1. **What is the timeline for updating our breakpoints for interpretation of antimicrobial susceptibility testing (AST) results?**

   Per CAP MIC.11385, laboratories subject to U.S. regulations must be up to date with breakpoints within 3 years of their publication by FDA. Laboratories not subject to U.S. regulations must update within 3 years of their publication by Standards Development Organizations (SDOs). This requirement is effective as of January 1, 2024.

   Note: SDOs with breakpoints currently acceptable for use by clinical laboratories include CLSI and EUCAST.

   Table 1 provides examples of when breakpoint revisions occur and what timeline is required of laboratories to update to current breakpoints based on the January 1, 2024 effective date.

   **Table 1: Timeline to Breakpoint Revision and Adoption by Laboratories**

<table>
<thead>
<tr>
<th>Year</th>
<th>Breakpoint version to update to</th>
</tr>
</thead>
<tbody>
<tr>
<td>2024</td>
<td>Must be up to date with FDA/SDO breakpoints published in 2021 standards (i.e., “catch up” to 2021 standards must be complete).</td>
</tr>
<tr>
<td>2025</td>
<td>FDA/SDO breakpoints updates from 2022 must be implemented</td>
</tr>
<tr>
<td>2026</td>
<td>FDA/SDO breakpoints updates from 2023 must be implemented</td>
</tr>
</tbody>
</table>

2. **Must I uniformly apply CLSI, EUCAST or FDA breakpoints to all antimicrobials that I test in my laboratory, or can I use a hybrid approach?**

   Laboratories are not required to implement FDA’s or one SDO’s breakpoints across all antimicrobials tested. However, laboratories should use the same breakpoint source if an antimicrobial is tested across multiple AST systems for the same organism.

   Example: Laboratory tests Enterobacterales against meropenem by both disk diffusion and by an automated AST system. The laboratory should apply breakpoints from the same source to both test systems (e.g., CLSI M100 S33 breakpoints for meropenem should be used for Enterobacterales on both AST systems, not CLSI for one and EUCAST for the other).

   Example: Laboratory applies CLSI M100 S33 Enterobacterales breakpoints to meropenem but EUCAST v.13.0 breakpoints to colistin. This is acceptable.

   Example: Laboratory applies CLSI M100 S33 *Pseudomonas aeruginosa* breakpoints to meropenem but EUCAST Enterobacterales breakpoints to meropenem. This is acceptable. In general, laboratories would apply breakpoints from one source primarily and only occasionally use alternative breakpoints, after consultation with their antibiotic stewardship team.
3. The most recent edition of M100 includes an update to the breakpoints for a specific antimicrobial/organism combination, but the FDA does not yet recognize this update. Must I update to the new CLSI breakpoints?
   No. Laboratories in the U.S. may wait to update the breakpoints until FDA recognizes the updated breakpoints. Once the FDA recognizes the breakpoints, the laboratory will have three years from the FDA publication date to verify/validate the breakpoints. If FDA update does not occur, or is different than CLSI, laboratory may choose to use current CLSI or FDA breakpoints.

4. How does the checklist item apply to laboratories from outside the US?
   Laboratories from outside the U.S. should follow local regulatory requirements and may choose to apply EUCAST, CLSI, or FDA breakpoints. Rarely, institution-specific breakpoints may be established (see question 12).

5. What if the CLSI breakpoints for a specific antimicrobial agent differ from those of the FDA?
   Laboratories (including those in the USA) may choose to use either CLSI or FDA breakpoints (with validation or verification, as appropriate). Be sure to apply the same breakpoints for a specific antimicrobial/organism combination across all AST systems.

6. How do I find FDA breakpoints?
   FDA breakpoints are listed here: https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
   For each antimicrobial agent (i.e., drug), the FDA provides information on whether CLSI breakpoints are recognized and whether there are exceptions or additions to CLSI breakpoints.

7. How do I find the date on which the FDA approved a new breakpoint?
   From the FDA STIC main page (see FAQ #6) click on “Notices of Updates”. The laboratory can also sign up to receive email updates for breakpoint changes.

8. How do I find CLSI breakpoints?
   Breakpoints for aerobic, anaerobic, and commonly encountered fastidious bacteria are published in CLSI M100 which is available for free online: https://clsi.org/all-free-resources/

9. How do I find the date of recent CLSI updates?
   These are listed in each CLSI M100, in the forward materials, “CLSI Breakpoint Additions Since 2010” and “CLSI Breakpoint Revisions Since 2010”

10. How do I know if I must validate/verify my AST system for updated breakpoints?
    First, the lab must determine what breakpoints are currently being applied to interpret AST results. The CAP Microbiology committee in conjunction with CLSI, ASM, and APHL, has created a “Breakpoints in Use” (BPIU) Excel template for laboratories to complete to assess compliance with currently accepted breakpoints. This template is publicly available as part of the new Breakpoint Implementation Toolkit on the CLSI website. Completion of the template will likely require the laboratory to contact their commercial AST system manufacturer (if appropriate) to understand what breakpoints are being applied based on the panel, software, and expert rules utilized. Discrepancies between currently accepted breakpoints and those being applied by the laboratory are identified. The laboratory should then work to verify/validate the breakpoint changes to be
compliant by January 1, 2024. If significant discrepancies exist, the laboratory should work with the antimicrobial stewardship team and clinical colleagues to prioritize the updates required.

11. What if my test system does not have dilutions low enough to accommodate the updated breakpoints?
The laboratory should contact the AST manufacturer as other panel configurations may be available with expanded dilutions. The laboratory may also consider utilizing manual tests (e.g., disk diffusion) if the antimicrobial is tested rarely. Additional approaches are discussed in Understanding and Addressing CLSI Breakpoint Revisions: a Primer for Clinical Laboratories by Humphries et al.

12. What if my antimicrobial stewardship team requests my laboratory to use breakpoints other than those published by FDA, CLSI or EUCAST?
Your antimicrobial stewardship team must provide written documentation describing the rationale for using alternative breakpoints. This documentation must include acknowledgment of acceptance by the CLIA laboratory director.

13. Are the CAP requirements the same for application of breakpoints to organisms beyond those listed in CLSI M100 (e.g., yeast, mycobacteria)?
Yes. This requirement applies to mycobacteria, fungi, and bacteria.

14. Where can I find CLSI breakpoints beyond those published in CLSI M100?
Breakpoints for additional fastidious or infrequently isolated bacteria, yeast, molds, and mycobacteria / aerobic actinomycetes are published in separate CLSI documents; M45, M27M44S, M38M51S, and M62, respectively. M38M51S and M62 documents are available for purchase from CLSI; M45 and M27M44S are available for free using the same link as for M100. https://clsi.org/all-free-resources/

15. What if my laboratory is unable to validate or verify an updated breakpoint?
In some circumstances, a laboratory may not be able to conduct a validation study necessary to update a breakpoint needed to remain compliant. In such cases, the laboratory may instead opt to test the combination by an alternate method using a current breakpoint. Laboratories should be aware, however, that manual methods, such as Kirby-Bauer disk diffusion and gradient strip diffusion, also have breakpoints assigned by the FDA that may differ from those of SDOs (CLSI, EUCAST). If a US laboratory wishes to use an SDO breakpoint with these manual methods that is different from the FDA’s, it is also required to validate the off-label breakpoint. Alternative options to validation/verification include suppressing the reporting of a particular result to the electronic health record and/or sending out testing to a referral laboratory that uses a reference or validated testing method.

16. What will an inspector look for to assess compliance?
Laboratories should be prepared to show inspectors:
- A list of which breakpoints are applied (including the source and publication year) to each antimicrobial-organism combination for AST. The Breakpoints In Use template that was used to assess current BPs may also be used for this purpose.
- Patient reports and proficiency testing results available demonstrating that AST results have been interpreted according to this policy.
• Documentation that breakpoints have been assessed at least annually to be kept up-to-date, including documentation of review by the institutional Antimicrobial Stewardship Committee, if applicable.
• If a laboratory has opted to use institution-specific breakpoints, documentation that these custom BPs were approved by the laboratory director and reviewed/approved by relevant stakeholders, such as the Antimicrobial Stewardship team, Pharmacy, and Infectious Disease, and the scientific and medical reasoning used in the review.

17. What resources are available to help our laboratory?

• **Antimicrobial Susceptibility Testing: Understanding New CAP Requirements** – This 1.25 hour activity provides expert insight into microbiology breakpoints, links to helpful resources, and knowledge checks to ensure understanding of new requirements
• **2023 Breakpoint Implementation Toolkit (2023 BIT)** - Together 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 Breakpoint Implementation Toolkit (BIT) to assist clinical laboratories in updating minimal inhibitory concentration (MIC) breakpoints.
• **CDC & FDA Antimicrobial Resistance (AR) Isolate Bank**
• **FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria (STIC)**
• **CLSI Free Resources** (including CLSI M100)