

**Immediately-in-effect guidance: Antimicrobial Susceptibility Test System Devices - Updating
Breakpoints in Device Labeling
December 5, 2023**

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello everyone and welcome to today's CDRH webinar. Thanks for joining us. This is Commander Kim Piermatteo of the United States Public Health Service and I serve as the Education Program Administrator in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be the moderator for today's webinar.

Today, we will discuss the immediately-in-effect guidance titled "Antimicrobial Susceptibility Test System Devices - Updating Breakpoints and Device Labeling," which was issued on September 29, 2023, and answer your questions about the guidance. This guidance is intended to provide industry and FDA staff with information regarding updating susceptibility test interpretive criteria, or STIC, which is synonymous with the term breakpoints, as well as provide information regarding associated performance data and device labeling for antimicrobial susceptibility test, or AST, system devices in response to breakpoint changes posted on the FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria website.

Before we begin, I'd like to provide a few reminders for the webinar. First, please make sure you've joined us through the Zoom app and not through a web browser to avoid technical issues. Second, the intended audience for this webinar is industry. Trade press reporters are encouraged to consult with the CDRH Trade Press Team at CDRHTradePress@fda.hhs.gov. And members of national media may consult with FDA's Office of Media Affairs at FDAOMA@fda.hhs.gov. And lastly, we look forward to interacting with you during the live question and answer segment of today's webinar. If you have a question, please wait and raise your hand at the end of today's presentation to get into the queue.

I now have the pleasure of introducing our presenters for today's webinar, Dr. Ribhi Shawar, Assistant Director of the Division of Microbiology Devices in the Office of Health Technology Number 7, or OHT7, for in vitro diagnostics, within the Office of Product Evaluation and Quality, or OPEQ, in CDRH. Joining Ribhi is Dr. Sarah Alsamara, Medical Officer in the Division of Microbiology Devices in OHT7 in OPEQ as well, and Dr. Natasha Griffin, Team Lead in the Division of Microbiology Devices in OHT7 in OPEQ as well.

We'll begin with a presentation from our presenters and then field your questions about our topic. Thank you all again for joining us. I'll now turn it over to Sarah to start today's presentation.

Sarah Alsamara: Thank you very much. I will now start the in-depth discussion of the immediately-in-effect guidance.

Our learning objectives from this webinar are to discuss the clinical significance of using updated breakpoints with AST system devices, to describe the background and scope of the guidance, and to describe the approaches outlined in the guidance for updating breakpoints in AST system devices.

I will first talk about the clinical significance of breakpoints.

First, we'll define an AST system device, which is an in vitro diagnostic device in which results are used to determine the susceptibility or resistance of a specific organism to a given antimicrobial agent, to inform therapeutic decisions, and importantly, to identify epidemiologic trends of antimicrobial-resistant organisms. And this is used to detect things like emerging resistance.

How are breakpoints established, and how are they used clinically? Well, breakpoints are well-established qualitative interpretations of quantitative results. They're determined based on microbiological, pharmacological, and clinical evidence to correlate interpretive categories with clinical outcomes. Importantly, breakpoints may be revised over time due to changing epidemiology and emerging resistance.

This slide explains the interpretive categories of breakpoints. So, the first is susceptible, meaning that there is a high likelihood of therapeutic success. Intermediate means that there is uncertain probability of therapeutic effect. And in the case of resistance, this means there's a high likelihood of therapeutic failure.

I will now share a clinical example demonstrating the use of breakpoints to inform clinical decision making. We see, in this example, we are looking at the organism enterobacterales and the antimicrobial ciprofloxacin. We can see that the breakpoints for this organism and antimicrobial combination have been revised. When we look at the graphical representation of this below, we see that at an MIC equal to one, under the old breakpoint interpretive criteria, this interpretive category would be susceptible, meaning that there would be a high likelihood of therapeutic success if this organism were treated with this antimicrobial agent. This would signal to clinicians that this antimicrobial could be effectively used.

However, when we look at the line below, using the new breakpoint, we see that with the most updated breakpoint, at an MIC of one, the interpretive category is actually resistant, meaning that there is a high likelihood of therapeutic failure. In this case, we see the importance of having updated breakpoints in order to guide clinicians to choose the most appropriate antibiotic to treat the infection. Using antibiotics that are ineffective against organisms can lead to progression of disease and undertreating of infection.

Now I will turn to Ribhi Shawar for the next part of this presentation.

Ribhi Shawar: Thank you, Sarah, for this highlight of the clinical relevance and importance of breakpoints for interpretation of results from AST devices.

Good afternoon, everyone. In the next few slides I'll provide some pertinent background and elaborate on the scope and applicability as they relate to this guidance.

But first, some background. As many on this call may be familiar, there are several guidance documents, initiatives, and other developments related to antimicrobial and antifungal drugs from CDER, the Center for Drug Evaluation and Research, and to AST devices from CDRH, the Center for Devices and Radiological Health. Without going too deep into history, in 2009, there was a need to revise guidance documents, including the joint CDER/CDRH guidance, as a result of multiple interactions and citizens' petition regarding appropriate breakpoints to use.

This guidance described a mechanism for updating breakpoints in AST system devices but did not provide specifics on processes. With the issuance of the immediate-in-effect AST guidance we are discussing today, that original 2009 was withdrawn. Now I want to take the opportunity to highlight some resources and initiatives that FDA had made throughout the years to facilitate and streamline development of AST devices and applicability of up-to-date breakpoints.

One such important development occurred as a result of the 21st Century Cures Act, signed into law on December 13, 2016. As a result, in 2017, a website was established by FDA referred to as a STIC, this is short for Susceptibility Test Interpretive Criteria, which provides in a single place a list of all FDA-recognized or established breakpoints for such drug organism or organism group combinations. This is pertinent to the discussions we are having at this webinar today since FDA-recognized breakpoints on the STIC website should be used when developing or updating AST devices. The slide contains a hyperlink to this website if you wish to go to it.

A couple of other initiatives are worth mentioning, as they are extremely valuable. One is the CDC and FDA Antimicrobial Resistance Isolate Bank, known as the AR Bank, or referred to as the AR Bank. The AR Bank was an FDA initiative established over eight years ago as an interagency agreement between FDA and CDC. I want to thank and acknowledge the hard work by our CDC colleagues for maintaining and continuing to support this effort. This has been a tremendously valuable source and resource of well-characterized isolates that can be used in developing or updating AST devices, as well as in clinical and public health laboratories. The isolates are provided free of charge and this slide contains a hyperlink to this website. Please visit it.

And the final point on this slide is the Coordinated Development Guidance, which was issued in 2019. This is, again, a combined CDER/CDRH guidance, offers steps that drug and device manufacturers can take to facilitate availability of AST devices for use in clinical lab in a timely manner after new drug approval.

Now let's turn our attention to the subject matter for updating breakpoints in AST devices. Since 2019, FDA has established a mechanism whereby an AST device manufacturer can include, along with their regulatory submission for clearance, a breakpoint change protocol, abbreviated here as BCP. But this does not flow from the tongue very well, at least not for me, so, I might just keep saying breakpoint change protocol. At any rate, this, in essence, is an SOP, standard operating procedure, which describes steps an AST device manufacturer will take to update the breakpoint information in labeling, or package insert, if certain conditions apply without the need to submit a regulatory application to FDA.

To date, FDA has reviewed and cleared over 60 AST device applications with such breakpoint change protocol and this facilitates availability of devices with updated information. However, up until recently, such breakpoint change protocols were only applicable to devices and drug-organism combinations for that specific drug-organism combination used on that device.

With the issuance of the immediate-in-effect guidance, AST device label can be updated using a predetermined change control plan, or PCCP, or a previously cleared, between brackets, breakpoint change protocol. Most importantly, this will be applicable to what we call legacy devices, which Dr. Griffin will describe in a few minutes in more details. Next, I will briefly go over the scope of this guidance.

As you know, there are multiple types of qualitative and quantitative manual or automated AST devices. The scope of this guidance is limited to those devices classified under the Code of Federal Regulations, or CFR, which appear on this slide, along with the product codes. Modifications to these devices, the device package inserts specifically, can be made if the conditions stated in a breakpoint change protocol or a PCCP reviewed and cleared by FDA are applicable.

Now I'm going to turn the floor over to Natasha to guide us through specifics outlined in this guidance and how this will all work. Natasha?

Natasha Hardesty: Thanks, Ribhi.

I will now provide details of the specific policies outlined in the guidance.

The immediately-in-effect guidance describes the use of a predetermined change control plan, or PCCP, to update breakpoints in AST system devices in the event of a future FDA-recognized breakpoint change. A PCCP is documentation provided in a premarket submission that proactively prespecifies and seeks premarket authorization for future changes as outlined in the PCCP. Please note that as it relates to AST devices, this documentation was referred to as a breakpoint change protocol prior to issuance of this guidance. As such, the specifications previously described in breakpoint change protocols are generally the same as those described in PCCPs.

The IIE guidance describes how to establish a PCCP, what content should be included in a PCCP, and how to utilize a PCCP in the event of a future FDA-recognized breakpoint change. I'll describe each in the upcoming slides.

As I mentioned, prior to issuance of the guidance, breakpoint change protocols were received and reviewed for AST devices. The breakpoint change protocols are now being received and reviewed as PCCPs. As such, the purpose, content, and subsequent action remain the same in that PCCPs can be provided for review and clearance with an AST device so that in the event of an FDA-recognized breakpoint change, the PCCP can be followed, and if certain criteria are met, the label can be updated and sent to the AST device's inbox without a new 510(k) submission.

The IIE guidance describes how to establish a PCCP to proactively seek clearance of updated breakpoints and labeling without a new 510(k). FDA is recommending that all AST device manufacturers include a PCCP in future submissions to ensure timely breakpoint updates in the event of a future FDA-recognized breakpoint change. In general, the PCCP should contain procedures that help ensure that the breakpoint update does not significantly change the performance of the previously cleared device.

In general, a PCCP will describe modifications determined to be appropriate for inclusion in the PCCP, as well as the protocol in place to adopt the modification. The guidance states that the PCCP should describe the applicability of the PCCP to AST system devices with the same technological characteristics. This is to allow use of a single PCCP across multiple AST devices, as I will describe later.

In addition, the PCCP should state that the breakpoints to be updated are those that are recognized on the FDA STIC web page. Importantly, the updated breakpoints should fall within the reporting range of the previously cleared device.

In addition, the PCCP should include procedures that will be performed to re-evaluate the clinical data provided in the most recent 510(k) clearance to support the updated breakpoints. This includes determining whether the re-evaluated data demonstrates acceptable performance, as well as includes a sufficient number of resistant isolates. Finally, the PCCP should describe how the AST device label will be updated, including sending the updated labeling to the AST device's inbox, which will be described next.

In the event of an FDA-recognized breakpoint change, an AST device that was cleared with a PCCP can utilize the PCCP to adopt the breakpoint update in accordance with the PCCP. Notably, there may be some scenarios in which the AST device label cannot be updated per the PCCP. In those cases, we recommend that manufacturers refer to the FDA guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device."

When updating the AST device label, it's important to note that the breakpoint update must be documented per the manufacturer's quality system. In addition, the updated labeling should be emailed to the AST devices inbox, ASTdevices@fda.hhs.gov.

To describe how to update breakpoints in AST devices with a PCCP, we've illustrated three different scenarios. In the first scenario, the PCCP is used with the AST device it was cleared with. In this example, an AST device for testing ciprofloxacin is cleared with a PCCP. At some point after clearance, CDER recognized updated breakpoints for ciprofloxacin. At that time, the manufacturer uses the PCCP, and updates the ciprofloxacin device label, and sends it to the AST devices inbox.

The guidance also describes how a PCCP, or breakpoint change protocol, that was cleared for an AST device can be used for a legacy device, which is a device that was cleared without a PCCP, or breakpoint change protocol. For the PCCP or breakpoint change protocol to be applicable, when compared to the AST device cleared with the PCCP or breakpoint change protocol, the legacy device should have been cleared under the same classification regulation and product code, have the same intended use, and have the same technological characteristics.

As previously described, the breakpoint update should be implemented in accordance to the cleared PCCP or breakpoint change protocol. This is because updates that are outside of the scope of the PCCP generally require submission of a 510(k) prior to updating the labeling. In addition, the breakpoint update must be documented per the manufacturer's quality system, as well as internally documented. This documentation should include a reference to the 510(k) submission of the AST device that had the cleared breakpoint change protocol or PCCP that was used. In addition, it should have a summary indicating that the breakpoint change protocol or PCCP that was used was appropriately followed and a final determination that the update falls within the enforcement policy, which is outlined in the guidance. The updated label, as well as the referenced 510(k) submission number, should be emailed to the AST devices inbox.

The second scenario describes use of a previously cleared PCCP or breakpoint change protocol with a legacy AST device. In this illustration, an AST device for testing piperacillin-tazobactam, or pip-tazo, is cleared. Later, an AST device for testing ciprofloxacin is cleared with a breakpoint change protocol or PCCP. At some point in the future, CDER recognizes updated breakpoints for pip-tazo. At that time, the manufacturer uses the breakpoint change protocol or PCCP that was cleared for ciprofloxacin to update the pip-tazo device label. The updated pip-tazo device label, as well as a reference to the ciprofloxacin 510(k) submission, are sent to the AST devices inbox.

The guidance also describes how to incorporate by reference a cleared breakpoint change protocol or PCCP in a future 510(k) submission. Similar to the legacy devices, new AST devices that incorporate cleared breakpoint change protocols or PCCPs by reference in a new 510(k) submission should have the same intended use and technological characteristics as the AST device that was cleared with the breakpoint change protocol or PCCP. As previously described, the breakpoint update should be implemented according to the cleared PCCP or breakpoint change protocol, be documented per the manufacturer's quality system, and the updated labels should be sent to the AST devices inbox.

The third and final scenario describes updating breakpoints with a breakpoint change protocol or PCCP that was incorporated by reference in a new AST device clearance. In this illustration, an AST device for testing ciprofloxacin is cleared with a breakpoint change protocol or PCCP. In the future, an AST device for testing sulbactam-durlobactam is cleared, along with a reference to the breakpoint change protocol or PCCP that was cleared with ciprofloxacin. At some point in the future, CDER recognizes updated breakpoints for sulbactam-durlobactam. At that time, the manufacturer uses the breakpoint change protocol or PCCP that was referenced in the sulbactam-durlobactam clearance, and updates the sulbactam-durlobactam device label, and sends it to the AST devices inbox.

In summary, we want to reiterate that the use of AST devices with updated breakpoints is essential to provide accurate results for patient care and to monitor the emergence of antimicrobial resistance. Breakpoint change protocols have been successfully used to update breakpoints in AST devices. Going forward, we anticipate that PCCPs will continue to be successful in ensuring timely updates to breakpoints.

The immediately-in-effect guidance provides least burdensome recommendations for manufacturers to update breakpoints in AST devices, including legacy AST devices. As such, manufacturers that have a cleared breakpoint change protocol can immediately begin using it to update breakpoints of legacy AST devices.

Further, AST device manufacturers without a clear breakpoint change protocol should submit a 510(k) for an AST device and include a PCCP for review. After clearance, the PCCP can be used to update breakpoints for legacy AST devices, as described in the guidance.

Here are the resources that were mentioned earlier in the presentation, along with the full URL that you can access after the presentation.

Although this immediately-in-effect guidance was implemented without prior public comment, comments may be submitted to the docket number FDA-2023-D-4045. FDA will consider all comments received and revise the guidance as appropriate.

Thank you for your time and attention. We look forward to answering your questions. I'll now turn it back over to Kim.

CDR Kim Piermatteo: Thank you Natasha. And thank you to Sarah and Ribhi for your presentation as well. We will now transition to our interactive question and answer segment.

Before we begin, I'd like to go over how we will manage this segment and give you a few reminders. First, to ask a question, please select the Raise Hand icon, which should appear on the bottom of your Zoom screen. I'll announce your name and give you permission to talk. When prompted, please select the blue button to unmute your line and then ask your question. When asking your question, please remember to limit yourself to asking one question only and try to keep it as short as possible. And we appreciate that you may have a very specific question involving your device or scenario; however, we might not be able to answer such specific questions. Therefore, we'll try to frame a broader response based on what's described in this guidance. After you ask your question, please lower your hand. And if you have another question, please raise your hand again to get back into the queue and I'll call on you as time permits.

While we await your questions, I would like to ask our presenters a few questions we've received regarding the immediately-in-effect guidance. So, Ribhi, I'd like to ask you this question. Why are disk devices outside of the scope of the guidance?

Ribhi Shawar: Alright, thank you, Kim. Yeah, I'd be happy to take that. The answer to this one is, we expect that question to have come, really, from several. For the majority of AST disk devices, as many of the people in attendance here will know, the clearance relies on leveraging information used to establish disk-to-MIC correlates as part of the antimicrobial drug review and approval. And so, we are actively working on an approach to allow a breakpoint change protocol, or revisions, or PCCP of some sort, to disk package inserts in order to allow for that updated information to get in the hands of users. In the meantime, if you have any specific questions, please submit them to ASTdevices@fda.hhs.gov inbox.

CDR Kim Piermatteo: Thanks, Ribhi. Now I'd like to ask Natasha a question. Natasha, the question is, if a manufacturer has a previously cleared breakpoint change protocol, do they need to submit a PCCP?

Natasha Griffin: Thanks. Thanks, Kim. No. A manufacturer with a previously cleared breakpoint change protocol does not need to submit a PCCP. As the least burdensome approach, the guidance allows manufacturers to use previously cleared breakpoint change protocols in lieu of submitting a PCCP. As noted in the guidance, previously cleared protocols can be applied to legacy devices and can also be incorporated by reference in future AST device premarket submissions.

CDR Kim Piermatteo: Great. Thanks, Natasha. And for this last question, Sarah, I'll be directing that to you. Sarah, the question is, how can end users and manufacturers easily identify FDA-recognized breakpoint updates?

Sarah Alsamarai: Thank you, Kim. So, for current up-to-date breakpoint information, you can go to the FDA STIC website, and this is also noted on the Resources slide of our PowerPoint. And note that when applicable, the FDA STIC website may refer to CLSI documents for current breakpoints. We also do recommend that manufacturers sign up to receive the FDA-recognized antimicrobial STIC breakpoints email notifications, available on the STIC website, to make sure that they receive notifications on future updates.

CDR Kim Piermatteo: Great. Thanks again, Sarah. Thanks for your response. We'll now take our first live question, which is coming from Briget. Briget, I have unmuted your line. Please unmute yourself and ask your question.

Briget, are you able to unmute yourself?

Alright, Briget if you are double muted, please check that and I will try to circle back to you in a few.

Our next, what I'd like to do is I'd like to circle back to Natasha and ask you a question we've received previously as well. And that question is, if a company did not have any previously cleared PCCP or BPC protocol, what should they do?

Natasha Griffin: Thanks, Kim. We are strongly encouraging manufacturers without a previously cleared PCCP or breakpoint change protocol to submit a 510(k) submission for their AST system device with a PCCP. As a reminder, before PCCP can be applied to legacy devices, it will need to first be reviewed and cleared by FDA.

CDR Kim Piermatteo: Thanks, Natasha. Alright, I'm going to call on Lacey. Lacey, I have unmuted your line. Please unmute yourself and ask your question.

Lacey Harbour: Hi, everyone. Can you hear me just fine?

CDR Kim Piermatteo: Yes, we can.

Lacey Harbour: Thank you. I'm actually curious on how you see the breakpoint change device and the PCCP, whatever you want to call it, would be overlapping with the letter to file process. You stated that you need to follow your internal quality management system. But I was wondering if you guys could go in a little bit more detail on what you see that process looking like and if it would be different from the BCPs versus the PCCPs.

CDR Kim Piermatteo: Thank you, Lacey. I'm going to turn it over to Ribhi to provide you a response.

Ribhi Shawar: Yeah. Thank you, Lacey, for this question. Clearly, any device manufacturer knows about the quality system that they need to follow. In essence, the breakpoint change protocol or PCCP are documents that a sponsor establishes for certain steps and processes that they want to follow within their own systems when certain conditions apply. So, in essence, this is still following up on their overall quality system regulation, irrespective of how they, as a manufacturer, intend to provide those documentations within their own system. So, this way, this is not a different approach or a, it in fact, is a least burdensome approach, such as no need for duplication of any type of effort. I hope I addressed that. But if not, then if we have time, we can maybe circle back with further information.

CDR Kim Piermatteo: Thanks, Ribhi. Lacey, did you have any follow-up questions?

Lacey Harbour: I don't. I think that that answers it. So you're not saying that if you had a letter to file method, that if you were following, if you did an analysis that proved that you were still within the PCCP, and you knew you had to update the labeling, you were going through that process, you had the procedures in place and the SOPs in place, that you don't need to then turn around to your letter to file procedure. You can just update your, am I understanding that you're saying, if someone were to update their letter to file procedures and reference that if there is a PCCP that's been established, that you

follow that? Or is that what you're saying, or something to that effect? I'm just trying to make sure that it's 100% understood.

Ribhi Shawar: Yeah. I'll try and clarify it further. But if not, please feel free to send us an email to the AST devices inbox and we can address it that way. But in general, as Natasha explained, there's the processes that need to be followed, meaning that a PCCP or breakpoint change protocol would have been reviewed by FDA, would have been concurred with, before any manufacturer on their own decided to do those kind of things. FDA needs to know and be informed about how these processes are working and that they concur with the SOP, if you will, of how things are to be applied. But again, please feel free to send us an email to the inbox if there are still questions.

Lacey Harbour: Thank you. Yeah, I'm partially asking because, as you are likely aware, software as a medical device has the new PCCP application guidance documents. And so, you as you have already established this process, just trying to understand how to use it for devices that are not just the ASTs. So, thank you so much. I think that made quite a bit, that added clarity. Thank you.

Ribhi Shawar: Thank you.

CDR Kim Piermatteo: Thanks Lacey for your question and thanks Ribhi for your response. Next, I am going to circle back to Sarah for a question we previously received. Sarah, the question is, can a manufacturer send in a 510(k) with only a PCCP? Or does the PCCP have to accompany a request for a device clearance?

Sarah Alsamarai: Thanks, Kim. So, no. As described in the guidance, a PCCP must accompany a premarket submission with a device.

CDR Kim Piermatteo: Great. Thanks for clarifying, Sarah. Next, I'd like to call on Sharon. Sharon, I have unmuted your line. Please unmute yourself and ask your question.

Sharon Cullen: Hi, this is Sharon. So first of all, thanks for the tremendous progress in establishing a process for legacy devices. So, I wanted to acknowledge that. Then I wanted to follow up with a question of, there are limited situations where we could use these PCCPs. Specifically, currently, if we test additional isolates or have to do additional testing, then it doesn't qualify for the PCCP. My question is, do you have plans to pursue further expansion of when we can apply the PCCP? And if so, what would that look like?

CDR Kim Piermatteo: Thank you Sharon for your question. Would anyone on the team like to provide a response? It does, Sharon, that does sound a little bit outside the scope of our webinar for today. I don't know, Ribhi or Natasha, if you wanted to expand on that or have-- I guess, Sharon, we would suggest you could email the AST email box if you wanted some specific information, or the docket that we had mentioned earlier.

Sharon Cullen: OK. STMA can probably then respond through the docket with a couple of questions. That would be a good approach.

CDR Kim Piermatteo: Great. Thanks, Sharon. Alright, our next question is coming from a number. That number is 10021728. I've unmuted your line. Please unmute yourself and ask your question.

Nathan Hardesty: Hi, yes. We have a quick question regarding indications for use and things that change within breakpoints. If we had a previously cleared organism group, and now the FDA changes the breakpoints, and only a specific organism is now recognized, does that mean that that is still covered under a PCCP or BCP? Or would we have to submit specifically to the new indication for use for that antimicrobial?

CDR Kim Piermatteo: Hi. Thanks for your question. If you could just provide your name real quick and...

Nathan Hardesty: Yes.

CDR Kim Piermatteo: Oh, go ahead.

Nathan Hardesty: Yeah, sorry. This is Nathan Hardesty.

CDR Kim Piermatteo: Great. Thank you, Nathan. I think we're going to turn it over to Ribhi. Did you want to provide a first response? Or if anyone else on the team has anything they want to add, please chime in.

Ribhi Shawar: Yes, I can give it a try. Thank you, Nathan. Appreciate the question. Changes to intended use, like the addition of an organism, taking out of an organism, is still outside of what exactly the intent of this, but could be a result of it, meaning that, as a result of applying something that your SOP stated, there will be changes to it. But again, I think the specifics and nuances for each device are really going to be very hard to cover in a webinar like this. Again, encourage you to either submit to the docket or submit to the AST devices, which I know you have done. But I'm going to also ask, maybe Natasha, if you have any additional thoughts on this, because we discussed those kind of things before.

Natasha Griffin: Nothing more than what Ribhi's already mentioned. So, I'll guess I'll reiterate. In the event that FDA removes breakpoints for a particular organism group, there is an expectation that from the manufacturer side that the intended use for that drug would be updated to reflect FDA's current thinking or decision for that antimicrobial. Again, it's outside the scope of the PCCP, but that is something that should be handled by manufacturers.

CDR Kim Piermatteo: Thanks, Natasha. And thanks, Ribhi. Nathan, I think we want to reiterate that we would like you to submit your comment via email, not through the docket. So, this would be something that you could submit to the AST devices email.

Nathan Hardesty: OK, thank you very much.

Ribhi Shawar: Kim, one other point, sorry this is Ribhi.

CDR Kim Piermatteo: Sure.

Ribhi Shawar: Since this is being recorded, perhaps, also, Pre-Submission depends, again, on the details and the intensity of it. A Pre-Submission might actually be a good one for those types of things because the details will be provided in that Pre-Submission rather than, a simple email might not contain all the information that is needed. So just a suggestion here also.

Nathan Hardesty: OK, sounds great. Thank you.

CDR Kim Piermatteo: Great. Thanks, Ribhi, for that clarification. Alright, I would like to come to Natasha again. Natasha, I'm going to ask you a question we've previously received. And that question is, does the PCCP have to include a listing of legacy devices to which the PCCP may apply?

Natasha Griffin: So, the short answer is no. A PCCP should not include a listing of legacy devices to which it may apply. As noted in the guidance, the PCCP should be generally written for an AST system device and not for a specific drug tested with that system. When updating breakpoints for legacy devices, manufacturers should reference the 510(k) submission number of the cleared PCCP when sending the updated label to the AST devices inbox. In addition, the PCCPs can be incorporated by reference in future AST device submissions.

CDR Kim Piermatteo: Thanks, Natasha. Alright Ribhi, I'm going to come back to you with a question that we have previously received. And that question is, what should happen if all breakpoints for a drug are completely removed from FDA STIC, or STIC?

Ribhi Shawar: Alright thank you, Kim, for the question. Again, those are really good questions, whoever submitted them. So, in general, marketing of an AST device to test for a drug organism combination for which there is no FDA breakpoints would not be in the interest of public health, because usually, this occurs when there is insufficient data to support testing or interpreting that particular combination.

As such, breakpoint information for this drug-organism combination should not be appearing in that label, it should be removed from the labeling. In general, device manufacturers are the ones responsible for ensuring, are responsible for ensuring the continued use of the device in a safe and effective manner, which, of course, includes labeling with up-to-date breakpoints and the removal of unrecognized breakpoints is appropriate. Again, this may be a detailed question and answer, but hopefully, that is clear. Since this is a submitted question, I think that that's all I can say at this point, unless Sarah or Natasha want to add anything.

CDR Kim Piermatteo: OK. Thanks, Ribhi. Hearing none from Sarah and Natasha, we're going to head and move on to another question that I'd like to direct towards Sarah. And Sarah, that question is, what type of submission can a PCCP be submitted with?

Sarah Alsamarai: So, a PCCP can be submitted with any premarket submission for an AST device, regardless of the purpose. And also note that acceptance of a PCCP in a premarket submission will be determined during the review.

CDR Kim Piermatteo: Thanks, Sarah. Alright at this time, I don't see any more raised hands. So, I'd like to make a call out, if you have a question that you would like to ask our presenters today on our topic, please click on that button in Zoom to raise your hand and we can call on you and you can ask our presenters your question.

While we wait for that, Natasha, I'm going to come back to you with another question we've received. And that question is, what is the difference between a breakpoint change protocol and a predetermined change control plan?

Natasha Griffin: So, documents submitted prior to issuance of the IIE guidance are referred to as breakpoint change protocols, while documents submitted after issuance are referred to as PCCPs. As noted in the presentation, the content, scope, and purpose remain the same between both documents. And please note that the format of the PCCP remains at the discretion of the manufacturer.

CDR Kim Piermatteo: Thanks, Natasha. Alright, I'm going to make one more call out. Does anyone on the call today have any questions that they would like to ask today?

If so, I need you to raise your hand in Zoom.

Alright, seeing none, then, we will go ahead and move to close our webinar. That will wrap up our question and answer segment today. Thank you to all of you for your questions and participation. And I'd now like to turn it back over to Ribhi to provide his final thoughts. Ribhi?

Ribhi Shawar: Thank you, Kim. Yes, happy to. So, thank you for attending this webinar. And we hope that the information we shared and the answers to your questions were helpful. As noted in the information we shared, the use of breakpoint change protocols was introduced by FDA several years ago and has shown success.

Many sponsors have taken advantage of the breakpoint change protocol and instituted changes to AST device labels upon FDA-recognized revisions to the breakpoints, such as on the STIC website, thus assuring safe and effective use of these devices. As explained, this new guidance formalizes the use of breakpoint change protocols, now referred to as predetermined change control plans, or PCCPs, to further facilitate the process of breakpoint updates in AST device labeling, while broadening the applicability of clear breakpoint change protocols or PCCPs to legacy AST devices, as Natasha had mentioned.

We strongly encourage manufacturers to take advantage of this least burdensome approach to update their labeling to ensure continued appropriate, safe, and effective use of AST devices. Thank you and have a great rest of your day.

CDR Kim Piermatteo: Thanks, Ribhi, for those final thoughts. For your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on this slide, under the section titled In Vitro Diagnostics. A recording of today's webinar and a transcript will be posted to CDRH Learn under the same section and subsection in the next few weeks. And a screenshot of where you can find these webinar materials has been provided on this slide as well.

Again, if you have additional questions about this guidance, please submit them to ASTdevices@fda.hhs.gov. And if you have additional questions about today's webinar, feel free to reach out to us in DICE at DICE@fda.hhs.gov.

And lastly, we hope you're able to join us for a future CDRH webinar. You can find a listing of all of our upcoming webinars via the link provided on the bottom of the slide at www.fda.gov/CDRHWebinar.

This concludes today's webinar. And thank you all again for joining us. Have a great day.

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