HOW TO DEVELOP & OBTAIN REGULATORY APPROVAL OF COMMERCIAL ANTIMICROBIAL SUSCEPTIBILITY TESTS IN A TIMELY MANNER

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Sept. 29, 2016

AGENDA

I. Introduction to STMA

II. Commercial AST Development

III. Challenges to Timely AST Development

IV. Proposals, Suggestions Moving Forward

DEVELOPMENT OF COMMERCIAL PRODUCTS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING

Bill Brasso, Sr. Staff Scientist,
R&D - ID/AST
BD Diagnostic Systems
STMA – Past-President, Active Member

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

STMA MEMBER COMPANIES

Accelerate Diagnostics, Inc.

BD Diagnostic Systems (Phoenix®)

Beckman-Coulter, Inc. (MicroScan®)

bioMérieux, Inc. (VITEK®2)

Bio-Rad Laboratories

Hardy Diagnostics

Mast Diagnostics

Thermo Scientific™ (Sensititre™)

ACCOMPLISHMENTS WHEN COMPETITORS WORK TOGETHER

- Participate in development of updates to FDA-CDRH Guidance Documents
- Advocates for recent Antimicrobial Resistance (AMR) legislation in US Congress
- Act as liaisons, representatives from AST industry on Standardization Committees (CLSI, USCAST)
  - Working groups
  - Ad Hoc WGs
  - Document reviewers
- "Roundtable" for Pharma to introduce new drugs
- Maintain the database for antimicrobic 'codes' for AST industry, regulatory agencies
- Central mechanism for supplying bulk antimicrobic powders to industry

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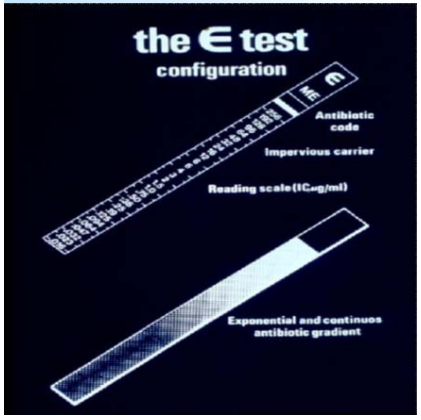
ANTIMICROBIC SUSCEPTIBILITY TEST (AST) METHODS USED BY CLINICAL LABS

AST devices provide therapeutic guidance to physicians and the clinical laboratory to determine

1. the **susceptibility** of a bacterial pathogen,
2. if the infecting organism is **resistant to the 'drug(s) of choice'**, or
3. **to detect emerging resistance** through surveillance.

Most labs use automated systems for AST. Some still use manual AST methods (disk diffusion, broth microdilution, macrotubes, etc.)

Picture from oncologynurseadvisor.com

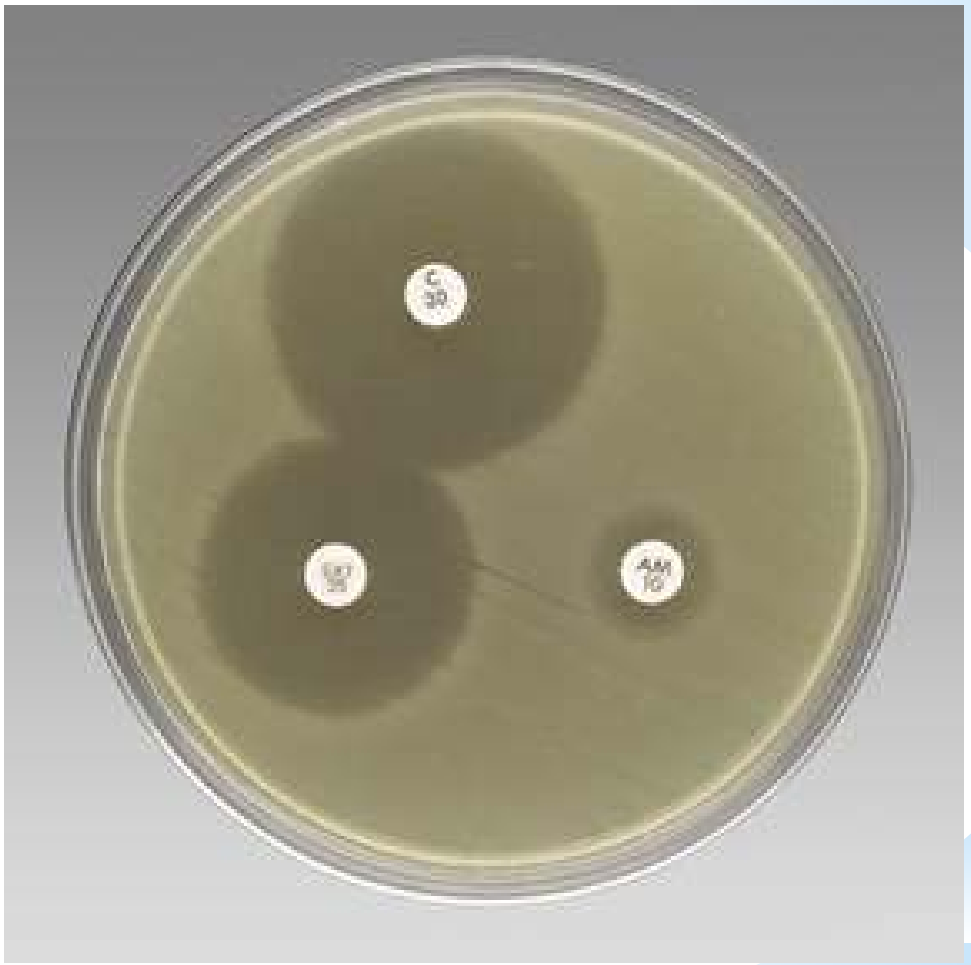


Commercial AST Methods

AST – K-B DISK DIFFUSION METHOD

Principle

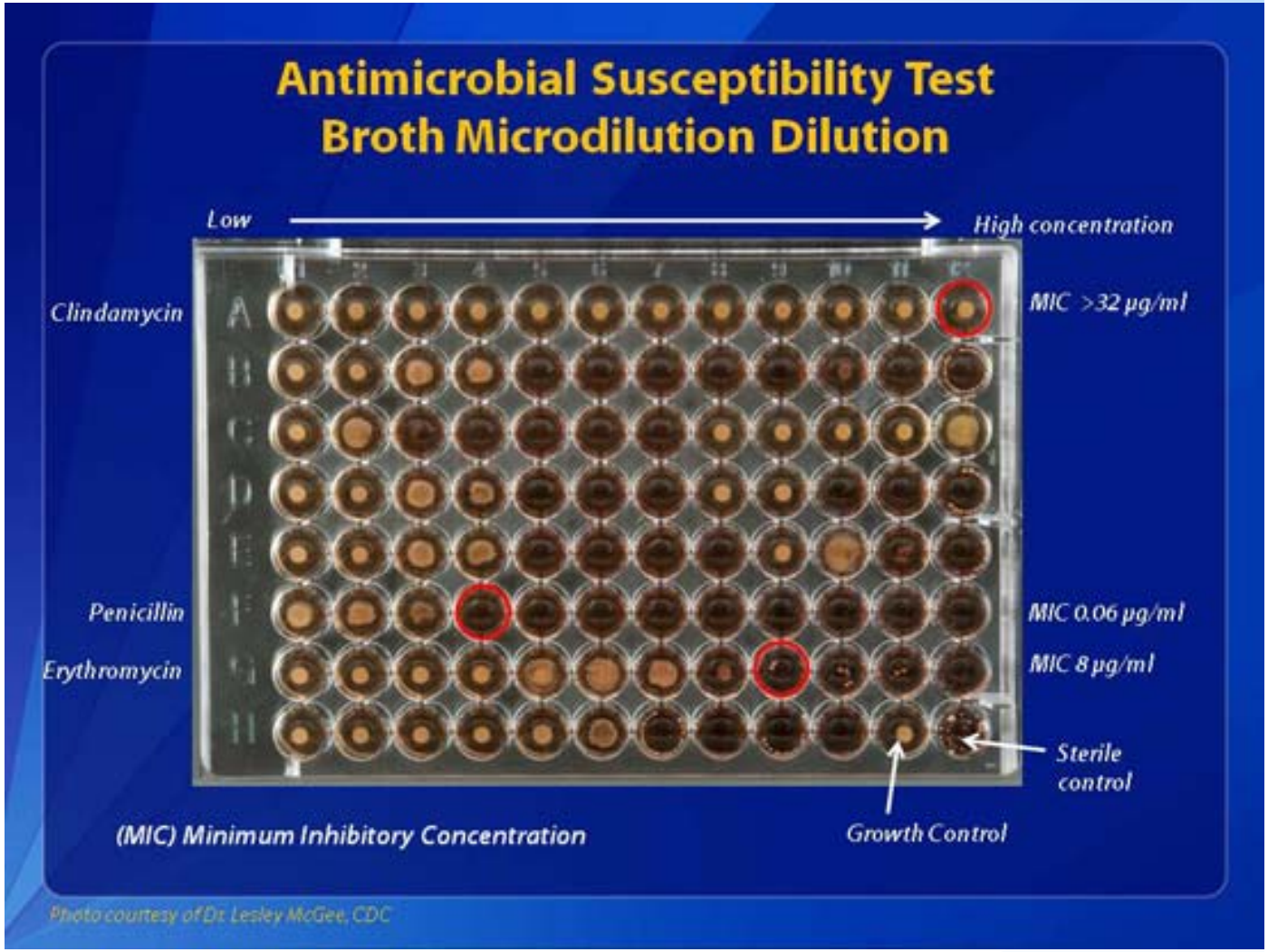
- MHA plate inoculated w/ uniform standardized suspension
- Place antimicrobic disks on surface
- Incubate overnight @ 35°C in ambient air
- Read zones of inhibition
- Interpret results
- Disks prepared commercially



AST - BROTH MICRODILUTION METHOD

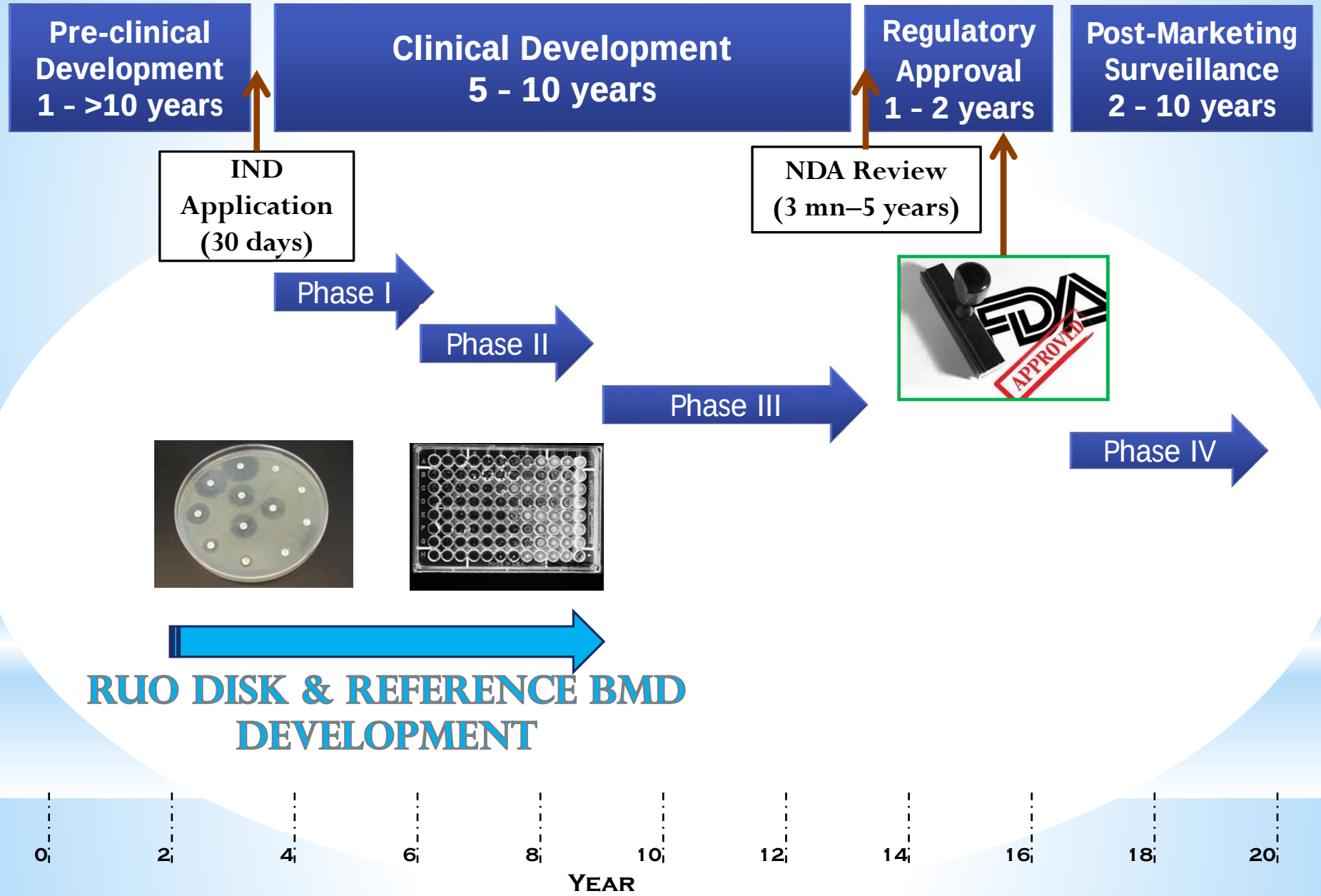
Principle

* Plastic tray inoculated w/ standardized suspension in CA-MHB
* Incubate overnight @ 35°C in ambient air
* Read MICs
* Interpret results
* Prepared in-house or commercially
* Agents dried, frozen or lyophilized



Picture courtesy of cdc.gov

NEW ANTIMICROBIC DEVELOPMENT PROCESSES FOR PHARMACEUTICAL COMPANIES



NEW ANTIMICROBIC DEVELOPMENT PROCESSES FOR PHARMACEUTICAL COMPANIES

Pre-clinical Development 1 - >10 years

Clinical Development 5 - 10 years

Regulatory Approval 1 - 2 years

Post-Marketing Surveillance 2 - 10 years

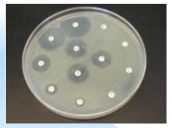
IN
Appli
(30 c

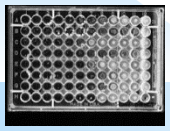
view
years)

Phase IV

The Food and Drug Administration has developed four distinct and successful approaches to making new drugs available as rapidly as possible:

- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- Fast Track





Rolling Review, a drug company can submit completed sections of New Drug Application (NDA) for review by FDA, rather than waiting until every section is completed.

NEW ANTIMICROBIC DEVELOPMENT PROCESSES FOR PHARMACEUTICAL COMPANIES & AST DEVICE MANUFACTURERS

Pre-clinical Development
1 - >10 years

Clinical Development
5 - 10 years

Regulatory Approval
1 - 2 years

Post-Marketing Surveillance
2 - 10 years

IND Application (30 days)

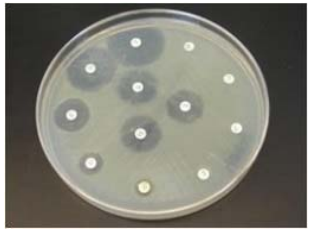
NDA Review (3 mn–5 years)

Phase I

Phase II

Phase III

Phase IV



Disk Development

0 2 4 6 8 10 12 14 16 18 20

YEAR

DISK DEVELOPMENT FOR AGAR DIFFUSION METHOD

Disk development can start during Phase 1, incorporated into testing during Phase 2 .

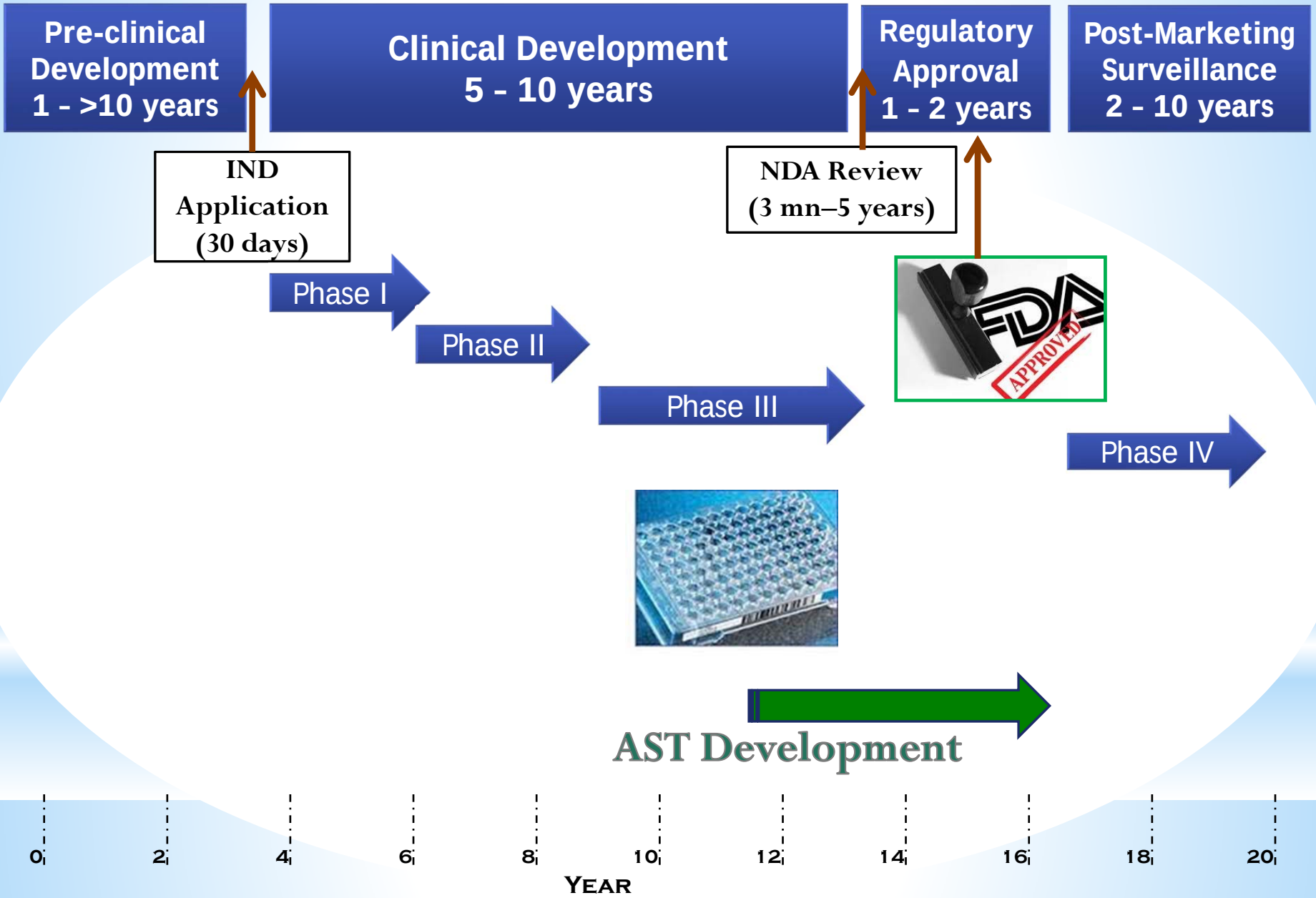
- **All CLSI M23 studies need to be done before any clinical testing.**
- **To develop a new disk from scratch for "research use only", the customer (Pharmaceutical Co.) provides the specs ("Product Development Package") for labeling development including:**
  - ✓ **Product description**
  - ✓ **concentration**
  - ✓ **disk code**

- **Other critical information needed:**
  1. **Is the compound (powder) sensitive to light, moisture, temperature , etc.?**
  2. **Is the compound water-soluble? Other solvent system required? The solubility is important to obtain a homogeneous solution for even distribution on the cards.**
  3. **What are the QC test strains, ranges and antibiotic class to develop and test the disks?**

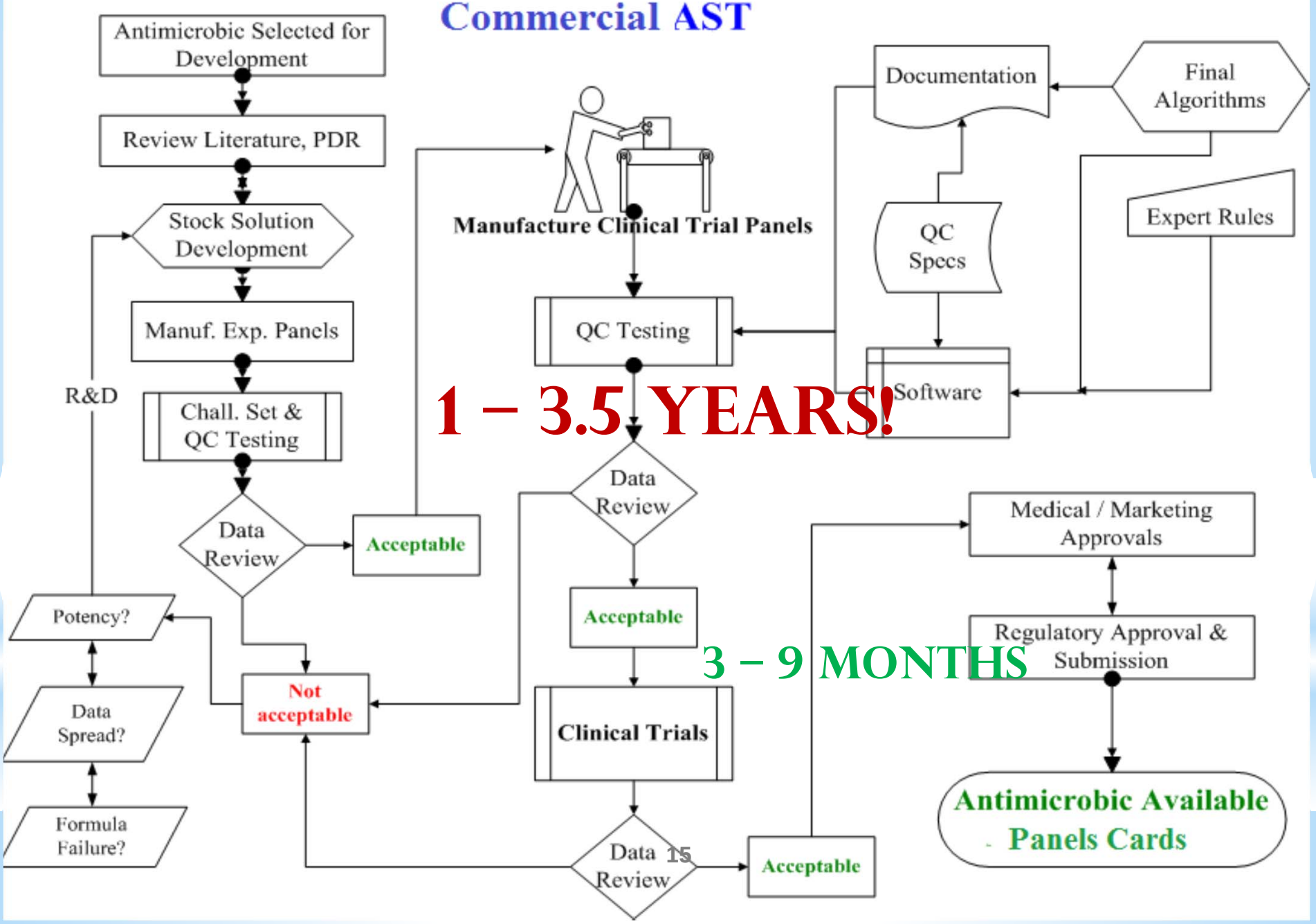
- **Usually 3 RUO lots made for testing potency, QC, performance, stability, etc.**

To later convert the disk to an IVD product for sale, Project Protocols, Technical Files, Expiration date approvals, etc., are considered with the manufacturer.

NEW ANTIMICROBIC DEVELOPMENT PROCESSES FOR PHARMACEUTICAL COMPANIES & AST DEVICE MANUFACTURERS



Antimicrobic Development for Commercial AST



AST DEVELOPMENT FOR BROTH MICRODILUTION (BMD) METHOD

- For AST development, Pharmaceutical companies usually approach AST manufacturers (STMA) during Phase 2.
- Some AST manufacturers can begin development early (~ Phase 2) if involved early in providing reference (BMD) panels. Others start development during Phase 3, so that their clinical trials will coincide with NDA submission and/or approval.
- **Considerations for selecting a drug for AST development**…
  1. Does this antibiotic look promising to make it through NDA approval?
  2. Does the drug address a current public health issue?
  3. Does this antibiotic require special conditions, additives, handling, etc., that will make development a challenge?
  4. Has the AST manufacturer already begun or in the middle of an AST development "cycle"? (Business decisions)
  5. Are there other pressing issues (new breakpoints for old drugs, new resistance markers identified, etc.)

CLINICAL TRIALS FOR FDA SUBMISSION

- 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, including premarket notification requirements 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**."[1]

FOR EACH ANTIBIOTIC AND INDICATION, A SEPARATE 510(K) IS REQUIRED.

[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.

FDA RECOMMENDATIONS FOR AST DEVICES

For Antimicrobics in MIC/"Breakpoint" Formats

- ✓ **Number of sites: 3**
- ✓ **Organisms:**
  - **100/site fresh (50%) & stock (50%)**
  - **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**

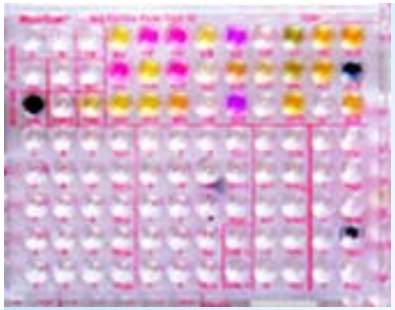
Many other recommendations for a successful outcome for the submission not listed here.

FDA CRITERIA FOR SATISFACTORY PERFORMANCE OF *IN VITRO* ANTIBIOTIC TEST DATA

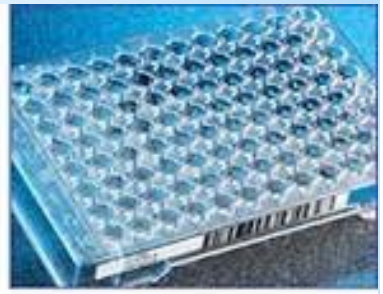
For Antimicrobics in MIC/"Breakpoint" Formats

- ✓ **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**

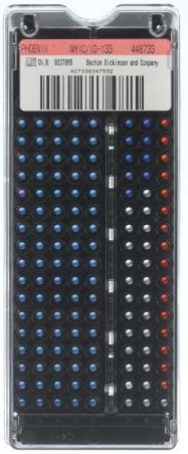
Required for Overall, as well as for each "Organism Group"!



COMMERCIALIZATION



* Drug X is ready to be introduced on a panel/card with other drugs! Need New Product Configuration (Cat #) for the panel.
* 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, possibly obsoleting some catalog numbers (data are maintained in software)
* Update Product Label Information (Customer Labeling, including box label, panel/card label)
* Package Insert with "Instructions for Use" in every box
* Therapy Guide and Expert System Guide updates
* Letter to the Customer (usually with background material)
* Notification of new codes to interface software vendors
* Building inventory
* Software installs



ANTIMICROBIAL SUSCEPTIBILITY TESTING: CHALLENGES TO GETTING TO MARKET

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Director Clinical Affairs
Beckman Coulter, Microbiology
STMA – Active Member

Challenges with Antimicrobial Drug Sponsors

* Phase 3 clinical strains cannot be used for AST device manufacturers clinical trial studies
* Long lead times for Material Transfer Agreements (MTA) to obtain antimicrobial agents and bacterial strains.
* Modification of formulation/process changes or frozen method by antimicrobial drug sponsor during AST device development or clinical trial
  * Invalidates data
  * Causes rework
* Antimicrobial agent could get discontinued
  * Wasted time and effort

Challenges with Antimicrobial Drug Sponsors

* Antimicrobial agent could be sold to another sponsor
  * New MTA and other new contracts need to be created

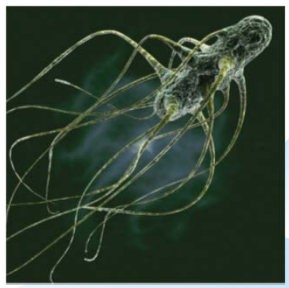
Recent positive changes:

* STMA has good working relationship with many antimicrobial drug sponsors
  * new agents presented at STMA meetings
* Antimicrobial drug sponsors creating organism sets for new agents

Challenges with FDA Approval Process

510K Criteria

* Inability to submit 510K until NDA approved
* Breakpoints and indicated organism, last part of the NDA reviewed by CDER
  * Can't finalize AST device clinical trial data until breakpoint and indications finalized in NDA
* Limiting organisms tested in 510K to antimicrobial package insert indicated organisms
* Acceptance criteria – does not take into account inherent variability of the frozen reference method
  * If wild type microbial distribution is close to the breakpoint – issue exacerbated



Frozen Reference Variability
C. freundii and Cefotaxime
(Breakpoints 1/2/4)

***C. freundii* 42086**

Incubation Temperature:		35°C		34°C		34°C		34°C		34°C		36°C		36°C		36°C		36°C	
Inoculum Plate Age:		20 hr		18 hr		18 hr		24 hr		24 hr		18 hr		18 hr		24 hr		24 hr	
Inoculum Density:		0.08		0.06		0.10		0.06		0.10		0.06		0.10		0.06		0.10	
MIC	Sum	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2
0.25	33	1	2	2	4	1	3	2	6		3	2	3		1	1	2		
0.5	134	9	8	8	6	7	4	8	4	9	6	8	7	9	8	7	6	10	10
1	5						1			1	1				1		1		
2	4					1	1							1		1			
4	0																		
8	2															1	1		

- ✓ Testing done on CLSI frozen reference panels
- ✓ Variables within CLSI reference method parameters described in M7-A10
- ✓ CLSI Ad Hoc working group looked at parameter refinement – determined further refinement could not be done

Challenges with FDA Approval Process

510K Criteria - Continued

* Study design requirement does not allow for the variability of the reference method
  * Current guidance does not allow for range of MIC results for a single isolate
  * Current guidance does not allow for repeat testing
    * ISO 20776-2, 5.2.7 Discrepancy resolution testing
* Data collection required for all inoculation methods and read methods for all phases of the study – separate 510K per procedural options

Challenges with FDA Approval Process

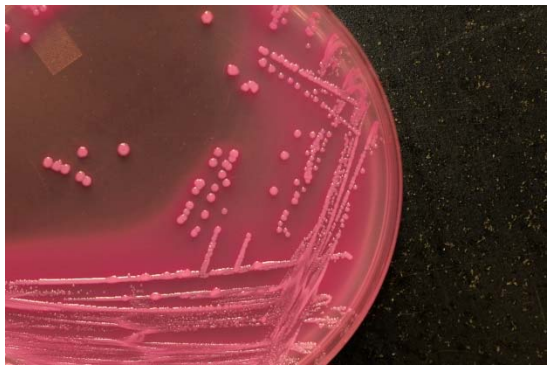
510K Criteria - Continued

- Testing requirements have expanded over time which results in longer clinical trials
  - Restricted organism testing
- Items missing in the current guidance document but are now expected criteria at time of review
  - Minimum numbers per species
  - Restriction of stock isolates to less than three years of age
  - More data on scale (hard with new agents)
  - Application of acceptance criteria to each organism group vs overall performance
  - Molecular characterization

Challenges with FDA Approval Process

510K Criteria - Continued

* Expanded data requirements for breakpoint changes now requiring extensive clinical trial testing
* Fresh isolates being less than 7 days – restricts availability of strains
  * Hospital workflow
  * Limits use of reference laboratories
  * Species not frequently encountered
  * New agents isolates are often susceptible



Challenges with FDA Approval Process

* AST device manufacturers need to balance demand for clinical trials
  * New antimicrobials agents
  * New breakpoints for existing antimicrobial agents
  * Agents targeting significant public health threat
  * Customer demand for new antimicrobial agent
* New antimicrobials typically have few resistant organisms, therefore it is difficult to show performance over the MIC therapeutic range
  * Limited by package insert organisms
* Fast-track status only available for antimicrobial drug sponsors via Generating Antibiotic Incentives Now (GAIN) Act

Antimicrobial Susceptibility Testing: Suggestions Going Forward

Bill Brasso and Darcie (Roe) Carpenter

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Suggestions moving forward

- Continue meetings like today
- Coordinated clinical development
  - Antimicrobial drug sponsors to provide AST device manufacturers access to clinical trial isolates and FDA to allow these isolates to be used as significant part of AST device manufacturers data collection
  - Same organisms would be used to for establishing breakpoint, drug approval and AST device manufacturer systems
- Have antimicrobial drug sponsors create a challenge set of isolates (subset of Phase 3 study isolates) for use as AST device test set
  - FDA involved – approve challenge set
  - Make large enough to replace efficacy and challenge testing under current guidance
  - Challenge – how to make available?
- Mechanism for concurrent review of drug and AST device manufacturers systems
  - Challenge – if breakpoints or indications change during review process – would require reprocessing of data from AST device clinical trial data if have to match

Suggestions moving forward

Revise Current FDA Guidance – Class II Special Controls Guidance Document: Antimicrobial Susceptibility Testing (AST) System (August 28,2009)

- **Fast Track opportunities for AST device manufacturers clinical trial and requirements**
- **Allow reporting of MICs for organisms not in the product insert**
- **Allow approval of MICs reporting when breakpoints are not available**
- **Revise requirements for removal of limitations**
- **Revise requirements for breakpoint changes**
- **Allow for replicate testing (compare to range rather than mode)**
  - **Takes into account the variability of the reference method**

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Suggestions moving forward

Revise Current FDA Guidance – Class II Special Controls Guidance Document: Antimicrobial Susceptibility Testing (AST) System (August 28,2009) - continued

- Allow for repeat testing
- Reduce data requirements
  - Primary method for all phases of the study
  - Alternate inoculation and read methods – Internal validation only, and/or Challenge data review
- Allow CLSI QC ranges in addition to FDA QC ranges in submissions
- Use the CDC/FDA Antibiotic Resistance (AR) Bank – to provide challenge sets for data requirement for breakpoint changes which require no product design change

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Suggestions moving forward

Revise Draft FDA Guidance – Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Device (September 21,2016)

* Drug sponsor and AST device manufacturer can meet together with the FDA
  * Logistics
    * **Results in five different meetings?**
    * **A sponsor/independent representing all AST device manufacturer?**
    * **One meeting for all AST device manufacturers?**
* Does this change when AST device manufacturers can submit 510K?
* What happens for break point changes? Not addressed in this document.

* Test Case – New process - Melinta Therapeutics has volunteered with Delafloxacin

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Suggestions moving forward

* **Support - H.R. 6 - 21st Century Cures Act**
* **PURPOSE.—It is the purpose of this Act to improve the current regulatory structure related to public notice of the susceptibility test interpretive criteria and to allow for greater flexibility for the Food and Drug Administration in carrying out its duty to update susceptibility test interpretive criteria for drugs and devices used to determine the susceptibility of organisms to that drug or device.**

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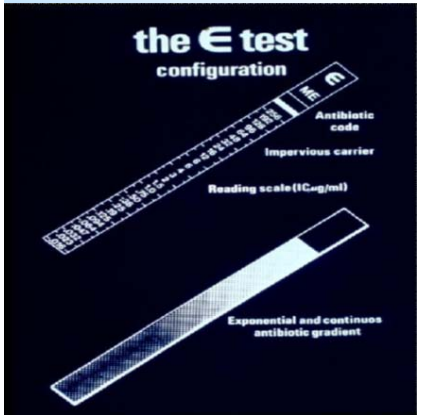
Conclusions

* **The AST device submission process has had small changes over time – Resulting in significant changes to AST device clinical trials**
* **The current process can be improved**
* **More coordination between antimicrobial drug sponsor, FDA and AST device manufacturers is vital**
* **Changes will require implementation of the draft guidance AND revisions to existing AST device guidance**
* **Fast track process has worked for antimicrobial drug sponsor**
  * **Fast track process would provide assurance of quality AST device results while providing accurate commercial AST methods to clinical labs sooner**
* **Current process impact:**
  * **Limit use of new antimicrobial drugs without AST test**
    * **Result - not on local formulary**
  * **Patient are currently being treated with new antimicrobial agents without an approved diagnostic test**

Thank you!!



Questions?