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MINIREVIEW

Impact of 21st Century Cures Act on Breakpoints and Commercial Antimicrobial Susceptibility Test Systems: Progress and Pitfalls

Romney M. Humphries,[a] Mary Jane Ferraro,[b] Janet A. Hindler[c]

[a]Accelerate Diagnostics, Tucson, Arizona, USA

[b]Departments of Medicine and Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[c]Department of Pathology and Laboratory Medicine, University of California, Los Angeles, California, USA

ABSTRACT Antimicrobial resistance is the most pressing medical challenge of the past decade. At the front line are clinical laboratories, which are responsible for accurately reporting antimicrobial susceptibility test (AST) results to clinicians and public health authorities. The ability of the laboratory to detect resistance has been hampered by several factors. In 2016, the 21st Century Cures Act was signed into law, marking an important step toward resolving many regulatory dilemmas that hampered development and updates to commercial AST systems (cASTs). We describe the pathway and history of U.S. regulation of cASTs and outline both the rewards and unmet needs possible from the 21st Century Cures Act.

KEYWORDS 21st Century Cures Act, antimicrobial susceptibility testing, Food and Drug Administration, Clinical and Laboratory Standards Institute, breakpoints

There is no question that antimicrobial resistance is one of the most pressing medical issues of the 21st century. Emerging resistance concerns include carbapenem-resistant *Enterobacteriaceae* and multidrug-resistant *Acinetobacter* and *Pseudomonas aeruginosa*, all of which have become endemic in many areas of the United States. Detection of these organisms by the clinical laboratory is critical not only to enable treatment, but also to reduce their spread (1). However, several regulatory and technical challenges have limited the ability of the laboratory to generate rapid and accurate susceptibility results for bacteria isolated from specimens from patients (2).

The 21st Century Cures Act, which was signed into law on 13 December 2016 by President Barack Obama, requires amendment of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) to ensure a more efficient process by which to update susceptibility test interpretive criteria to recognize antimicrobial resistance. On 13 December 2017, the FDA launched the Antimicrobial Susceptibility Test Interpretive Criteria website (3), which includes recognition of many of the disk diffusion and MIC interpretive criteria (also known as breakpoints) published in Clinical and Laboratory Standards Institute (CLSI) document M100, and some of those published in the CLSI M45, M24-A2, M43-A, and M27-S3 documents, as part of meeting the provisions of the 21st Century Cures Act (4). While this is an important step toward enabling a more rapid response to emerging antimicrobial resistance, many unmet needs remain to be addressed. This minireview evaluates the current challenges associated with antimicrobial susceptibility testing (AST) in the United States and discusses measures, including the 21st Century Cures Act, that will aid in their resolution. A timeline for these issues is given in Table 1.

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Address correspondence to Romney M. Humphries, rhumphries@axdx.com.

TABLE 1 Timeline of AST dilemmas

Yr	Activity
1972	CLSI (formerly National Committee for Clinical Laboratory Standards [NCCLS]) initiates publication of breakpoints
1980–1990s	FDA-recognized breakpoints begin to be printed in the drug label
Pre-2006	FDA permits AST clearance with CLSI and/or FDA breakpoints
2005	CLSI votes to approve revisions to *Enterobacteriaceae* cephalosporin/aztreonam breakpoints
2006	FDA beings to enforce restriction of cAST labeling to include only FDA breakpoints, and these can be applied only to specific organisms in list 1 (where there are clinical outcome data)
2006, 2007	CLSI submits citizen petition to FDA to request continued use of CLSI breakpoints in cAST labeling
2007	FDA rejects CLSI petition, publishes revision to class II special controls document stipulating that FDA breakpoints must be used for cAST clearance
2007	FDAAA enacted, allowing FDA process to update breakpoints in drug label
2009	FDA publishes guidance for industry on approach to comply with FDAAA
2010	CLSI publishes revisions to *Enterobacteriaceae* cephalosporin, aztreonam, and carbapenem breakpoints[a]
2013	FDA updates drug label for *Enterobacteriaceae* cephalosporin, aztreonam, and carbapenem breakpoints
2014	CLSI updates *Enterobacteriaceae* cefepime breakpoints
2015	FDA updates *Enterobacteriaceae* cefepime breakpoints
2015	CLSI begins to publish ECV if insufficient data are available for clinical breakpoint
2016	21st Century Cures Act signed into law
2017	FDA establishes AST Interpretive Criteria website, recognizing CLSI breakpoints

[a]For a complete list of CLSI breakpoints updated since 2010, see reference 5.

HOW BREAKPOINTS ARE ESTABLISHED IN THE UNITED STATES

In the United States, three organizations currently establish breakpoints for antimicrobial agents. These include one regulatory body, the Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER), and two standards development organizations (SDOs), i.e., CLSI (founded in 1967) and the National Antimicrobial Susceptibility Testing Committee for the United States (USCAST) (founded in 2015). FDA antibacterial breakpoints (until very recently, as discussed further below) were published only in the drug prescribing information (drug label), CLSI antibacterial breakpoints are published in the M100 standard (5) and the M45 guideline (6), and USCAST breakpoints are listed on their website. FDA staff are active advisors to the CLSI AST Subcommittee. No laboratory accreditation agencies specify which breakpoints clinical laboratories must use, and some laboratories have even developed internal breakpoints to address unique antimicrobial resistance or stewardship issues in their institution. However, manufacturers of commercial antimicrobial susceptibility test systems (cASTs) must adhere to FDA-recognized breakpoints when obtaining clearance for their systems. In contrast, laboratories usually rely on CLSI standards to inform clinical practice, which is a dilemma for the >90% of laboratories that use cASTs (7).

FDA CONSTRAINTS ON BREAKPOINTS FOR cASTS AND INDICATIONS

In 2007, with revision in 2009, FDA published the class II special controls guidance document for AST systems (8), which required cAST manufacturers to abide by FDA breakpoints alone. For the preceding 20 years, FDA permitted cAST clearance with CLSI or FDA breakpoints. Although these were usually the same, there was little scrutiny by FDA or manufacturers to identify any differences at that time. As part of the revised pathway, the FDA also stipulated that "the practice of reporting results should be discouraged when the antimicrobial agent has not been proven to be effective for treating infections caused by the organism" (8). In other words, results from cASTs should be reported only for those species for which *in vivo* efficacy of the antimicrobial has been demonstrated, as listed in the antimicrobial's instructions-for-use (IFU) section of the drug label. *In vivo* efficacy is demonstrated during the phase II/III clinical trial for

the agent and includes only those species encountered in patient infections during the trial that were treated with the antimicrobial. This list of species for which an antimicrobial has been shown to be active both *in vitro* and *in vivo* is sometimes referred to as "list 1" of the antimicrobial's IFU, as opposed to "list 2," which includes the organisms for which *in vitro* activity alone has been demonstrated.

Several challenges resulted from the new pathway established in 2007: (i) many breakpoints present in drug labels at the time were out of date and unreliable for detection of emerging mechanisms of resistance, (ii) several older drug labels had only disk diffusion breakpoints and no MIC breakpoints, and (iii) the number of "list 1" organisms was (and remains) very limited, excluding many organisms that are both clinically important and commonly treated with a given antimicrobial. For example, the list 1 aerobic and facultative anaerobic Gram-negative bacteria for meropenem include *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. Clearly, other clinically important organisms are commonly treated with meropenem, including other members of the *Enterobacteriaceae* and *Acinetobacter baumannii*. However, manufacturers of cASTs were restricted in providing performance data that focused primarily on organisms from list 1. In this case, sponsors could no longer obtain FDA clearance for meropenem and *A. baumannii*. The Center for Devices and Radiological Health (CDRH) continued to permit submission of data to support testing of non-list 1 organisms but did so only if these represented no more than 5% of the data set submitted and for organisms that were biologically similar (e.g., other members of the *Enterobacteriaceae*) and associated with the type of infection for which the antimicrobial is indicated. cASTs cleared prior to 2007 were not limited by the constraints imposed by the 2007 pathway and could continue to test and report off-label organisms.

In 2006 and again in 2007, the CLSI submitted citizen petitions (9, 10) to FDA to outline the challenges associated with the new stipulations ultimately outlined in the special controls document (8) and to request that cASTs continue to be cleared using CLSI breakpoints. FDA rejected these petitions, reinforcing their stance that breakpoints cleared on a cAST should be consistent with breakpoints published with the drug label. In the response to the 2006 petition, FDA suggested that the pharmaceutical manufacturer could request a change to the breakpoints or that CLSI could submit a citizen petition to FDA to request a change to the breakpoints published in the drug label. In 2006 and 2007, CLSI submitted petitions to FDA to request updates to the vancomycin drug label to update *Staphylococcus aureus* breakpoints to those endorsed by CLSI (11) (docket 2006P-0348) and updates to the penicillin drug label to include the newly published CLSI *Streptococcus pneumoniae* nonmeningitis breakpoints (12) (dockets 2007P-0273 and 2007P-0274). FDA responded to both petitions by requesting further time for review, and to date, no formal response has been provided to CLSI. In the interim, Baxter, the primary manufacturer of generic forms of both vancomycin and penicillin, voluntarily updated the drug label with CLSI breakpoints.

In 2007, the FDA Amendments Act (FDAAA) was signed into law, section 1111 of which described a requirement that FDA periodically update susceptibility test interpretive criteria for antibacterial agents and make those findings publicly available (13). FDA's compliance with this law included evaluation of both pharmaceutical company-initiated drug product labeling updates and susceptibility test interpretive criteria published by SDOs, with supporting information, and publication of updates annually in a Federal Register notice. However, it remained clear that the indications-for-use ("list 1") organisms were not to change, based on these assessments, without sufficient clinical trial data to support these changes.

These constraints on cASTs have presented significant dilemmas in the past 10 years. First, cAST manufacturers were reluctant to correct performance issues on cASTs cleared prior to 2007, when doing so would result in loss of the ability to test list 2 organisms. Second, newer cASTs were at a disadvantage compared to those cleared prior to 2007, as the number of organisms that could be tested against a given antimicrobial was severely limited. From a patient perspective, the impact was tremen-

dous, since 19 to 43% of critically ill patients receive off-label antimicrobials (14) and clinicians were often denied laboratory data to inform therapy.

UPDATING BREAKPOINTS TO CONFRONT ANTIMICROBIAL RESISTANCE

Since 2010, CLSI, FDA, and USCAST have published several breakpoint updates (for CLSI breakpoints, these are listed in document M100). These revisions are based on more sophisticated pharmacokinetic/pharmacodynamic (PK/PD) analyses, including the use of Monte Carlo simulations of probability of target attainment, and improved detection of emerging resistance. Importantly, the revised breakpoints are intended to provide a more accurate evaluation of the likelihood of clinical success when the antimicrobial is used to treat serious infections than do historical breakpoints (15–17). Historical breakpoints for most broad-spectrum agents were established before resistance to these agents existed, and it was difficult to determine their future reliability to predict treatment outcomes. As an example, the historical ceftriaxone breakpoints were established in the early 1980s, before extended-spectrum-β-lactamase (ESBL)-producing *Enterobacteriaceae* were common. Some isolates that harbored ESBLs generated MIC results interpreted as susceptible by these historical breakpoints and were associated with treatment failures (16). A temporary fix was introduced in 1994, with the recommendation for clinical laboratories to perform an ancillary ESBL test on selected isolates and edit cephalosporin and aztreonam susceptible results to resistant if an ESBL was detected. However, it quickly became apparent that ESBLs were evolving, that detection by the test was unreliable, and that many laboratories did not perform ESBL testing at all, requiring a more permanent solution to this dilemma.

In 2005, CLSI approved adjustments to the cephalosporin and aztreonam breakpoints for the *Enterobacteriaceae* (16). However, CLSI did not publish these revisions until 2010, as it took 5 years for CLSI leadership and FDA (CDER and CDRH) to establish a path forward for these changes, including awaiting for the FDAAA to be enacted. It then took a further 3 years (until 2013) for the drug labels to be updated with the revised breakpoints, at which point cASTs were able to submit data to CDRH for clearance with the revised breakpoints. To date, not all cAST manufacturers have gone through the process to modify their cASTs with the revised breakpoints, including the manufacturers of the two cASTs most used by clinical laboratories in the United States: Vitek 2 (bioMérieux, Durham, NC) and MicroScan (Beckman Coulter, Sacramento, CA). While use of the revised breakpoints is encouraged by the FDA, updating devices is voluntary. The primary reason why cAST manufacturers have not updated their devices is the FDA restrictions discussed above; i.e., cAST manufacturers were reluctant to update their systems to accommodate revised breakpoints when these updates came at a loss of the number of organisms that could be claimed by the 2009 pathway.

Laboratories have the ability to manually edit breakpoints used on cASTs and to report patient results using the current breakpoints. However, this is a modification of the FDA-cleared instructions for use, which renders the test a laboratory-developed test (LDT). The process of verifying an LDT is more complex than verification of an unmodified FDA-cleared test, a task that many laboratories find difficult to accomplish. Furthermore, performance of cASTs is not always as accurate at the lower antimicrobial agent concentrations needed to implement the current breakpoints. Manufacturers of some cASTs did not evaluate these low concentrations with their original FDA submissions, and for certain agents, the low concentrations are not even included on the marketed panels (18). As a result, many laboratories have yet to adopt current breakpoints. A recent survey in California found that 26% of laboratories are not using the current carbapenem breakpoints for the *Enterobacteriaceae* (7), which is dangerous for both patient care and infection control.

SUMMARY OF ISSUES AND RESOLUTION WITH THE 21ST CENTURY CURES ACT

To summarize the discussion above, three primary AST dilemmas exist: (i) multiple breakpoint-setting organizations that publish differing breakpoints; (ii) FDA restriction of cASTs to allow testing only using breakpoints published by FDA; and (iii) significant

delays between updates to breakpoints, which are designed to meet critical patient care or public health needs, and their implementation by cASTs and laboratories. The provisions of the 21st Century Cures Act specific to AST begins to address all three issues.

First, the 21st Century Cures Act requires FDA to establish a website listing all FDA-recognized breakpoints, within 1 year of enactment. This website was posted by FDA on 13 December 2017. Furthermore, the act allows FDA to recognize, in whole or in part, breakpoints established by SDOs; at present, CLSI is the only SDO that both has met the criteria stipulated by the law to serve as an SDO for this purpose and has responded to the Federal Register for breakpoint recognition. Breakpoints must be removed from drug labeling by 13 December 2018, and cAST manufacturers can submit for FDA clearance cASTs using breakpoints recognized by FDA and listed on the website. To date, FDA has recognized antibacterial breakpoints in part from the CLSI's M100 (27th edition) standard, M45 (3rd edition) guideline for infrequently isolated or fastidious bacteria, M24-A2 guideline for mycobacteria, nocardiae, and aerobic actinomycetes, and M43-A guideline for human mycoplasmas. Only antifungal susceptibility test interpretive criteria from CLSI's M27-S3 standard are recognized. Of note, M27-S3 is the historical standard, and the species-specific *Candida* breakpoints published by CLSI in 2012 in the M27-A4 document have not been recognized by FDA. This means that multiple breakpoints still exist, but it is believed that through a process of data review, FDA will recognize the majority of CLSI breakpoints, leading to a single, harmonized set of breakpoints housed on the FDA website. Breakpoints established by other SDOs may be recognized if the SDO submits to the Federal Register a request for review of the supporting data for these. Importantly, this process provides a pathway for collaboration between FDA and SDOs to ensure that breakpoints are up-to-date with the most current evidence.

Second, the law decouples susceptibility testing and breakpoints from an antimicrobial's drug label indications section and requires inclusion of a disclaimer in the cAST package insert stipulating that the safety and efficacy of the antimicrobials listed on the FDA's breakpoint website in treating clinical infections may or may not have been established in adequate and well-controlled clinical trials. These steps are critical because when combined, they allow cASTs to be cleared for organisms that are not on "list 1" but that have a breakpoint, which is a major advancement from FDAAA. As an example, many cAST manufacturers are planning to submit for clearance current meropenem breakpoints for the *Enterobacteriaceae*, as all members could now be included in the cAST indications, as opposed to only *K. pneumoniae*, *E. coli*, and *P. mirabilis* by the old rules. However, the caveat to this is that the organism to be included should share biological properties with those included in the indications for use of the drug and be associated with infections similar to those caused by the indicated list 1 species and that cAST data are available to demonstrate acceptable performance compared to reference standard broth microdilution.

Third, FDA is required to update the website at least every 6 months with new and any revised breakpoints. This definitive timeline allows a more rapid adoption of revised breakpoints and a more streamlined pathway for cAST manufacturers to submit and obtain clearance for their devices with the most up-to-date standards.

REMAINING cAST DILEMMAS AND UNANSWERED QUESTIONS

While the progress with the 21st Century Cures Act is a giant step toward resolving many of the issues as outlined above, several outstanding issues exist. The FDA's Susceptibility Test Interpretive Criteria website is in its infancy, currently listing (with a few exceptions) only those breakpoints where FDA and CLSI were already in alignment but with expansion to include list 2 organisms. FDA will continue to update the website, requesting data from CLSI, drug manufacturers, and other sources to justify breakpoints that are not currently recognized by FDA or are different from FDA-recognized breakpoints. However, a major risk is that, much like the case for FDAAA, the timeline for review of each breakpoint is not defined; the only requirement is

that updates to the website must occur every 6 months. Furthermore, the exact data required and the assessment process for the data are not fully defined. Many breakpoints published by CLSI that are not recognized by FDA were established years ago (for example, the *Stenotrophomonas maltophilia* breakpoint for trimethoprim-sulfamethoxazole, the *Burkholderia cepacia* complex breakpoints, many of the streptococcal and staphylococcal breakpoints, etc.). FDA may not accept breakpoints generated for organisms that do not reflect contemporary bacterial populations or that were established using outdated methodologies to establish breakpoints, regardless of the current applicability of the breakpoint. CLSI has updated the M23 guideline (17), which stipulates the process for establishing breakpoints and breakpoint revision, to ensure that all breakpoints in the M100 standard are evaluated for current applicability. However, it is unknown whether an absence of data to suggest that a breakpoint is in need of revision will suffice for justifiable evidence for FDA to recognize the breakpoint on the website or whether data demonstrating the clinical validity of the breakpoint will need to be generated. For many older antimicrobials, it is unlikely that these data will ever exist.

While we are hopeful that AST manufacturers will update cASTs and obtain FDA clearance with the current breakpoints in a timely manner, there again remains the issue that this process is voluntary. Prioritization of cAST development by diagnostic manufacturers for addition of new antimicrobials, new breakpoints, and (now) new organisms to be claimed can be complex. To provide evidence of the performance of the devices, such modifications often require completion of a new clinical trial to generate data for 510(k) submission, in addition to the complexities of product design, software updates, and customer implementation. Ultimately, cAST manufacturers generate very little, if any, revenue from these activities. While subsidies now exist for development of new antimicrobials (the GAIN Act), no such incentives exist for cAST manufacturers. The Reinvigorating Antibiotic and Diagnostic Innovation (READI) Act was introduced to congress in 2015 (19). This act starts to address this issue by proposing tax credits for clinical testing expenses for qualified infectious disease products and rapid (<4-h) diagnostic tests. However, the READI Act is designed to subsidize tests for new antibiotics and novel diagnostics but not necessarily reformulation of existing cASTs to accommodate breakpoint revisions.

Finally, a major dilemma remains for those important antimicrobial-organism combinations for which insufficient data exist to establish a clinical breakpoint. In particular, those antimicrobials that are generic do not have a vested sponsor to support studies to gather required data. In these instances, CLSI has started to use MIC distribution data alone to establish an epidemiological cutoff value (ECV), which allows differentiation of isolates with and without acquired or mutational resistance mechanisms but does not necessarily correlate with treatment outcomes (20). As an example, an ECV was established by CLSI in 2017 for colistin and the *Enterobacteriaceae*, as opposed to a clinical breakpoint, due to the absence of PK/PD and clinical outcome data. However, there is currently no pathway by which to obtain clearance for cASTs with an ECV. This is a critical issue; as CLSI continues to revise breakpoints and finds insufficient PK/PD or clinical outcome data to fully support a clinical breakpoint, the number of ECVs may increase. The community can benefit from discussions among all stakeholders to assess the utility of ECVs. A pathway to obtain FDA clearance, with appropriate disclaimers, may be needed.

CONCLUSIONS

The goal of performing AST is to provide actionable data to the treating clinician on the relative susceptibility of an organism to a given antimicrobial. Ideally, these data provide the clinician with a probability of success of therapy with the antimicrobial, based on the most current pharmacodynamic/pharmacokinetic, clinical outcome, and resistance mechanism data, through the use of an interpretive breakpoint. As outlined above, this process of establishing, revising, and applying breakpoints is complex. However, antimicrobial resistance is a growing concern, which requires coordinated

efforts on the parts of FDA, all SDOs, advocacy groups, pharmaceutical companies, diagnostic manufacturers, clinicians, and clinical laboratories. While the 21st Century Cures Act is an important step forward, continued efforts, such as the READI Act, ongoing breakpoint review and update by SDOs, and implementation of these by diagnostic manufacturers and laboratories, are needed to ensure accurate and timely detection of antimicrobial resistance by clinical laboratories.

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R.M.H is a current voting member of the CLSI AST Subcommittee, J.A.H. is a former voting member, and M.J.F. is a former chairholder and voting member. M.J.F. presently serves on the CLSI board of directors.

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