. Gitterman several times already mentioned, there's actually the need for really changing some of our paradigms and working

together. Let me just explain it towards two concrete examples. One of them is in -- really the 21st Century Cure provision allows us now to address some of the breakpoint changes much faster. This is, of course, an extreme benefit, but also a headache for everybody because can you imagine that as it was mentioned this morning, more and more devices need to be processed faster? There are initiatives to kind of do this and to develop maybe faster approaches. But I encourage everybody here in this workshop, please don't just go home and say: Somebody will fix it. But be encouraging and you'll see it here in the slide as well. Please provide us your feedback. Provide us in the docket. Provide us as emails or in this queue subs where we have an opportunity to think beyond what we already do and maybe get some ideas from your side.

The other one is also -- and it was extremely clear this afternoon, the new technologies are so interesting, but still so much challenging as well. The interpretation of the (inaudible) are

not there. There are tools to kind of provide some of this interpretation, but we need to find means of helping the physicians to really then effectively make the final decisions. And that is very exciting I think to everybody that we are moving fast, yeah? But we need to kind of find out some of the tweaks, and some of the report and structures that we can use to really help people to use that information most effectively. But I can also share with you, you saw the team that has been involved in preparation of this workshop. Everybody wants to move this environment forward. There's nobody kind of trying to hinder anything. We really are interested allowing to move and -- and have a positive impact in this environment.

And before I close this workshop, I would really like to thank several people. First of all the FDA workshop organization team, Dr. Gitterman, Dr. Shava, Dr. Wilhelm, Ms. Convel, Dr. Anderson, and Dr. Werseo, as well as Ms. Sheer, Kim Sconce, Dr. Whitney, and Dr. Roth. This organizational and these communication educational meetings don't

happen without additional help from our team on the educational office, Susan Warren and Peggy Ronan, and also would like to extend to the conference management Alissa Polovoy, approved by Jason Conti. And please join me to give them a small appreciation.

(Applause.)

MR. SCHERF: Lastly, I would also like to thank the speakers and the panelists. I think it was really, really helpful to get your information and your perspective from a clinical perspective as well as from the laboratory perspective. So thank you very much for providing us, and thank you all who attended this meeting and provided the feedback, and have a safe trip back and thank you very much for coming.

(The meeting concluded at 5:06 p.m.)

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