Antimicrobial Susceptibility Test Devices-

Disk (Disc) Update

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FDA-Industry IVD Roundtable
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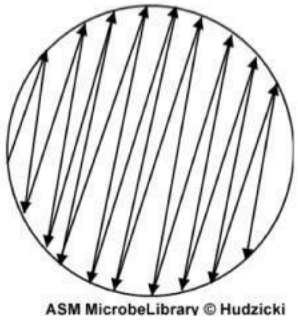
Outline

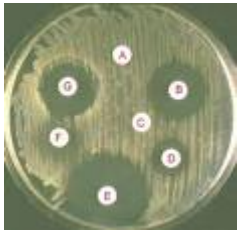
- Background
  - Disks-What are they?
  - Regulation, Classification, Review and Oversight
- Concerns
- FDA/Stakeholders Interactions
  - Point/Counter-Point
  - Accomplishments
- Studies and Future Direction

Bauer-Kirby-Sherris-Turck Test (AKA: Kirby-Bauer)

- Bauer, AW; Kirby, WM; Sherris, JC; Turck, M (April 1966). "Antibiotic susceptibility testing by a standardized single disk method". American journal of clinical pathology. 45 (4): 493–6. PMID 5325707.
- Bauer, AW; Kirby, WM; Sherris, JC; Turck, M (March 1966). "Antibiotic susceptibility testing by a standardized single disk method". Technical bulletin of the Registry of Medical Technologists. 36 (3): 49–52. PMID 5908210

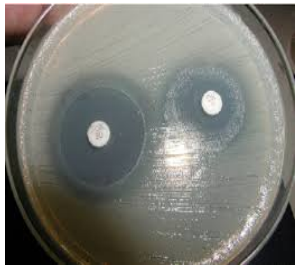
- From 1966 onward:
- Standard procedure
- Standard inoculum
- Standard culture media
- Standard concentration
- Established quality control strains and parameters
- Established/Approved interpretative criteria =S, I, R, to correlate to MIC
- Popular, easy to use
- Often first tests available for newly approved drugs
- Provide valuable results that impact patient management



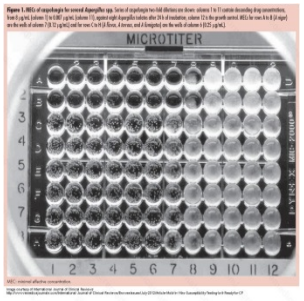


https://www.youtube.com/watch?v=sx1uDYSfINA

Antimicrobial Susceptibility Test (AST) Methods Landscape



- Diffusion Methods
  - Disk (zone, qualitative, surrogate)
  - Etest Gradient Agar Diffusion (MIC)
- Dilution Methods
  - Minimum Inhibitory Concentrations (MIC)
  - Interpretive criteria (the world of S, I, R)
  - Manual or automated
  - Novel devices
- Resistance Detection
  - Growth-Based, Culture Media
  - Culture-independent, Resistance Markers, Molecular (w/wo ID)
  - Future……



Regulations and Review of AST

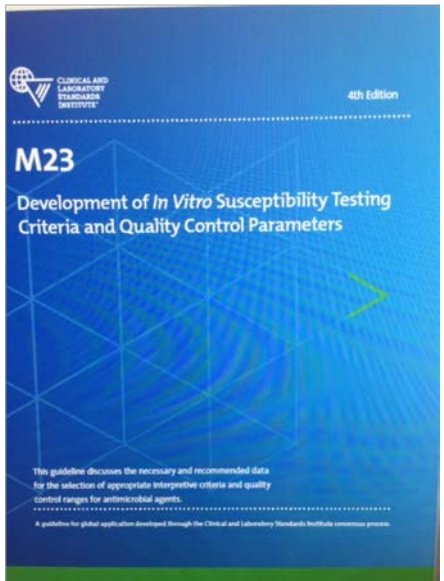
- AST devices
  - All are Class II, require review and 510(k) premarket notification (i.e., non-exempt)
  - 510(k) MDUFA timelines
  - Regulations:
    - 21 CFR 866.1640 and 21 CFR 866.1645
    - multiple product codes depending on device type
  - Studies, data requirements and evaluation criteria:
    - Several CDER and CDRH guidance documents
    - Several recognized CLSI standards and guidelines

Disk Diffusion Review/Clearance

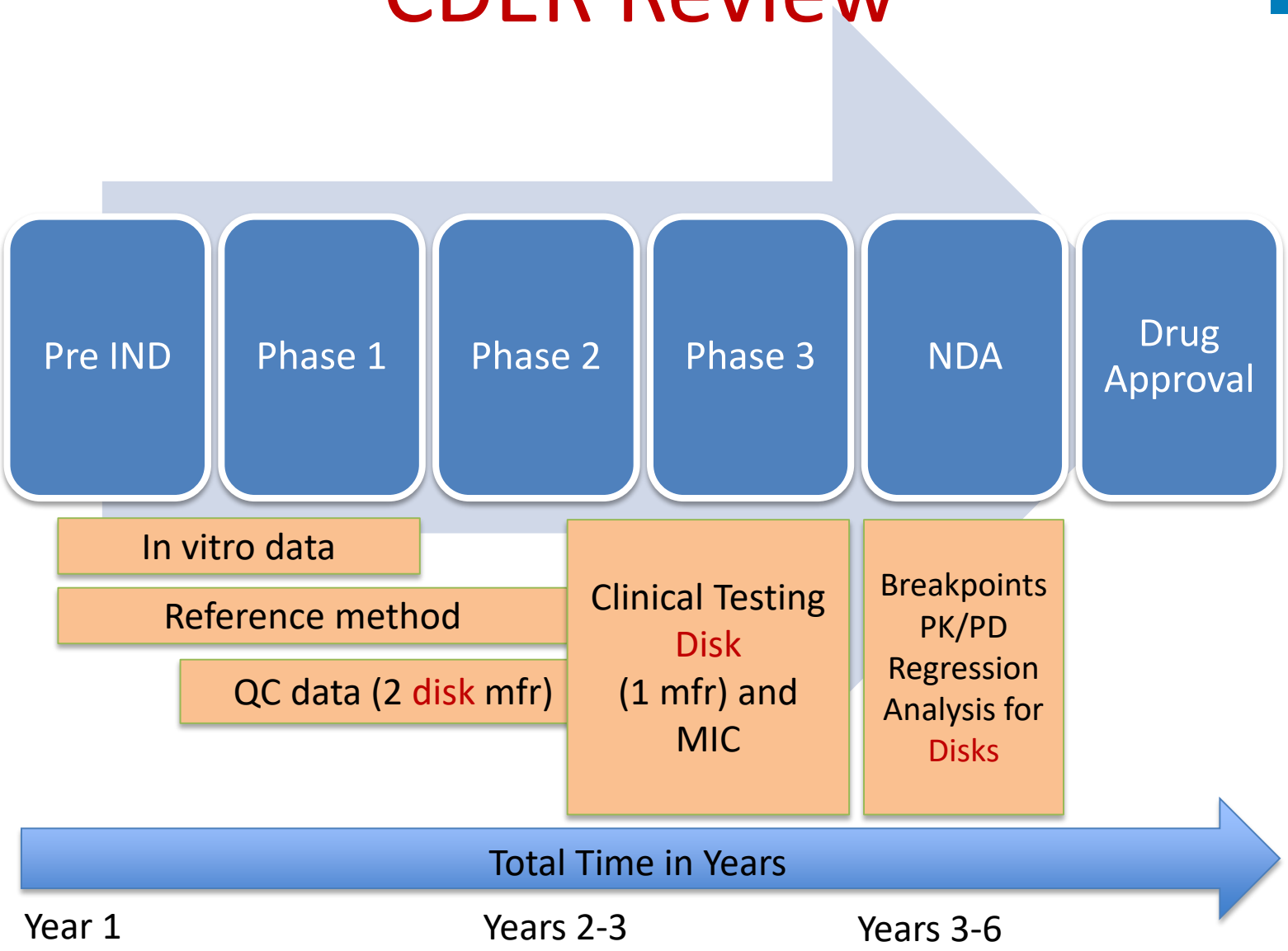
- Disk brands utilized as part of drug evaluation and included in the data evaluated in the NDA can be cleared shortly after drug approval based on the NDA data.
- 510(k)s for disk brands not utilized in the drug evaluation have historically been submitted and cleared through a "labeling review" without submission of data describing their performance.
  - Limited number of disk manufacturers
  - Cross communication between FDA Centers

Disk Diffusion Review/Clearance

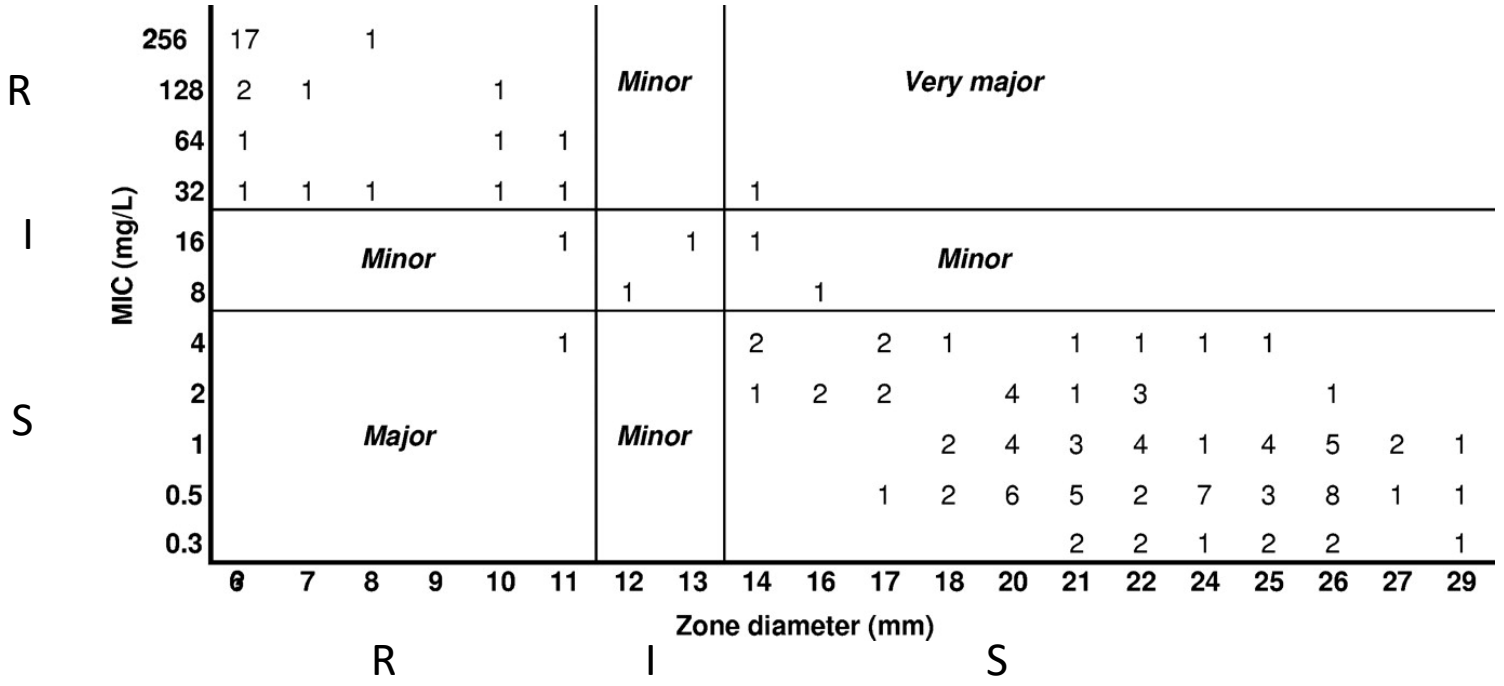
- Disks (brands) data reviewed during drug evaluation
  - Disk content/stability
  - Quality control isolates and zone diameters established
  - FDA Guidance and CLSI guidelines (M-02,M-23) studies
  - Correlation between zone diameters and MICs
  - Isolate testing to determine drug efficacy



CDER Review


Pre IND
Phase 1
Phase 2
Phase 3
NDA
Drug Approval
In vitro data
Reference method
QC data (2 disk mfr)
Clinical Testing
Disk
(1 mfr) and
MIC
Breakpoints
PK/PD
Regression
Analysis for
Disks
Total Time in Years
Year 1
Years 2-3
Years 3-6

"Scattergram" of MICs versus zone diameters



Turnidge, J. et al. 2007. Clin. Microbiol. Rev. 20(3):391-408

Drug – year of approval	Months: Drug Approval to Disk Clearance	Device Man.	Cleared based on			
			QC and Breakpoint Data from NDA	QC and Clinical Data from NDA	QC Data Only from NDA	New Study to CDRH
Doripenem 2007	3	A	X			
	7	B	X			
Ceftaroline 2010	2	A	X			
	12	B	X			
Ceft/Tazo 2014	11	A		X		
Ceftz/Avi 2015	9	A		X		
	8	B			X	
Delaflox 2017	2	A		X		
Mero/Vabor 2017	2	A		X		
	14	C				X 2018
Plazomicin 2018	< 1	A		X		
Eravacycline 2018	1	A		X		

Disk Diffusion Review/Clearance

- Disks (brands) data reviewed during drug evaluation
  - Disk content/Stability
  - Quality control isolates and zone diameters established
  - FDA Guidance and CLSI guidelines (M-23) studies
  - Correlation between zone diameters and MICs
  - Isolate testing to determine drug efficacy
- Disks (brands) data NOT reviewed during drug evaluation

FDA Concerns

1. Performance (Safety and Effectiveness) of new disks
   - Class II
   - 510(k) needed for new brand
2. Indicators of Performance Issues
   - Recalls
   - Literature
   - Variability of disk quality
   - Data from CLSI (M23 Tier 2 QC Study)
   - Disk issues observed during NDA

FDA Concern 1

- Disks are Class II Devices
- In a 510(k) paradigm, performance data are needed to demonstrate substantial equivalence.
- The principles of safety and effectiveness underpin the substantial equivalence determination in every 510(k) review.
- Newly developed antimicrobial agents are sometimes used for treating the sickest patients.

FDA Concern-2

Even though the drug developer defines drug component specifications, there is evidence that disks from various manufacturers can have different quality and may lead to variable results.

- Recent Class 2 Recalls
  - 11 recalls in past 5 years
- Recent literature and scientific data [a]
- Indicators of variability of disk quality [b]
  - Evaluation of results with QC strains with disks from 9 manufacturers
  - Some disks for some drugs completely out of range
- Disk data from a single manufacturer during M23 Tier 2 QC studies [c]
  - Out of range disk results (high and low) from prospective range
- Specific Disk issues observed during NDA
  - Disk content, disk stability and occurrence of very major errors as compared to BMD

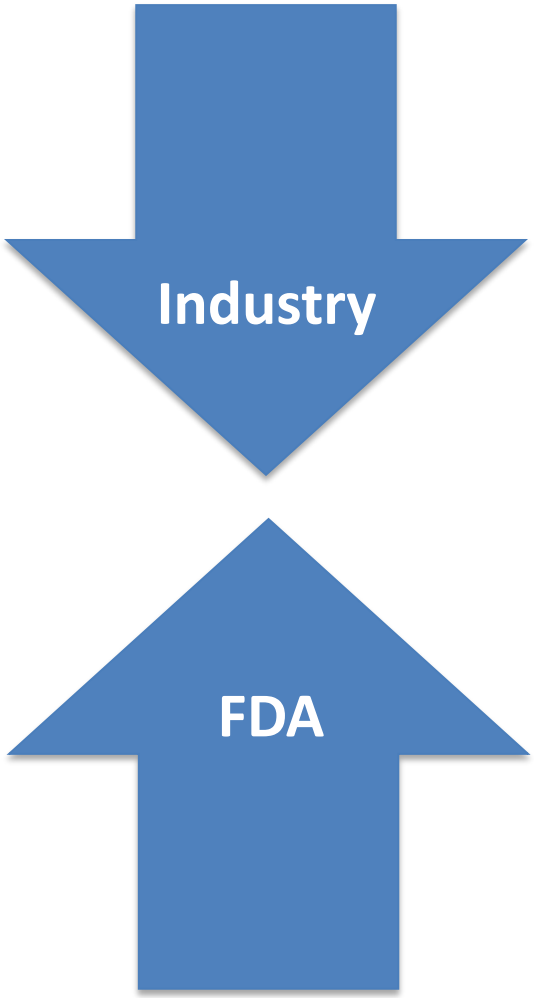
[a] Cohen, D and G. Swift. 2013. Laboratories and Regulator Misled over Antibiotic Susceptibility Test Discs. BMJ. 346:f837

[b] http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/Warnings/Summary_Evaluation_of_selected_disks_from_nine_manufacturers_Update_June_2016.pdf

[c] CLSI AST Subcommittee

Point/Counter-point on Disk Review

Point/Counter-point on Disk Review



1. Additional studies will delay the availability of AST disks
2. Disks evaluated during the NDA are not required to perform reproducibility studies
3. Disks are made to the same specifications, so performance should be equal

1. Disk included in the NDA will be available shortly after drug approval. Coordinated Development allows for early interaction on studies
2. Disk evaluated during the NDA are included in extensive studies with clinical isolates and in comparison to broth microdilution
3. Scientific Evidence suggest disk manufacture can vary and data is needed to support clearance

"New"
Disk Study Data for CDRH Review

1. Sites
2. Isolates
3. Reproducibility
4. Reference Method
5. Quality Control

1. Sites

FDA Original	FDA Revised
1 External Site	1 Internal Site
3 Independent Operators	
Even distribution of isolates to mimic 3 sites	
	Study design to avoid bias in zone interpretation by manual read

2. Isolates

FDA Original	FDA Revised
300 clinical isolates (75 contemporary, 275 stock)	For new agents: 300 indicated organisms (no requirement for contemporary or stock)
← 75 additional Challenge with known resistance mechanisms →	
	For targeted species, minimum of 100 strains
	Organisms can be obtained from any source including from the drug company

3. Reproducibility

FDA Original	FDA Revised
1 external site	1 site, can be internal
2 operators with isolates evenly distributed to mimic testing at 3 sites	3 readers with isolates evenly distributed to mimic testing at 3 sites (blinded)
10 organisms for 3 days	15 organisms for 3 days
← 2 disk lots →	
2 media lots	1 cleared media lot
240 data points	270 data points

4. Reference Method

FDA Original	FDA Revised
Compare to MIC data from the NDA or Compare to another cleared disk	
	Organisms from any source (see isolates)

No Cleared Disk Available

- Reference = MIC

Cleared Disk Available

- Reference = MIC or
- Comparator = Cleared Disk

5. Quality Control

FDA Original	FDA Revised
Performed each day of testing	
At least 60 replicates for each QC isolate	
Different media lots	1 media lot
Different disk lots	2 disk lots

Take Home Message…

- Disk brands included in the NDA may be cleared "soon" after drug approval with data collected during the drug study
- Disk brands not included in the NDA need to provide results of comparative studies performed with their disks
  - New Clearance (9/27/2018)-See Decision Summary:
    - Meropenem/Vaborbactam Antimicrobial Test Disk (https://www.accessdata.fda.gov/cdrh_docs/reviews/K181975.pdf)

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U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?


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