Antimicrobial Susceptibility Testing (AST) Devices

Agenda

I. Introduction and Evolution of STMA
II. Antibiotic Development and Pre-release Quality Control Requirements
III. Software and Expert Systems
IV. FDA Requirements and Clinical Trials
V. AST Device and Antibiotic Approvals
VI. Commercialization
VII. Overview of Commercial Methods
VIII. The Clinical Microbiology Laboratory
IX. Q&A

STMA
SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

EVOLUTION OF THE STMA

SUSCEPTIBILITY **T**ESTING **M**ANUFACTURERS **A**SSOCIATION

- 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 (One officer/company, rotating)
- Yearly Fees

STMA
SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Current STMA Officers

- Dee Shortridge, President
- Jenny Lorbach, Vice-President
- Bill Brasso, Secretary
- Blaine Leppanen, Executive Director

STMA
SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Mission Statement

- To stimulate and enable cooperative interaction between the AST industry, pharmaceutical industry, regulatory agencies, standardization groups, laboratories, etc. regarding joint issues related to the field of susceptibility testing.

- Ongoing education of the members regarding antimicrobial agents under development in the pharmaceutical industry.

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SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

STMA Member Companies

- BD Diagnostic Systems
- bioMérieux, Inc.
- Bio-Rad Laboratories
- Hardy Diagnostics
- Mast Diagnostics
- Siemens Healthcare Diagnostics (MicroScan)
- Thermo Fisher Scientific, Inc.
- TREK Diagnostic Systems

Accomplishments

- Mechanism for Supplying Bulk Drug Powder to Industry
- Participation in Developing new Guidance Documents for both CDER and CDRH
- Representatives from AST industry on Standardization Committees
- Database for Antibiotic Abbreviations for Regulatory Agents
- Standardized Validation Procedures for Frozen/Dried Panels

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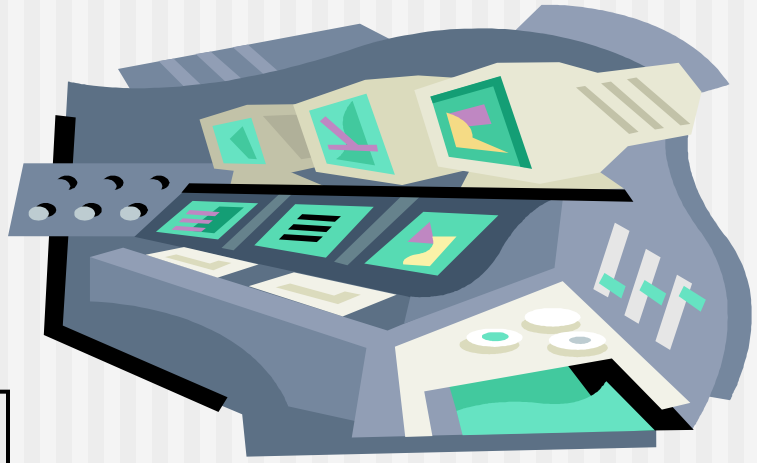
The Three Components of AST Systems



Instrument

Biological Reagents
Cards
Trays
Strips

Software

Mechanical

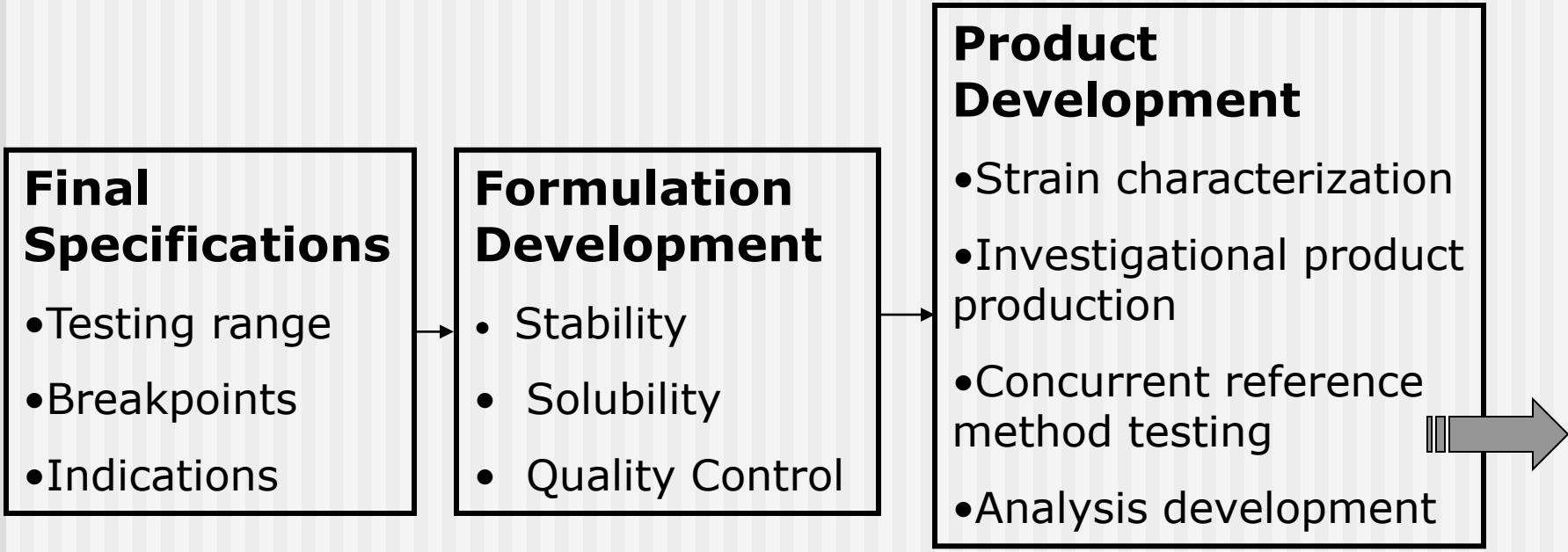
Reading/ Results/Algorithms

Knowledge base (Expert System)

Each new drug or update of current drug requires development of reagents/software in parallel

II. Antibiotic Development and Pre-release Quality Control Requirements

Antibiotic Qualification -- MIC



Antibiotic Qualification -- MIC

Final Specifications

- Testing range – What concentrations of antimicrobial agent will be on the panel?
- Breakpoints – Manufacturers, FDA, CLSI, EUCAST, Japan, and any others
- Indications – What bacteria/yeast exactly is the drug used for? e.g. Inducible Clindamycin

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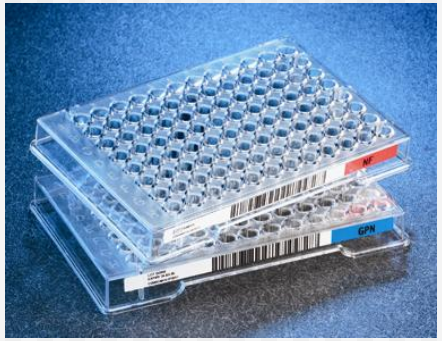
Antibiotic Qualification -- MIC

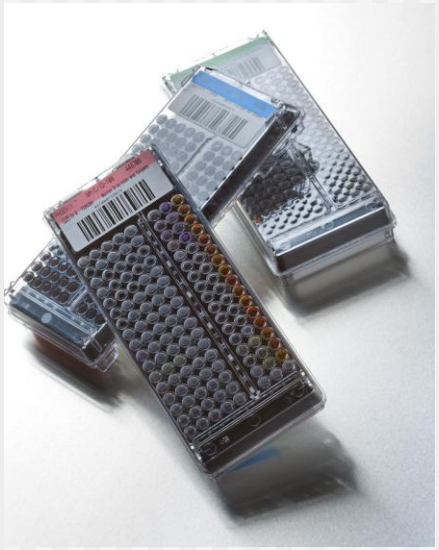
Formulation Development

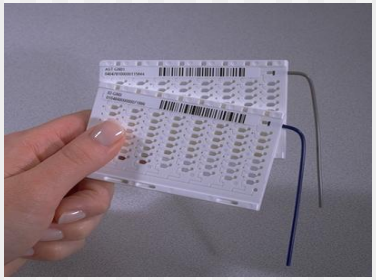
Products are NOT a frozen reference panel and are formulated to be dried

Panel/Card may look like it has “15 drugs” but to manufacturers it has 96 small containers needing something inside them

- Stability
- Solubility







SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Antibiotic Qualification -- MIC

Product Development

- Strain characterization – need resistant and susceptible strains. Helpful if mechanisms of resistance is known. All resistance is not created equal.
- Concurrent reference method testing – the Mueller Hinton Broth question, they are different
- Investigational product production – feasibility lots, scale up to production
- Manufacturing of proposed low breakpoint concentrations of antimicrobials (+/- 2 dilutions) may be impossible for both test and reference methods
- Analysis development – HPLC or other assays

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Manufacturing Quality Control

- QC specifications are based on a combination of physical and microbiological characteristics established for each product.
  - The sampling plan is determined by the size of the lot produced.
  - Physical Inspection
    - Card, panel, strip or other product are inspected for physical defects prior to packing in pouch.
    - Pouch label and outer package label are inspected for defects.
  - Bioload Testing
    - To verify that the product does not have an unacceptable level of contamination.
    - For some products this may include sterility testing.

Manufacturing Quality Control

- Microbiological testing: Confirms that the preparation of each well in the panel or strip was performed correctly.
  - Each lot manufactured is tested with a specific set of isolates chosen for each antibiotic and may include strains with on-scale MIC values as well as known resistance mechanisms. The results are compared to expected values.
  - Testing may also include chemical analysis of wells.

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Manufacturing Quality Control

- Each product has Package Insert Organisms (ATCC strains and includes CLSI QC strains) that are recommended as isolates that a customer may or be required to run with the product.
  - The recommended Package Insert isolates are tested with each product.

- Once QC has determined all of the Physical and Microbiological requirements have been met, the product is then released into Finished Goods Inventory.

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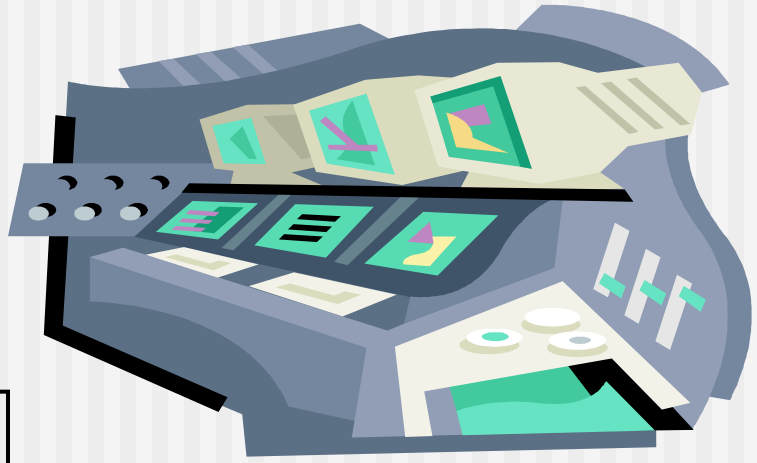
III. Software and Expert Systems

Software and Expert Systems



Instrument

Biological Reagents
Cards
Trays
Strips

Software

Mechanical

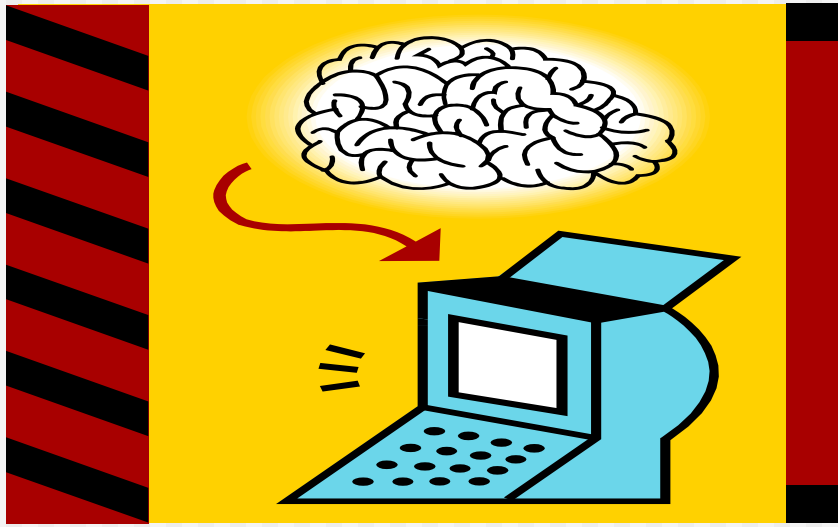
Reading/ Results/Algorithms

Knowledge base (Expert System)

Each new drug or update of current drug requires development of reagents/software in parallel

Software of AST Systems
The Brains of the Instrument

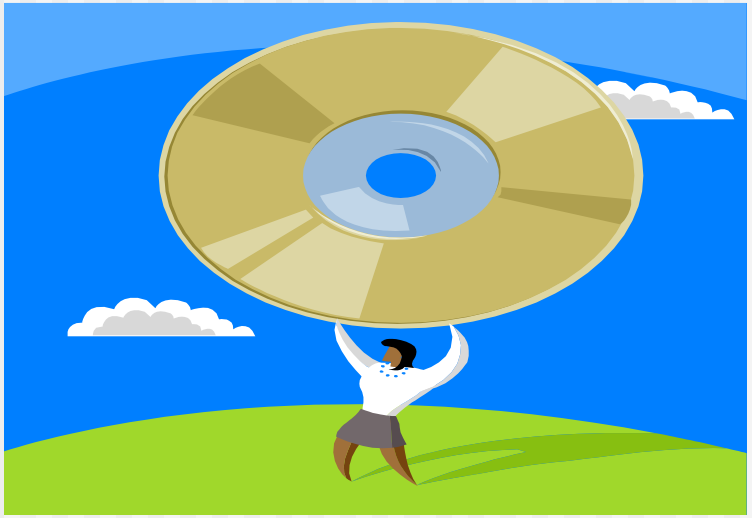
- **Readings/Results/Interpretation**
  - **Interface with Database**
  - **Algorithms/Analysis**
  - **Expert System**
- **Mechanical (Robotics)**
  - **Movement of reagents through the instrument**
- **User Interface**
  - **Patient data/Loading/ Status updates and results**
- **LIS Interface**
  - **Interaction with other systems to generate reports**



Software of AST Systems

Every Change (e.g. new drug, new breakpoints, new resistance mechanism, etc) requires software:

- **Development**
- **Verification**
- **Validation**
- **Regulatory clearance**
- **Installation**
  - **May be time limited**
  - **Site visit may be required**
  - **Instrument may be down for some period of time**
  - **User custom settings may need to be re-entered**



Software of AST Systems
Expert Systems

Computer Aided Decision Support

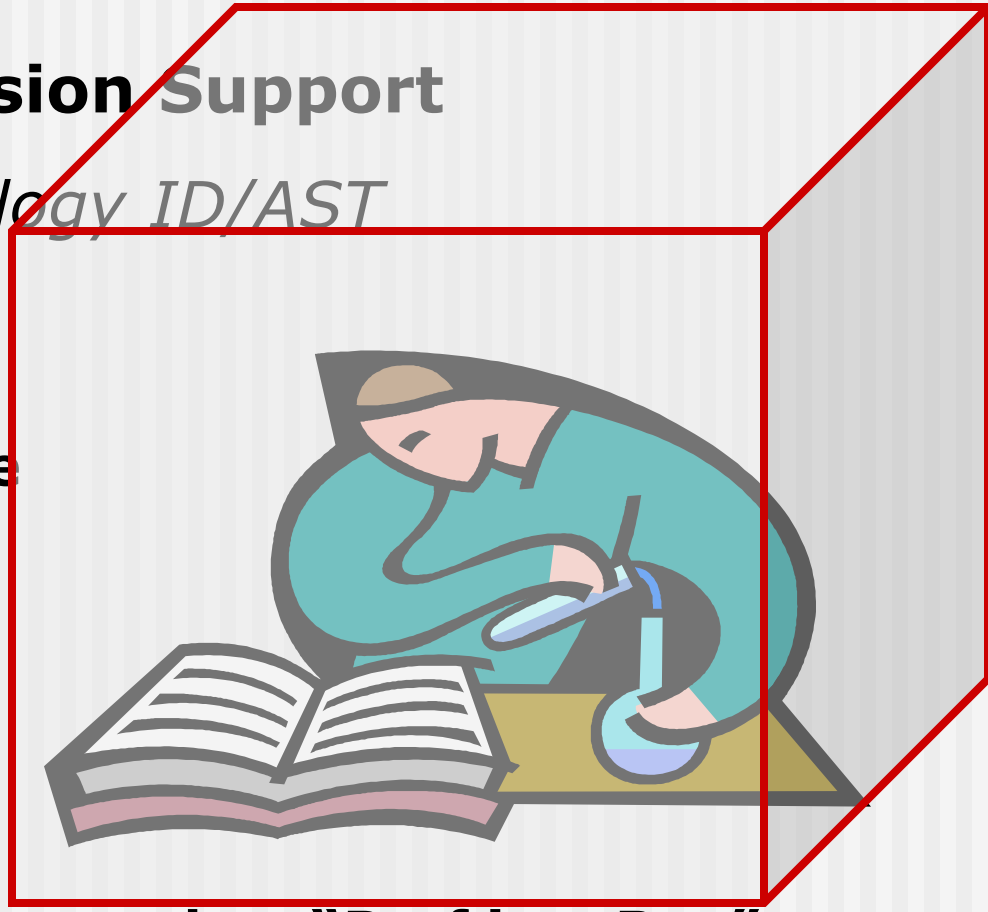
- **Computer programs that use logic to draw inferences**
- **Conclusions are based on carefully formulated information**
- **Rules are defined according to a set of conditions with a specific action to be taken when those conditions are met**

Software of AST Systems
Expert Systems

Computer Aided Decision Support

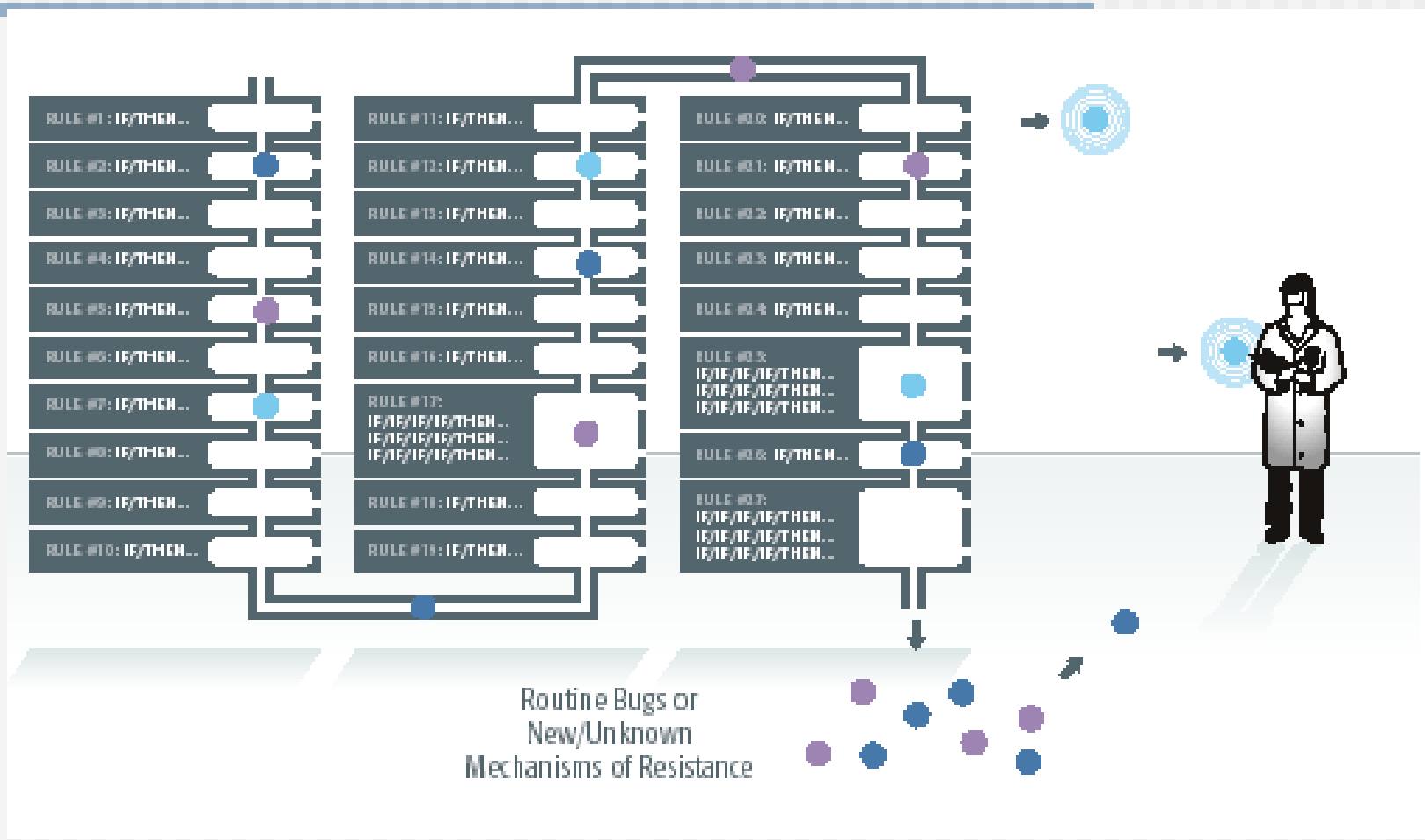
As it relates to Microbiology ID/AST

- **Body of data (logic) used to make inferences based on the identification (ID) and susceptibility (AST) patterns of microorganisms**



a.k.a. "Prof in a Box"

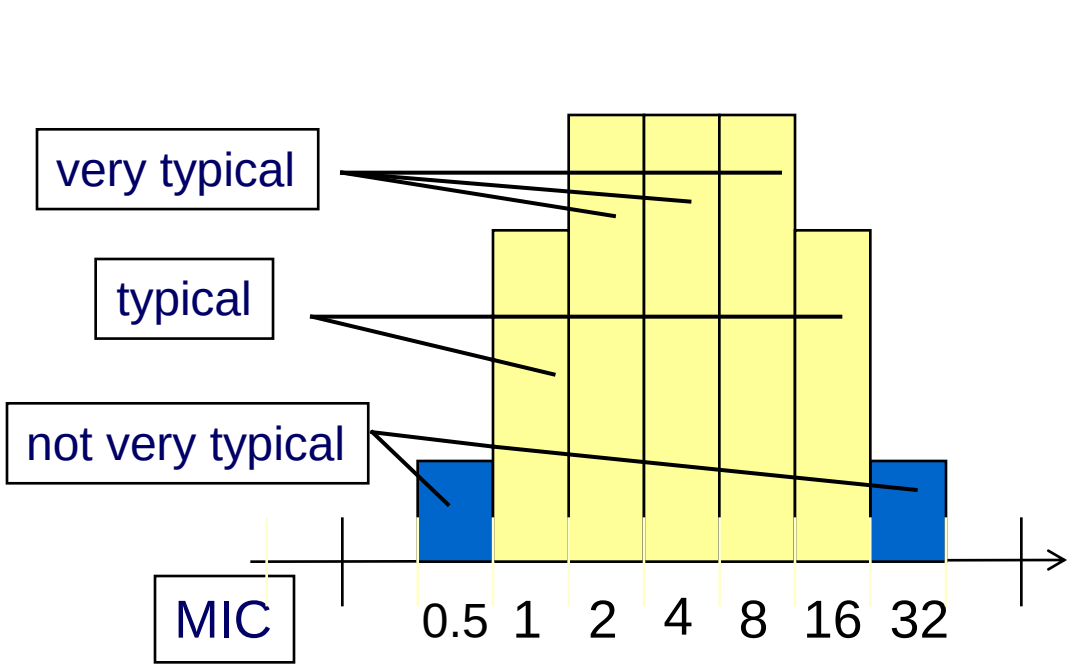
Software of AST Systems
Rule-Based Expert Systems

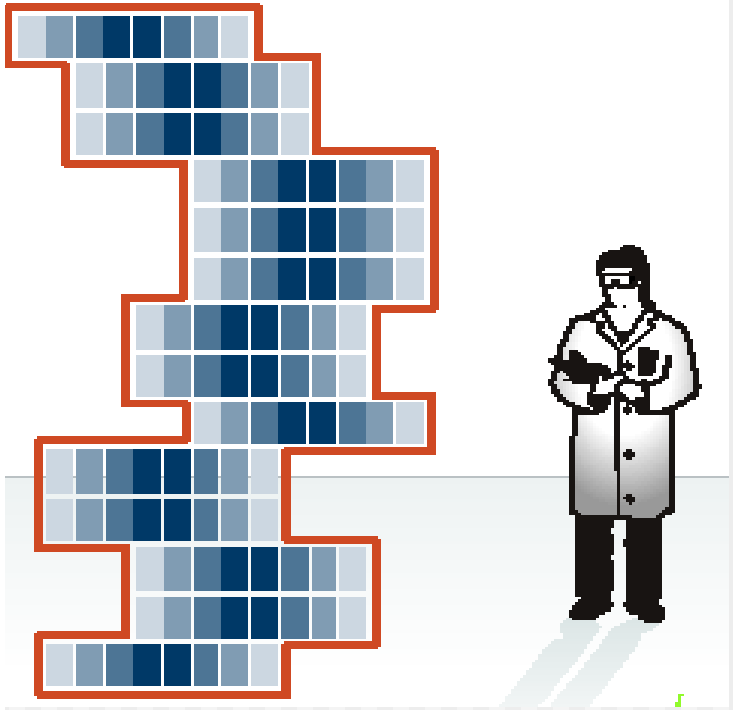


Software of AST Systems
Rule-Based Expert Systems

- **Typically employs a series of 'rules' developed either by the individual user or by the AST system manufacturer (or both) for evaluating results**
- **Based on "If - Then" statements**
- **Most common approach is to use simple linear logic based on interpretive categories (S, I, R)**
  - **e.g. IF organism is *S. aureus* AND oxacillin is R, THEN convert all beta-lactams to R**
- **User-defined rules often include antibiotic/ organism specific comments to help guide clinical decision-making**
  - **e.g. "*S. aureus* isolates resistant to oxacillin (MRSA) are considered resistant to all beta-lactam antibiotics"**

Software of AST Systems
Phenotype-Based Expert Systems





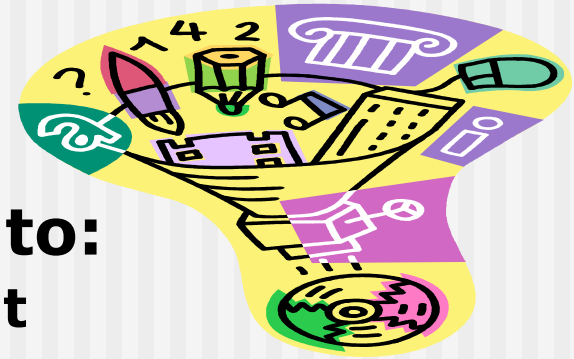
MIC frequency distributions for each organism/drug phenotype combination are compared to a data base to create a probability assessment

Software of AST Systems
Expert Systems

- **Expert System knowledge bases are programmed with certain facts:**
  - **Antimicrobials**
  - **Organisms**
  - **Current microbiological information as defined by CLSI/EUCAST and/or published scientific data**
- **For each susceptibility result, Expert Systems software:**
  - **Applies the rules**
  - **Asks the knowledge base"Is this result correct given what is contained in the knowledge base about this organism's identification and susceptibility?"**

Software of AST Systems
Expert Systems

- **For each analysis, Expert Systems can offer guidance to the technologist:**
  - **Are the results correct?**
  - **Are there therapeutic corrections that should be made?**
  - **Are results consistent?**



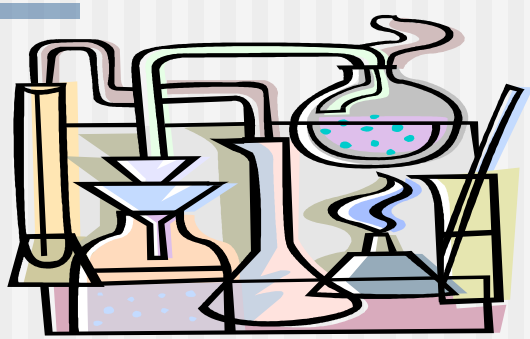
- **The technologist can decide to:**
  - **Accept the Expert System result**
  - **Repeat the test**
  - **Disregard the Expert System recommendation**
  - **Flag results for review**

Software of AST Systems
Expert Systems

- **For each analysis, Expert Systems offer the opportunity to separate out the routine/"normal" results that do not need human assessment, freeing the laboratory scientist to focus on those results that are unexpected/unusual which do need further investigation**

- **Comments can be automatically generated to provide valuable information from the microbiology laboratory to the clinician to aid in patient management**

Software of AST Systems
Expert Systems



- **Why use an Expert System?**

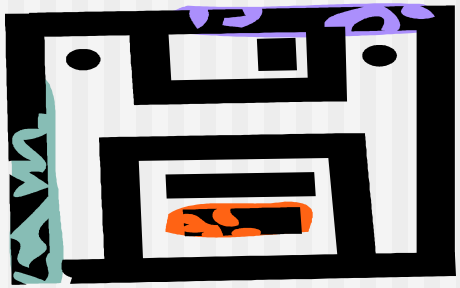
  Automatically detect
  - **Technical errors**
  - **Result anomalies**
  - **Natural and acquired resistance patterns**

- **Clinical Utility**
  - **Enables rapid and accurate identification and susceptibility result reporting**
  - **On-line validation of susceptibility results**
  - **More efficient microbiology laboratory identification and susceptibility review and validation process**

Software of AST Systems
Expert Systems

Considerations when using an Expert System

- **Dependent on accuracy/presence of rules or phenotypes in instrument database**
- **Regular updating of rules and database is required**
- **Lack of adequate data on certain organisms**
- **Dependence on antibiotics tested**



Software of AST Systems Summary

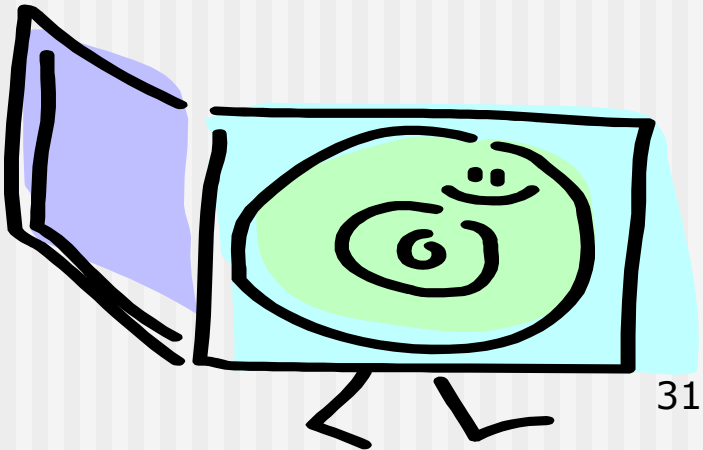
The Software is the brains of the Instrument

- **Changes such as new organism/drug combinations, new breakpoints, new resistance mechanisms require new or updated software**
- **Development of new/updated software generally proceeds in parallel with development of reagents**

Software of AST Systems Summary

Expert Systems provide computer aided decision support

- **Body of data (logic) used to make inferences based on the ID/AST patterns of microorganisms**
- **Goal is to separate out the usual from the unusual to enhance rapid, relevant, and accurate reporting**



IV. FDA Requirements and Clinical Trials

FDA Requirements and Clinical Trials

- All antimicrobic susceptibility test (AST) systems, and all antimicrobics included for distribution and sale in the U.S. in these systems, must receive premarket clearance from the FDA.
- "a manufacturer who intends to market a device of this generic type should

  (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E,

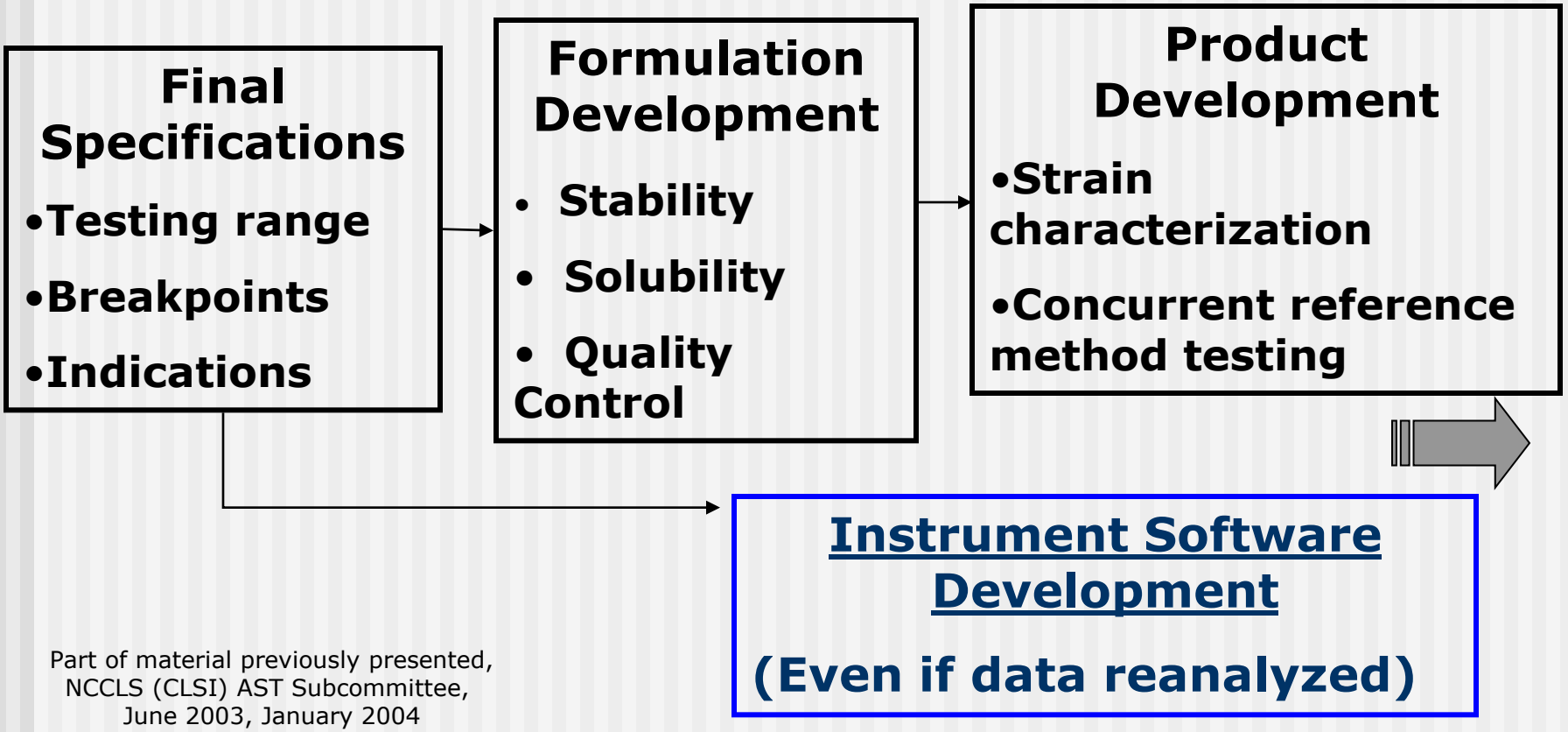
  (2) address the specific risks to health associated with automated short-term incubation cycle AST system identified in this guidance and,

  (3) obtain a substantial equivalence determination from FDA prior to marketing the device (see also 21 CFR 807.85)."[1]

[1] From Guidance for Industry and FDA. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems, U.S. Dept. of Health and Human Services, Center for Devices and Radiological Health. Issue date Aug. 28, 2009.

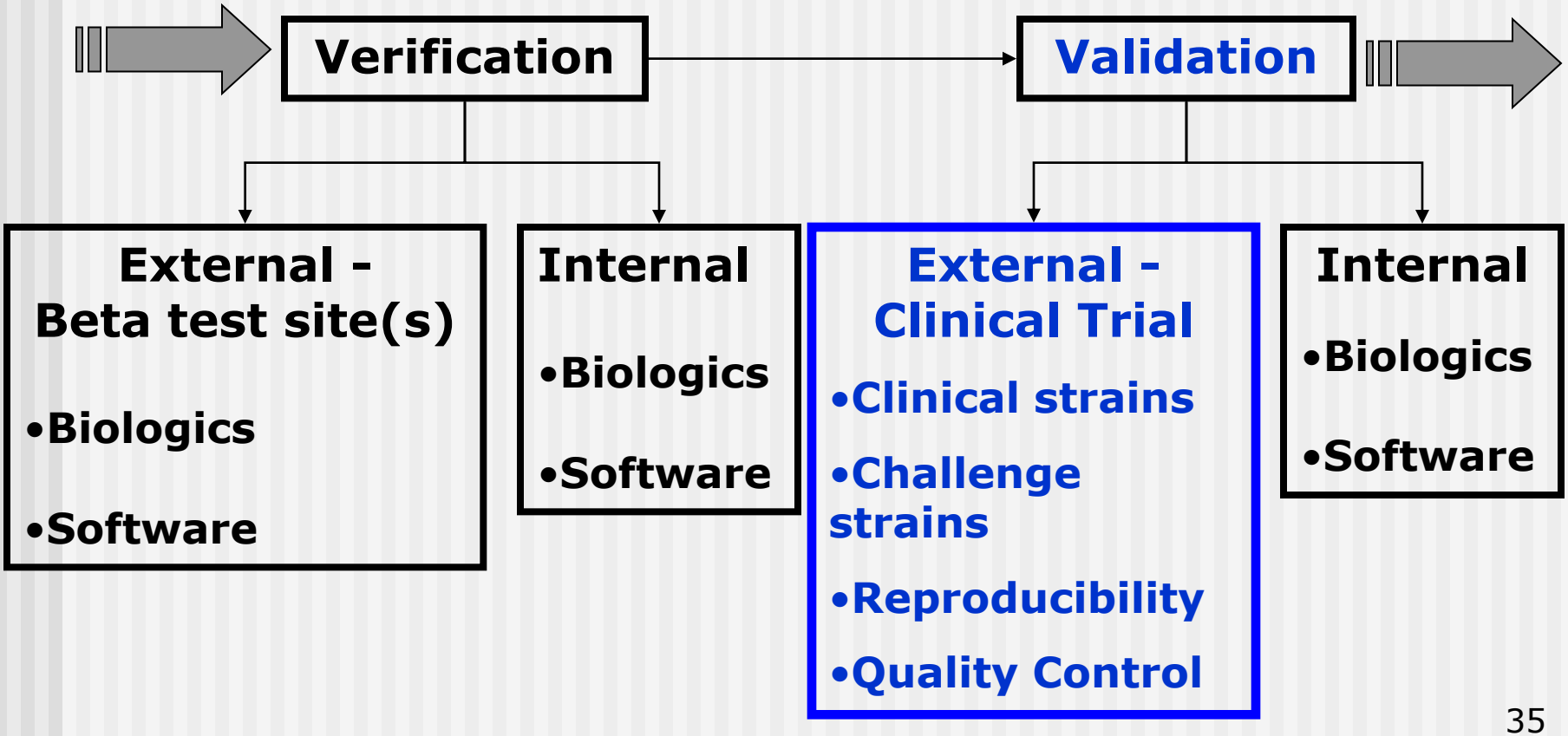
Antibiotic Development and Qualification Process for AST Systems -- MIC

For each new antibiotic and indication,



Part of material previously presented, NCCLS (CLSI) AST Subcommittee, June 2003, January 2004

Antibiotic Development and Qualification Process for AST Systems -- MIC



FDA Guidelines for 510(k) Study Design for Antimicrobics in AST Devices

For each antibiotic **AND** indication, a separate 510(k) is required.

- Reference Method = CLSI Standard Methods for aerobic bacteria (M7)
- Inoculation Methods - include both manual and automated methods, where applicable.
- Reading Methods - include manual, visual and automated methods, where applicable.

FDA Guidelines for 510(k) Study Design for Antimicrobics in AST Devices

For each antibiotic **AND** indication,

- Test Organism Selection - include "organisms for which clinical efficacy and *in vitro* activity have been demonstrated" and "that represent the clinical indications of the antimicrobial agent and are within its spectrum of activity."[1] Include known resistance markers.
- Include isolates from 1) routine clinical cultures (fresh), 2) clinical stock strains and 3) Challenge set organisms ("should favor R strains, and include organisms for which the antimicrobial agent's MICs are on-scale"[1]).
- Must include CLSI QC isolates

On-scale MICs

On-scale MICs are considered "evaluable" as they do not include inequality values

On-scale concentrations for this series = 0.5 - 32

0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32

MICs of <=0.25 and >32 are considered "off-scale"

FDA Recommendations for AST Devices

For MIC/"Breakpoint" Formats

- ✓ Number of sites: 3
- ✓ Organisms:
  - 100/site fresh & stock
  - 75 Challenge Set
- ✓ Reproducibility: 25/site or 10x3x3/site
- ✓ Interpretive Standards: FDA
- ✓ Stability: 3 lots (real-time data)
- ✓ QC (Reference & Test Device)
  - CLSI Strains - 20 results/site
  - At least 1 QC strain on-scale
- ✓ Inoculum Density Checks – QC, fresh and reproducibility

FDA Criteria for Satisfactory Performance of *in vitro* Antibiotic Test Data

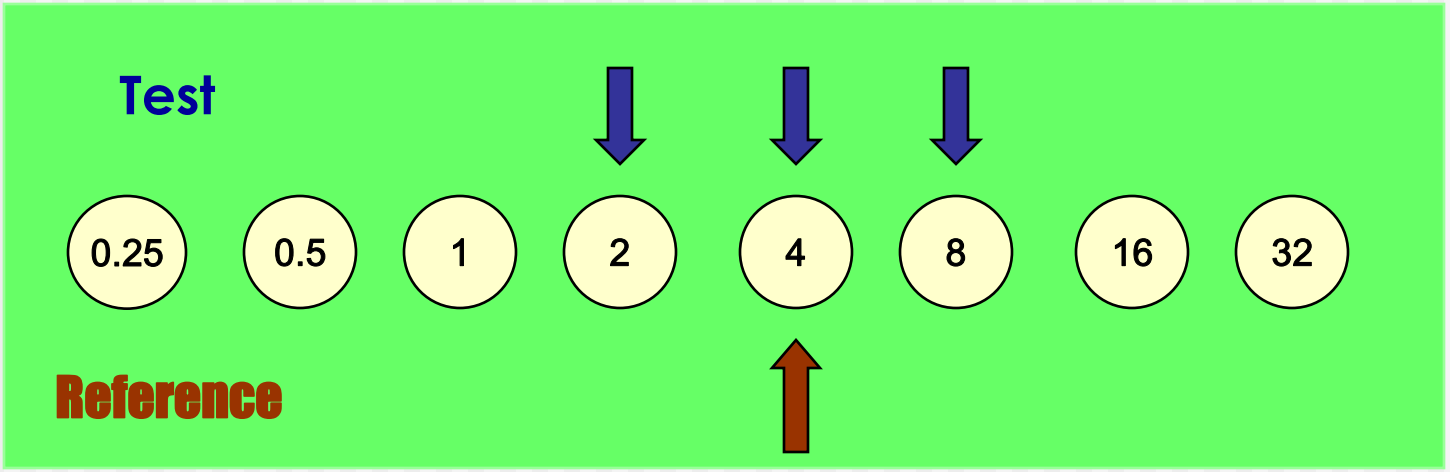
For MIC/"Breakpoint" Formats

- ✓ Accuracy (Fresh, stock & Challenge Set) :
  - Percent EA and CA ≥ 90%
  - VME rate ≤ 1.5% of "R" isolates (statistical criteria includes upper 95% conf. limit of 7.5% and lower 95% conf. limit of 1.5%)
  - ME rate ≤ 3% of "S" isolates
  - Growth failure rate < 10 for any genus or species
- ✓ Reproducibility: ≥ 95%
- ✓ QC Test Device: ≥ 95% within expected range

AST: Evaluating Performance

Essential Agreement (EA)

Agreement of the test system to the reference within +/- one dilution.

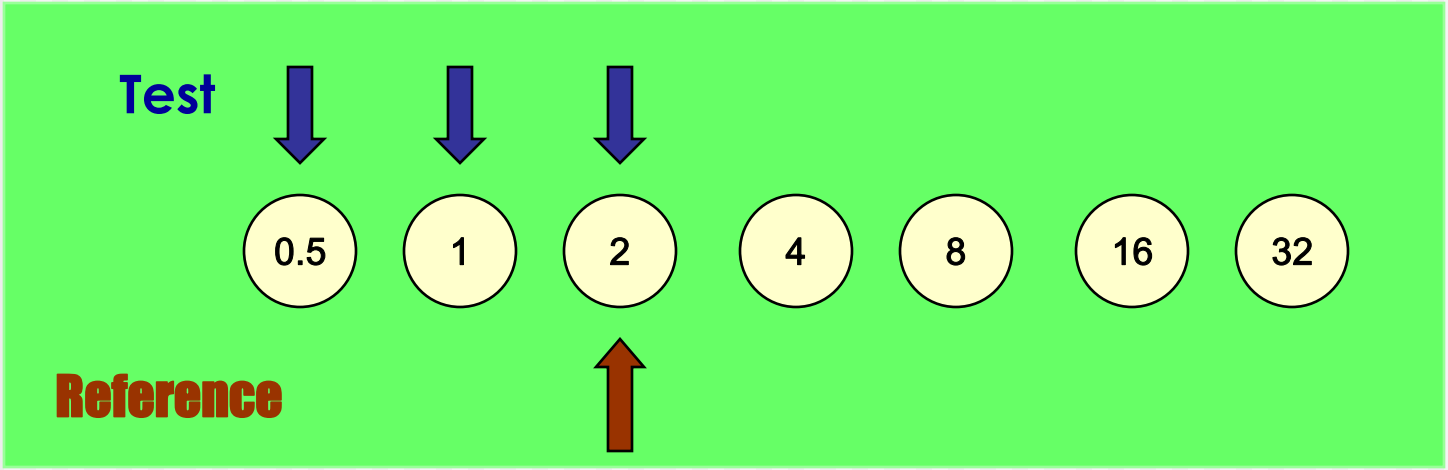


NOTE: The antibiotic and breakpoints are not requirements for EA calculation.

AST: Evaluating Performance

Categorical Agreement (CA)

Agreement of the test system to the reference within category.



LVX Breakpoints for the *Enterobacteriaceae*
S<=2, I=4, R=>8

AST: Category Agreement Without Essential Agreement

*With permission from J. Patel

- Hypothetical experiment: 30 isolates of Enterobacteriaceae were tested for meropenem susceptibility by reference MIC method and an AST device.
- New MEM breakpoints: **S/I/R = 1/2/4**

Test MICs

Reference MICs	0.125	0.25	0.5	1	2	4
0.125						
0.25			6	10		
0.5			4	8		
1				2		
2						
4						

Essential agreement = 66%

Category agreement = 100%

AST: Essential Agreement Without Categorical Agreement

- Hypothetical experiment: 30 isolates of Enterobacteriaceae were tested for meropenem susceptibility by reference MIC method and an AST device.
- New MEM breakpoints: **S/I/R = 1/2/4**

Test MICs

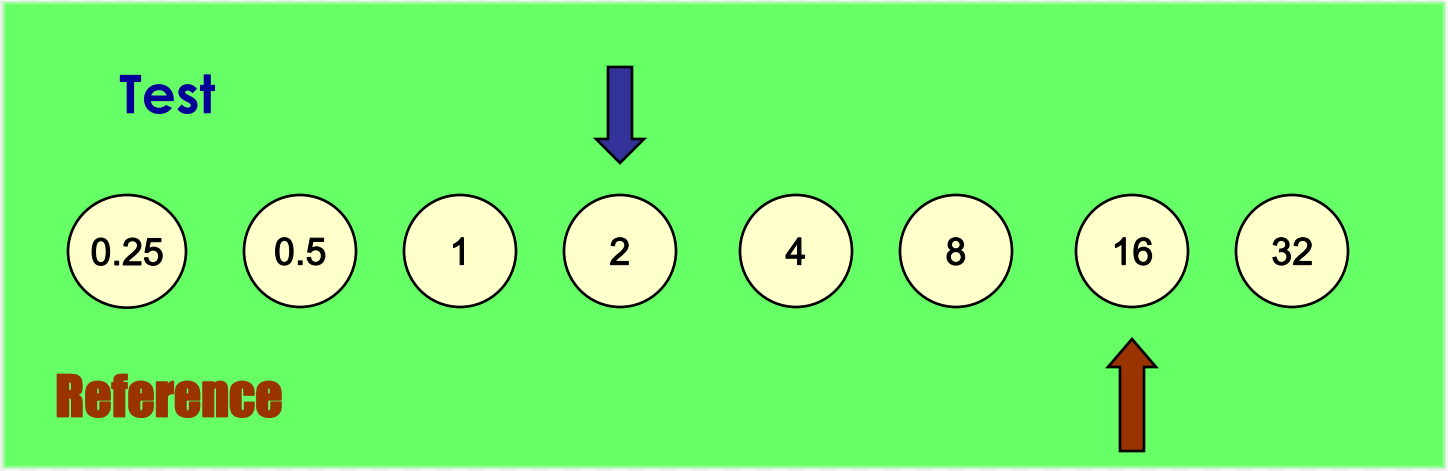
Reference MICs	0.5	1	2	4
0.5	3			
1		15	9	
2				2
4				1

Essential agreement = 100%

Category agreement = 63%

AST: Evaluating Performance

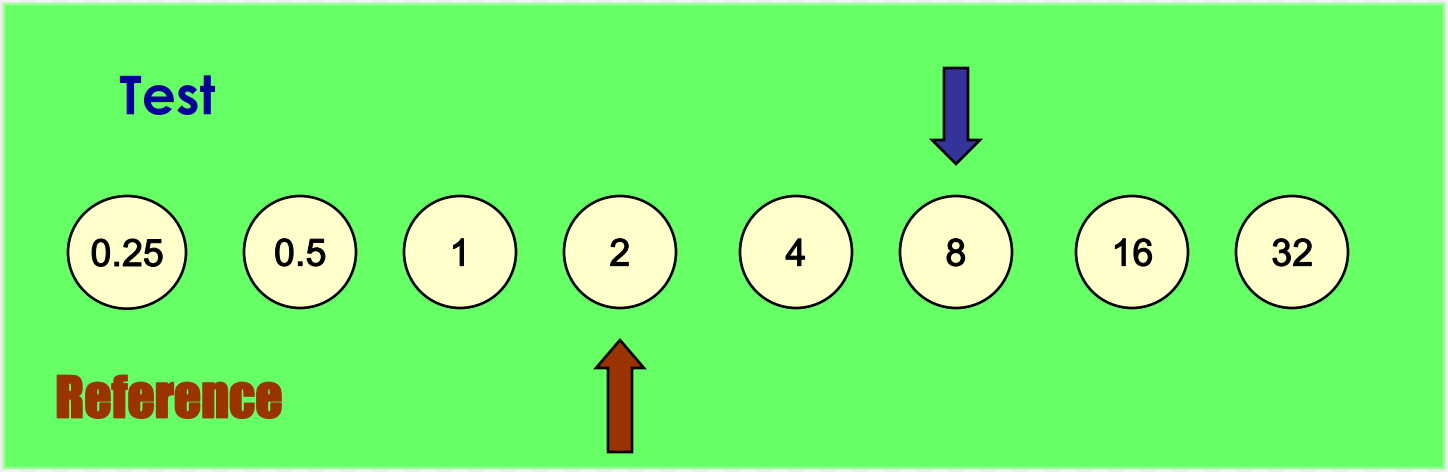
<u>Discrepancies</u>:
Very Major Error (VME):
Reference = R, Test System = S



LVX Breakpoints for the *Enterobacteriaceae*
S<=2, I=4, R=>8

AST: Evaluating Performance

<u>Discrepancies</u>:
Major Error (ME):
Reference = S, Test System = R



LVX Breakpoints for the *Enterobacteriaceae*
S<=2, I=4, R=>8

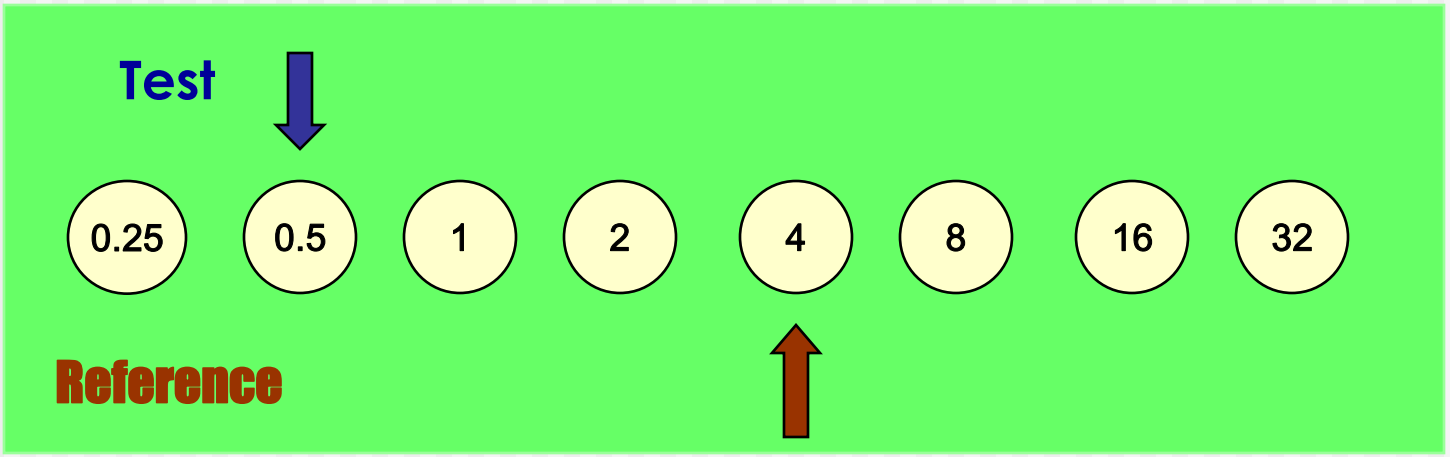
AST: Evaluating Performance

Discrepancies:

Minor Error (miE):

Reference = S or R, Test System = I;

Reference = I, Test System = S or R.



LVX Breakpoints for the *Enterobacteriaceae*

S<=2, I=4, R=>8

AST: Evaluating Performance

Discrepancies:

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Reference = S or R, Test System = I;

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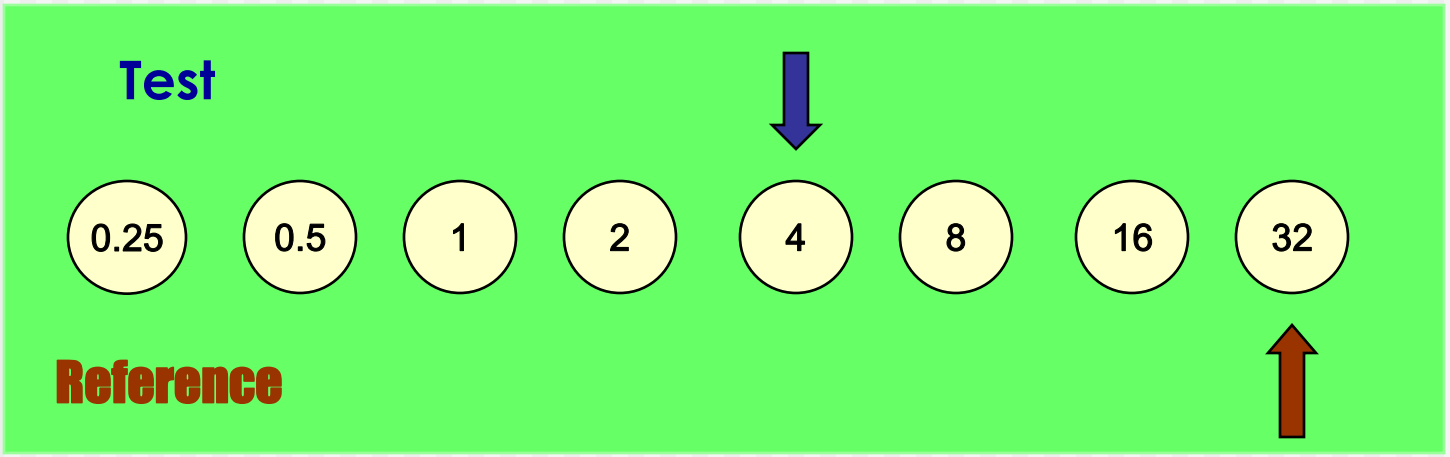


LVX Breakpoints for the *Enterobacteriaceae*

S<=2, I=4, R=>8

Affect of “S” Only vs. “S / I / R” Breakpoints on Agreement Rates

S / I / R Breakpoints

	REFERENCE MICs										
	<=	=		S	I	R			>	Grand Total	
TEST_MICs	0.125	0.25	0.5	1	2	4	8	16	16		
<= 0.125	93	3	2							98	
0.25	12	3	1	1						17	
0.5	1	4	2		1					8	
1		1	3	3	1	1				9	S
2		1	1	1	2					5	I
4		1		1		1				3	R
8					1	1	4	1		7	
16							5	10	1	16	
> 16								4	21	25	
Grand Total	106	13	9	6	5	3	9	15	22	188	

S = 134 I = 5 R = 49

EA	176
EA%	93.6
CA	179
CA%	95.2
VME	1
VME%	2.0
ME	2
ME%	1.5
MiE	6
MiE%	3.2

Affect of “S” Only vs. “S / I / R” Breakpoints on Agreement Rates

Susceptible / Non-susceptible BPs

	REFERENCE MICs										
	<=	=			S	NS			>	Grand Total	
TEST_MICs	0.125	0.25	0.5	1	2	4	8	16	16		
<= 0.125	93	3	2							98	
0.25	12	3	1	1						17	
0.5	1	4	2		1					8	
1		1	3	3	1	1				9	S
2		1	1	1	2					5	NS
4		1		1		1				3	
8					1	1	4	1		7	
16							5	10	1	16	
> 16								4	21	25	
Grand Total	106	13	9	6	5	3	9	15	22	188	

EA	176
EA%	93.6
CA	180
CA%	95.7
VME	3
VME%	6.1
ME	5
ME%	3.7
MiE	NA
MiE%	NA

S = 134 I = 5 R = 49

Satisfactory Performance of *in vitro* Antibiotic Clinical Trial Test Data

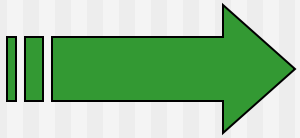
For MIC/"Breakpoint" Formats, once all of these criteria are satisfactory,…

- ✓ Accuracy (Fresh, stock & Challenge Set) :
  - Percent EA and CA ≥ 90%
  - VME rate ≤ 1.5% of "R" isolates (statistical criteria includes upper 95% conf. limit of 7.5% and lower 95% conf. limit of 1.5%)
  - ME rate ≤ 3% of "S" isolates
  - Growth failure rate < 10 for any genus or species
- ✓ Reproducibility: ≥ 95%
- ✓ QC Test Device: ≥ 95% within expected range

…you are now ready to begin preparing for the FDA submission (510(k) or PMA). Suggested formats for data presentation are included in the Guidance document.

FDA and/or other Regulatory Submissions

510(k) Submission



FDA Review

- **Labeling (Intended use)**
- **Indications**
- **Performance**
- **Limitations**

Once received, the submitted document will be reviewed within 60 – 90 days.

V. AST Device and Antibiotic Approvals

AST Device and Antibiotic Approvals

- In response to a Citizens Petition from CLSI; CDER & CDRH published

  "Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

  - Provides for Acceptance of Voluntary standards **such as CLSI**
  - Defines Drug Manufacturers responsibilities
  - Defines AST Manufacturers responsibilities

- CDRH in March, 2009, updated our guidance Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

FDA Recommendations

- Establish performance characteristics by agreement with the CLSI standard reference method for each antimicrobial agent and the organisms intended for testing.
- Because variations in test procedures can affect performance, conduct agreement studies on all procedural options included in the package insert. Such procedural options include, inoculation preparation methods and reading of results, for example:
    - growth inoculation preparation method
    - direct colony suspension inoculation method
    - visual reading
    - automated readings.

Submission Contents

- Submissions for antimicrobial susceptibility testing (AST) systems should include only one drug, one method of reading, and one method of inoculation.

- You may bundle gram-negative and gram-positive claims (provided the same methods of reading and inoculation are used for both). For more information, refer to the FDA guidance

Limitations

- You must include a statement of limitations of the procedure. 21 CFR 809.10(b)(10). If the device has software-generated interpretations, these limitations should be incorporated into the software. Examples of some limitation statements:
  - You should recommend the use of an alternative method for testing prior to reporting of any results when the spectrum of activity for any antimicrobial agent includes organisms with either unacceptable very major discrepancy or major discrepancy rates.
  - If you did not test sufficient resistant organisms with an approved indication for use for the antimicrobial agent, you should include a statement in the labeling similar to this.

When CLSI Changes BKPTS

- Drug application holder submits an appropriate labeling supplement to CDER for review and approval (see 21 CFR 314.70).
- AST Manufacturer validates that the new criteria does not change performance (reevaluate previously collected data or perform a new comparative study)
- If no change, submit an Add-to-File
- If performance drops below acceptable, submit new 510(k).

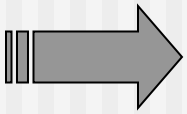
Comparative Study

- Similar group of organisms as those groups that provided the original Essential Agreement or Category Agreement results
- Representative number from all groups of organisms that might be affected by modifications to the device

VI. Commercialization

Commercialization

Once clearance is received,
Once stability is completed,
Once panels are implemented in the software,
Once expert rules are written,
Once interface configurations are completed
Once the software is validated,
Once it is released by QA,



Commercialization

- **New Product Configuration**
- **Update Product Information**
- **Build Inventory & Change Catalog Numbers**
- **User Software Installation**
- **User Education**

Then the work really begins

Commercialization: New Product Configuration Drug X is ready to be on a panel/card with other drugs!

- Generally, configuration is completed early. For systems with multiple antibiotics on a panel: what is the best fit of antibiotics for a particular need? (e.g. Neg, Pos, Fermenter, Nonfermenter, Breakpoint, MIC, Urine, Combo)
- It's decided much earlier what panel type this will go on and in what dilutions
- The new product gets a name and number early on (e.g. NBPC50 = Neg Breakpoint Combo 50)
- For companies with many products, decisions are made on older products to eventually obsolete (data are maintained in software)

Commercialization: Update Product Information

You get Customer Labeling:

- Instructions for Use ("IFU") in every box contain performance information for every drug – it may be different for MIC and BP configurations
- Box label, panel/card label
- Therapy Guide – details what interpretation goes with which organism and which MIC
- Expert System Guide update
- Letter to the Customer (usually with some background material)
- New "glossies" listing all panel types

Commercialization: Update Product Information

Non- Customer Labeling:

- Notification of new codes to interface software vendors
  - An historic fact: “ESBL” was 4 letters and was 1 letter too many for some interfaces
  - Some of this still continues with various interfaces, e.g. SDD is sometimes transmitted as “S”, or “D”

Commercialization: Build Inventory & Add Catalog Numbers

- Catalog numbers are added to the system to be available on line (sounds so simple)
- Enough of the new panel/card with updated IFU are made for customers in the country of release to order and located in appropriate storage at distribution center
- Enough software disks are duplicated
- Direct distribution vs. distribution center
- Customer software disks and letters are sent out! New panels/cards/etc. available!

Commercialization: User Software Installation

- Once the user has software, needs to be loaded on system – customer or technical specialist, usually detailed loading instructions
  - Save/backup/merge old data with new
- Customer needs to work with their hospital LIS system for new drugs
- Customizing expert system option for some systems

Commercialization: User Education (and Sales/Technical/Hot Line)

Usually involves web/phone training for internal personnel – so they can train customer

Depends on the antibiotic and its application, – sometimes needs to be basic

May involve local or in-site training to customers

The “hot line” needs to know all about the drug, what it is likely used for, how it is implemented in the software – so that when you call them, they know the answer

Commercialization: User Education (and Sales/Technical/Hot Line)

Some examples of what users may need to know:

How does cefoxitin work? How does it work in software with/without oxacillin?

Why are there many BPs for S. pneumoniae and penicillin and how should I put that in my software?

Why aren't there CLSI breakpoints for Drug X in the software?

And, of course, what about those new cephalosporin breakpoints….

VII. Overview of Commercial Methods

Commercial Methods

- Phoenix and Sensi-Disc (BD Diagnostic Systems)
- Vitek 2 and E-test (bioMérieux, Inc.)
- MicroScan (Siemens)
- Sensititre (TREK Diagnostic Systems)

VIII. The Clinical Microbiology Laboratory

The Clinical Microbiology Laboratory

- Linda Mann, PhD, D(ABMM)

Senior Staff Clinical Microbiologist, Clinical Affairs, Siemens

Bench technologist and former laboratory director

Provide internal and external education about AST issues at Siemens

- Dyan Luper, MT(ASCP) SM, MB

Staff Scientist, R&D

BD Diagnostic Systems

Former bench technologist and microbiology supervisor

BDXpert team lead

Clinical Lab AST Issues

- Methods used in clinical laboratories
- Breakpoint changes
- Issues:
  - Agents without FDA-approved breakpoints
  - Species specific breakpoints
  - Organisms not covered by CLSI tables or FDA breakpoints
  - Disease or body site specific breakpoints
  - Agents without CLSI breakpoints
  - Other reporting issues
  - Proficiency testing issues

Methods Used by Clinical Labs

- Most clinical labs use automated systems for AST.
  - Some labs still use disks as the primary method.
  - Only rare labs use frozen panels or agar dilution methods routinely.
- Some labs maintain two automated systems – for backup and filling any gaps.
- Many (but not all) labs will also maintain supplies, procedures, competency testing, and perform verification, and validation activities for supplemental methods such as disk diffusion, screening agars, or Etest strips. Materials may expire if rarely needed.

Automated AST Systems

- Interpretive criteria are built into our software and applied to appropriate organisms.
  - Easy to report/not report based on ID
  - Easy to report/not report based on formulary
  - Harder to implement based on site of infection since labs define sources differently and have to customize the systems to their sources
- Expert/Alert systems can warn users about inconsistent or unusual results.
- Systems may be customized to procedures used in that laboratory to handle results – “verify results” may become “perform mecA before reporting”.

Customer Education

- Not many labs have staff or resources. to maintain an expertise in AST.
- Training is provided for operation of our systems
  - Several levels of training may be offered.
- Field Support by Technical Specialists
- Seminars/Symposiums/User Group Meetings
  - CME – not marketing events
  - Training may go out to the field.
- Newsletters
- Technical Support Bulletins
- CME on our websites

Complaints/Product Issues

- Quality Regulations require us to track and deposition product complaints.
  - Direct complaints from customers
  - Publications reporting issues
  - The most comment complaints are probably QC-related and are organism related.
  - Thresholds are set – for example, more than 3 complaints in a year may trigger an investigation but major issues are investigated when reported.
- Confirmation of a serious problem results in field corrective actions – remove product, customer letters, effectiveness checks, implementation of corrective and preventive actions.

Breakpoint Changes

- Can provide lower dilutions needed to support laboratories in the implementation of lower breakpoints
- Cannot implement breakpoint changes in our software prior to FDA clearance – requires the drug labels to be updated and approved
- Can provide software that allows users to customize breakpoints in their systems "after appropriate validation/verification"
- What does verification of BPs mean?
  - Verification is not judging the appropriateness of the breakpoint – confirmation that the automated system still gives accurate interpretations (CA) at the new breakpoints.

Why Verify the New Breakpoints?

- EA is measured across the dilutions for which the device is cleared.
- EA for any particular dilution may vary. Noise tends to increase in the lower dilutions.
- If the breakpoint is at a dilution with a lower EA, the CA may suffer.
- Just because an automated system has clearance for the dilutions that encompass the new breakpoints, it does not mean that CA would meet FDA requirements for clearance.

Do I Do It Now or Wait?

- I don’t have the staff, the budget, the organisms I need to perform the verifications.
- Who covers the cost of the supplies needed for the verification?
- I don’t do disk testing now so I need to set up that method before I verify my system?
- I can’t get time with my IT folks.
- CLSI does give me options, so it is not that important, is it?
- Won’t this affect my antibiogram data?
- Won’t I just have to do it again next year – more new breakpoints or new agents to add?

If a New Panel/Card is Needed

- Select a new panel/card with appropriate dilutions and desired drugs
- Set up pricing, manage orders and inventory
- Implement new panels in LIS – may require getting IT support from outside the laboratory
- Verify that new panels meet performance claims (acceptable for use) prior to reporting patient results if new agents added or new breakpoints implemented
- Perform 20-30 days of daily QC testing for any new agents; if successful, implement weekly testing
- Train staff, update procedures, communicate with medical staff and pharmacy, etc.

Agents without FDA-Approved BPs

- FDA establishes breakpoints for agents only for bacterial species/groups with approved indications.
- What if I have to test other organisms for which there are no breakpoints?
  - Why can't my automated system report results for these organism?
  - Do I maintain other methods ($$$) for these isolates?
  - Do I delay results by sending these organisms out for testing ($$$)
- What if I change the ID in my system to one that will report the AST results that I want? Will the results be valid for the real organism?
  - For some systems/panel types, the MIC value depends on the identification.

Agents without FDA-Approved BPs

- What if there are no FDA breakpoints at all for an agent? How do I test and report?
- Example colistin – CLSI breakpoints exist; agent used to treat MDRO in very sick patients.
- Automated systems cannot get clearance to test in US.
- Devices could provide accurate MICs (compared to frozen reference method) without SIR interpretations.
- Labs can obtain RUO/IUO AST products but must sign a waiver saying they will not use the results clinically.

Species Specific BPs

- Breakpoints are getting very species specific.
  - If an agent has BPs for *Staphylococcus aureus*, why not coagulase-negative staph?
  - What about *Pseudomonas* species not *P. aeruginosa*, *Acinetobacter* other than *A. baumannii,* and then what about *Achromobacter*, *Stenotrophomonas*,, etc?
  - Species specific dilutions requirements: *Salmonella* spp. – Fluoroquinolones (require more real estate, reduces number of agents that can be included on the device)
- Labs must be able to test and report results to help guide therapy. If devices cannot, at the least, report an MIC value, alternative methods must be used. Critical results may be delayed.

Disease/Body Site Specific BPs

- Ideally this may be a very good way to approach reporting of AST results.
- *S. pneumoniae* – Penicillin (meningitis, nonmeningitis, oral); Cefotaxime, ceftriaxone, cefepime (meningitis, nonmeningitis)
  - Blood or sputum culture isolate of *S. pneumoniae* – Does the patient have meningitis?

- Practically, this is hard to implement in the laboratory as specimen type reported may correspond to various types of infections. MIC numbers are not well understood by all physicians.

Agents without CLSI BPs (only FDA BPs)

- Laboratories use the CLSI documents as their reference for susceptibility testing. Missing breakpoints cause confusion.
- Example tigecycline – No CLSI breakpoints published since breakpoints have not been requested.
- Laboratories must check drug package inserts to find breakpoints if not using an automated systems.

Other Reporting Issues

- CLSI has warnings about some misleading results.
  - Newer agents do not get breakpoints for organisms for which the agent is ineffective or when there is no approved indication.
  - May be hard for the laboratory to distinguish between the two reasons for having no breakpoints.
- Not every physician who uses antibiotics is an infectious disease specialist.
- Streamlining results (cascade reporting) to report only the best agents for that organism/source could be a good thing but can be misleading.
  - May apply results of one drug to predict other agents
  - May miss unexpected resistance later in the cascade

Real Case Example

- Patient has *Acinetobacter baumannii* in urine.
- Laboratory reported the isolate as susceptible to imipenem.
  - Did not report ertapenem – not indicated, no BP criteria, no expert system rule
- Physician misinterprets this to mean that the isolate should also be susceptible to ertapenem.
- Sometimes reporting that "obvious" R adds to patient safety (intrinsic resistance).

- Other examples include *P. aeruginosa* R to imipenem but still S to meropenem, etc.

Proficiency Testing Issues

- CLSI Table 1s list agents *suggested* for reporting based on FDA approved indications.
- How do I know when to report or not report other agents?
- Not all proficiency providers understand that Tables 1 listings are *suggested* reporting guidelines.

- Do I use FDA or CLSI BPs to report survey results? (Should use what you report for patients.) How will I be graded?
- CAP encourages use of new breakpoints. Should they penalize those that do not?
- Not all proficiency providers understand the FDA/CLSI BP issues

Summary

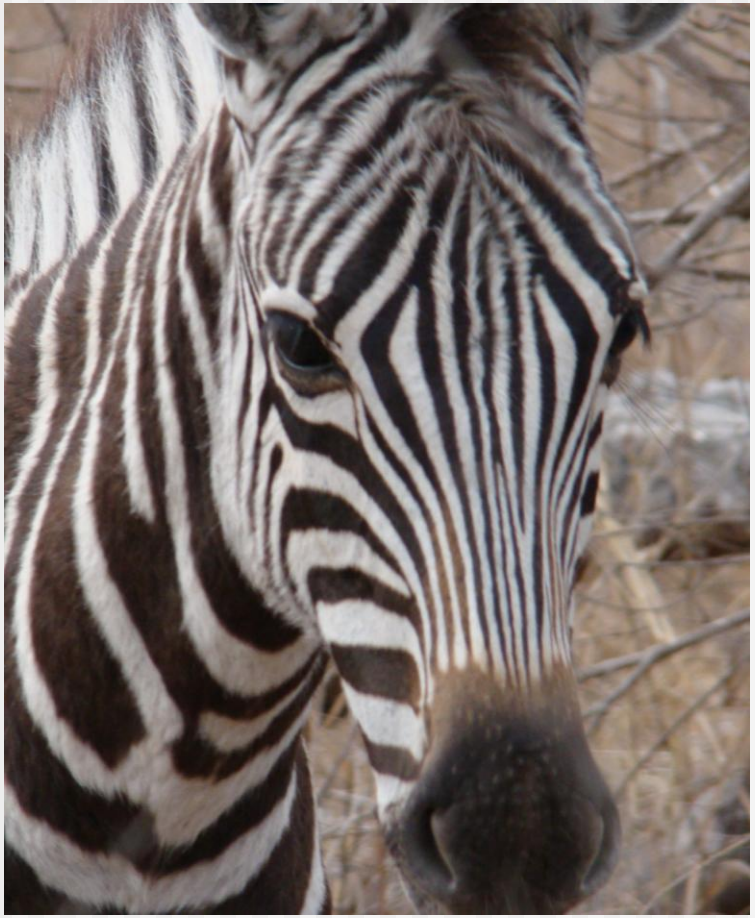
- Automated systems help laboratories but are limited by breakpoint issues.
- Not every infection is caused by an organism that will earn BPs at FDA or CLSI.
- Cost of supplies and staff time to maintain alternative methods for organisms they cannot test on the automated system are issues for many laboratories.
- Sending isolates to the reference laboratory for additional testing delay results.

Summary

- Automated susceptibility systems help laboratories that lack personnel with expertise with Expert/Alert systems and customer education.
- In the future, we need to address limitations created by species specific breakpoints for new antibacterial agents.

Summary

- Laboratories want to provide accurate and timely results needed by the physician to guide therapy and positively affect patient outcomes.
- We need the help of CLSI and FDA to find a way to help laboratories provide results critical to patient care for all types of infections and all types of organisms.



IX. Q&A