

INDUSTRY PERSPECTIVE ON THE ADVANTAGES AND CHALLENGES OF NOVEL AST METHODS

Registration of Novel AST Methods

- General recommendations
- Address reference method challenges
- Drive efficiency during the review process
- Device development and performance demonstration consistent with FDA criteria
- Reports and interpretation issues

1. A reference or two

General Recommendations

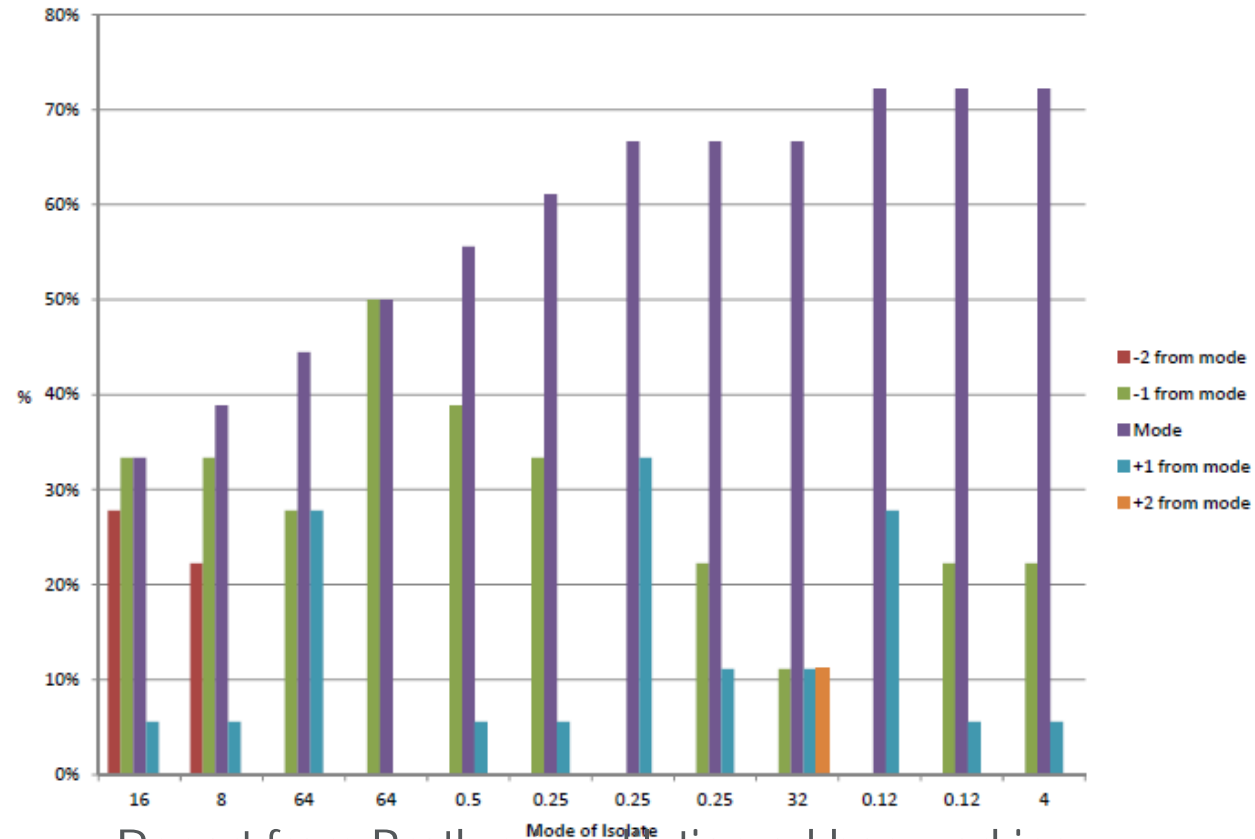
- Utilize the pre-submission mechanism to:
 - Clarify classification
 - Discuss submission strategy (single or multiple submissions)
 - Align on performance requirements
 - Describe technology fundamentals
- Time invested correlates with the degree of benefit
 - Present organized thoughtful content, it will be appreciated
 - CLSI documents are particularly useful for analytical study guidance, other guidance documents are available (e.g., ID and AST guidance, etc.)

1. A reference or two

BMD Variability From Frozen Isolates



**E. coli Isolates, Replicate Testing, Cefotaxime
Distribution of MIC for each isolate around it's mode**



Report from Broth microdilution ad hoc working group

Root Causes

for Reference METHOD Variability

Process
inconsistency

Transfer approach of AXDX
Broth Microdilution factory

Biological
variability

Compare to BMD mode

Non-selective
subculture bias
from specimens

Perform studies using
representative populations

Control with Reference site approach

Consistent training & **Methodology**

Equipment (i.e., incubator and other **Machines**)

Lab personnel / **Manpower** (single site)

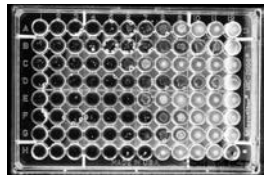
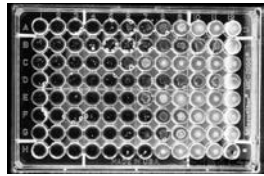
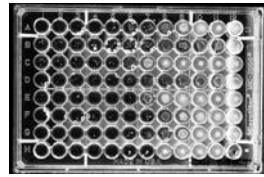
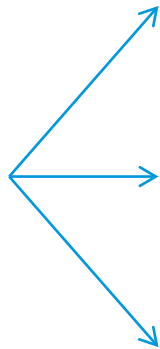
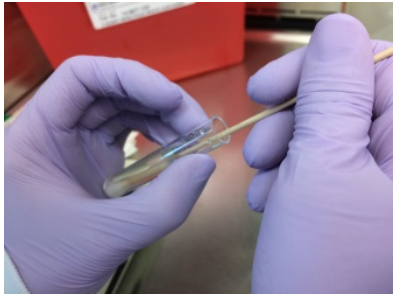
Materials (raw materials / controlled shipment)

Measurement (BMD transcription error detection)

Mother nature and environmental factors (single site)

Broth microdilution **replication**

single MF* Preparation

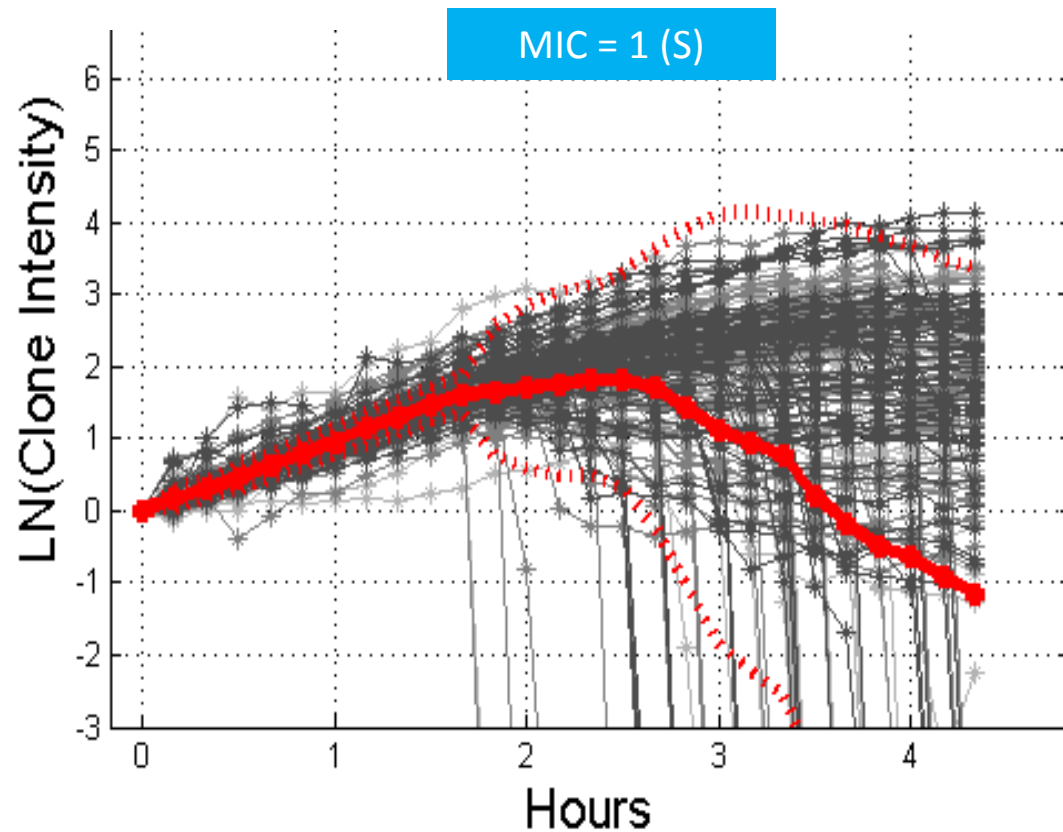


TRIPLICATE BMDs

Compare test device to BMD mode

*MF preparation described as part of sampling strategy

Variability factored into the trial design

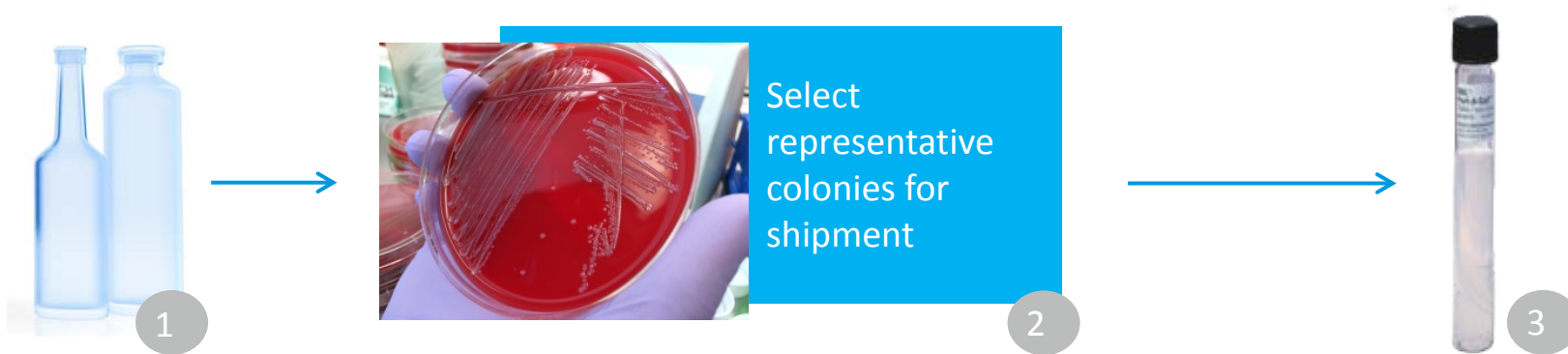


AXDX MIC is representative of the clonal population

- Individual clones, (subsampled)
- Average response
- ⋯ 2 σ from the average response

Addressing Variability at Clinical Trial sites

Biased colony selection during isolation is a risk



Industry Perspective:

Address Reference Method Challenges

- Drive consistency with manufacturing controls
- Compare test device to BMD modal result
- Thoughtful sampling of specimens to insure comparison to representative populations

1. A reference or two

Facilitating Efficient Review

- Accelerate PhenoTest™ BC kit clinical study scope
 - Single submission for ID and AST
 - 1,850 positive blood cultures
 - 14 different species of bacteria and 2 species of yeast that cause bloodstream infections
 - Antibiotic sensitivities across 18 select antibiotics
 - Analytical studies in excess of clinical studies
- Mutual interest to drive to conclusion as quickly as possible
 - Tools provided to increase efficiency of review
 - Align on line listing format

1. A reference or two

Formatted Line Listings

AXDX AST Excel Tool_final.xlsxm - Microsoft Excel

File Home Insert Page Layout Formulas Data Review View Developer Add-Ins

From Access From Web From Text From Other Sources Existing Connections Refresh All Connections Sort & Filter Filter Clear Reapply Advanced Text to Columns Remove Duplicates Data Validation Consolidate What-If Analysis Group Ungroup Subtotal Outline Analysis

D117 71_1070_521

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	AMK Line Listings												
2					Gray Shade	index only, not test records							
3		SUBTOTAL	402		Red	AST Errors (vmj, maj, min)							
4													
5		SubjID	SampleType	Exp	ExpDate	BottleType	TimeToPos	BottleWait	Genus	Species	StrainID	RefGS	SoCID
111	x	9240062	FRESH	71_1069_490	2016-03-01 10:0:	BACTEC LYTIC/1/5.266666667	4.517777778		Enterobacter	cloacae	N/A	GNRods	Enterobacter cl
112	x	9240069	FRESH	71_1070_498	2016-03-03 14:2:	BACTEC PLUS AE 2.633333333	3.107777778		Escherichia	coli	N/A	GNRods	Escherichia coli
113	x	9240070	FRESH	71_1068_500	2016-03-04 10:3:	BACTEC PLUS AM 112.0833333	3.069722222		Escherichia	coli	N/A	GNRods	Escherichia coli
114	x	9240075	FRESH	71_1071_505	2016-03-04 14:5:	BACTEC LYTIC/1/23.18333333	7.02		Pseudomonas	aeruginosa	N/A	GNRods	Pseudomonas :
115	x	9240079	FRESH	71_1068_511	2016-03-08 10:4:	BACTEC LYTIC/1/14.56666667	7.038888889		Klebsiella	pneumoniae	N/A	GNRods	Klebsiella pneu
116	x	9240080	FRESH	71_1069_512	2016-03-08 10:4:	BACTEC PLUS AE 11.03333333	5.941944444		Escherichia	coli	N/A	GNRods	Escherichia coli
117	x	9240084	FRESH	71_1070_521	2016-03-11 11:1:	BACTEC PLUS AE 19.06666667	6.796944444		Pseudomonas	aeruginosa	N/A	GNRods	Pseudomonas :
118	x	9240085	FRESH	71_1071_520	2016-03-11 11:0:	BACTEC PLUS AE 19.93333333	7.766111111		Klebsiella	pneumoniae	N/A	GNRods	Klebsiella pneu
119	x	9240093	FRESH	71_1071_532	2016-03-16 12:0:	BACTEC LYTIC/1/13.06666667	2.4675		Escherichia	coli	N/A	GNRods	Escherichia coli
120	x	9240094	FRESH	71_1071_535	2016-03-17 10:4:	BACTEC LYTIC/1/4.933333333	7.143333333		Serratia	marcescens	N/A	GNRods	Serratia marces
121	x	9240098	FRESH	71_1069_542	2016-03-21 11:1:	BACTEC PLUS AE 11.63333333	4.559444444		Escherichia	coli	N/A	GNRods	Escherichia coli
122	x	9240099	FRESH	71_1070_543	2016-03-21 11:1:	BACTEC LYTIC/1/8.05	4.803055556		Escherichia	coli	N/A	GNRods	Escherichia coli
123	x	9240102	FRESH	71_1070_548	2016-03-23 09:3:	BACTEC LYTIC/1/10.73333333	5.697777778		Klebsiella	oxytoca	N/A	GNRods	Klebsiella oxyt
124	x	9240105	FRESH	71_1068_550	2016-03-23 14:4:	BACTEC PLUS AE 16.36666667	3.190277778		Pseudomonas	aeruginosa	N/A	GNRods	Pseudomonas :
125	x	9240107	FRESH	71_1070_554	2016-03-24 10:2:	BACTEC PLUS AE 12.78333333	7.533333333		Citrobacter	koseri	N/A	GNRods GPCoc	Citrobacter kos
126	x	9240120	CHALLENGE	71_1070_573	2016-04-01 10:4:	BACTEC PLUS AE 12.75	6.764722222		Escherichia	coli	IHMA-150461	GNRods	N/A
127	x	9240124	FRESH	71_1070_577	2016-04-04 11:0:	BACTEC PLUS AE 16.08333333	3.711666667		Enterobacter	cloacae	N/A	GNRods	Enterobacter cl
129	x	9240134	CHALLENGE	71_1070_591	2016-04-08 13:5:	BACTEC PLUS AE 18.36666667	2.393611111		Pseudomonas	aeruginosa	NA-M1118	GNRods	N/A
130	x	9240138	FRESH	71_1069_595	2016-04-11 11:1:	BACTEC PLUS AE 7.45	7.980277778		Escherichia	coli	N/A	GNRods	Escherichia coli
131	x	9240139	FRESH	71_1071_596	2016-04-11 11:1:	BACTEC LYTIC/1/9.9	3.875555556		Escherichia	coli	N/A	GNRods	Escherichia coli
133	x	9240172	FRESH	71_1068_640	2016-04-26 09:2:	BACTEC PLUS AE 9.9	3.262222222		Klebsiella	oxytoca	N/A	GNRods	Klebsiella oxyt
134	x	9240173	CHALLENGE	71_1069_649	2016-04-28 13:3:	BACTEC PLUS AE 13.9	5.163055556		Acinetobacter	baumannii	IHMA-975433	GNRods	N/A
135	x	9240174	CHALLENGE	71_1068_643	2016-04-27 11:4:	BACTEC PLUS AE 10.75	7.728888889		Escherichia	coli	IHMA-1031141	GNRods	N/A
136	x	9240175	CHALLENGE	71_1069_644	2016-04-27 11:4:	BACTEC PLUS AE 10.58333333	7.901944444		Escherichia	coli	IHMA-1043203	GNRods	N/A

Ready Filter Mode 100%

Facilitating Efficient Review

- Relatively small investment in software tools can facilitate rapid review
- Line listings for large datasets take time to construct definition in advance leads to efficiencies in supporting review process

1. A reference or two

Registration of Novel AST Methods

- Performance of novel devices and how to meet FDA performance goals
 - Fresh sample balancing is critical
 - Access to challenge isolates is a key to success
 - Be prepared to power studies required to demonstrate performance
- Reports and interpretation issues
 - FDA vs CLSI breakpoints
 - Expert rules

1. A reference or two



Thank you.

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