

Breakpoint Implementation Toolkit

Clinical laboratories performing antimicrobial susceptibility testing (AST) should use breakpoints currently recognized by Clinical and Laboratory Standards Institute (CLSI) or US Food and Drug Administration (FDA). CLSI, Association of Public Health Laboratories (APHL), American Society for Microbiology (ASM), College of American Pathologists (CAP), and Centers for Disease Control and Prevention (CDC), have jointly developed this toolkit to assist clinical laboratories in updating minimal inhibitory concentration (MIC) breakpoints. It is provided in a streamlined format and designed to guide performance of a verification or validation study required to update breakpoints. There are links to other resources that explain the rationale behind breakpoint updates, regulatory requirements for updating breakpoints, and detailed instructions for performing an AST breakpoint validation or verification. Manufacturers of AST systems can provide guidance on breakpoints used and clearance status with their systems.

Contents

Introduction

- How to Use Breakpoint Implementation Toolkit
- Definitions/References/Resources
- Pathway for Updating Breakpoints (Figure 1)

Part A. Breakpoints in Use

- Template for Documenting Breakpoints in Use

Part B. CLSI vs FDA Breakpoints

- Listing of all current CLSI breakpoints (M100-Ed34) and corresponding FDA breakpoints

Part C. Breakpoint Implementation Summary

- Template for documenting results of a validation study to update breakpoints

Part D. CDC and FDA AR Bank BIT Isolate Sets

- CDC and FDA Antibiotic Resistance Isolate Bank isolate sets available for use in breakpoint verification and validation studies

Part E. Instructions for Use of BIT Part F

- Instructions for using the prefilled Excel workbook

Part F. AR Bank Data Entry and Calculations

- Excel workbook prefilled with the AR Bank BIT set isolates and their results

Part G. Blank Form for Data Entry

- Template for validations or verifications using isolates other than those listed in the AR Bank BIT sets included in this toolkit

How to Use Breakpoint Implementation Toolkit

It is assumed that those using this toolkit have some knowledge of the need to update AST breakpoints. Please check references in the list below for more detailed information about updating breakpoints.

The APHL-ASM CRO Breakpoint Implementation Toolkit published in 2022 and accessible [here](#) contains detailed instructions, as well as worksheets and forms for validating updated carbapenem breakpoints, and is based on the CAP Breakpoint Implementation Toolkit (2012, no longer available). These instructions can be adapted to verification or validation of other breakpoints when following guidance included in the Breakpoint Implementation Toolkit.

In brief, it is suggested that you proceed as follows:

1. Determine what breakpoints are in use in your laboratory.
2. Determine which of these breakpoints are old or out of date (eg, no longer recognized by CLSI or FDA) and would require updating for continued reporting.
3. Develop a priority list and a plan for updating breakpoints.

Refer to the flowchart in [Figure 1](#) that highlights a detailed pathway for updating breakpoints.

Refer to Part A [here](#) to assist you in documenting breakpoints in use.

IMPORTANT NOTES:

1. Laboratories are encouraged to implement updated CLSI breakpoints as listed in M100, 34th ed.
2. If CLSI breakpoints differ from FDA breakpoints, (see [Part B](#)) a laboratory can elect to use current CLSI or FDA breakpoints.
3. Manufacturers of commercial AST must use FDA breakpoints that are current at the time they submit a test for FDA clearance.
4. A laboratory should NOT use breakpoints that are no longer recognized by CLSI or FDA.
5. As of January 2024, CAP-accredited laboratories may be penalized if they use breakpoints that are no longer recognized by CLSI or FDA. US laboratories must at least adopt breakpoints within three years of the date of official publication by FDA accepting the revised breakpoints.

Definitions/References/Resources

In the context of updating to current CLSI breakpoints:

Verification is used to evaluate the performance of breakpoints which have been FDA cleared for use on a device manufacturer's AST system (ie, FDA recognizes the CLSI breakpoints, and the manufacturer has obtained clearance by FDA for the current CLSI/FDA breakpoints on their AST system).

Validation refers to any other scenario not covered by verification and when the laboratory is modifying an FDA-cleared test (eg, using breakpoints that are different from those that are FDA cleared for use on the device manufacturer's AST system).

NOTE: Details regarding how AST device manufacturers implement updated breakpoints for their system can be found in Table 3.

Table 1. Situations Where Breakpoint Verification or Validation Is Required to Use Updated CLSI Breakpoints

Updated Breakpoint Status	Commercial Antimicrobial Susceptibility Testing System Status	Performance Assessment Required ^a
CLSI=FDA	CLSI breakpoints are FDA cleared and available on panel/software.	<ul style="list-style-type: none"> • Verification^b • 10 to 15 isolates/drug
CLSI=FDA	Device manufacturer has notified customers that the device has received FDA clearance with updated CLSI/FDA breakpoints and has advised customers how to implement breakpoints with their panels/software.	<ul style="list-style-type: none"> • Verification^b • 10 to 15 isolates/drug
CLSI=FDA	Device manufacturer has not received FDA clearance of the device with updated CLSI/FDA breakpoints.	<ul style="list-style-type: none"> • Validation (if desire to use CLSI breakpoints) • 30 isolates/drug
CLSI≠FDA	Manufacturer must provide FDA breakpoints; use of CLSI breakpoints would be off label.	<ul style="list-style-type: none"> • Validation (if desire to use CLSI breakpoints) • 30 isolates/drug

^a Consensus suggestions from authors of 2023 Breakpoint Implementation Toolkit

^b If no change to the test has been made by the AST manufacturer (eg, no reformulation of drug dilutions), a verification of reporting may be sufficient. This would involve ensuring MIC results are interpreted correctly on patient reports.

Table 2. Resources for Updating Breakpoints

Resource	Location	Comments
Current CLSI Breakpoints	<u>Performance Standards for Antimicrobial Susceptibility Testing, 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.</u>	Updated annually, usually in February
Current FDA Breakpoints	<u>Susceptibility Test Interpretive Criteria (STIC)</u>	Updated as new information is obtained from CLSI and/or pharmaceutical company and reviewed by FDA
CLIA regulations for verification and performance specifications	<u>CLIA §493.1253(b)(1);</u>	No specific details for verification of AST systems
CAP requirements for updating Breakpoints	Contact CAP to obtain complete checklist; see below for specific breakpoint requirements	(Available to CAP-accredited laboratories)
CLSI. Verification of Commercial Microbial Identification and Antimicrobial Susceptibility Testing Systems. 1st ed. CLSI guideline M52. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.	<u>Purchase from clsi.org</u>	1st edition is currently under revision; describes verification in detail; validation is discussed briefly in Appendix B
APHL-ASM CRO Breakpoint Implementation Toolkit	<u>APHL Implementation Toolkit</u>	Contains extensive instructions, worksheets, and forms for validating updated carbapenem breakpoints

Table 3. Considerations for Updated Breakpoint Implementation in Commercial AST Devices

<ul style="list-style-type: none"> • FDA clearance status of a test for an AST device may not be synonymous with up to date FDA breakpoints (ie, clearance may have been granted with previously published FDA breakpoints). • If a test was FDA cleared, and breakpoints were subsequently updated by CLSI, the manufacturer must wait for FDA to review rationale documentation^a and update the FDA Susceptibility Test Interpretive Criteria (STIC) website to reflect FDA acceptance of the updated CLSI breakpoints. • The AST manufacturer can re-submit performance data to FDA for authorization to update the breakpoints for the test for that device only when the FDA STIC website update has occurred.

^a Rationale documents prepared by CLSI when breakpoints are updated can be found [here](#) with a companion webinar [here](#).

References

References Addressing Potential Negative Impact of Using Obsolete Breakpoints

Ambrose PG, Bhavnani SM, Andes DR, et al. Old *in vitro* antimicrobial breakpoints are misleading stewardship efforts, delaying adoption of innovative therapies, and harming patients. *Open Forum Infectious Diseases*. 2020;7(7). doi: <https://doi.org/10.1093/ofid/ofaa084>.

Humphries RM, Hindler JA, Epton E, et al. Carbapenem-resistant Enterobacteriaceae detection practices in California: what are we missing? *Clin Infect Dis*. 2018; 66(7):1061-1067. doi: <https://doi.org/10.1093/cid/cix942>.

Johnson WM, Clark JA, Olney K, et al. Changing times: The impact of gram-negative breakpoint changes over the previous decade. *Antimicrob Stewardship & Healthcare Epidem*. 2022;2(1). doi: <https://doi.org/10.1017/ash.2022.301>.

Yarbrough ML, Wallace MA, Potter RF, et al. Breakpoint beware: reliance on historical breakpoints for Enterobacteriaceae leads to discrepancies in interpretation of susceptibility testing for carbapenems and cephalosporins and gaps in detection of carbapenem-resistant organisms. *Eur J Clin Microbiol Infect Dis*. 2020;39(1):187-195. doi: <https://doi.org/10.1007/s10096-019-03711-y>.

References Addressing Understanding Breakpoint Updating

Humphries RM, Abbott AN, Hindler JA. Understanding and addressing CLSI breakpoint revisions: a primer for clinical laboratories. *J Clin Microbiol*. 2019;57(6). doi: <https://doi.org/10.1128/JCM.00203-19>.

Newitt VN. AST and safety at core of microbiology checklist changes. *CAP Today*. October 2021. <https://www.captodayonline.com/ast-and-safety-at-core-of-microbiology-checklist-changes/>
Accessed March 16, 2023.

Simner PJ, Rauch CA, Martin IW, et al. Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints. *Open Forum Infectious Diseases*. 2022;9(3). doi: <https://doi.org/10.1093/ofid/ofac007>.

To access the entire BIT Toolkit, visit <https://clsi.org/bit-toolkit/>.