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Emerging Resistance, New Antimicrobial Agents ... but No Tests! The Challenge of Antimicrobial Susceptibility Testing in the Current US Regulatory Landscape

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Accurate and timely performance of antimicrobial susceptibility testing (AST) by the clinical laboratory is paramount to combating antimicrobial resistance. The ability of laboratories in the United States to effectively perform ASTs is challenged by several factors. Some, such as new resistance mechanisms and the associated evolution of testing recommendations and breakpoints, are inevitable. Others are entirely man-made. These include unnecessarily strict US Food and Drug Administration (FDA) limitations on how commercial AST systems can be used for diagnostic testing, the absence of up-to-date performance data on these systems, and the lack of commercially available FDA-cleared tests for newer antimicrobial agents or for older agents with updated breakpoints. This viewpoint will highlight contemporary AST challenges faced by the clinical laboratory, and propose some solutions.

Keywords. antimicrobial susceptibility testing; breakpoints; Food and Drug Administration.

Antimicrobial resistance is a critical public health and safety dilemma. We have witnessed a seemingly inexorable increase in the number of infections due to carbapenem-resistant Enterobacteriaceae, multidrug-resistant (MDR) *Pseudomonas aeruginosa*, MDR *Acinetobacter baumannii*, and vancomycin-resistant *Enterococcus faecium*. Public cries for action have led to several national initiatives, including a National Report on Combating Antimicrobial Resistant Bacteria in 2014, appointment of a Presidential Advisory Committee in 2015, the Centers for Disease Control and Prevention's (CDC) Antibiotic Resistance Solutions Initiative, and formation of the National Institute of Allergy and Infectious Diseases' Antimicrobial Resistance Leadership Group, as well as efforts on the part of the Biomedical Advanced Research and Development Agency, the Agency for Healthcare Research and Quality, the CDC's National Healthcare Safety Network, and the US Food and Drug Administration (FDA).

In the backdrop of these national efforts is an emerging and neglected struggle by the clinical laboratory to generate accurate and actionable antimicrobial susceptibility reports. Key challenges include extensive delays between the update of a clinical breakpoint and its clearance on commercial antimicrobial susceptibility testing (cAST) devices; significant lags between approval of new antimicrobials and marketing of FDA-cleared cASTs; strict regulation by FDA over which drug/bug combinations can be tested

by cAST devices; and lack of active, periodic review of the performance of cAST devices as resistance emerges (Table 1). This viewpoint will evaluate these challenges and some potential solutions to these entirely man-made problems.

BACKGROUND: THE CONTEMPORARY LANDSCAPE OF AST IN THE UNITED STATES—DEVICES AND BREAKPOINTS

Commercial AST Devices

In the United States, cAST devices must be cleared by FDA as in vitro diagnostic (IVD) devices, and used by laboratories according to manufacturer's instructions listed in the FDA-cleared product insert. IVD devices available to laboratories in the United States include automated systems (bioMérieux Vitek2; BD Phoenix; Beckman Coulter MicroScan; and Thermo Scientific Sensititre), the manual Etest, and disk diffusion methods. Compared to manual methods, automated systems provide streamlined workflow, objective measurement of results, and sophisticated software to aid interpretation [1]. As such, nearly all US laboratories use automated systems exclusively, with the majority using either Vitek2 or MicroScan.

The cASTs are class II devices, meaning FDA clearance is achieved through a premarket notification, or 510(k) process, by which the manufacturer documents that the cAST performs comparably to reference broth microdilution (BMD) [2, 3]. For devices that yield a minimum inhibitory concentration (MIC), both categorical agreement (ie, the same susceptible, intermediate, or resistant interpretation) and essential agreement (ie, MICs within $\pm 1 \log_2$ dilution of reference BMD results) is required. FDA mandates >89.9% essential and categorical agreement with BMD, for each drug/bug combination, and minimal

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Table 1. Challenges and Possible Solutions Associated With Use of Commercial Antimicrobial Susceptibility Testing Systems by Clinical Laboratories in the United States

Challenge	Why This Impacts Patient Care	Possible Solutions
Updated FDA breakpoints are not available on cAST devices.	Patient safety compromised as laboratories may not detect resistance. Emerging resistance may go undetected.	FDA and diagnostic manufacturers work together to identify optimal plan for updating breakpoints. Identify a regulatory mechanism to set time limits for IVD breakpoint update. FDA and CDC to develop set of challenge isolates ^a for testing with updated breakpoints as soon as it becomes apparent that breakpoint needs updating; add to new FDA-CDC Antimicrobial Resistance Bank. Interim solution for laboratory: Verify MIC breakpoints off label—CDC provides verification plan/ isolates for clinical laboratory use. FDA and CDC provide in vitro data to explain clinical and public health impact of using old or updated breakpoints.
Tests for newer drugs not available on cAST devices.	Patient safety compromised. Some drugs cannot be used (eg, ceftazidime-avibactam, ceftolozane-tazobactam) without AST. Emerging resistance may go undetected.	FDA, pharmaceutical manufacturer, and diagnostic manufacturers work together prior to NDA submission to identify optimal plan for adding drug to IVD. Make FDA breakpoints available to diagnostic manufacturers as soon as possible so they can begin test development. Pharmaceutical company works with FDA and CDC to develop set of challenge ^a isolates for testing with new drugs during new drug development; add to new FDA-CDC Antimicrobial Resistance Bank.
FDA does not provide breakpoints for organisms that may not have been included or did not perform reliably during pharmaceutical manufacturer's clinical trial (eg, meropenem and <i>Acinetobacter</i>).	Only FDA breakpoints are cleared on cASTs. Patient safety compromised as antimicrobial agents are frequently used off label (eg, MDR isolates; polymicrobial infection; similar agent unavailable due to formulary considerations or drug shortage).	FDA to reconsider the need for clinical data to determine that an in vitro test performs reliably and pros and cons to patient safety and to public health of various breakpoint-setting rules.

Abbreviations: AST, antimicrobial susceptibility testing; cAST, commercial antimicrobial susceptibility testing; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; IVD, in vitro diagnostic; MDR, multidrug resistant; MIC, minimum inhibitory concentration; NDA, new drug application.

^a Challenge isolates represent organisms that can be used by IVD manufacturers to update breakpoints for existent drugs or develop tests for new drugs.

very major (false-susceptible) and major (false-resistant) errors. Any major change to a cAST device requires FDA re-review and clearance. However, FDA does not have the legal authority to compel cAST device manufacturers to reevaluate performance of their systems when new resistance mechanisms are recognized. Many drug/bug combinations tested on cASTs by laboratories today were cleared before resistance was widespread. For example, fluoroquinolone cASTs were cleared before fluoroquinolone resistance was common. More robust, periodic reviews of cAST device performance may prevent cAST product recalls, such as occurred for piperacillin-tazobactam on the Vitek2 in 2011 and Etest in 2015.

Breakpoints

MIC and disk zones are interpreted using clinical breakpoints. In the United States, breakpoints are established by 2 organizations: FDA and the Clinical and Laboratory Standards Institute (CLSI), who use differing approaches. FDA establishes breakpoints in the context of an individual new drug application (NDA) or upon request of the drug manufacturer for older agents [4]. FDA has no legal authority to compel drug manufacturers to submit a request to revise breakpoints; this is especially problematic for older generic drugs, as few manufacturers will invest time and money to update breakpoints for these agents. FDA breakpoints are listed in the approved drug prescribing information. A list of breakpoints newly approved or updated by FDA since 2010

is available at: <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm275763.htm>.

CLSI, a multidisciplinary, volunteer organization, sets consensus standards followed by laboratories worldwide. CLSI updates breakpoints for older agents according to criteria outlined in their M23 guideline [5]. These criteria include recognition of a new resistance mechanism, availability of new pharmacokinetic/pharmacodynamic data, simplification of laboratory testing, or harmonization of breakpoints with those of FDA and/or their European counterpart, the European Committee on Antimicrobial Susceptibility Testing. For new drugs, CLSI either publishes FDA-granted breakpoints, or, sometimes, alternative breakpoints but only 2 years after the drug's initial approval by FDA. CLSI may reevaluate breakpoints independent of requests made by drug manufacturers, if M23 criteria are met. CLSI breakpoints are provided in the M100S standard [6], which is updated annually and is available free of charge at: <http://www.clsi.org/m100/>. Laboratories can use either FDA or CLSI breakpoints if performing AST by noncommercial methods (such as BMD or disk diffusion); however, by US law, cAST devices must use FDA breakpoints.

CHALLENGE 1: UPDATED BREAKPOINTS

In 2010, CLSI updated aztreonam, cephalosporin, and carbapenem breakpoints for the Enterobacteriaceae. Carbapenem and

piperacillin-tazobactam breakpoints for *P. aeruginosa* and carbapenem breakpoints for *A. baumannii* were updated in following years [6, 7, 8, 9]. FDA subsequently updated breakpoints for most of these antimicrobials (Table 2). Use of updated breakpoints is the most effective method to detect clinically relevant cephalosporin and carbapenem resistance, in face of the multitude of β -lactam resistance mechanisms among gram-negative bacteria [9]. For instance, laboratories that use revised Enterobacteriaceae carbapenem breakpoints detect significantly more carbapenem-resistant Enterobacteriaceae than do laboratories that use historical breakpoints [10].

FDA guidance suggests that cAST devices update breakpoints within 90 days of an FDA breakpoint update to the drug label [4], but this almost never occurs. For instance, FDA updated ertapenem, imipenem, and meropenem Enterobacteriaceae breakpoints in 2012–2013, but only 1 automated cAST manufacturer (BD) has obtained clearance for all 3 breakpoints on its system.

One manufacturer has not obtained clearance for any of the updated carbapenem breakpoints to date (Table 2). Continued delay in updating breakpoints on cASTs compromises patient safety in the United States, but there is no indication that cASTs will update breakpoints in a timely manner unless a regulatory mechanism is developed to require diagnostic manufacturers to do this. At present, FDA does not have the legal authority to require cAST manufacturers update breakpoints, even though these companies no longer comply with current FDA regulations.

Data required by FDA for clearance of an updated breakpoint may differ by device. If the device does not need redesign to accommodate the updated breakpoint and existing data demonstrate acceptable performance, FDA may exercise enforcement discretion, allowing the manufacturer to bypass the 510(k) process. However, if redesign is needed, a new clinical trial to establish the performance of the redesigned device must be performed and these data submitted through the 510(k) pathway.

Table 2. Minimum Inhibitory Concentration Breakpoints for Gram-Negative Bacteria That Have Been Updated Since 2010^a

Antimicrobial	CLSI MIC (μ g/mL) Breakpoint ^b			FDA MIC (μ g/mL) Breakpoint ^c			Year CLSI Breakpoint Updated	Year FDA Breakpoint Updated ^d	No. of cAST Systems With Current FDA Breakpoints ^e
	Susc	Int	Res	Susc	Int	Res			
Enterobacteriaceae									
Aztreonam	≤ 4	8	≥ 16	≤ 4	8	≥ 16	2010	2013	1
Cefazolin (systemic)	≤ 2	4	≥ 8	≤ 1	2	≥ 4	2010, 2011	2013/2015	0
Cefazolin (urine)	≤ 16	...	≥ 32	No breakpoints available			2014	...	0
Cefepime	≤ 2	4–8 ^f	≥ 16	≤ 2	4–8	≥ 16	2014	2014	1
Cefotaxime	≤ 1	2	≥ 4	≤ 1	2	≥ 4	2010	2015	0
Ceftazidime	≤ 4	8	≥ 16	≤ 4	8	≥ 16	2010	2014/2015	0
Ceftriaxone	≤ 1	2	≥ 4	≤ 1	2	≥ 4	2010	2013/2015	3
Doripenem ^g	≤ 1	2	≥ 4	≤ 0.5	2010	2012	1
Ertapenem	≤ 0.5	1	≥ 2	≤ 0.5	1	≥ 2	2010, 2012	2012	3
Imipenem	≤ 1	2	≥ 4	≤ 1	2	≥ 4	2010	2012	2
Meropenem	≤ 1	2	≥ 4	≤ 1	2	≥ 4	2010	2013	2
<i>Pseudomonas aeruginosa</i>									
Cefepime ^h	≤ 8	16	≥ 32	≤ 8	...	≥ 16	No update	2014	1
Ceftazidime ^h	≤ 8	16	≥ 32	≤ 8	...	≥ 16	No update	2014/2015	0
Doripenem ^g	≤ 2	4	≥ 8	≤ 2	2012	2012	1
Imipenem	≤ 2	4	≥ 8	≤ 2	4	≥ 8	2012	2012	2
Meropenem	≤ 2	4	≥ 8	≤ 2	4	≥ 8	2012	2013	1
Piperacillin-tazobactam	$\leq 16/4$	32/4–64/4	$\geq 128/4$	$\leq 16/4$	32/4–64/4	$\geq 128/4$	2012	2013	2
<i>Acinetobacter</i> spp									
Doripenem ^g	≤ 2	4	≥ 8	≤ 1	2014	2012	1
Imipenem	≤ 2	4	≥ 8	≤ 4	8	≥ 16	2014	No update	...
Meropenem	≤ 2	4	≥ 8	No breakpoints available			2014

Abbreviations: cAST, commercial antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; FDA, US Food and Drug Administration; Int, intermediate; MIC, minimum inhibitory concentration; Res, resistant; Susc, susceptible.

^a Both CLSI and FDA lowered breakpoints (not shown here) for ciprofloxacin and *Salmonella* species (FDA for *Salmonella* Typhi only); CLSI also lowered breakpoints for levofloxacin and ofloxacin for *Salmonella* species; no cAST system manufacturer has updated these breakpoints.

^b As listed in [6].

^c As listed in 1 or more pharmaceutical manufacturer's labels as of 20 February 2016.

^d As listed under "Date of Most Recent FDA Review of Microbiology Susceptibility Interpretive Criteria" at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm275763.htm> (accessed 20 February 2016); the date the specific FDA breakpoint was updated occurred at or prior to the date listed here; multiple years are listed as included on this website.

^e The 4 FDA-cleared cAST systems reviewed include: bioMérieux Vitek2, BD Phoenix, Beckman Coulter MicroScan, and Thermo Scientific Sensititre.

^f Interpretive category is susceptible–dose dependent.

^g Breakpoints introduced to CLSI M100 tables for the first time in 2010.

^h Breakpoints not updated by CLSI, but have been updated by FDA.

Manufacturers have indicated that considerable resources are required to reformulate cAST devices to accommodate revised breakpoints, hampering progress and innovation in other areas [11].

Interim Solution: Clinical Laboratory Verification of Updated Breakpoints

Manual override of the interpretations generated by cAST systems was viewed as a temporary method by some laboratories to allow use of updated breakpoints. However, deviation from the manufacturer's instructions, including interpreting MICs by a breakpoint other than that listed in the device product insert, is modification of the test, rendering it a laboratory-developed test. Laboratories that make such modifications are considered diagnostic device manufacturers by FDA and by US law must perform in-house studies to ensure analytical performance of the modification prior to reporting patient results. The extent of such verification studies is at the laboratory director's discretion, but must include confirmation of accuracy, reproducibility, and reportable and reference ranges. Such studies are critical because cAST devices were manufactured to optimize accuracy and reproducibility of MIC interpretations with the old breakpoints and may not perform as well with revised breakpoints. Few laboratories have the resources to execute these studies and as such continue to use old breakpoints. There is a dearth of peer-reviewed, independent data on cAST device performance that laboratories can draw on to inform their decision to update breakpoints off-label. Only 2 reports in the literature have evaluated the performance of automated cAST devices with updated Enterobacteriaceae carbapenem breakpoints; these documented performance ranging from suboptimal to acceptable [12, 13].

Long-term Solution: Changes to Establishment of Breakpoints and the Regulatory Structure of cAST Device Clearance

Ultimately, a mechanism to enforce breakpoint update timelines is needed for FDA-cleared cAST devices. These may be longer than the currently suggested 90 days if new product development is necessary, but should not exceed 1 year, given the

critical nature of updated breakpoints to patient safety. FDA should notify each diagnostic manufacturer in writing when a breakpoint is updated, and provide the manufacturer with a deadline for when they are expected to submit data to support updating the breakpoint on their cAST. Aiding this process is the recent development of a CDC/FDA organism bank, comprised of well-characterized bacterial isolates with known antimicrobial resistance profiles, for development and evaluation of updated breakpoints (<http://www.cdc.gov/drugresistance/resistance-bank/>). This organism bank could be expanded to include isolates appropriate for evaluation of new antimicrobial agents or agents with updated breakpoints. In addition, manufacturers should notify clients, in writing, that their cASTs are not up-to-date with current FDA breakpoints, and may generate erroneous results.

CHALLENGE 2: NEW ANTIMICROBIALS

There are no-to-few FDA-cleared cAST devices currently available for the 6 antibacterial agents approved since implementation of the 2012 Generating Antibiotic Incentives Now provisions to the FDA Safety and Innovation Act (Table 3). The recent pattern for clearance of cASTs for new antimicrobial agents is a several-year lag between the approval of the drug for clinical use and the availability of a cAST device. The rate-limiting step to date has been submission of data by the cAST manufacturer to FDA for review, rather than delays at the agency level for review and clearance of the device. Much of this delay is due to ambiguous FDA submission requirements. Ceftaroline is the most recent "new" antimicrobial cleared on automated, cAST devices. Ceftaroline was approved in 2010 for treatment of acute bacterial skin and soft tissue infections and community-acquired pneumonia. While ceftaroline disks were available 1 month after ceftaroline's approval, the manufacturers of Vitek2, Phoenix, and MicroScan took 2.5–3.5 years to achieve clearance of this drug on their systems.

While vexing, the lack of FDA-cleared cAST devices for ceftaroline was not critical, given the very high baseline susceptibility of

Table 3. Newly Approved Antimicrobial Agents and Availability on Commercial Antimicrobial Susceptibility Testing Systems

Antimicrobial	Year Drug Approved by FDA	RUO Disk Available	RUO Etest Available	FDA-Cleared Test Available ^a	Surrogate Agent Available for Predicting Susceptibility
Ceftazidime-avibactam	2015	Yes	Yes	Sensititre ^b (in progress)	No
Ceftolozane-tazobactam	2014	Yes	Yes	Sensititre	No
Dalbavancin	2014	No	No	Sensititre (in progress)	Vancomycin [14]
Oritavancin	2014	No	No	Sensititre	Vancomycin [15]
Televancin	2014	Yes	Yes	Sensititre	Vancomycin [16]
Tedizolid	2014	No	No	Sensititre	Linezolid [17]
Ceftaroline (<i>Staphylococcus aureus</i>)	2013			BD Phoenix MicroScan Sensititre Vitek 2	No

Abbreviations: FDA, US Food and Drug Administration; RUO, research use only.

^a May only be available on custom panels.

^b Thermo Scientific Sensititre System.

gram-positive bacteria, including MRSA. However, for newer antimicrobials, including ceftolozane-tazobactam and ceftazidime-avibactam, susceptibility is far less predictable. The inability of laboratories to produce susceptibility results seriously cripples the use of these antimicrobials for patient care. Indeed, FDA labels for these drugs indicate they should only be used for patients proven or strongly suspected to have susceptible organisms, although testing to determine susceptibility is not possible at present.

Several pharmaceutical companies have made available research use only (RUO)-labeled disks and Etests for newly FDA-approved antimicrobials (Table 3) that are intended for local surveillance studies. Laboratories that request these must sign an agreement indicating they will not be used for clinical purposes. The RUO designation means they have not been cleared by FDA, and their performance is therefore unknown. RUOs cannot be billed for by the laboratory and cannot be reported to physicians to guide treatment decisions. Many hospitals prohibit use of RUO tests due to liability concerns. While use of these may aid hospitals in gaining a better appreciation of the overall susceptibility of organisms in their regions, they are not a solution for routine diagnostic testing.

Interim Solution: Use of Surrogate Agents to Predict Susceptibility

In some cases, as listed in Table 3, antimicrobials tested by FDA-cleared cAST devices can be used as surrogates to predict susceptibility of antimicrobials with no FDA-cleared cAST. For example, a vancomycin-susceptible result predicts an isolate's susceptibility to oritavancin, dalbavancin, and telavancin [14–16], even though resistance to these agents in *S. aureus* is exceedingly rare (<2%) and further data are required to determine the true predictive value of these surrogate agents. Furthermore, if an isolate is resistant to vancomycin (common for the enterococci), it may be either susceptible or resistant to these antimicrobials [14–16]. For high-stakes cases, confirmation of susceptibility of these agents may be specifically required.

No surrogate agent can predict ceftolozane-tazobactam or ceftazidime-avibactam activity. Ceftolozane-tazobactam had activity against 93.9% of isolates of *P. aeruginosa*, but only against 63.2% of MDR isolates [18], making AST necessary prior to use of this agent. Similarly, while ceftazidime-avibactam resistance can be predicted if an isolate harbors a metallo- β -lactamase (which few laboratories can reliably test for), isolates that harbor the more common *Klebsiella pneumoniae* carbapenemase (KPC) carbapenemase are typically susceptible, although at least 1 KPC-producing isolate has been documented to be ceftazidime-avibactam resistant [19], making specific MIC or disk testing of an isolate's susceptibility to this drug imperative.

Interim Solution: Pharmaceutical Company-Supported Reference Laboratories

Some pharmaceutical companies offer services of a reference laboratory to test isolates against their agent. Such reference laboratory testing is associated with reporting delays, may

only be performed if resistance is suspected, and is often only permitted for isolates that were recovered from specimens consistent with the FDA indications for the drug (eg, urine or intra-abdominal sources for ceftolozane-tazobactam). These programs have been cut back due to concerns regarding compliance with the Sunshine Act (ie, free-of-charge susceptibility testing may be viewed as a kickback to prescribing that company's drug).

Long-term Solution: Coordination Between Pharmaceutical Companies, Diagnostic Manufacturers, and FDA

At present there is a major disconnect between the pharmaceutical companies, the diagnostic companies, and the divisions of the FDA that regulate each (Center for Drug Evaluation and Research [CDER] and Center for Devices and Radiological Health [CDRH], respectively). All too often, priorities of these organizations do not align, resulting in extensive delays between drug approval and clearance of cASTs. For instance, NDA data submitted to CDER include disk-to-MIC correlates to support inclusion of disk breakpoints and quality control ranges in the drug label. These data should require minimal supplemental studies (if any) to obtain FDA clearance of the disks. However, these data must be submitted independently by the disk manufacturer to CDRH, to obtain clearance of the disk. Cosubmission of disk data to CDRH and CDER would streamline the process, but companies have been reluctant to do so, in case breakpoints proposed by the drug sponsor are not those ultimately assigned by CDER. A process at FDA to limit these concerns and obtain clearance of disks at the time of antimicrobial approval is needed. FDA is cognizant of this issue, and both CDER and CDRH are developing draft guidance on coordinated development of antimicrobials and cASTs.

Not all agents can be tested reliably by disk diffusion (eg, oritavancin and dalbavancin), and MIC methods are generally better at detecting emerging resistance. Ultimately, an expedited process is required for adding newer agents to automated cAST devices, as most US laboratories use these instruments. Such development will require collaboration between diagnostic manufacturers, pharmaceutical companies, and the FDA and recognition by cAST manufacturers of the urgent nature of this pursuit.

CHALLENGE 3: REPORTING RESTRICTIONS

Commercial AST devices are only cleared for testing and reporting antimicrobials using FDA breakpoints and only for organisms listed in the drug label for which the antimicrobial is "active both in vitro and in clinical infections." However, every day, antimicrobials are prescribed to treat infections caused by organisms not specifically listed in the clinical indication section of a drug label. There are many examples to this; for instance, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria meningitidis*, *P. aeruginosa*, and *Proteus mirabilis* are the only gram-negative organisms listed in the

meropenem drug label. As such, meropenem could not be reported for *A. baumannii* or other Enterobacteriaceae. Similarly, trimethoprim-sulfamethoxazole could not be reported for *Stenotrophomonas maltophilia*, nor daptomycin for *E. faecium*. Manufacturers of cASTs were historically granted FDA clearance for their device to test and report these drug/bug combinations, using CLSI breakpoints. In 2007, FDA stopped granting clearance of these “off-label” organisms, and required exclusive use of FDA breakpoints by cASTs. This challenge is poorly appreciated at the present date, due to the fact that the vast majority of cASTs performed by laboratories use commercial devices cleared prior to 2007. The number of drug/bug combinations that can be tested on cAST devices will inevitably dwindle, as devices are modified to accommodate new breakpoints and improve performance. This regulation may ultimately limit redesign of existing devices, as doing so will remove testing options currently available to the laboratory. Similarly, this may limit use of novel AST devices, as laboratories will be able to perform testing on a greater breadth of organisms using devices cleared before 2007.

Potential Solution

To our knowledge, no adverse events have been associated with testing these “off label” drug/bug combinations. We believe knowledge of in vitro MICs and CLSI interpretation provides a safety margin for physicians who choose to use these agents off-label. CDRH evaluation of the AST device should include evaluation of whether the test works as compared to BMD, and not whether the drug should or should not be used in clinical practice against a given organism. Ultimately, revision of the Code of Federal Regulations that governs FDA practice to assign breakpoint setting to a single organization, and publication of those breakpoints outside the drug label, can meet this challenge. Fortunately, language in the 21st Century Cures Act has been proposed to Congress to make these changes. Having a single breakpoint-setting organization will significantly improve the challenges associated with AST, as FDA and CLSI breakpoints do not align for many antimicrobials (Table 2).

CONCLUSIONS

Antimicrobial resistance is discovered almost exclusively through frontline testing performed by the clinical laboratory, by methods that are the same as those used in clinical laboratories more than 40 years ago. There is no doubt that new and novel tools are needed. However, recent trends in the regulatory policies that govern cAST devices in the United States may hamper the utility of these novel tests, just as they limit a laboratory’s ability to reliably detect antimicrobial resistance today. Prompt attention to these man-made challenges at a national level is essential, as these cripple laboratories’ ability to perform AST and generate clinically relevant data on antimicrobial resistance.

Notes

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