

Commercial Antimicrobial Susceptibility Test Systems

**Implications of Multiple Breakpoints,
Indications and Dosing Requirements for
Bacterial Isolates and a Single
Antimicrobial Agent**

**Anti-Infective Drugs Advisory
Committee Meeting
Thursday, Oct. 17, 2013**



THE SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION (STMA)

- Informal Group Started in 1994 at CLSI Meeting
- Formal Group Formed 2002
- Membership Limited to AST Companies and Other Support Companies.
- Three Meetings per Year
- Elected Officers
- Yearly Fees





Current STMA Member Companies

BD Diagnostic Systems

bioMérieux, Inc.

**Siemens Healthcare
Diagnostics Inc.**

ThermoFisher (Trek)

Bio-Rad

Hardy Diagnostics

Mast Group Ltd.



Current STMA Officers

- Bill Brasso, BD - President
- Sharon Shinn, Siemens - Vice-President
- Sheila Farnham, bioMérieux - Secretary
- Blaine Leppanen, Executive Director



Accomplishments

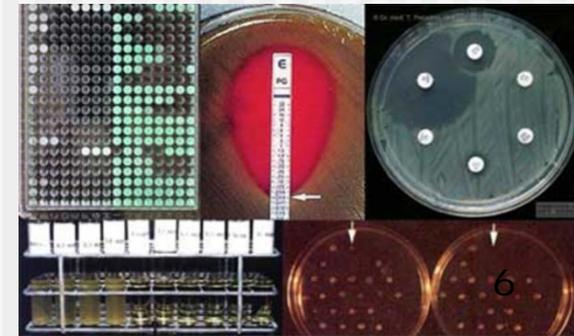


- Participation in Developing new Guidance Documents for both CDER and CDRH
- Representatives from AST industry on Standardization Committees, FDA Anti-Infective Advisory Committees, etc.
- Database for Antibiotic Abbreviations for Regulatory Agents
- Mechanism for Supplying Bulk Drug Powder to Industry
- Standardized Validation Procedures for Frozen/Dried Panels
- Represented by one voting member and one non-voting advisor on the CLSI AST Subcommittee
- Participation by all members on CLSI Working Groups
- Continuing education of standardization committees and pharmaceutical companies on requirements of AST industry

So, Why Are We (STMA) Here?

What does an AST Device Company do?

- We provide AST results (MIC and SIR interpretation) to the clinical laboratory for a cultured microbiology isolate
- We provide software and expert systems to assist with the interpretation of the results
- We are regulated by the FDA – both the MIC and SIR are subject to strict criteria in comparison to a reference method.
- We are not involved in PK/PD analyses nor dosing regimens
- We do not practice medicine, nor do we advise laboratories in the practice of medicine.



AST Systems and Each Antibiotic are regulated by the FDA

FDA 510(k) clearance is obtained based upon:

1) demonstration of substantial equivalence to a predicate device, and

2) meeting the requirements of special controls, i.e., satisfactory performance compared to a reference method.

✓ **Test MIC vs. Reference MIC (essential agreement)**

✓ **Categorical agreement and Error Rate (based upon FDA breakpoints)**

Currently, no acceptance criteria for different indications.

No acceptance criteria for different dosing.

No acceptance criteria for multiple breakpoints.*

***Several recent exceptions, e.g., *S. pneumoniae* vs. Penicillin**

“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

1. Can AST Systems manage multiple breakpoints for a single drug?

Answer: Some AST Systems can provide all interpretive criteria, for different indications while others provide a single criteria and expert rules for guidance of the other criteria.

○ Example: Penicillin vs. *S. pneumoniae*

	<u>S</u>	<u>I</u>	<u>R</u>
Parenteral non-meningitis	≤ 2	4	≥ 8
Parenteral meningitis	≤ 0.06	-	≥ 0.12
Oral penicillin V	≤ 0.06	0.12 - 1	≥ 2

“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

2. Can AST Systems currently manage both Intermediate (“I”) and Susceptible, Dose-Dependent (“S-DD”)?

Answer:

Some currently have this capability, while others will need to have software modifications to provide the S-DD category.

“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

3. ISSUE - Labs rarely receive information regarding the indication being treated.

- The specimen is usually labeled with a source – such as urine, blood or wound.**
- Using 3 separate breakpoints would require the lab (and the AST system) to provide separate SIR interpretations for each possible indication, in case the patient has one of them.**

“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

In the FDA Briefing Doc., Table 6 (p. 18): Susc. Bkpts. for *E. coli*, an instrument MIC of 2 mcg/mL for DRUG B would be interpreted as **Susceptible** if the patient had an ABSSSI or cIAI, but **Resistant** if the infection was a HABP. (Note: The laboratory received a blood culture. How should it be determined which indication is being treated when any of the indications could result in a positive blood culture with *E. coli*?)

<u>MIC</u>	<u>SIR</u>	
0.5	S	if ABSSSI
2.0	S	if cIAI
4.0	R	if HABP

The Lab
NEVER
gets this
info!



“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

4. Should AST Systems provide the laboratory* with dosing information on the AST report?
 - Is this actionable for the physician?
 - Is this easily available via Laboratory Information System (LIS), then to the Electronic Medical Record (EMR)?

* The clinical laboratory receives the AST System report, which is then uploaded via the institute's LIS.

In fact,...

“What are the practical implications for AST Manufacturers of having an antibiotic with different breakpoints for different indications?”

➤ In CLSI M100-S23, pg. 29, Sect. III

- ❖ “ In cases where specific dosage regimens are important for proper application of breakpoints, the dosage regimen is listed [in the Interpretive Criteria Tables]. These dosage regimen comments are NOT intended for use on individual patient reports.”**
- ❖ In Table 2, General Comments, CLSI states, “When implementing new breakpoints, it is strongly recommended that laboratories share this information with Infectious Disease practitioners, pharmacists”, etc.**

“What are the (im)practical issues regarding conveying this information to a clinician reviewing a patient’s susceptibility data?”

- **The interface between the AST system and all of the various LIS systems will require extensive modification to accomplish this task at a large cost to the laboratory.**
- **Making the transfer to the Electronic Medical Record (if present) is another hurdle.**

All of this must happen before the physician actually sees the results on the patient ‘chart’.

ADDED ISSUE - This information may not be transmitted to the LIS or HIS in the same format generated by the AST system.

How Will AST Data be Reviewed by FDA if Different Bkpts for a Single Drug?

		Broth Microdilution Reference Result												
		0.125	0.25	0.5	1	2	4	8	16	>16			Totals	
AST System Result	0.125	36	4	1							41	EA	227	
	0.25	6	27	2	3						38	EA%	94.6% √ (≥90%)	
	0.5		5	18	5	1	1				30	CA		
	1		1	9	16	6	1	1			34	CA%		(≥90%)
	2				6	8	3				17	VME		
	4				1	4	11	5			21	VME%		(<1.5% of R)
	8					1	6	8	2		17	ME		
	16						2	8	12	1	23	ME%		(< 3% of S)
	>16									19	19	MiE		
	Totals	42	37	30	31	20	24	22	14	20	240	MiE%		(-)

Typical dataset comparing AST System MIC results to reference (Broth microdilution) results for previous Drug B with multiple breakpoints.

How Will AST Data be Reviewed by FDA if Different Bkpts for a Single Drug?

		Broth Microdiution Reference Result												
		0.125	0.25	0.5	1	2	4	8	16	>16	Totals	EA	227	
AST System Result	0.125	36	4	1							41	EA%	94.6%	✓ (≥ 90)
	0.25	6	27	2	3						38	CA	205	
	0.5		5	18	5	1	1				30	CA%	85.4%	X
	1		1	9	16	6	1	1			34	VME	2	
	2				6	8	3				17	VME%	2.0%	X
	4				1	4	11	5			21	ME	0	
	8					1	6	8	2		17	ME%	0.0%	✓ ($\leq 3\%$ of S)
	16						2	8	12	1	23	MiE	33	
	>16									19	19	MiE%	13.8%	(-)
	Totals	42	37	30	31	20	24	22	14	20	240			
				S	I	R								

For ABSSSI, $S \leq 0.5$, $I = 1$, $R \Rightarrow 2$

With a “S” bkpt of **0.5**, this dataset would not pass the FDA criteria for 2 of the 4 “agreement” requirements

How Will AST Data be Reviewed by FDA if Different Bkpts for a Single Drug?

		Broth Microdiution Reference Result												
		0.125	0.25	0.5	1	2	4	8	16	>16				Totals
AST System Result												EA	227	
	0.125	36	4	1							41	EA%	94.6%	√ (≥90)
	0.25	6	27	2	3						38	CA	215	
	0.5		5	18	5	1	1				30	CA%	89.6%	√ (≥90)
	1		1	9	16	6	1	1			34	VME	1	
	2				6	8	3				17	VME%	1.8%	X
	4				1	4	11	5			21	ME	1	
	8					1	6	8	2		17	ME%	0.6%	√ (< 3% of S)
	16						2	8	12	1	23	MiE	23	
	>16									19	19	MiE%	9.6%	(-)
Totals	42	37	30	31	20	24	22	14	20	240				
					S	I	R							

For cIAI, S ≤ 2, I = 4, R ⇒ 8

With a “S” bkpt of 2, this dataset improves, but still does not pass the FDA criteria for 1 of the 4 “agreement” requirements.

How Will AST Data be Reviewed by FDA if Different Bkpts for a Single Drug?

		Broth Microdiution Reference Result												
		0.125	0.25	0.5	1	2	4	8	16	>16				Totals
AST System Result	0.125	36	4	1							41	EA	227	
	0.25	6	27	2	3						38	EA%	94.6%	✓ (≥90)
	0.5		5	18	5	1	1				30	CA	215	
	1		1	9	16	6	1	1			34	CA%	89.6%	✓ (≥90)
	2				6	8	3				17	VME	0	
	4				1	4	11	5			21	VME%	0.0%	✓ (≤ 1.5% of R)
	8					1	6	8	2		17	ME	2	
	16						2	8	12	1	23	ME%	1.1%	✓ (≤ 3% of S)
	>16									19	19	MiE	23	
	Totals	42	37	30	31	20	24	22	14	20	240	MiE%	9.6%	(-)
						S		I						

For HABP, S ≤ 4, I = 8, R ≥ 16

With a “S” bkpt of 4, this dataset passes the FDA criteria for all 4 “agreement” requirements. **What to do?**

In Conclusion, AST Devices and Manufacturers will continue to:

- Provide AST results (MIC and SIR interpretation) to the clinical laboratory for cultured microbiology isolates
- Provide software and expert systems to assist with the interpretation of the results
- Be regulated by the FDA – both the MIC and SIR are subject to strict criteria in comparison to a reference method.
- Not practice medicine, nor advise laboratories in the practice of medicine.
- (Should) not be required to provide dosage regimen comments on individual patient reports.