Regulatory Challenges in Antimicrobial Diagnostics

Committee on the Long-Term Medical and Economic Effects of Antimicrobial Resistance
Diagnostics and Susceptibility Testing
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Regulatory Challenges in Antimicrobial Diagnostics
Today's Agenda

- AST Testing and General Types of Diagnostic AST (or resistance marker) assays
- Phenotypic assays:
  - Commercial manufacturers with MIC devices, gradient diffusion (variation on MIC), or disk
  - Manufacture of an automated AST assays is a multiyear regulated project
- FDA requirements for disk diffusion manufacturers and 2017 changes
- FDA requirements for AST devices
- Ideal scenario: to have new drug, or old drug with breakpoints, available ASAP
  - FDA activities
- Discussions around industry proposals for changes to FDA requirements
- Breakpoints changes & devices, some history, 21st Century Cures Act, and the STIC
- When is a submission for a breakpoint change required? And some consequences

Antimicrobial Susceptibility Testing

- Performed on microorganisms suspected of causing disease. Also important in resistance surveillance, epidemiology studies, and in comparison of new and existing antimicrobial agents
- Tests performed on microbial isolates, not directly from specimen
- Phenotypic assays: Quantitative/qualitative dilution test or qualitative disk diffusion test
  - Dilution procedures used to determine MIC (minimum inhibitory concentration) – lowest concentration of agent that, under defined conditions, prevents appearance of visible growth in a defined period of time. Broth microdilution is most common method for MIC testing. Gradient diffusion also is part of this class
  - Disk diffusion gives a zone of inhibition
  - Reference test procedures defined by CLSI and ISO and are generally the same procedure
- Breakpoint – MIC or zone diameter value used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, non-susceptible.
  - Interpretive categories derived from microbiology characteristics, PK/PD parameters, & clinical outcome data, when available (CLSI M23). CLSI & EUCAST breakpoints are only sometimes the same.
- Molecular assays for determination of some defined resistance genes, eg MRSA, VRE

Antimicrobial Susceptibility Testing

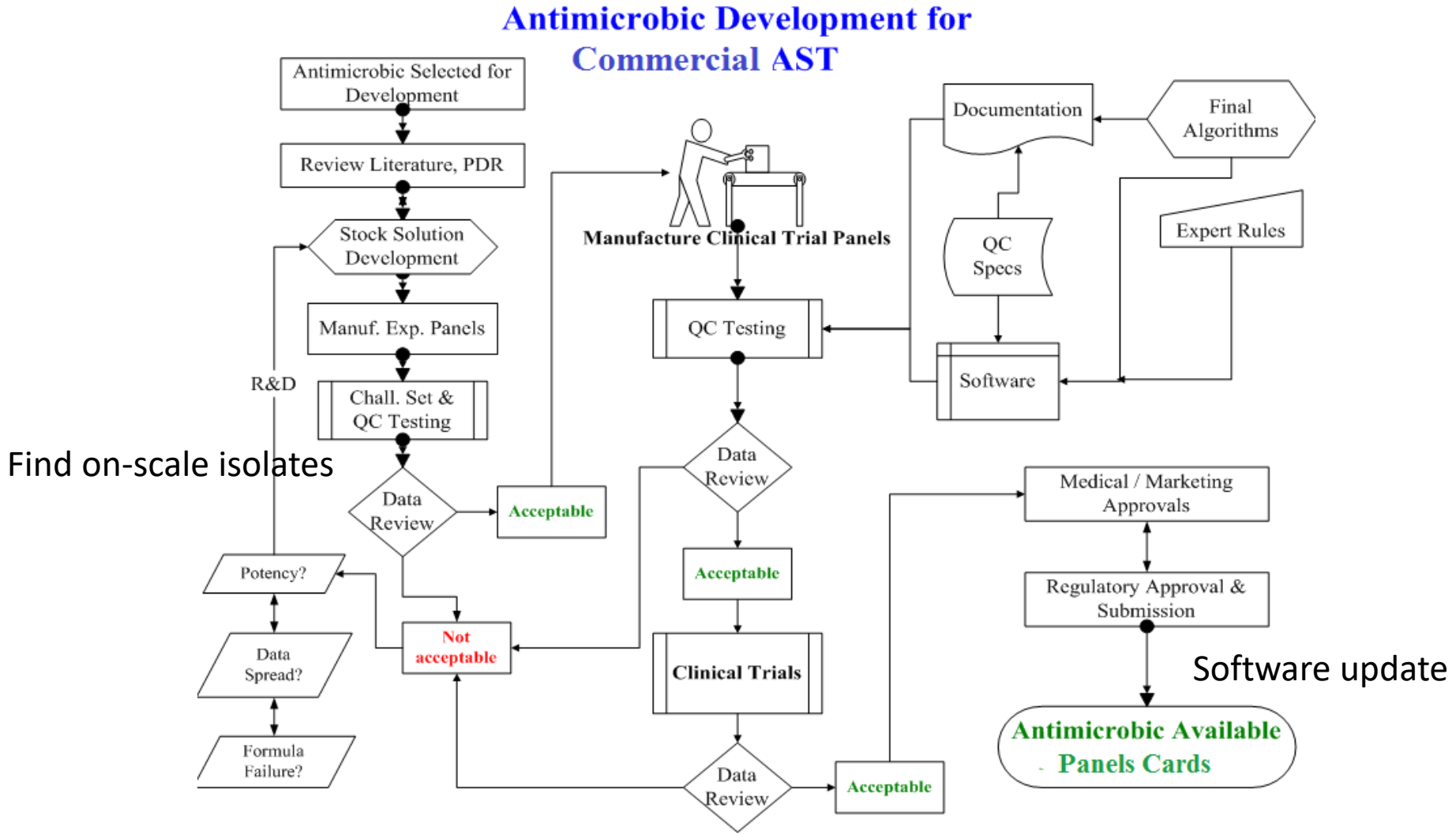
Susceptibility Testing Manufacturers Association (STMA) with phenotypic FDA-cleared product

(pre-2000)
Beckman-Coulter, Inc. (MicroScan®)
bioMérieux, Inc. (VITEK®2 & ETEST®)
Thermo Scientific™ (Sensititre™ & Oxoid Disks™)

BD Diagnostic Systems (Phoenix™ (2005) & Sensi-Disc™)

Accelerate Diagnostics, Inc. (PhenoTest™)
Bio-Rad Laboratories
Hardy Diagnostics
Mast Group Ltd.
Liofilchem

Antimicrobial Susceptibility Testing:
A Multiyear Regulated Process for the Manufacturer



Antimicrobial Susceptibility Testing:
FDA Requirements for Phenotypic Tests

- Regulated by US FDA for human clinical isolates
- Disks: Historically, disk formulation would be tested for clinical efficacy during the antibiotic NDA studies.
- All disk manufacturers would submit a labeling 510(k) after antibiotic NDA approval to receive FDA clearance. Disks were historically first diagnostic on market.
- October 2017 – Disk manufacturers informed during the process of disk labeling 510(k) submissions that FDA will require clinical isolate data for 510(k) clearance
  - 2018 on – STMA, Pharma & FDA participate in numerous discussions to better understand these new requirements

Antimicrobial Susceptibility Testing: Regulatory Requirements - Disks 2017

- Disks can be cleared if included in the pharma NDA data.
- If not included:

Sites: 1 internal site with 3 independent operators with even distribution of isolates to mimic 3 clinical sites

Reference method: Compared to MIC data from the NDA or compared to another cleared disk

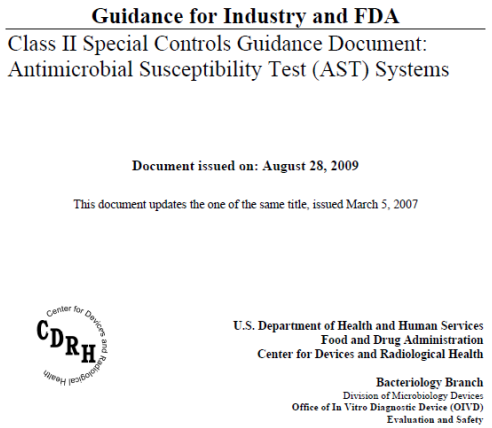
Quality Control: Performed each day of testing; at least 60 replicates for each isolate; 1 media lot; 2 disk lots

Isolates: 300 indicated organisms; 75 challenge isolates with known resistance mechanisms; minimum of 100 strains for the targeted species

Reproducibility: 1 site with 3 readers reading 15 organisms each for 3 days; 2 disk lots; 1 cleared media lot; 270 data points

Antimicrobial Susceptibility Testing:
FDA Requirements for Phenotypic Tests

- Regulated by US FDA for human clinical isolates
- MIC devices: Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 28, 2009
  510(k)
  - “Rapid” (<16h) were once considered PMA & now 510(k). Accelerate Dx device was “de novo” – combined ID and rapid AST directly from positive blood culture. Now 510(k)
  - Appendix in July 2015 gives presentation format and further information



Guidance for Industry and FDA

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

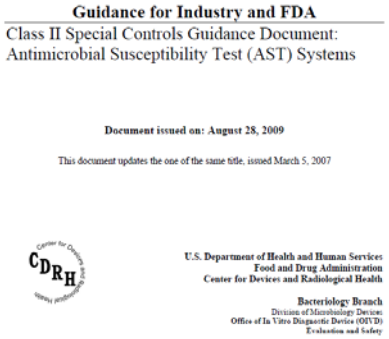
Document issued on: August 28, 2009

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

Antimicrobial Susceptibility Testing: Regulatory Requirements - MIC Devices



Guidance for Industry and FDA

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Sites: 3 clinical testing sites, 1 of which may be manufacturer's laboratory

Reference Method: Comparator is frozen reference microbroth dilution, prepared according to CLSI M7 (and ISO 20776-1)

Quality Control: CLSI and any other on-scale QC organisms on each day of testing, at least 20 test points per lab per organism

Isolates:

- Efficacy isolates, generally 100/site. A recent FDA change is 25 Contemporary and 75 Stock isolates, with an emphasis for on-scale organisms. Generally at least 20/genus of intended-use organisms; more for larger organism group.
- Challenge isolates – generally resistant isolates, or those with known MICs near the breakpoint (may be tested only at 1 site)

Reproducibility: at least 10 isolates, more recent requirement for on-scale MICs

All inoculation methods and all reading methods (so for MicroScan systems: turbidity and Prompt inoculation methods; manual, AS4 and WalkAway reads)

Antimicrobial Susceptibility Testing: Regulatory Requirements - MIC Devices

Quantitative MICs

- Efficacy and challenge isolates: **on-scale results only used since 2015 in most calculations** (so not the very S or very R isolates). **Evaluation at species level.**
- 90% Essential Agreement (+/-1 doubling dilution difference from reference MIC)
- 90% Category Agreement
- <1.5% very major errors (false S) calculated only from reference panel resistant results
- <3% major errors (false R) calculated only from reference panel susceptible results
- Reproducibility >/= 95%; QC >/= 95%
- **Generally little opportunity to resolve discrepancies. Trending statements required in labeling.**
- Recent FDA discussion: When categorical agreement doesn't meet the acceptance criteria, some additional analysis or testing may be allowed. If no Intermediate category, higher error rates may be allowed if essential agreement is high

Antimicrobial Susceptibility Testing: Regulatory Challenges

- **Ideal scenario to have new drug available on automated device shortly after drug approval**
- FDA has presented concerns about the lag in availability of new drugs on devices
- FDA issued “Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices” in 2016 to encourage early interactions and any synergies between new antibiotic applications and AST device applications, but FDA clearance separate
- CDC AR Isolate Bank established. Resistant bacteria gathered, data analyzed, and isolates are free
- More to come on 21st Century Cures Act

Antimicrobial Susceptibility Testing: Regulatory Challenges

- Series of discussions and actions around the 2009 Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems
  - December 2016 – STMA submitted comments to docket to FDA-2000-D-0128 with the goal of making the Class II requirements “less burdensome” for AST device manufacturers with maintaining efficacy and quality
  - September 2017 – FDA held workshop for public comment. STMA presented slides on docket comments.
  - December 5, 2017 – STMA meets with FDA to discuss FDA’s responses to STMA comments (the “low-hanging fruit” meeting) to streamline study designs and submission process
  - 2018 – 2019 to Feb 2020 - continued discussions, with AdvaMed involvement
- It would be nice to “bundle” submissions instead of 1 drug/submission (besides just the $$$ associated)
- STMA as a trade association was given permission to submit a pre-sub to FDA requesting the ability to change breakpoints without submitting a 510k, for 1 scenario

Antimicrobial Susceptibility Testing: Regulatory Challenges

Ideal scenario to have new drug available or **an older drug with new breakpoints on automated device shortly after breakpoint change (& acceptance by FDA)**

- Breakpoint changes….ongoing as resistance changes. Large set of CLSI changes for cephalosoporins and carbapenems discussed beginning in 2005 and published in mid-2010.
- Original guidance for AST manufacturers required submission of 510(k) **by drug** when updating breakpoints
- Prior to 2007, could apply breakpoints to broader organism group (eg all Enterobacterales) or report MICs only.
- 2007-2017 – AST device limited to indications in drug label. For older agents, greatly reduced organism reporting for AST device. Acinetobacter spp. rarely listed in drug label. (eg meropenem was restricted to 21 organisms).
- This was somewhat of a challenge for all

Antimicrobial Susceptibility Testing: Regulatory Challenges

- December 2016: FDA 21st Century Cures Act enacted, with implementation by December 2017. As part of this Act, FDA – CDER recognizes CLSI as a standards setting organization, recognizes some (but not all) CLSI breakpoints. Website is updated as some (but not all) breakpoints are recognized. A great step forward, but still challenges.

Cefazolin – Injection products

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Exceptions to the recognized standard of CLSI M100

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	≤1	2	≥4	-	-	-

S = Susceptible; I = Intermediate; R = Resistant
Interpretive criteria are based on a dose of 1 g every 8 hr.

Separate susceptibility test interpretive criteria for Enterobacteriaceae for therapy of uncomplicated urinary tract infections are not recognized at this time.

Antimicrobial Susceptibility Testing:
Regulatory Requirements – BP changes: When is a Submission Required?

Topic	Current AST SC Requirements	FDA Comment
Breakpoint Changes • Data available • No modifications or new dilutions • Sufficient R strains in original 510(k)	• CDER Guidance (withdrawn) requires submission of 510(k) when updating BPs	• Recalculate Categorical Agreement from original study • Pre-submission with summary of data, FDA letter allowing marketing with new breakpoints
Breakpoint Changes • Same as above but insufficient R strains in original 510(k)	• Same as above	• 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)
Breakpoint Changes • Data available • No modifications or new dilutions • Performance with breakpoints don't meet acceptable criteria	• Efficacy 3 sites, 100 isolates each, • Challenge 1 site 50-75 isolates	• 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.
Breakpoint changes New breakpoints not covered by existing drug concentrations or device is modified	• Traditional study and 510(k)	• No change

Example of consequence of changing breakpoints for commercial AST devices: Antibiotics without FDA-Recognized Breakpoints

- December 2016: FDA 21st Century Cures Act enacted, with implementation by December 2017. As part of this Act, FDA – CDER recognizes some (but not all) CLSI breakpoints. Website is updated as breakpoints are recognized.
- Some organism groups are not listed in the drug package insert so FDA - CDER does not have or recognize a breakpoint. Organisms that are not as common (e.g. *Burkholderia*) generally tend to not be listed in the drug package insert. CLSI generally has breakpoints for organism groups if the drug is used.
- Implementation of revised breakpoints for one organism group in the US may come with a cost to AST manufacturers for reporting MIC results for other organism groups.
- My example is MicroScan panels (established manufacturer) and meropenem.

Example: Meropenem CLSI and FDA breakpoints

- June 2010: CLSI published revised meropenem breakpoints for *Enterobacteriaceae* (</=1, 2, >/=4)
- Jan. 2012: CLSI published revised meropenem breakpoints for *P. aeruginosa* (</=2, 4, >/=8)
- Jan. 2014: CLSI published revised meropenem breakpoints for *Acinetobacter* spp. (</=2, 4, >/=8)
- CLSI also has meropenem breakpoints for *Burkholderia cepacia* and Other Non-*Enterobacterales* (</=4, 8, >/=16). These have not been revised.
- 2018: FDA recognized meropenem CLSI breakpoints for *Enterobacteriaceae* and *P. aeruginosa*. FDA does not recognize breakpoints for any other organisms.
- January 2, 2020: FDA recognized meropenem CLSI breakpoints for *Acinetobacter* spp.

Example: Meropenem on MicroScan panels

- 2002: MicroScan panels received FDA clearance for testing meropenem with Gram-negative organisms. This includes *Enterobacteriaceae, P. aeruginosa, Acinetobacter* spp., *B. cepacia* and Other Non-*Enterobacteriaceae*
- 2019: Beckman Coulter submitted revised contemporary breakpoint change data to FDA for *Enterobacteriaceae* and *P. aeruginosa.* Data were also submitted for *Acinetobacter* spp. Contemporary non-fermenters other than *P. aeruginosa* were also tested to ensure that MicroScan panel MIC results match reference MICs (since we previously had clearance and the breakpoints have not changed).
- 2019 : Beckman Coulter received clearance for new meropenem breakpoints for *Enterobacteriaceae* and *P. aeruginosa.* We had to withdraw data for *Acinetobacter.*
- With the breakpoint clearance in the USA, and because FDA does not recognize meropenem breakpoints for the other organisms, MicroScan **would not be able to report MICs or interpretation for the rest of the non-fermenters (despite previous clearance).**
- 2020*: Acinetobacter* meropenem breakpoint rationale document was accepted by CDER for this breakpoint. Beckman Coulter resubmits (with $$$) *Acinetobacter* data & receives clearance.
- What are US laboratories supposed to do for everything else? One cannot self-validate breakpoints without a MIC.

Consequences of changing breakpoints for commercial AST devices

- Implementation of revised breakpoints for one organism group in the US may come with a cost to AST manufacturers for reporting MIC results for other organism groups. There may be no reason not to report that result, and it is reported OUS.
- It would be helpful to be able to report the MIC without a breakpoint if FDA does not recognize the breakpoint.

Antimicrobial Susceptibility Testing: Regulatory Challenges

- Regulatory challenges for disk manufacturers and MIC device manufacturers.
- Issues with the AST special controls guidance are longstanding and have been the subject of industry/FDA discussion. There also were discussions specific to disk diffusion testing
- There is some increased flexibility in approach from FDA on case-specific bases for which formalization would be helpful.
  - Eg “fresh” versus “contemporary” isolates
  - Increasing the allowable very major error rates when there is no intermediate category, and essential agreement is high
  - Breakpoint changes when contemporary data exist, and future protocols
- Other steps forward from the FDA include coordinated development guidance, the establishment of the STIC website implementing provisions in the 21st Century Cures Act.
- However, regulatory challenges remain. Industry would greatly like to redline and update the special controls guidance to modernize both in terms of approach and existing technology to speed safe and effective ASTs to market to benefit patients and public health.
  - Eg The upcoming ISO 20776-2:2021 document for AST performance evaluation provides a less restrictive approach, and will be used by EUCAST