

Implementation of the 21st Century Cures Act for for Breakpoints and Interpretive Categories

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San Diego, California, USA

Implementation of the 21st Century Cures Act for Breakpoints and Interpretive Categories

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What is 21st Century Cures? (and why are we talking about it at CLSI?)

21ST CENTURY CURES ACT

GOALS OF THE LEGISLATION

RESEARCH



Remove barriers to research collaboration



Invest in STEM education



Provide new incentives for the development of rare disease drugs

GETTING TREATMENTS TO PATIENTS MORE QUICKLY



Foster coordination to find cures more quickly



Modernize clinical trials to increase access to drugs and treatments



Incorporate patient feedback in drug development and review process

KEEPING JOBS HERE AT HOME



Ensure U.S. remains a global leader in medical innovation, protecting and creating jobs at home



Encourage development of new medical apps to save lives and create jobs

#CURESatOne

E&C

Subtitle E—Antimicrobial Innovation and Stewardship

Sec. 3041. Antimicrobial resistance monitoring.

Sec. 3042. Limited population pathway.

Sec. 3043. Prescribing authority.

Sec. 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices.

Some jargon

- STIC = susceptibility test interpretive criteria
 - AKA, “breakpoint” or “interpretive criteria”
- SDO = standard development organization
 - E.g., CLSI

Sec 3044 of 21st C Cures Act

1. Establishment and maintenance of STIC website
2. Permits listing of STIC established by a qualified SDO
3. Requires disclaimers on STIC website re: STIC may/may not have been established for safety or adequacy, clinical significance is unknown; look at the approved product labeling
4. Requires STIC website be reviewed every 6 months
5. Requires removal of breakpoints from drug labels
6. Permits AST manufacturers to use breakpoints listed on the STIC website, or other standard recognized by FDA

So... what does that mean?

1. FDA can recognize CLSI breakpoints
2. AST manufacturers can use any breakpoint on the STIC website
3. Indications for use list (i.e. “list A”) no longer an issue for AST manufacturers (i.e., one could test off-label organisms)?

What is the CLSI AST Subcommittee doing?

1. Identifying and prioritizing breakpoints that differ between CLSI and FDA
2. Generating rationale documents to submit to federal register for breakpoint review by FDA
3. Generating public awareness on the topic:

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 and Janet A. Hindler^c

ACCEPTED MANUSCRIPT

21st Century Cures Act and Antimicrobial Susceptibility Testing: Clinical Implications in the Era of Multidrug Resistance

Romney M Humphries ✉, Janet Hindler, Mary Jane Ferraro, Amy Mathers

Clinical Infectious Diseases, ciy432, <https://doi.org/10.1093/cid/ciy432>

This workshop

FDA Center for Drug Evaluation and Research (CDER) Speaker: John Farley FDA, Center for Drug Evaluation and Research	Susceptibility Test Manufacturers Association (STMA) Speaker: Sharon Cullen Beckman Coulter
FDA Center for Devices and Radiological Health (CDRH) Speaker: Patricia Conville FDA Center for Devices and Radiological Health	Pharmaceutical Industry perspective (15 minutes) Speaker: Linda Miller CMID Pharma Consulting

Q&A / panel discussion: 50 minutes



Implementation of the 21st Century
Cures Act for Breakpoints and
Interpretive Categories
FDA CDER Perspective

John Farley MD MPH

Deputy Director

Office of Anti-Microbial Products

CDER FDA



Introduction

- Enabling physicians to select appropriate antibacterial or antifungal drugs is critical to individual patient care and public health.
 - Laboratories and AST device manufacturers need to be able to use up-to-date susceptibility test interpretive criteria (STIC) or breakpoints for the reports provided to physicians to inform appropriate treatment choices.
 - Identification of patients who have certain types of resistant bacteria is also essential for infection control practices.



The 21st Century Cures Act

- 21st Century Cures Act was signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
 - Section 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices
 - Added Section 511A to the Federal Food, Drug and Cosmetic Act
 - Section 3041. Antimicrobial Resistance Monitoring
 - Section 3042. Limited Population Pathway for antibacterial and antifungal drugs (LPAD)

<https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf>



Challenges Addressed by Section 511A

- A laborious, duplicative, and time consuming process to update STIC that depended upon each drug sponsor updating its drug labeling with new or updated STIC. Only then could updated STIC be incorporated in AST devices.
- A clinical need for STIC for organisms not listed in the Indication section of drug labeling.



- In the Cures Act, Congress recognized the importance of improving the process of updating STIC.

Section 511A:

- Clarifies FDA's authority to recognize the standards established by standards development organizations (SDOs).
- States that FDA retains full authority to accept a standard in whole or in part or to establish alternative STIC.
- Clarifies that sponsors of AST devices may rely upon these FDA recognized or listed STIC to support pre-market authorization of their devices.

Implementation Progress: SDO Requirements for Recognition



- FDA now has authority to recognize standards established by a national or internationally recognized SDO that:
 - Establishes and maintains procedures to address potential conflicts of interest and ensure transparent decision making;
 - Holds open meetings to ensure that there is an opportunity for public input by interested parties, and establishes and maintains processes to ensure that such input is considered in decision making; and
 - Permits its standards to be made publicly available, through the National Library of Medicine or another similar source acceptable to the Secretary of Health and Human Services.
- After publishing a Federal Register Notice on October 30, 2017 inviting submissions, FDA determined that CLSI fulfills these statutory requirement at this time.
- Other SDOs could submit information in the future regarding how they fulfill these requirements.



Implementation Progress: FDA STIC Recognition or Identification

- On December 13, 2017, FDA established the Interpretive Criteria webpages (www.fda.gov/STIC).
 - These webpages list STIC by therapeutic category (antibacterial or antifungal).
 - These webpages list FDA recognized or identified STIC by antibacterial and antifungal drug.
- FDA recognizes consensus standards for performance standards, methods standards, and quality control parameter standards for antimicrobial susceptibility testing on separate webpages.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfsstandards/search.cfm>

Implementation Progress: Updates



- FDA has established a Notice of Update webpage as part of (www.fda.gov/STIC).
- At least every 6 months, FDA will publish a notice that recognizes new or updated STIC standards or parts of standards, withdraws recognition of standards or parts of standards, or makes any other necessary updates.
- Interested parties can sign up on this webpage to receive an email notification when FDA posts new updates.

Currently Reformatting Individual Drug Webpages for Clarity



Example: Doxycycline – Oral, Injection Products

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
<u>Pathogen</u>						
Enterobacteriaceae	M100 standard is recognized					
<i>Acinetobacter</i> spp.	M100 standard is recognized					
<i>Streptococcus pneumoniae</i>	M100 standard is recognized					
<i>Bacillus anthracis</i>	M45 standard is recognized			-	-	-
<i>Brucella</i> spp.	M45 standard is recognized			-	-	-
<i>Franciscella tularensis</i>	M45 standard is recognized			-	-	-
<i>Yersinia pestis</i>	M45 standard is recognized			-	-	-
<i>Vibrio cholerae</i>	M45 standard is recognized			-	-	-
<i>Nocardiae</i> and other aerobic <i>Actinomyces</i> spp.	M24-A2 standard is recognized			-	-	-

S = Susceptible; I = Intermediate; R = Resistant

Exceptions to the recognized standard of CLSI M100

For the bacteria listed below, susceptibility test interpretive criteria are not recognized at this time:

Other Non-Enterobacteriaceae, *Staphylococcus* spp., *Enterococcus* spp.

Implementation Progress: Submitting Information Regarding STIC Recognition



- On March 1, 2018, FDA posted a Federal Register notice requesting comments by interested third parties on FDA's initial STIC recognition and listing determinations on the Interpretive Criteria web page. <https://www.regulations.gov/docket?D=FDA-2017-N-5925>
 - Interested third parties or drug sponsors may provide information that FDA could use as a basis for recognizing new or updated STIC.
 - Alternatively, drug sponsors may submit data supporting changes to STIC recognition to their annual report.



Implementation Progress: Updating Drug Labeling

- On December 13, 2017, FDA published a guidance providing recommendations on fulfilling the new labeling requirements for STIC for prescription systemic antibacterial and antifungal drugs.
 - Section 511A(d)(2) requires that, within one year of establishment of the STIC webpages, STIC and related information be removed from labeling and replaced with a reference to the STIC webpages.

Current Challenges and Opportunities



- Obtaining updated information to support the recognition of clinically important not yet recognized STIC, with the goal of providing physicians with the best available information to guide treatment choices.
- Ensuring that physicians receiving laboratory reports based on STIC and making treatment decisions are aware of the dosing regimen that supported those STIC.
- Leveraging information from electronic health record (EHR) systems to provide updated clinical outcome information to support STIC recognition decisions.



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Implementation of the 21st Century Cures Act for Breakpoints and Interpretive Categories: CDRH Perspective

Patricia Conville, MS, MT
Division of Microbiology Devices
CDRH, FDA



Disclosure

Nothing to disclose



Outline

- Historical Perspective
- CDRH use of the STIC webpage
- Examples of various recognitions
- Updating breakpoints
- Coordinated Development
- CDRH Activities related to AST Testing



Guidance for Industry and FDA

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

Document issued on: August 28, 2009

This document updates the one of the same title, issued March 5, 2007

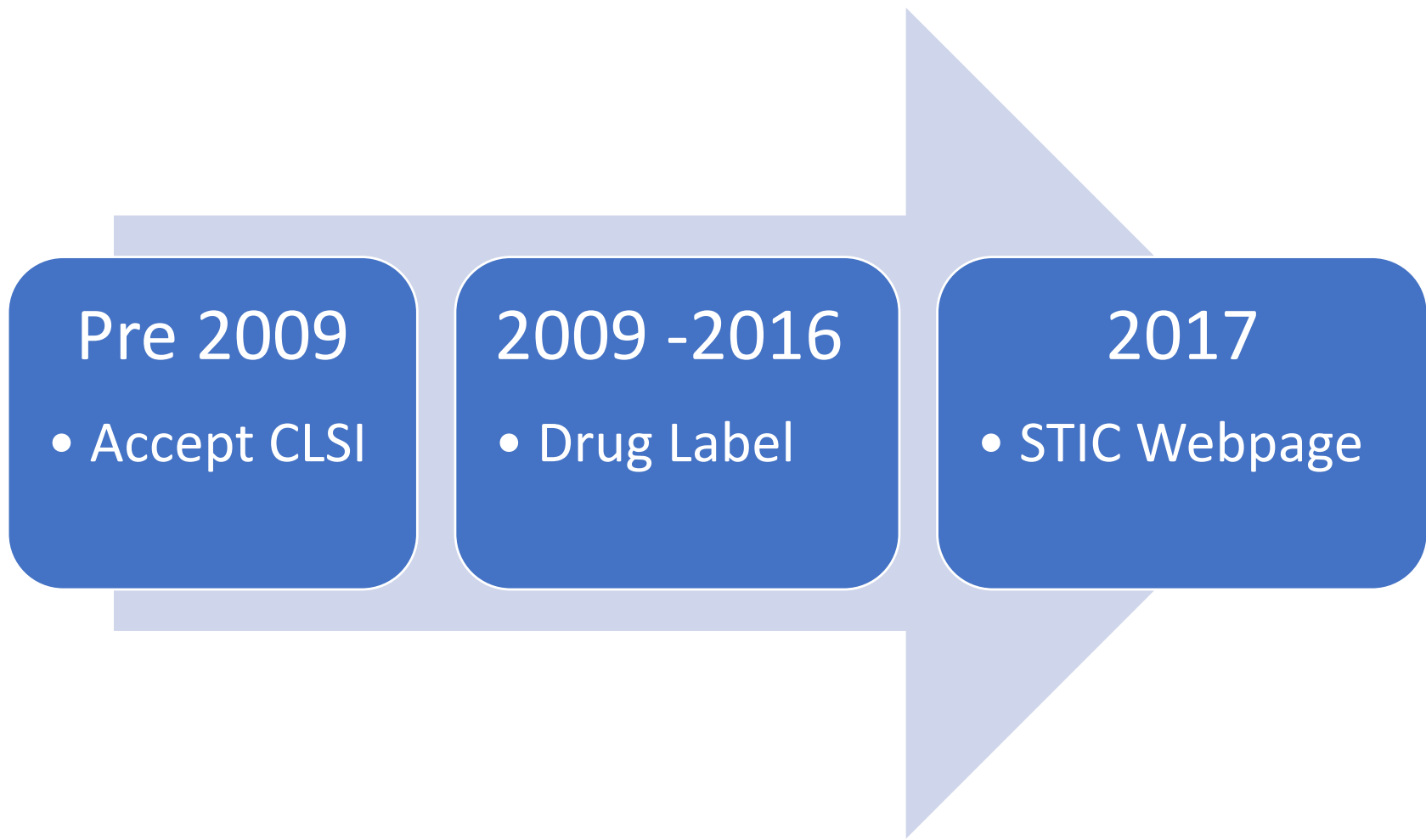


**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Bacteriology Branch
Division of Microbiology Devices
Office of In Vitro Diagnostic Device (OIVD)
Evaluation and Safety**



CDRH Device Review Breakpoints and Indicated Organisms





CDRH Review Pre 21st Century Cures

- Based on data reviewed by CDER during drug evaluation – Reference List Drug Label
- Section 12.4 Microbiology
 - List 1: Lists organisms for which drug has been shown to be active both *in vitro* and in clinical infections
 - List 2: Lists organisms for which *in vitro* data was available but clinical significance of the activity is unknown



Ceftazidime Drug Label

List 1

- *Citrobacter* spp.
- *Enterobacter* spp.
- *E. coli*
- *Klebsiella* spp.
- *P. mirabilis*
- *P. vulgaris*
- *Serratia* spp.
- *P. aeruginosa*



Active *in vitro* and in clinical infections

List 2

- *Acinetobacter* spp.
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Providencia* spp.
- *Salmonella* spp.
- *Shigella* spp.
- *Morganella morganii*
- *Yersinia enterocolitica*



In vitro data available but clinical significance is unknown



Breakpoints in Drug Label

Table 8. Susceptibility Breakpoints for Meropenem/Vancomycin/Colistin/Tobramycin/Polymyxin B/Linezolid/Avibactam

<i>Pathogen</i>	<i>Minimum</i>	<i>Disk Diffusion Zone Diameter (mm)</i>	
	<i>S</i>	<i>S</i>	<i>R</i>
Enterobacteriaceae	≤ 10	≥ 21	≤ 20
<i>Pseudomonas aeruginosa</i>	≤ 10	≥ 21	≤ 20

QC Ranges in Drug Label



Ceftazidime-Avibactam

Table 9. Acceptance Control Limits for Susceptibility Testing

<i>Quality Control Organism</i>	<i>Concentration (mg/L)</i>	<i>Disk Diffusion Zone Diameter (mm)</i>
<i>Staphylococcus aureus</i> ATCC 29213	16	-
<i>Staphylococcus aureus</i> ATCC 25923	-	16 - 22
<i>Escherichia coli</i> ATCC 25922	0.5	27 - 35
<i>Escherichia coli</i> ATCC 35218	0.06	28 - 35
<i>Pseudomonas aeruginosa</i> ATCC 27956	0.06	25 - 31
<i>Klebsiella pneumoniae</i> ATCC 700603	0.06	-
<i>Haemophilus influenzae</i> ATCC 49619	0.06	28 - 34
<i>Haemophilus influenzae</i> ATCC 4976	0.01 - 0.06	-
<i>Streptococcus pneumoniae</i> ATCC 49619	0.25 - 2	-

STIC Webpage



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Drugs

Home > Drugs > Development & Approval Process (Drugs) > Development Resources

Development Resources

- Antibacterial Drug Development Task Force
- FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria**
- Ingredients
- Medical Imaging and Drug Development
- Model-Informed Drug Development Pilot Program
- Pediatric Product Development
- Clinical Outcome Assessment Compendium
- Over-the-Counter (OTC)

FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria

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- [Antibacterial Susceptibility Test Interpretive Criteria](#)
- [Antifungal Susceptibility Test Interpretive Criteria](#)

Looking for recent updates? Please see: [Notices of Updates](#)

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These web pages provide information about the *in vitro* susceptibility of bacteria or fungi to certain drugs. The safety and efficacy of these drugs in treating clinical infections due to such bacteria or fungi may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown. The approved product labeling for specific drugs provides the uses for which the product is approved.



STIC Webpage

Drug	Route of Administration	STIC for Drug Included in CLSI M100 Standard	Exceptions or Additions to CLSI M100 Standard	Last Updated
Amikacin	Injection	Yes	No	12/13/17
Ceftazidime	Injection	Yes	Yes	12/13/17
Meropenem and vaborbactam	Injection	No	Yes	12/13/17
Capreomycin*	Injection	No	No	12/13/17

*No STIC are recognized by FDA for this drug at this time.



1. Standard Recognized - Amikacin

List 1: *E. coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Pseudomonas* spp., *Acinetobacter* spp.
List 2: *C. freundii*

Drug	Route of Administration	STIC for Drug Included in CLSI M100 Standard	Exceptions or Additions to CLSI M100 Standard	Last Updated
Amikacin	Iniection	Yes	No	12/13/17

Table 2A. Enterobacteriaceae (Continued)

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL			
			S	SDD	I	R	S	SDD	I	R
AMINOGLYCOSIDES										
(32) WARNING: For <i>Salmonella</i> spp. and <i>Shigella</i> spp., aminoglycosides may appear active <i>in vitro</i> but are not effective clinically and sho										
A	Gentamicin	10 µg	≥ 15	-	13-14	≤ 12	≤ 4	-	8	≥ 16
A	Tobramycin	10 µg	≥ 15	-	13-14	≤ 12	≤ 4	-	8	≥ 16
B	Amikacin	30 µg	≥ 17	-	15-16	≤ 14	≤ 16	-	32	≥ 64



2. Standard Partly Recognized - Ceftazidime

Drug	Route of Administration	STIC for Drug Included in CLSI M100 Standard	Exceptions or Additions to CLSI M100 Standard	Last Updated
Ceftazidime	Injection	Yes	Yes	12/13/17

Exceptions to the recognized standard of CLSI M100

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
<i>Pseudomonas aeruginosa</i> ^a	≤ 8	-	≥ 16	≥ 18	-	≤ 17

S = Susceptible; I = Intermediate; R = Resistant

^a For *P. aeruginosa*, susceptibility interpretive criteria are based on a dose of 2 grams IV every 8 hours in patients with normal renal function

CLSI MIC: ≤4, 8, ≥16

CLSI Disk: ≥21, 18-20, ≤19



Standard Partly Recognized - Ceftazidime

Exceptions to the recognized standard of CLSI M100:

For the bacteria listed below, susceptibility test interpretive criteria are not recognized at this time:

Acinetobacter spp. disk diffusion interpretive criteria (Interpretive criteria for MIC are recognized.)

Burkholderia cepacia complex disk diffusion interpretive criteria (Interpretive criteria for MIC are recognized.)

Other Non-*Enterobacteriaceae*

Neisseria gonorrhoeae

Table 2B-5
Other Non-*Enterobacteriaceae*
M07

Table 2F
Neisseria gonorrhoeae
M02 and M07



3. New Drugs Not in M100 – Meropenem-Vaborbactam

Drug	Route of Administration	STIC for Drug Included in CLSI M100 Standard	Exceptions or Additions to CLSI M100 Standard	Last Updated
Meropenem and vaborbactam	Injection	No	Yes	12/13/17

FDA-Identified Interpretive Criteria

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤4/8	8/8	≥16/8	≥17	14-16	≤13

S = Susceptible; I = Intermediate; R = Resistant

List 1: *E. cloacae*, *E. coli*, *K. pneumoniae*

List 2: *C. freundii*, *C. koseri*, *K. aerogenes*, *K. oxytoca*, *M. morgani*, *P. mirabilis*, *Providencia spp.*, *Serratia marcescens*, *P. aeruginosa*



Summary

- Look at breakpoint exceptions
- Look at methods not recognized (disk diffusion)
- Look at organism groups not recognized
- Device manufacturers should still test organisms on List 1 and List 2.

- QC – all QC ranges as listed in M100 recognized



Pre-submissions

- Drug/organism combinations may not fit these examples
- Pre-submissions welcome!

Statement Required for all AST Devices



- *The safety and efficacy of [drug] in treating clinical infections due to [organism group] other than [species] may not have been established in adequate and well-controlled clinical trials. The clinical significance of such susceptibility information in those instances is unknown.*

Updating Breakpoints for AST Devices

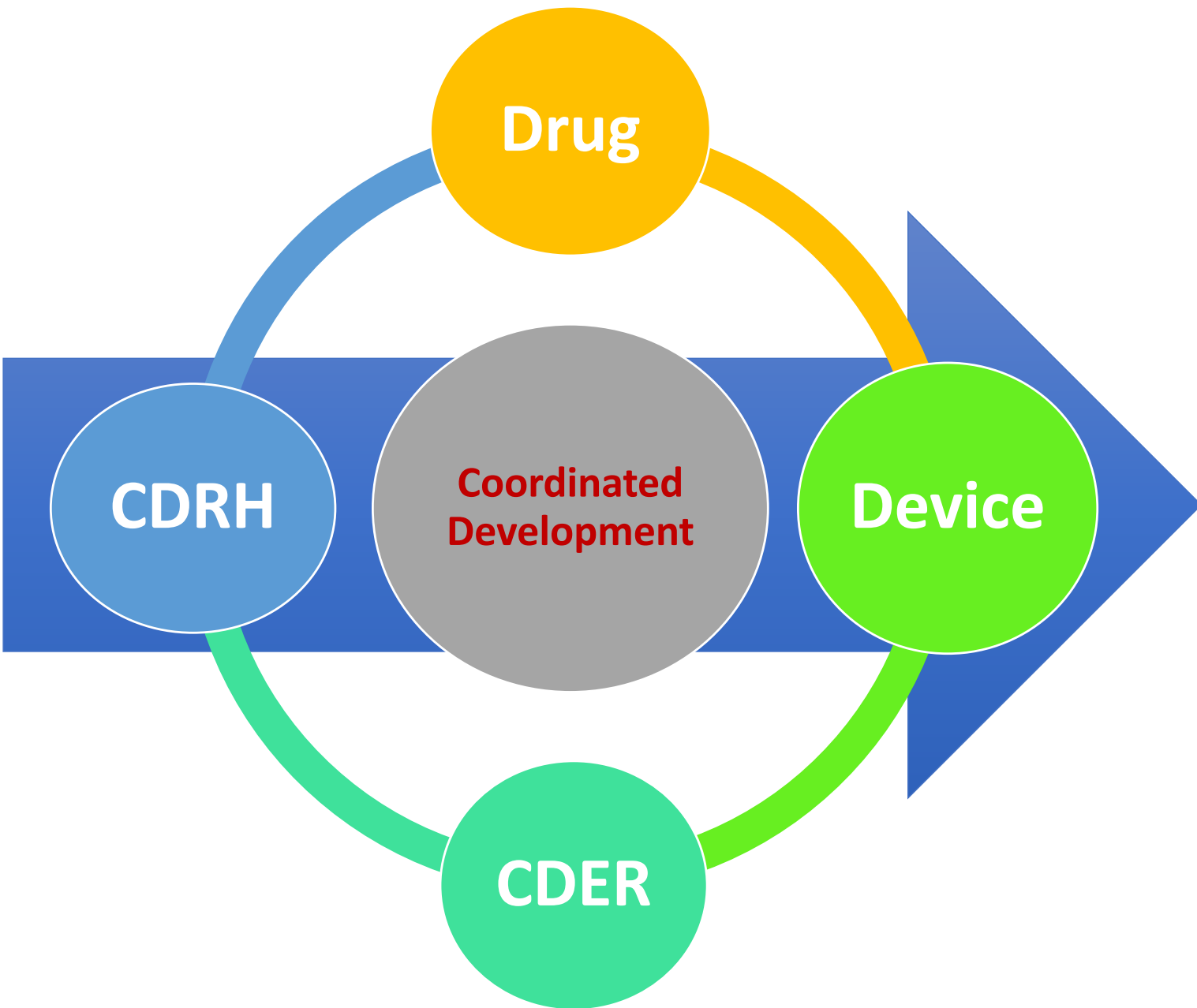


- Extent of additional testing depends on:
 - The information available from the original submission (variety of species/resistant strains)
 - Antibiotic dilutions on the device contain new breakpoints
 - No modifications to the device
- Submission type can range from:
 - Pre-submission with summary
 - Special 510(k)
 - Traditional 510(k)
- Pre-submissions Welcome!



ECVs

Currently not considered in device review



**Improved
Patient
Care**

Coordinated Development



- Discussions among drug developers, Device manufacturers and CDER should occur early and often regarding potential breakpoints and indicated organisms
- Device manufacturers should provide plans data collection and analysis related to coordinated development to CDRH for device review
- 510(k) submission to CDRH should coincide with submission of NDA/drug approval



Recent Interactions with Stakeholders

- **September, 2016**
 - Public Workshop - Coordinated Development and Draft Guidance
- **September, 2017**
 - Public Workshop – Antimicrobial Resistance
- **December, 2017**
 - Discussions regarding broth microdilution regulatory issues (FDA/STMA)
- **March, 2018**
 - Discussions regarding disk diffusion test regulatory issues (FDA/STMA)

CDC & FDA Antibiotic Resistance Isolate Bank

[CDC](#) > [Antibiotic / Antimicrobial Resistance](#)



Hello! Are you enjoying the new AR Isolate Bank web page? [Email us](#) with any feedback or issues.



The [CDC & FDA Antibiotic Resistance \(AR\) Isolate Bank](#) provides curated collections of resistant organisms to help microbiologists, drug and diagnostic manufacturers, and researchers combat one of the world's greatest infectious disease threats.

Isolates are gathered through CDC's outbreak response and surveillance programs, validated and sequenced for testing, and then thoughtfully curated to increase lab efficiencies and public health innovations. The isolates represent samples from healthcare-associated, foodborne, gonorrhea, and community-associated infections.

The isolates are available at no cost to recognized and approved institutions.

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580 isolates

1060 orders

135 registered users



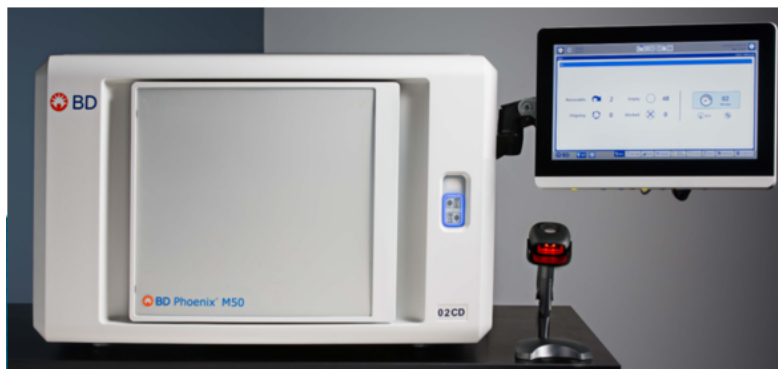
New Isolates - March 2018

[Isolates with New or Novel Antibiotic](#)



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21st Century Cures Act STMA Perspective



21st Century Cures Act STMA Perspective

- I. Highlights on STMA's Perspective of 21st Century Cures Act
- II. 2007 - 2016 AST Device Challenges
- III. Recent Progress – 2017 to Present
- IV. Summary of FDA & STMA Discussions
- V. Proposed Next Steps and Future Opportunities

Highlights STMA Perspective 21st Century Cures Act

- **Able to implement breakpoints from standards development organizations (SDOs).**
- **Able to report larger number of organisms with AST devices**
 - Prior to 2007, able to apply breakpoints to broader organism groups and/or report MIC only
 - Since 2007, AST device limited to indications in FDA drug label
 - Newer agents - small number of species (*Acinetobacter* spp rarely included)
 - Older agents - reduced organism reporting capabilities when submitting 510k for revised AST (e.g., 25%, 50%)
 - Can now include organism groups with SDO breakpoints e.g. *Enterobacteriaceae*, *Acinetobacter* spp, Other Non-*Enterobacteriaceae*, M45 organism groups
 - Include labeling statement “clinical efficacy not established”
 - **Ability and approach to report MIC only for species without breakpoints - TBD**
- **Large pipeline of new/revised antimicrobial agents is overwhelming**
 - Limited financial incentives to AST manufacturers for revised antimicrobial agents (e.g., revised panels/cards for existing users)
 - Reducing scope of study designs and streamlining submissions can help to address capacity issues.



2007–2016 Challenges

■ Device study requirements increased

- Greater focus of on-scale organisms,
- Test larger number of indicated organisms, less overlap of organisms when testing multiple drugs in single study
- Expanded testing for secondary methods (e.g., inoculum prep, panel/card dispense, multiple instrument types)

■ Large workload e.g., new antimicrobial agents, breakpoint changes, screening tests

■ Acceptance criteria not achievable resulting in labeling limitations or no submission

- Wild-type closer to the breakpoint (affects CA, Mj, VME)
- Greater variability of MICs with some newer agents (e.g., ESBLs, expression of resistance/enzymes)
- Criteria applied to individual organisms or groups (vs overall)
- Unable to do repeat testing to resolve discrepancies

■ Only able to report FDA breakpoints

- Some drugs not updated with revised CLSI breakpoints

■ Not able to report MICs for organisms without FDA breakpoints

- Older drugs with no breakpoints in drug insert (e.g., colistin, amphotericin B)
- Not able to report MICs and support surveillance studies, ECVs/ECOFFs
- Limited data for organisms with multidrug resistance and limited treatment options (e.g. Acinetobacter)

Recent Progress—2017 to Present

■ STMA-FDA collaboration and improvements

- Streamlined studies (e.g., fresh/stock isolates, breakpoint changes, new/revised QC, secondary methods)
- Pre-submission for some breakpoint changes
- Criteria more achievable (e.g. excluding 1 dilution errors from CA, ability to do reference method repeats to resolve discrepancies, prospective replicate testing when variability expected)
- Established method and criteria to evaluate bias

■ New challenges

- New clinical testing and data requirements for disk 510(k) submissions

■ Continuing challenges

- Inability to report MICs for organisms without breakpoints
- Extensive studies/cost to support secondary methods
- Formal guidance (FAQs) not yet available
- Capacity to support breakpoint changes: on-going changes, authorization for recently recognized CLSI breakpoints
- Capacity to implement changes AND launch new ASTs (e.g. software, labeling, panels, cards, disks)
- Availability of on-scale and resistant organisms (applicable for each drug)
- Resolving discrepancies is still burdensome and acceptance criteria not always achievable
- Reproducibility request for breakpoint changes for older drugs



STMA / FDA 510(k) Discussions

- **Class II Special Controls Guidance Document for AST Systems (primarily MIC methods):**
 - December 2016: STMA formally submitted proposed changes and rationale (docket FDA-2000-D-0128)
 - September 2017: FDA workshop “Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices”
 - December 5, 2017: STMA/FDA met to identify and gain agreement on “low hanging fruit”
 - **Present: Awaiting FDA response to minutes & FAQs, further discussions on remaining issues TBD**
- **“New” FDA Disk Clearance Requirements:**
 - Historic: Disk method established during NDA, individual manufacturers submit 510(k) with labeling summary
 - ~October 2017: FDA responded to disk manufacturer 510(k) submissions indicating clinical data now required.
 - November 20, 2017: STMA & FDA teleconference to discuss new FDA requirements and STMA concerns.
 - January 27, 2017: STMA & FDA met to further discuss STMA concerns and potential alternatives
 - March 12, 2017: STMA & FDA teleconference. FDA summarized proposals and presented rationale.
 - **Present: Awaiting FDA response to minutes & FAQs, addressing questions individually with Pre-Submission process, further discussions on open questions TBD**
- Highlights on the following slides
 - + Streamlined/improved processes
 - Approach still burdensome/additional opportunities could be explored
 - Proposals under consideration or additional comments



FDA Class II Guidance Modifications

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
Isolates for Clinical Studies	<ul style="list-style-type: none"> 50 fresh (≤ 7 days) per site 	<ul style="list-style-type: none"> 25 “contemporary” (≤ 6 months/can be frozen) per site 	<ul style="list-style-type: none"> + Duration not constrained by fresh isolates, focuses on more relevant isolates Working with Pharma to get more on-scale and relevant isolates Limited number of on-scale isolates with highly active agents.
	<ul style="list-style-type: none"> No more than 50 stock (≤ 3 years) per site 	<ul style="list-style-type: none"> 75 stock (no time requirement) per site 	
	<ul style="list-style-type: none"> Include on-scale isolates 	<ul style="list-style-type: none"> Emphasis on on-scale isolates 	
Trending/Bias	<ul style="list-style-type: none"> Analysis and acceptance criteria for trending are not defined in SC guidance 	<ul style="list-style-type: none"> Supports STMA statistical analysis <i>Bias = (% test results above reference) – (% test results below reference)</i> A trend $\geq 30\%$ will be reflected in the labeling 	<ul style="list-style-type: none"> + Better statistical model than current approach. Establishes criteria. Propose to apply criteria to overall/combined results and not individual species

FDA Class II Guidance Modifications - Continued

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
Breakpoint Changes <ul style="list-style-type: none"> • Data available • No modifications or new dilutions • Sufficient R strains in original 510(k) 	<ul style="list-style-type: none"> • CDER Guidance (withdrawn) requires submission of 510(k) when updating BPs 	<ul style="list-style-type: none"> • Recalculate Categorical Agreement from original study • Pre-submission with summary of data, FDA letter allowing marketing with new breakpoints 	<ul style="list-style-type: none"> + Streamlined regulatory approaches saving \$10k fee. If acceptable, no additional studies needed. • Explore ability to include multiple drugs in one submission (e.g., same class)
Breakpoint Changes <ul style="list-style-type: none"> • Same as above but insufficient R strains in original 510(k) 	<ul style="list-style-type: none"> • Same as above 	<ul style="list-style-type: none"> • Test additional resistant strains (e.g., 50 of prevalent species, internal OK) to supplement original data • Recalculate performance (original and supplemental). • No reproducibility needed • Most are Special 510(k) 	<ul style="list-style-type: none"> + Same as above. Testing approach focuses on evaluation of breakpoint change. • Bundling could reduce fees and allow for efficient reviews and consistency within drug classes.

FDA Class II Guidance Modifications - Continued

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
Breakpoint Changes <ul style="list-style-type: none"> • Data available • No modifications or new dilutions • Performance with breakpoints don't meet acceptable criteria 	<ul style="list-style-type: none"> • Efficacy 3 sites, 100 isolates each, • Challenge 1 site 50-75 isolates 	<ul style="list-style-type: none"> • Test additional strains externally: 25 contemporary, 75 stock, 75 challenge (include R and on-scale) • Recalculate performance (original and supplemental). • Reproducibility: reanalyze or do new study if not on-scale. 	<ul style="list-style-type: none"> + Streamlines study requirements and focuses supplemental testing on evaluation of breakpoint change. - Proposal for reproducibility is burdensome and not needed to evaluate breakpoint changes • Explore ability to test internal for more flexibility
Breakpoint changes New breakpoints not covered by existing drug concentrations or device is modified	<ul style="list-style-type: none"> • Traditional study and 510(k) 	<ul style="list-style-type: none"> • No change 	<ul style="list-style-type: none"> • Agree with no change

FDA Class II Guidance Modifications - Continued

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
Acceptance Criteria	<ul style="list-style-type: none"> Acceptable # ME: $\leq 3\%$ of susceptible isolates Acceptable # VME $\leq 1.5\%$ of resistant isolates Acceptable CA (exact) $\geq 90\%$ 	<ul style="list-style-type: none"> Eliminate the use of Table 8 in the SC document Increase acceptable # VME to $\leq 2\%$ Additional analysis excluding 1 dilution errors from CA 	<ul style="list-style-type: none"> - Ability to meet VME criteria depends on # of resistant isolates and ability to resolve discrepancies
Variability of Reference Method/ Discordant Evaluation	<ul style="list-style-type: none"> Performance of reference method in triplicate for clinical and challenge 	<ul style="list-style-type: none"> Determine variability of ref. method through drug manufacturer prior to beginning device studies Perform replicate testing of ref. method at each site or single site and use mode or median value (for all isolates or isolates determined to be variable prior to testing). Retest percentage of concordant results when retesting discordants 	<ul style="list-style-type: none"> + Prospective triplicate testing for species with known variability. + Resolution of discrepancies recognizes variability of reference method and improves ability to meet criteria - FDA proposal for large # concordant retesting is burdensome • Explore ability to do repeats internally and replicates for AST device

FDA Class II Guidance Modifications - Continued

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
Evaluation of Secondary Inoculation Methods - <u>existing assays</u> , same technology	Agreement studies should be performed on all procedural options	<ul style="list-style-type: none"> Sites – one internal, mimic 3 users, QC - 60 replicates, Organisms - 1 from each group, Drugs - 1 from each class, Compare to primary method, Special 510(k) 	<ul style="list-style-type: none"> - Proposal is burdensome. • Propose streamlined studies and submission approaches (e.g., internal verification of optical density of inoculum, dispense volume into AST)
Evaluation of Secondary Inoculation Methods - <u>new assays</u> , same technology	Agreement studies should be performed on all procedural options	<ul style="list-style-type: none"> QC - 20 replicates at 3 external sites Organisms - Challenge set at 1 site Each drug Compare to reference method, Traditional 510(k) 	<ul style="list-style-type: none"> - Proposal is burdensome. • Propose internal verification. Not necessary to re-validate a method already shown to be substantially equivalent to the primary method.

FDA Disk Clearance Requirements

Topic	Current AST SC Requirements	FDA Comment	STMA Comment
<p>Rationale for Disk 510(k) clearance requirement changes</p>	<p>Historical: disk method reviewed in NDA; individual disk manufacturer submitted labeling 510(k) only</p> <p>2017 - scope of 510(k) increased to now include clinical data review (similar to AST Guidance requirements)</p>	<p>FDA concerns leading to additional requirements:</p> <ul style="list-style-type: none"> • Disks are Class II devices which require data to determine safety and effectiveness • FDA cited recent “disk recalls, BMJ article, and a EUCAST disk QC study showing variability with some manufacturers & antimicrobial agents 	<p>– Proposal is burdensome.</p> <ul style="list-style-type: none"> • Safety issue/public health need for additional clinical testing by each disk manufacturer is unclear. • Recalls have been lot specific related to manufacturing issues which more stringent clearance requirements will not prevent • Majority of disk performance issues occurred with Non-US disks

FDA Disk Clearance Requirements - Continued

Topic	FDA Comment	STMA Comment
New Disk 510(k) clearance requirements	<p>New disk evaluation guidelines:</p> <ul style="list-style-type: none"> • Sites: 1 internal site with 3 independent operators to mimic 3 clinical sites. • Isolates: 300 indicated orgs (no fresh/age specifications); 75 challenge isolates with known resistance mechanisms • Reproducibility: Performed at 1 site (can be internal) with 3 readers reading 15 orgs each for 3 days to yield 270 data points. 2 disk lots and 1 media lot must be used. • Reference method: Compare to MIC data from the NDA OR compare to another cleared disk • Quality Control: Performed each day of testing; at least 60 replicates for each isolate; 1 media lot; 2 disk lots 	<ul style="list-style-type: none"> – Reproducibility study is burdensome • Represents significant increase in testing (510k historically for labeling only) • STMA members are proceeding with studies to support 510(k) for disks for new antimicrobial agents • Propose use of CLSI M23 Tier 2 QC study to demonstrate reproducibility of disk manufacturer or conduct small reproducibility study • Propose to use strains for efficacy/challenge study with known MICs to prevent need to retest reference method. May need different set of organisms than those used in NDA studies.

Next Steps – STMA Members

- Individual manufacturers will continue to
 - Incorporate FDA feedback into new study designs/510(k) submissions (as appropriate)
 - Assess priority and ability to support new antimicrobial agents, improvements and revised breakpoints
 - Large number of new/revised assays in pipeline (globally)
 - Limited financial incentives/revenues for revised antimicrobial agents
- STMA will continue to
 - Work with FDA to streamline study designs and submissions
 - Reducing scope of study designs and streamlining submissions can help to address capacity issues.
 - Work with SDOs, Pharma and CDC to make characterized organism sets available for AST evaluations
 - Reduces effort for AST manufacturers
 - Improves quality and consistency of device evaluations.



Next Steps - FDA

- Need continued progress to streamline device studies and submissions
 - Focus on study parameters key to quality of evaluation, reduce/streamline others
 - Improved efficiency potentially increases availability of AST results for all stakeholders
 - Provides data for clinicians to make informed decisions when treatment options are limited
 - Better evaluation/more efficient than individual laboratory validation studies
- Class II Special Controls Guidance for AST Device:
 - FDA FAQ sheet to address low hanging fruit – pending
 - Further discussion on remaining issues/opportunities - TBD
- Disk Clearance Requirements:
 - Pre-submission feedback,
 - Lengthy process, limited and unique to individual antimicrobial agents
 - General approach is still being defined
 - STMA members are proceeding with studies/510(k) with information available
 - FDA FAQ sheet new disk 510(k) data requirements – TBD
 - Further discussion on remaining issues/opportunities – TBD

Next Steps - Future Opportunities

- CLSI and/or Pharma Support:
 - Evaluate reproducibility of reference (MIC and disk) with new drugs
 - Include as improvement in M23 (e.g., use to establish reference method, assist in setting the breakpoint)
 - Known variability useful to AST manufacturers for development and 510(k) studies (e.g. prospective replicate testing, resolving discrepancies)
 - Identify organism sets to develop and evaluate AST device performance
 - Include all applicable resistance mechanisms targeted
 - Establish expected result with minimum 3 replicates on reference (e.g., MIC, disk)
 - Make readily available to all AST manufacturers (e.g., CDC AR bank, pharma, central lab)
- Request to FDA to allow reporting MIC only for organisms with no clinical breakpoints
 - Performance based on Essential Agreement and assessment of bias.
 - MIC data supports multiple stakeholders & objectives
 - Surveillance and epidemiology
 - ECV/ECOFFs
 - Provides data for clinicians to make informed decisions when treatment options are limited
 - Better evaluation/more efficient than individual laboratory validation studies

Thank You



Implementation of the 21st Century Cures Act for Breakpoints and Interpretive Categories

A Pharmaceutical/Biotechnology Industry Perspective

June 2, 2018

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Disclosure:

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CMID Pharma Consulting, LLC

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The opinions expressed in these slides are my own and do not necessarily reflect the opinions of my former employer, GSK, my current clients or colleagues who shared their views with me.

21st Century Cures Act

Broken Business
Model for Anti-
bacterial Drug
Development

- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
 - Section 3041: Antimicrobial Resistance Monitoring
 - Section 3042: Limited Population Pathway for antibacterial and antifungal drug (LPAD)
 - **Section 3044:**
 - **Susceptibility test interpretive criteria (breakpoints) for microorganisms**
 - **Antimicrobial susceptibility testing devices**

A Pharma/Bio's Perspective on Section 3044

<https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf>

Susceptibility breakpoints for microorganisms FDA label & website

- Organisms listed in Microbiology Section of FDA drug label:
 - List 1: associated with a labeled indication
 - List 2: efficacy has not been established in clinical trials; microorganisms should be relevant to a labeled indication
- Breakpoints will now be on STIC website and not in drug label
 - www.fda.gov/STIC
 - It might be helpful for website to include the actual recognized breakpoints and not just links to CLSI

Susceptibility breakpoints for microorganisms FDA label & website

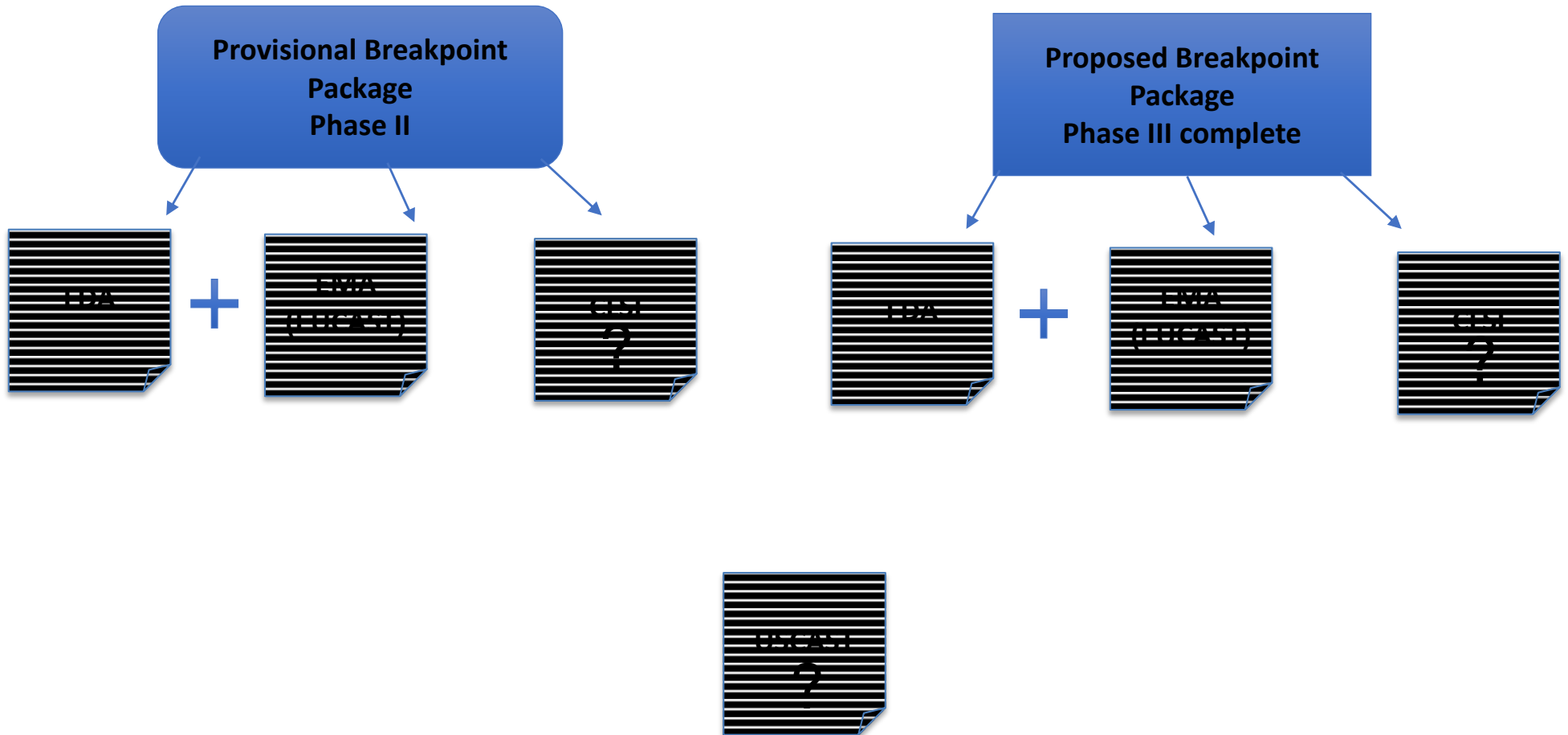
- Are FDA recognized breakpoints on STIC website limited to those organisms that are included in List 1 ONLY?
 - **Not necessarily** - FDA presentation at CLSI January 2018:
 - “There might be need for interpretive criteria for organisms not listed in the Indication section of drug labeling”
 - “The website includes breakpoints for organisms that are not included in the first list when such breakpoints are supported by adequate scientific justification”
 - Clarity needed on “adequate scientific justification”
 - ECV + PK/PD target attainment? Other?

FDA Susceptibility breakpoints for microorganisms

Potential Pathways for Breakpoint approvals

Assume Goal is US/EU label

Assume EU label desired and sponsor accepts EUCAST as Breakpoint reviewer for EU label



Pros/Cons of Engaging CLSI Prior to NDA Submission

Pros

- External Expert advice
- Could help facilitate FDA review
- Early input could solve potential problems; may provide “adequate scientific justification” for breakpoints
- Could support breakpoints for List 2?

Cons

- Additional time for document preparation/internal company review
- There may be requests for data not necessarily needed by FDA
- Breakpoint setting an “art” not a “science” – what happens when there are discrepancies due to judgment or emphasis on different criteria
- Public access to confidential data prior to NDA submission

Susceptibility breakpoints for microorganisms

Changes to breakpoints of previously approved drugs

- **Application holders will have 1 year following establishment of the website to remove breakpoints from label and replace with reference to website. Part of annual reportable change.**
 - Not a significant issue for drug developers/license holders.
 - Potential increased responsibility for generic companies
-
- **FDA will conduct periodic (every 6 months) review of breakpoints**
 - More frequent than in the past
 - This seems reasonable as new science or new data emerges
 - Will become part of post-approval regulatory requirements
 - Increases opportunity for “level playing field”
 - Need to understand requirements to assess potential impact for drug developers/license holders.
 - Potential increased responsibility for generic companies

Antimicrobial susceptibility testing devices

Is there also a Broken Business Model for Diagnostic Device Development?

- More frequent changes in breakpoints likely in future
 - How will AST manufacturers keep devices current with changing breakpoints?
 - Will there be more delays in the availability of new drug AST devices?

Summary

- Section 3044 of 21st Century Cures Act has significant changes for breakpoints and antibiotic drug development.
- Ability of FDA to adjust breakpoints according to new data/science is good
- Presentation at CLSI (or any future SDO) is not required
 - Therefore sponsors can decide on individual basis to utilize SDO process.
 - Confidentiality issue could be significant barrier for new drug pre-approval
- Pharma/Bio have concerns about delays in AST device systems for new drugs & how Section 3044 regs could affect timelines

The Breakpoint Setting Process & Harmonization is the Bigger Challenge – Significant Role for next M23

Thank you

- Nicole Scangarella-Oman
- Mary Motyl
- Patricia Bradford
- Greg Moeck

Questions?