U.S. FOOD & DRUG ADMINISTRATION

Welcome To Today's Webinar

Thanks for joining us!
We'll get started in a few minutes

Today's Topic:
Immediately-in-effect guidance: Antimicrobial Susceptibility Test (AST) System Devices – Updating Breakpoints in Device Labeling

December 5, 2023

Immediately-in-effect guidance: Antimicrobial Susceptibility Test (AST) System Devices – Updating Breakpoints in Device Labeling

Ribhi Shawar, PhD (ABMM)
Assistant Director
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Sarah Alsamarai, MD MS
Medical Officer
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Natasha Griffin, PhD
Team Lead
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Center for Devices and Radiological Health
U.S. Food and Drug Administration

Sarah Alsamarai, MD, MS
Medical Officer
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Immediately-In-Effect (IIE) Guidance

Antimicrobial Susceptibility Test (AST) System Devices – Updating Breakpoints in Device Labeling issued on September 29, 2023

www.fda.gov/regulatory-information/search-fda-guidance-documents/antimicrobial-susceptibility-test-ast-system-devices-updating-breakpoints-device-labeling

Learning Objectives

- Discuss the clinical significance of using updated breakpoints with AST system devices
- Describe the background and scope of the guidance
- Describe the approaches outlined in the guidance for updating breakpoints in AST system devices

Clinical Significance of Breakpoints

AST System Device

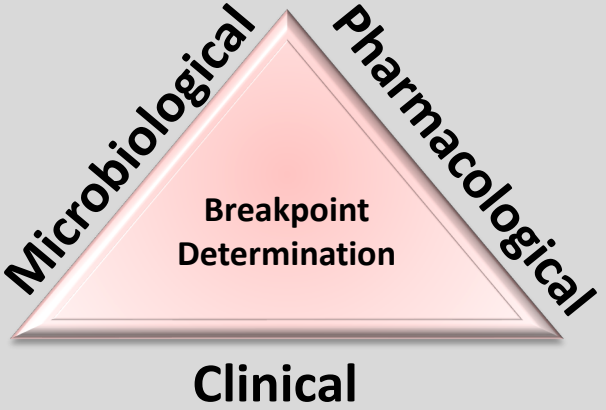
An *in vitro* diagnostic device in which results are used to:

- Determine the susceptibility or resistance of a specific organism to a given antimicrobial agent
- Inform therapeutic decisions
- Identify epidemiologic-trends of antimicrobial-resistant organisms (such as emerging resistance)

Establishment and Use of Breakpoints

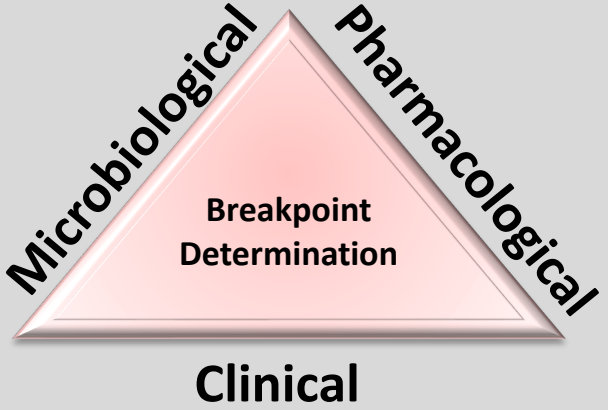
Breakpoints are:

- well-established qualitative interpretations of quantitative results
- determined based on microbiological, pharmacological and clinical evidence to correlate **interpretive categories** with clinical outcomes
- may be revised over time due to changing epidemiology and emerging resistance



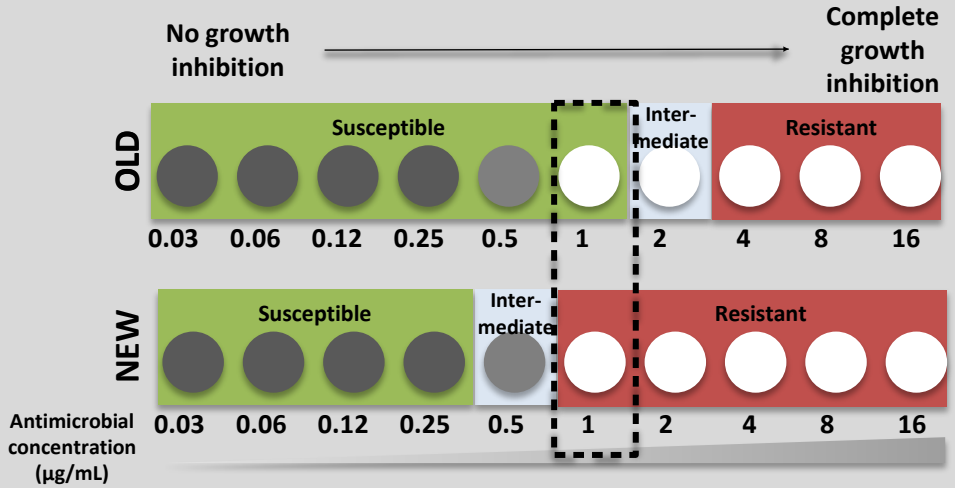
Interpretive Categories (i.e., Breakpoints)

- **Susceptible (S)**
  - High likelihood of therapeutic success
- **Intermediate (I)**
  - Uncertain probability of therapeutic effect
- **Resistant (R)**
  - High likelihood of therapeutic failure



AST System Device Performance Evaluated with Breakpoints

Enterobacterales - Ciprofloxacin	Breakpoints (S,I,R)	
	OLD	NEW
MIC value (µg/mL)	≤1, 2, ≥4	≤0.25, 0.5, ≥1



Susceptible
(High likelihood of therapeutic *success*)

Resistant
(High likelihood of therapeutic *failure*)

Ribhi Shawar, PhD (ABMM)
Assistant Director
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Background and Scope

Background

- **FDA (CDER/CDRH) Labeling Update Guidance** (2009)
  - Described an enforcement policy for updating STIC in AST system device labeling
  - Did not describe the procedures for using a breakpoint change protocol (BCP)
  - Withdrawn with issuance of IIE guidance

- **CDC & FDA Antimicrobial Resistance Isolate Bank** (2015)
  - Provides challenge isolates to verify/validate breakpoints

- **FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria (STIC) website** (2017)
  - Required by the 21st Century Cures Act to provide up-to-date breakpoint information online
  - Limited use of FDA-recognized breakpoints to those that appear on the FDA STIC webpage

- **FDA (CDER/CDRH) Coordinated Development Guidance** (2019)
  - Outlined steps to facilitate timely availability of AST Devices in a timely manner at the time of drug approval or shortly thereafter.

CDER – Center for Drug Evaluation and Research
CDC – Centers for Disease Control and Prevention

Paths to Update Breakpoints on AST System Devices

Pre-IIE Guidance Issuance

- Update AST device label using BCP
  - To date, FDA has cleared >60 AST devices with BCPs and updated labels consistent with the BCP
- Only applied to AST devices cleared with a BCP

Post-IIE Guidance Issuance

- Update AST device label using predetermined change control plan (PCCP) or previously cleared BCP
- May be applied to legacy AST system devices

Scope of Guidance

Limited to:

- AST devices classified under the regulation numbers and with the product codes summarized in table
- Modifications related to breakpoint updates

Regulation Number	Product Code	Device Type
21 CFR 866.1640	LRG	Instrument For Auto Reader & Interpretation Of Overnight Suscept. Systems
	JWY	Manual Antimicrobial Susceptibility Test Systems
	LTT	Panels, Test, Susceptibility, Antimicrobial
	JTT	Susceptibility Test Powders, Antimicrobial
	LTW	Susceptibility Test Cards, Antimicrobial
	NGZ	Susceptibility Test Plate, Antifungal
21 CFR 866.1645	LON	System, Test, Automated, Antimicrobial Susceptibility, Short Incubation
21 CFR 866.1650	PRH	Positive Blood Culture Identification And Ast Kit

CFR – Code of Federal Regulations

Natasha Griffin, PhD
Team Lead
Division of Microbiology Devices
Office of In Vitro Diagnostics (OHT7)
Office of Product Evaluation and Quality

Policies Outlined in the Guidance

Updating Breakpoints in AST System Device Labeling: PCCP

- A PCCP is documentation proposed in a premarket submission that proactively prespecifies and seeks premarket authorization
  - *For AST system devices, this documentation was referred to as a BCP prior to issuance of the IIE guidance*
- IIE Guidance addresses updating AST system device labeling in the event of an FDA-recognized breakpoint change, as follows:
  - How to establish a PCCP
  - What content should be in a PCCP
  - How to utilize a PCCP

PCCP for AST System Devices

Why: Approach to update breakpoints in AST devices without a new 510(k)

What: Documentation for evaluating breakpoint changes

Who: AST device manufacturer generates PCCP with FDA feedback

When: Submitted for review and clearance with an AST device 510(k) submission

How: PCCP is followed in the event of an FDA-recognized breakpoint change

Result: If PCCP is appropriately followed (that is, no deviations), updated label sent to ASTdevices@fda.hhs.gov *without* a new 510(k).

NOTE: BCPs are now being received and reviewed as PCCPs

Establishing a PCCP

- AST device manufacturers can propose a PCCP to proactively seek clearance of updated breakpoints in labeling without the need for a new 510(k)
- FDA recommends that all AST system device submissions include a PCCP in future submissions
- PCCP should contain procedures to help ensure that breakpoint updates do not significantly change the performance

See Section IV.A(1) of guidance for full establishment recommendations

Content of a PCCP

- Description of Modifications
  - Describes the applicability to AST system devices with same technological characteristics
  - Updated breakpoints being adopted:
    - Identical to the relevant breakpoints on the FDA-recognized STIC website
    - Fall within the previously-cleared reporting range
- Modification Protocol
  - Procedures to re-evaluate clinical data in most recent 510(k) clearance
    - Acceptable performance
    - Sufficient number of resistant isolates
  - Planned updates to AST labeling

See Section IV.A(3) of guidance for full content recommendations

Utilizing a PCCP

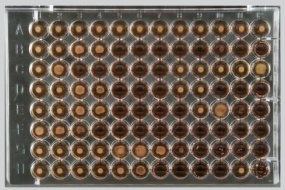
- With a PCCP that has been reviewed and cleared in a 510(k) for an AST system device:
  - Breakpoint update can be implemented according to the cleared PCCP
    - Refer to the FDA guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device" for changes outside of the scope
  - Breakpoint update must be documented per the manufacturer's quality system
  - Updated labeling should be emailed to ASTdevices@fda.hhs.gov

See Section IV.A(2) of guidance for full utilization recommendations

Approach to Update Breakpoints in AST System Devices *with a PCCP*

Scenario #1: Use PCCP with the AST system device it was cleared with

Ciprofloxacin device cleared with PCCP



CDER recognizes updated breakpoints for ciprofloxacin

Center for Drug Evaluation and Research

PCCP used and updated ciprofloxacin device label sent to ASTdevices@fda.hhs.gov

See Section IV.A(2) of guidance for full utilization recommendations

A *Legacy* AST System Device

- Compared to the device cleared with the BCP/PCCP, the ***legacy*** device should:
  - Be previously 510(k) cleared under the same classification regulation and product code,
  - Have the same intended use, and
  - Have the same technological characteristics

Utilization of a BCP/PCCP for *Legacy* AST System Devices

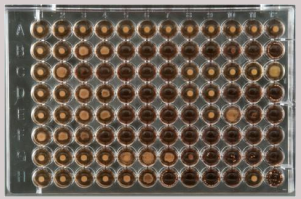
- Breakpoint update should be implemented according to the cleared BCP/PCCP
  - Breakpoint updates that are not specified in, or implemented in accordance with, the cleared BCP/PCCP generally require submission of a 510(k) prior to updating the labeling
- Breakpoint update must be documented per the manufacturer's quality system
- Internal documentation should include:
  - Reference to 510(k) submission number of cleared BCP/PCCP
  - Summary that the protocol was appropriately followed
  - Determination that update falls within the enforcement policy outlined in this guidance
- Updated label and referenced 510(k) submission number should be emailed to ASTdevices@fda.hhs.gov

See Section IV.B of guidance for full recommendations for legacy AST devices

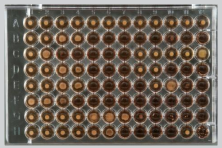
Approach to Update Breakpoints in *Legacy* AST System Devices

Scenario #2: Use cleared BCP/PCCP with legacy AST system device

Piperacillin-tazobactam device cleared



Ciprofloxacin device cleared with BCP/PCCP



CDER recognizes updated breakpoints for piperacillin-tazobactam

Center for Drug Evaluation and Research

BCP/PCCP (cleared for ciprofloxacin device) used and updated piperacillin-tazobactam device label sent to ASTdevices@fda.hhs.gov

See Section IV.B of guidance for full recommendations for legacy AST devices

Utilization of a BCP/PCCP *incorporated by reference* for AST System Devices

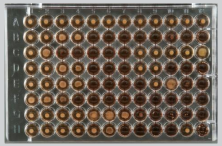
- Manufacturers may reference cleared BCP/PCCP with new 510(k) submissions
  - *New AST device should have the same intended use and technological characteristics as the device cleared with the BCP/PCCP*
  - Submission should include the 510(k) submission number of the cleared BCP/PCCP
- Breakpoint update should be implemented according to the cleared BCP/PCCP
- Breakpoint update should be documented per the manufacturer's quality system
- Updated label should be emailed to ASTdevices@fda.hhs.gov

See Section IV.C of guidance for full recommendations to incorporate by reference

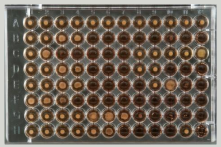
Approach to Update Breakpoints in AST System Devices *with a referenced BCP/PCCP*

Scenario #3: Use a cleared BCP/PCCP that was incorporated by reference with an AST system device clearance

Ciprofloxacin device cleared with BCP/PCCP



Sulbactam-durlobactam device cleared with referenced BCP/PCCP



CDER recognizes updated breakpoints for sulbactam-durlobactam

Center for Drug Evaluation and Research

BCP/PCCP (cleared for ciprofloxacin device) used and updated sulbactam-durlobactam device label sent to ASTdevices@fda.hhs.gov

See Section IV.C of guidance for full recommendations to incorporate by reference

Summary

- Use of AST devices with updated breakpoints is essential to provide accurate results for patient care and to monitor emergence of resistance

- BCPs have been successfully used to update breakpoints in AST devices

- IIE guidance provides least burdensome recommendations to update breakpoints in AST devices, including legacy AST devices

- Manufacturers of AST devices with a cleared BCP can ***immediately*** begin applying it to legacy AST devices

- Manufacturers of AST devices without a cleared BCP should submit a 510(k) submission 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 outlined in the guidance

Resources

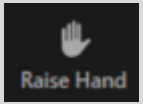
Slide Number	Cited Resource	URL
13	Antimicrobial Susceptibility Test (AST) Systems - Class II Special Controls Guidance for Industry and FDA	www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/antimicrobial-susceptibility-test-ast-systems-class-ii-special-controls-guidance-industry-and-fda
13	FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria	www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
13	21st Century Cures Act	www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act
13	Coordinated Development	www.fda.gov/media/124382/download
13	CDC & FDA Antimicrobial Resistance (AR) Isolate Bank	www.cdc.gov/drugresistance/resistance-bank/index.html
22	Deciding When to Submit a 510(k) for a Change to an Existing Device	www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device

Submit Comments to Docket

- Although implemented without prior public comment, comments may be submitted to the docket number **FDA-2023-D-4045** (www.regulations.gov/docket/FDA-2023-D-4045), in accordance with the Agency's good guidance practices.
- FDA will consider all comments received and revise the guidance as appropriate.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Let's Take Your Questions

- **To Ask a Question:**
  - Raise your hand in Zoom 

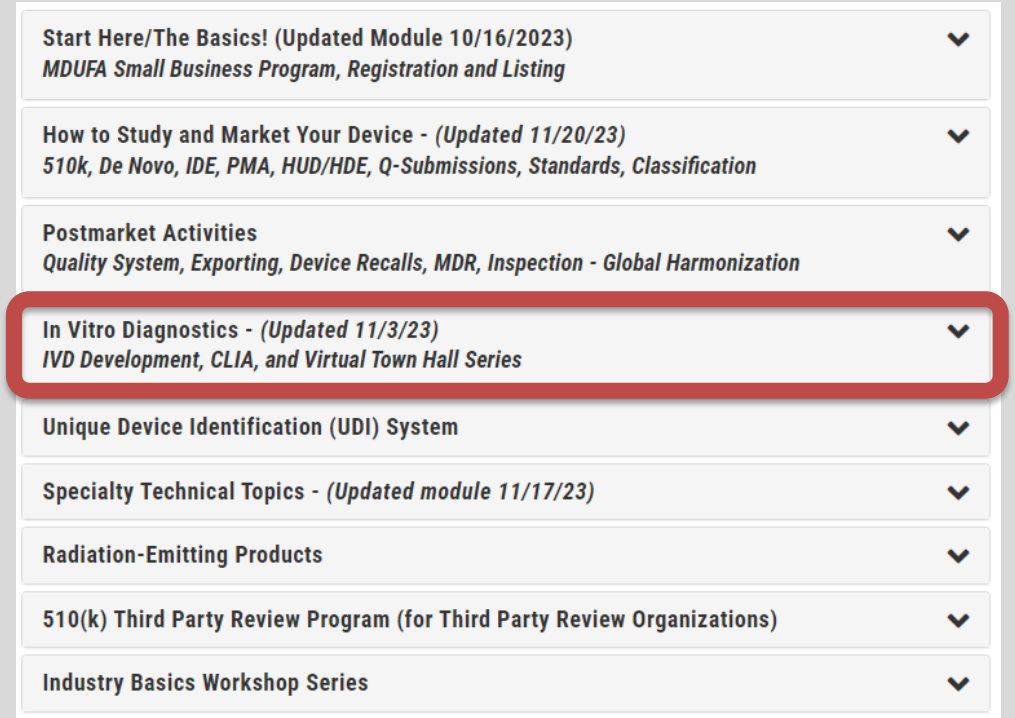
  - Moderator will announce your name and invite you to ask your question
  - Unmute yourself when prompted in Zoom to ask your question

- **When Asking a Question:**
  - Ask one question only
  - Keep question short
  - No questions about specific submissions

- **After Question is Answered:**
  - Mute yourself and lower your hand
  - If you have more questions - raise your hand again

Thanks for Joining Today!

- **Presentation and Transcript will be available at CDRH Learn**
  - www.fda.gov/Training/CDRHLearn
- **Additional questions about today's presentation**
  - Email: DICE@fda.hhs.gov
- **Upcoming Webinars**
  - www.fda.gov/CDRHWebinar




FDA
U.S. FOOD & DRUG
ADMINISTRATION