FDA Perspective and Experience with Review of AST Device Applications

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Antimicrobial Susceptibility and Resistance:
Addressing Challenges of Diagnostic Devices Workshop

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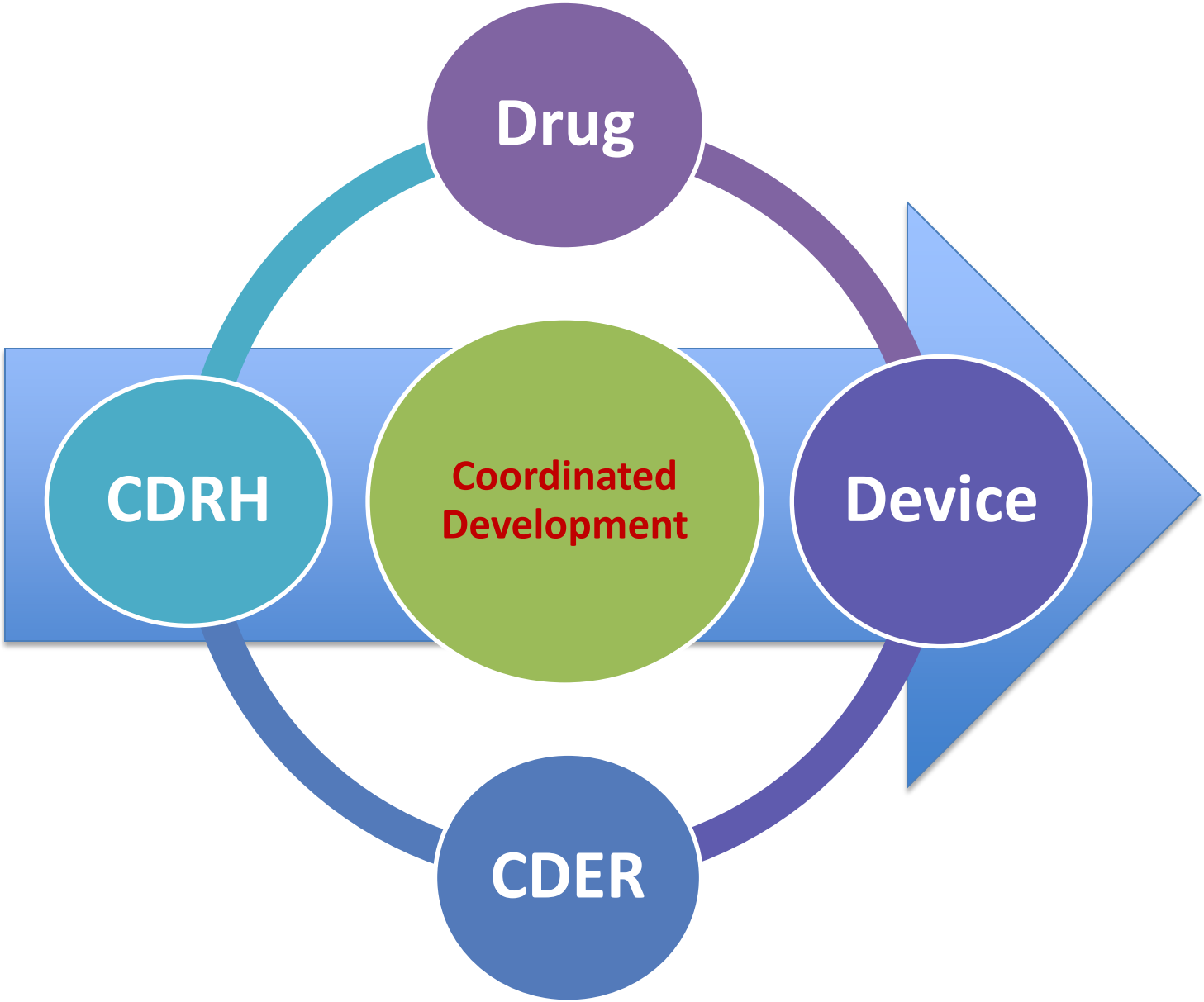
Disclaimer

- The contents of this presentation are for discussion and summary purposes only and do not describe the full extent of requirements applicable to devices under discussion in this workshop. Please see the Federal Food, Drug, and Cosmetic Act and Chapter I of Title 21 of the Code of Federal Regulations (CFR), especially Subchapter H that has requirements specific to medical devices

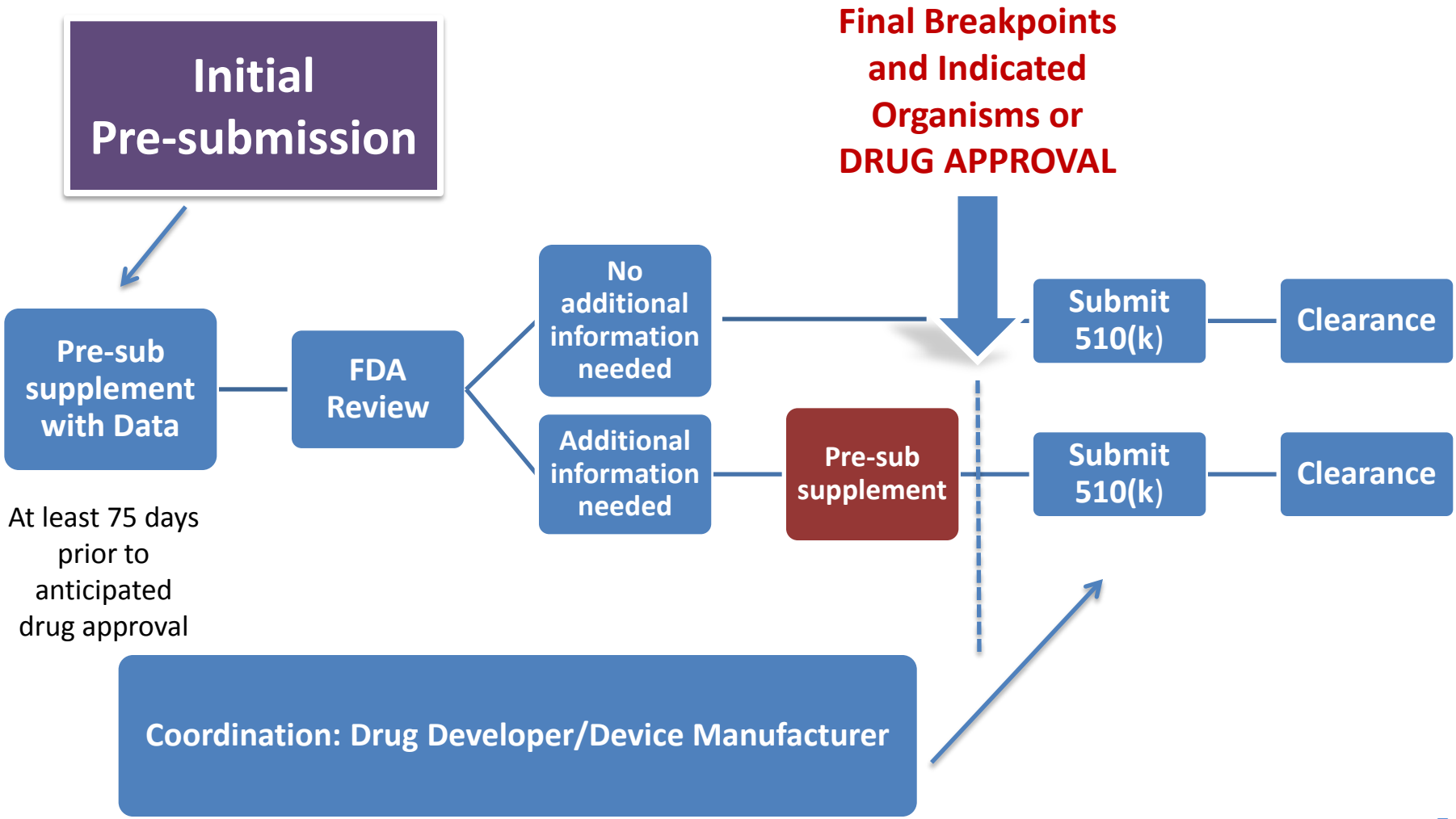
Outline

- Coordinated Development
- AST device review and experience with reference broth microdilution (BMD)
- AST device review challenges and solutions

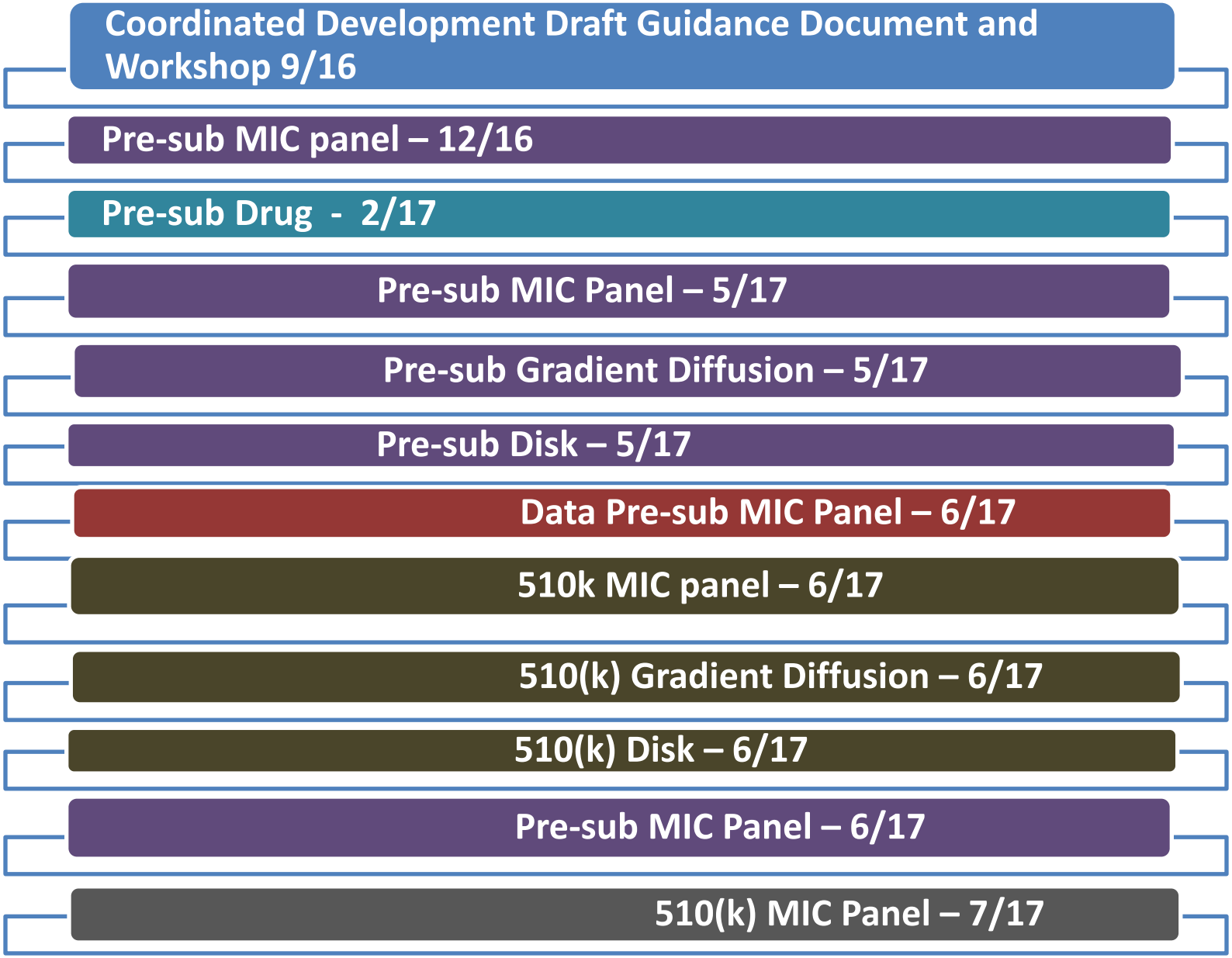


Improved Patient Care

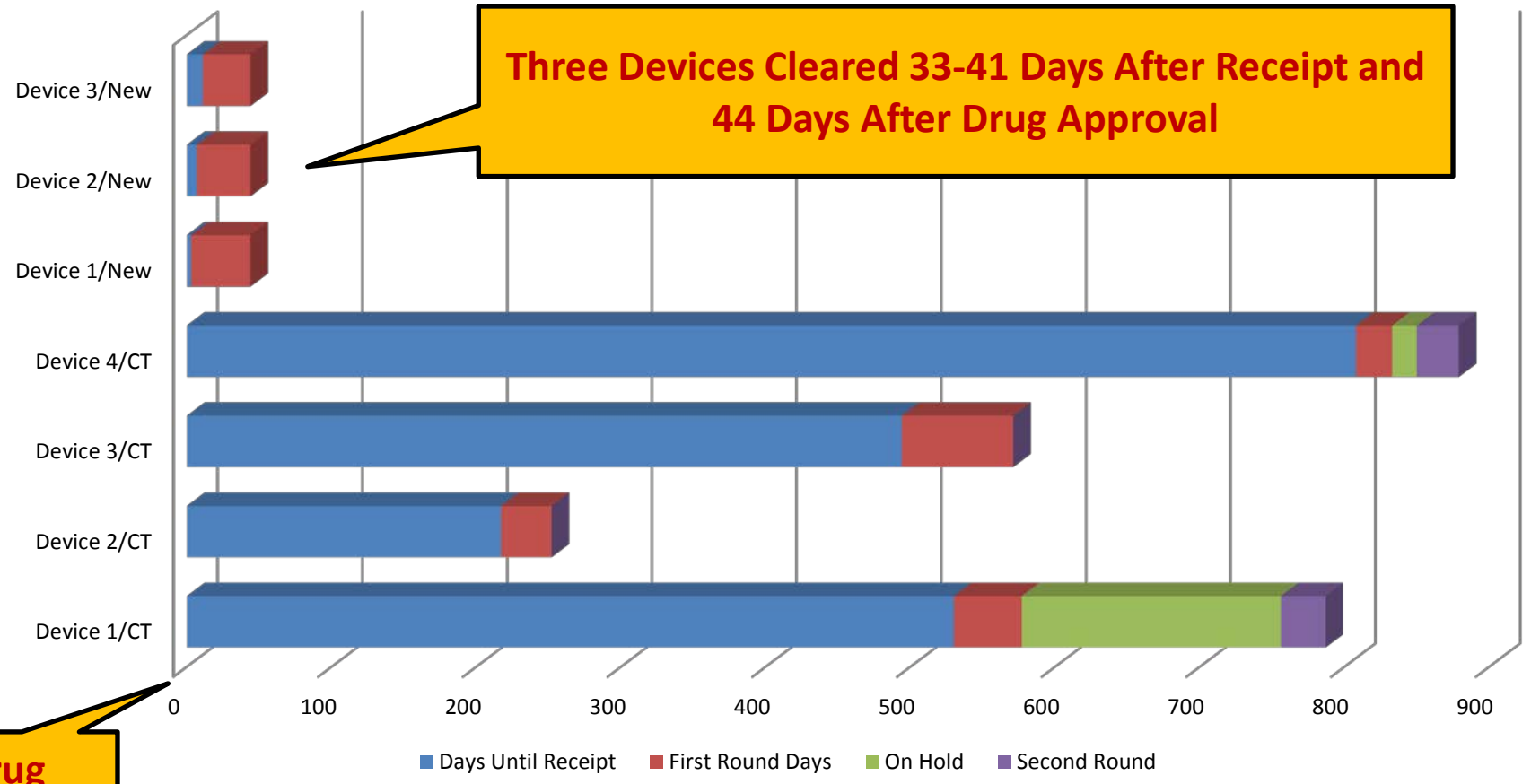
Coordinated Development Submission Process



Activities: September 2016 to Date



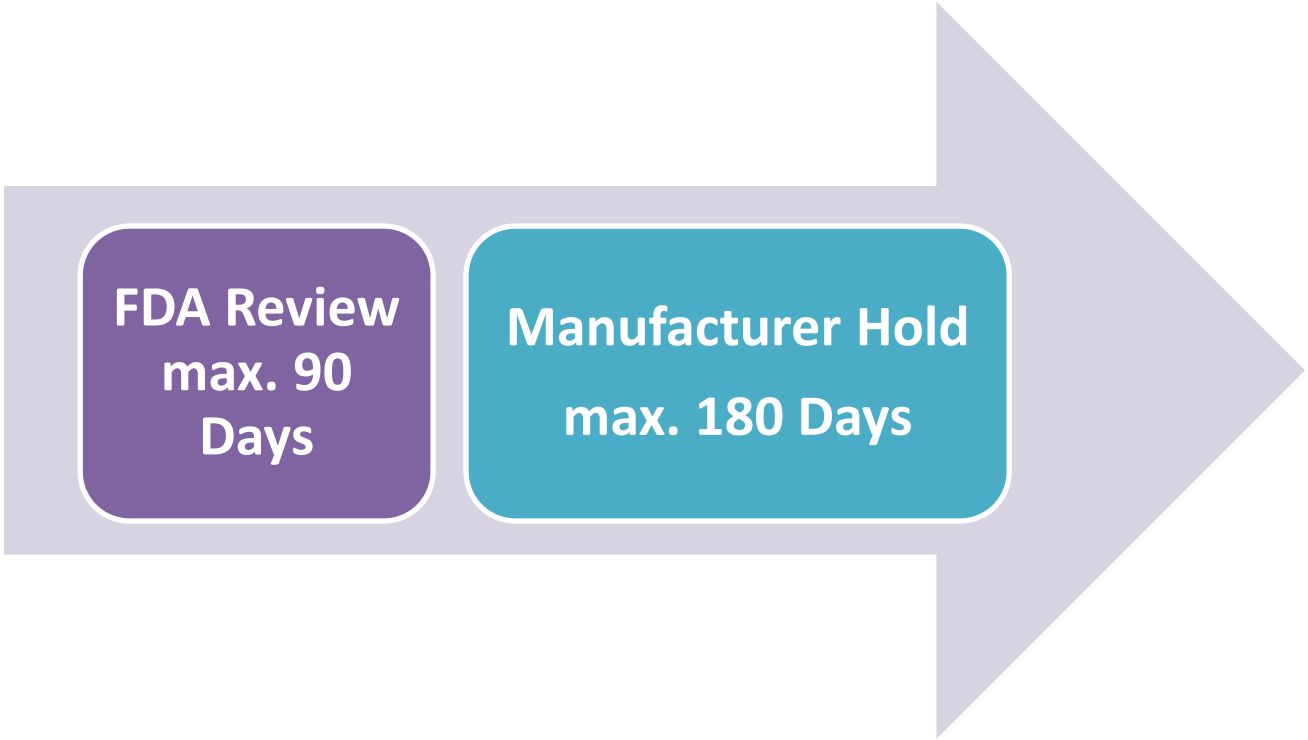
Days Until 510(k) Clearance After Drug Approval



Drug Approved

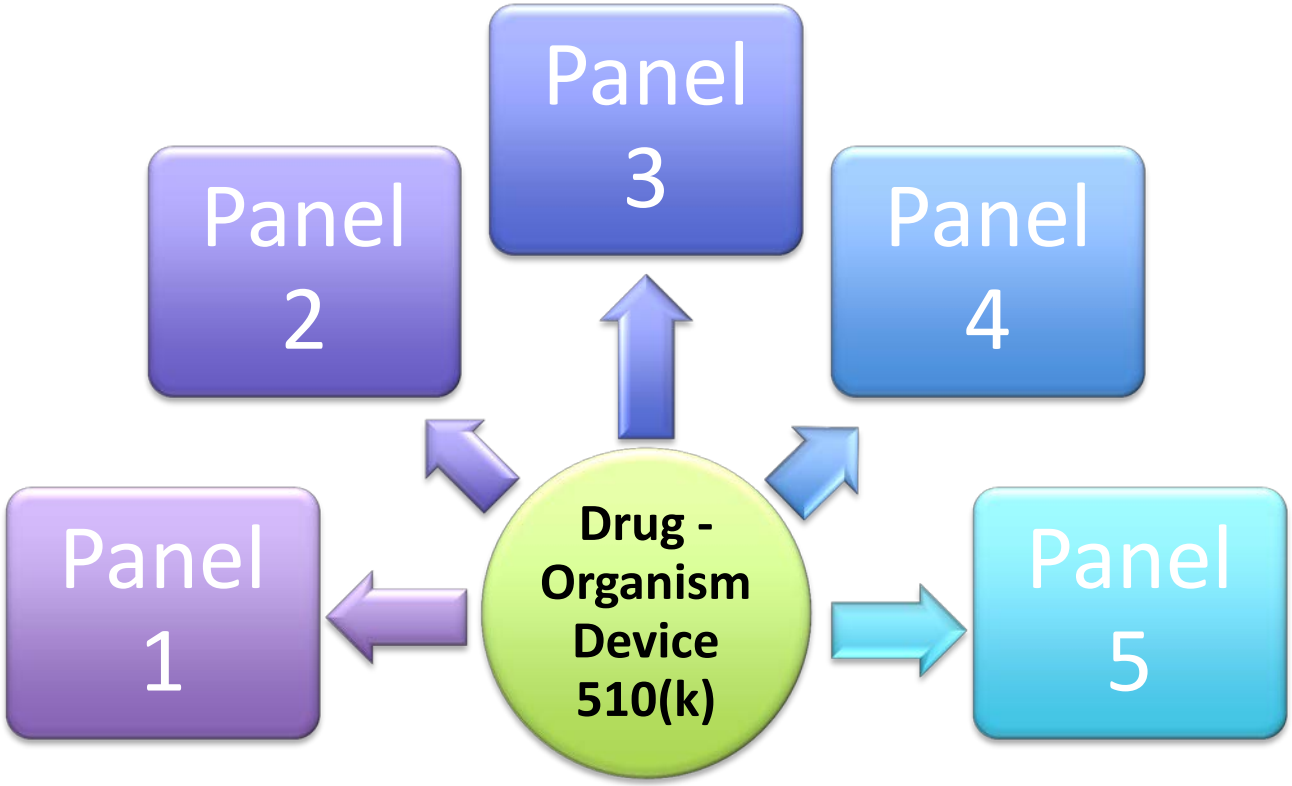
FDA Data On File

The 510(k) MDUFA Timeline



Total Max Days: 270

From One 510(k) Come Many



Clearance for a drug/organism combination allows incorporation of that drug/organism combination on any panel type manufactured by the sponsor.

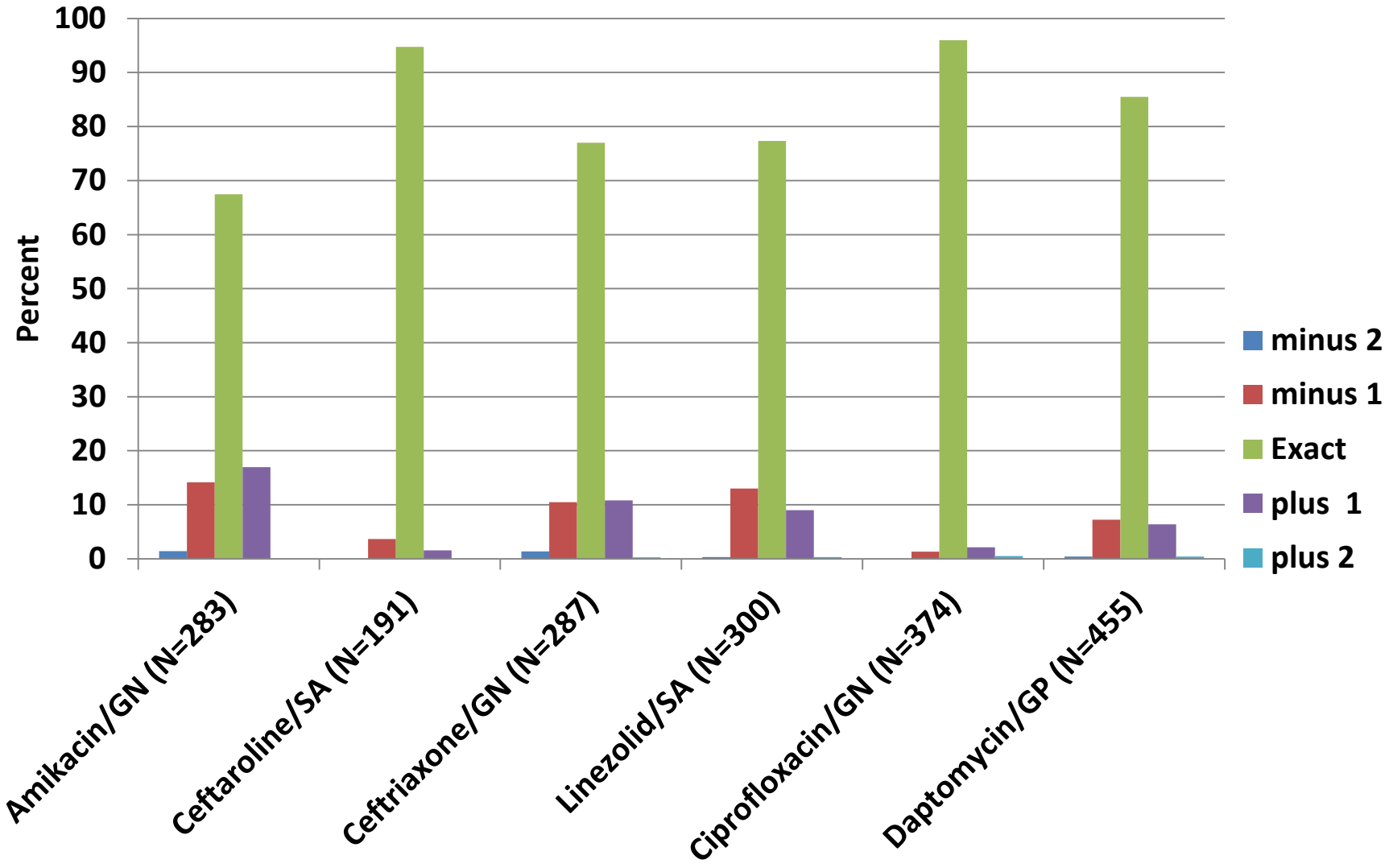
Assessment of BMD Variability

- Reproducibility of the ref. BMD method is addressed in CLSI M23

- Assessment of ref. BMD variability is important when planning a new AST device for clearance
  - Consider replicate testing of the reference method

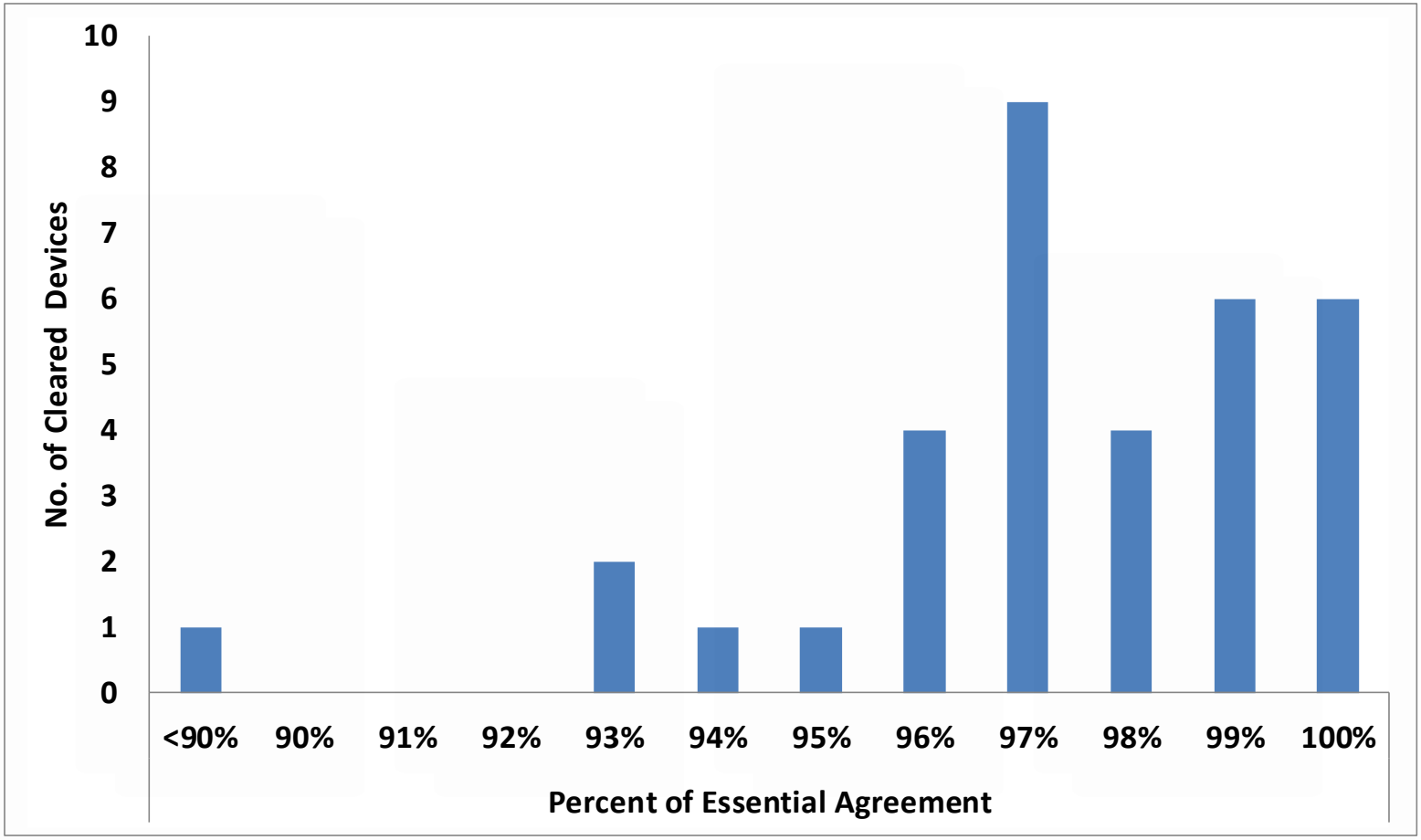
- Interactions between drug developers and device manufacturers are critical in understanding ref. BMD variability

Results of Duplicate BMD Testing



FDA Data On File

High % Essential Agreement: Data From 34 Cleared Devices, 2014-2017



FDA Data On File

Repeat Testing of Ref. BMD

- Testing multiple replicate of ref. BMD can be used as part of the study plan
- Discordant analysis results cannot be used to change original performance
- Repeat testing may be appropriate in cases where there was evidence of a technical error
  - The data analysis is conducted using the repeat results

AST Device Review Requirements, Challenges, and Solutions

- Species spectrum and number of isolates
- Importance of evaluating CA, MAJ/VMJ errors
  - Adjustment of errors; Drugs without “I” BP
- Importance of “on-scale” MICs
- Evaluation of bias/trending
- Submission scenarios when BPs change

Species Spectrum and Number of Isolates

- All claimed species should be evaluated
- Isolates should **predominantly** be from the list of organisms for which the drug has been shown to be active both in vitro and in clinical infections
- FDA allows inclusion of isolates representing species from the “in vitro only” list in the FDA drug label

Isolates for AST Testing

Isolate Type	Total Number	No. per site	Time from isolation	Value
Fresh	75	25	7 days from isolation	• Real world conditions • Not preselected
Recent	75	25	Up to one year from isolation	• On-scale organisms with MICs near the breakpoints • Organisms with currently circulating resistance mechanisms • Because organisms to be tested are pre-selected, it is possible that isolates with better performance are presented in results of device evaluation
Stock	150	50	Up to three years from isolation	
Challenge	75	75 (one site)	Not specified	
Total	375	-	-	

Importance of Evaluating Categorical Agreement/Errors

- Evaluation of category agreement is implied in the regulations regarding AST devices (866.1640 and 866.1645):
  - Results from AST tests are "*used to determine the antimicrobial agent of choice to treat bacterial disease*"
  - Test reporting must provide the interpretive criteria users should use for each antimicrobial agent

- The interpretive category (S,I,R) is a component of device labelling that is provided in patient report
  - Physicians and HCP are familiar with S,I,R results in the patient reports

Adjustment of Errors/No "I" BP

		Reference				
		Susceptible			Resistant	
		0.5	1	2	4	>4
Device	0.5					
	1	12	8	3		
	2	1			11	9
	4		1			7
	>4			1	2	287
	Total	13	9	4	13	303

Very major errors

In EA

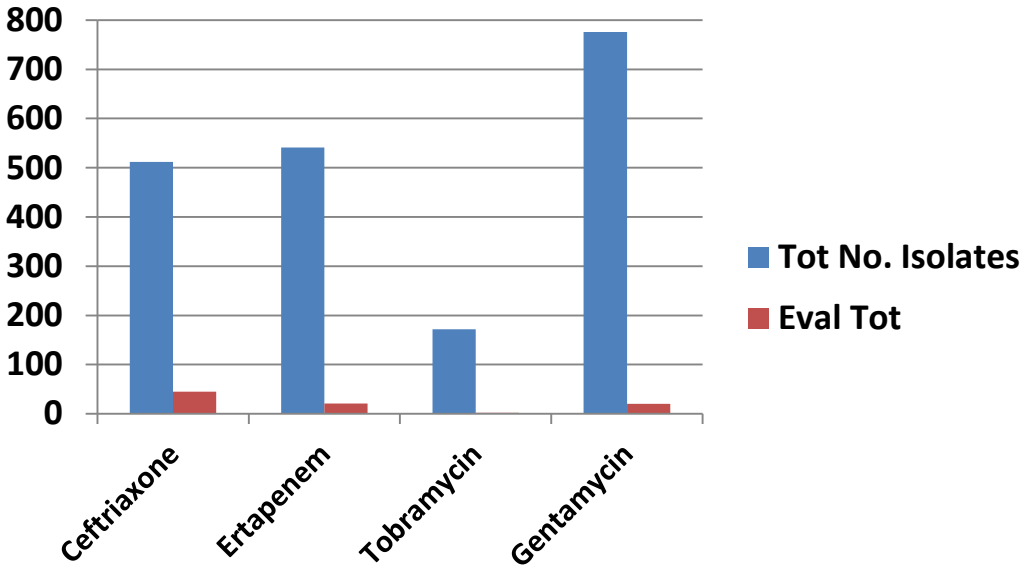
Not in EA

Major errors

Not in EA

Total Resistant = 316
No. vmj errors = 20 (6.3%)
No. vmj in EA = 11
Adjusted vmj = 9 (2.8%)*
*acceptable per Table 8 AST Special Controls Document

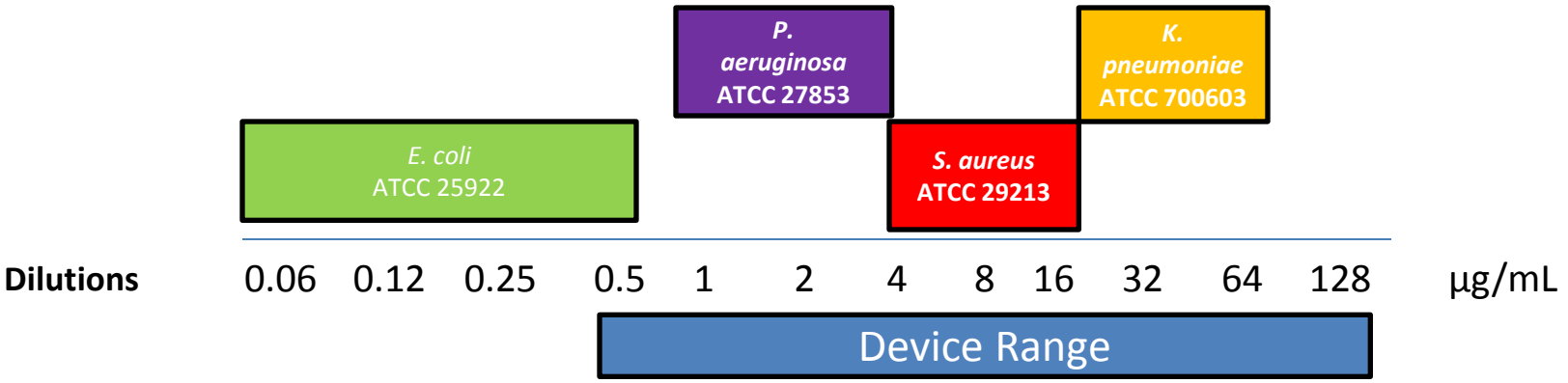
Examples of Cleared Devices Evaluable "On-Scale" Results



- AST Special Controls Guidance: "*The new device and the reference panel should include a sufficient number of two-fold dilutions around the S and R thresholds*"
- With limited evaluable data, FDA is unable to determine true EA
- FDA may request additional testing and/or a footnote in labeling

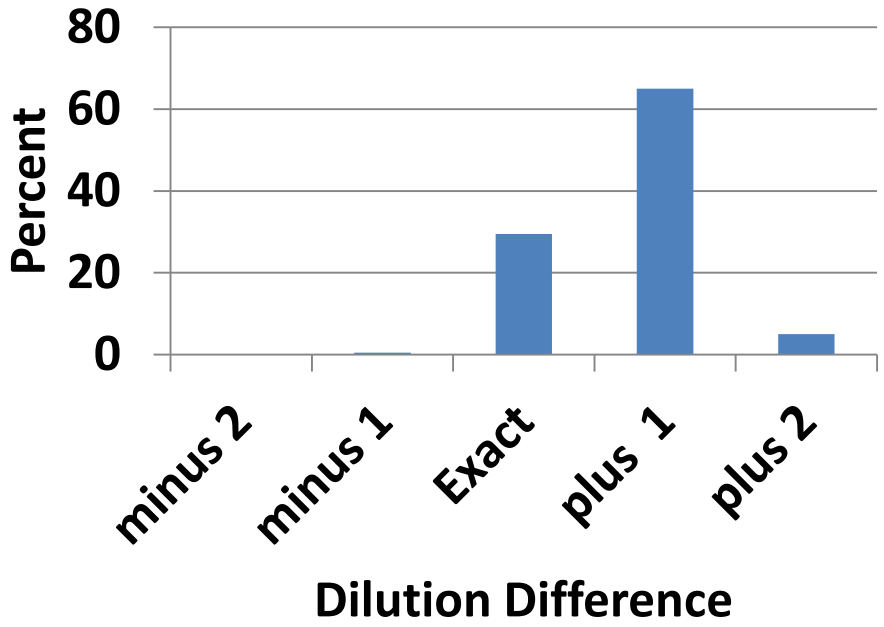
FDA Data On File

Example of On-scale and Off-Scale QC Ranges-Ceftazidime



- There should be at least one QC organism that will produce on-scale results for each antimicrobial/media
- Concentration/reporting ranges on the panel should allow on-scale evaluation of the selected QC strains
  - Some device designs may not fully cover the range
  - Assess the need to validate new strain (e.g. CLSI M23-type studies)

MIC Trending Analysis



- FDA AST Guidance Recommends Evaluation of Trending to assess impact on interpretation of patient results
- FDA requests the following footnote in labeling:

  "The device MIC values tended to be higher by one or more dilution compared to the reference method"

Different Scenarios When Breakpoints Change

1. Previously collected data exists that includes resistant organisms and new breakpoints are covered in drug concentrations on the device
   - No device modifications needed
     - Recalculate performance with new breakpoints
     - If performance acceptable submit
     - If performance unacceptable – conduct a new study
   - Device modifications needed
     - Conduct a new study
2. Previously collected data exists that includes resistant organisms and new breakpoints are not covered in the drug concentrations on the device
   - Conduct a new study

Future Direction

- Implementation of 21st Century Cures Act
  - Implications for AST submissions and reviews
- Address comments on Coordinated Development Guidance with the goal to finalize
- Interacting with STMA and other stakeholders
  - FDA is planning a Frequently Asked Questions Guidance to address common issues and streamline submissions and reviews

Thank You!