Coordinated development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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FDA-Industry IVD Roundtable
November 29, 2017

Outline

- The AST landscape and FDA review process
- Concerns over time lag between drug approval and AST device availability
- FDA initiatives on coordinated development and streamlining the process
- FDA and stakeholders interactions to date
  - Promising early experiences
- Resources

The Landscape

- Disk Diffusion Based Devices (Zone Diameter)
- Dilution Based Devices (MIC)
  - Agar Gradient Diffusion
  - Visually (Manually)-Read Panels
    - Multiple inoculation methods, organism/drug specific adaptations in media, etc.
  - Instrument-Read Panels/Automated, Algorithm-Driven Devices
    - Multiple inoculation methods, organism/drug specific adaptations in media, complex software, instruments, etc.
- Resistance Detection
  - Growth-Based, Culture Media
  - Culture-independent, Resistance Markers, Molecular (w/wo ID)
  - Future……

Guidance for Industry and FDA

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

Document issued on: August 28, 2009

This document updates the one of the same title, issued March 5, 2007

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Bacteriology Branch
Division of Microbiology Devices
Office of In Vitro Diagnostic Device (OIVD)
Evaluation and Safety

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080564.htm

Microbiology Information: Drug and AST Device

Antimicrobial Drug Timeline

IND/Phase I
- Basic microbiology profile
- R&D test methods evaluation
- Spectrum, MOA, Resistance, etc.

Phase II-III
- Drug-specific reference method established and used to generate data
- QC organisms and ranges established
- Disk potency studies
- Provisional MIC (and/or disk) BP

NDA Approval
- Microbiology data from clinical trials
- Conformation of MIC/Disk BP correlates and QC parameters
- CDER reviews and approves QC ranges and BP
- Disk diffusion information is included in drug labeling

AST Device TimeLine (Disk)*

R&D
- Drug manufacturer works with disk manufacturer (A, B, C, etc.) to produce IUO/RUO disks during phase II-III

510(K)
- Disk manufacturer (A, B, C, etc.) submits no new data to CDRH
- Application to CDRH, references drug label information
- CDRH consults with CDER to confirm that manufacturer data was provided and that it passes performance criteria
- Device FDA review is **90 days or less unless additional information/data is needed**

*Assuming no issues were identified to prevent development/approval of disk correlates

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NDA-Approval

- Microbiology data from clinical trials
- Conformation of MIC/Disk BP and QC parameters
- Information is included in drug labeling

AST Device TimeLine (MIC)

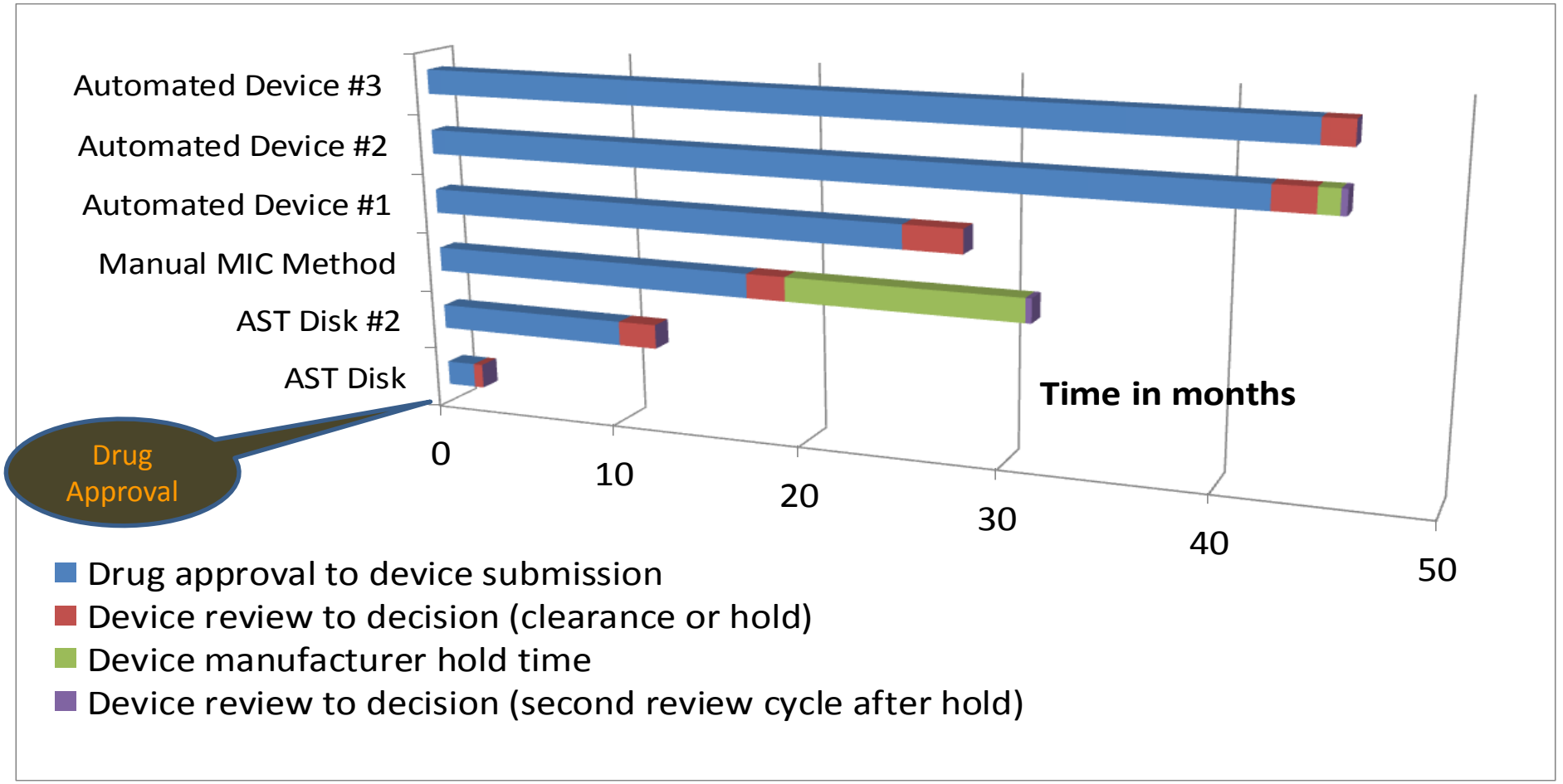
R&D

- Optional: Sponsor contacts FDA with questions using the presubmission process.
- Device manufacture conducts R&D
- Once final design is complete, formal studies are conducted

510(K)

- Sponsor submits a 510(K) and data in conformance with AST Special Controls Guidance,
- CDRH evaluates data in comparison to head to head reference method data
- MIC BP and indicated organisms must be as in drug label.
- Device FDA review is **90 days or less unless additional information/data is needed**

New Drug Approval to AST Device Clearance: Elapsed Time (Months)



Contains Nonbinding Recommendations

Draft – Not for Implementation

Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: September 21, 2016

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document that relate to CDRH, contact Ribhi Shawar, at 301-796-6698, or ribhi.shawar@fda.hhs.gov. For questions for CDER, contact Joseph Toerner at 301-796-1400, or joseph.toerner@fda.hhs.gov.

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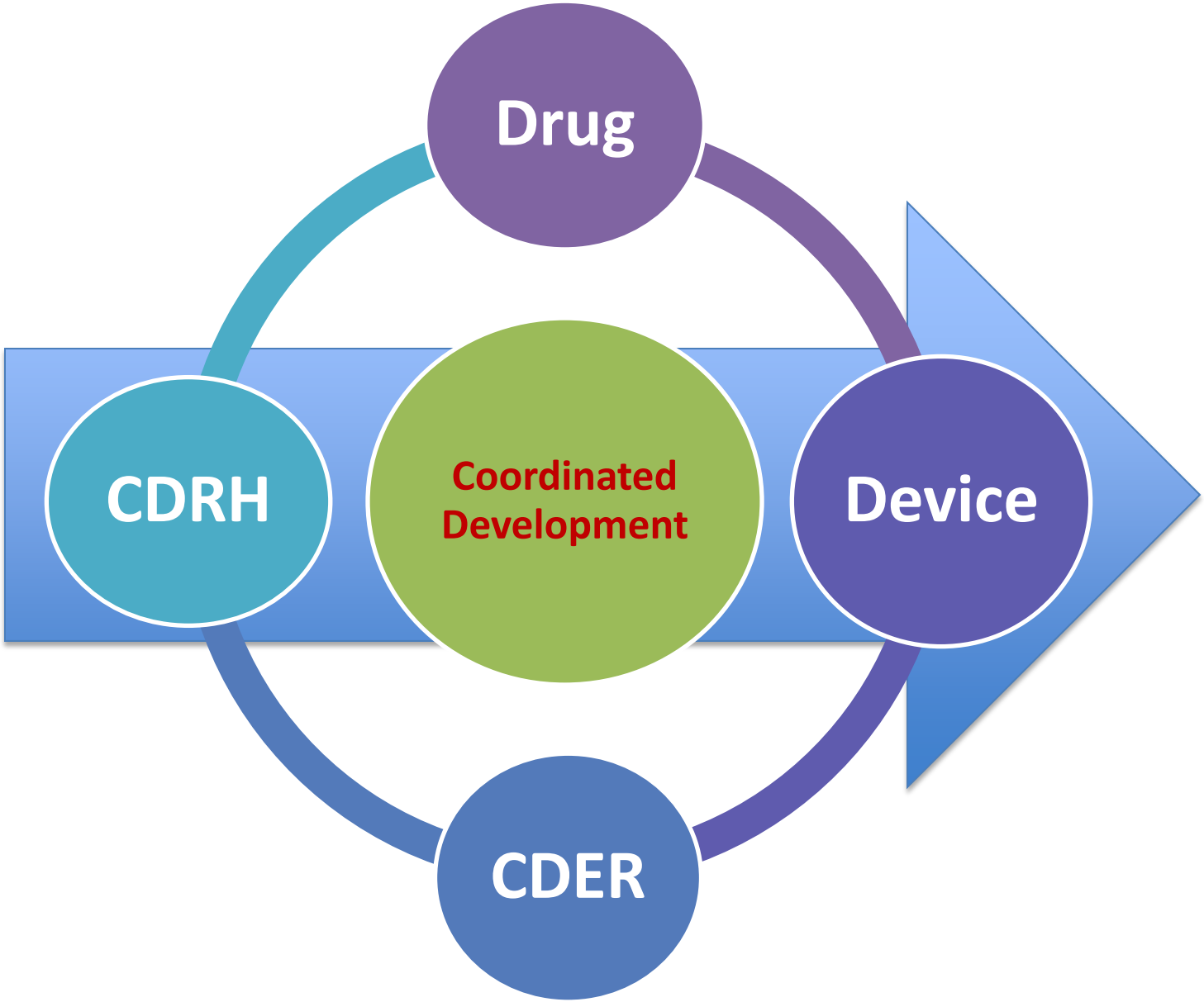
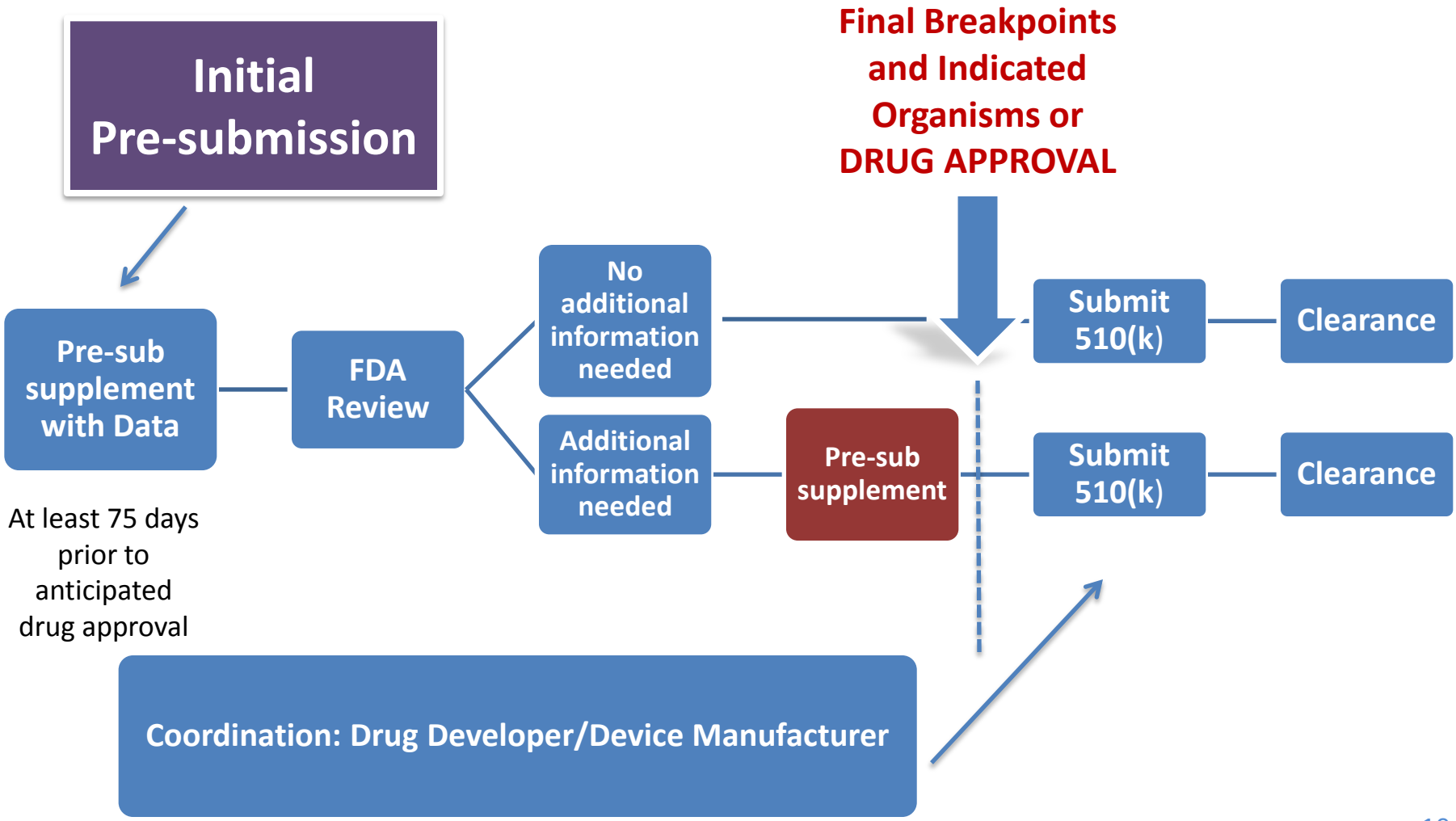
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research



Improved Patient Care

Coordinated Development Submission Process



Coordinated Development

Can Do

- Streamline the time between drug approval and device clearance - AST device availability coincides with drug approval
- Promote meaningful discussion between drug developers, device manufacturers and the FDA
- Provide drug developers access to AST device technology during clinical studies
- Provide device manufacturers access to organisms obtained during drug development
- Improve patient care

Cannot Do

- Change existing regulatory requirements or timelines for drug or device review and approval or clearance

Pre-submission Supplement for AST Device Review

- Contains the same data as required for 510(k)
  - Clinical performance – EA and CA and error rates with provisional breakpoints and preliminary indicated organisms
  - Challenge performance – EA and CA and error rates with provisional breakpoints and preliminary indicated organisms
  - Reproducibility Studies
  - Quality Control
  - Evaluate alternate inoculation and read methods

Pre-submission Supplement for AST Device Review

- Any additional information specific to the drug
  - Specific resistance mechanisms
  - Special reporting instructions
    - Cross resistance with other resistance mechanisms
    - Organisms with intrinsic resistance
    - Specific media or supplements

Agreements

Appropriate confidentiality agreements should be in place to allow drug developers, device manufacturers any other involved party to share pertinent information with CDRH and CDER regarding the NDA and device review.

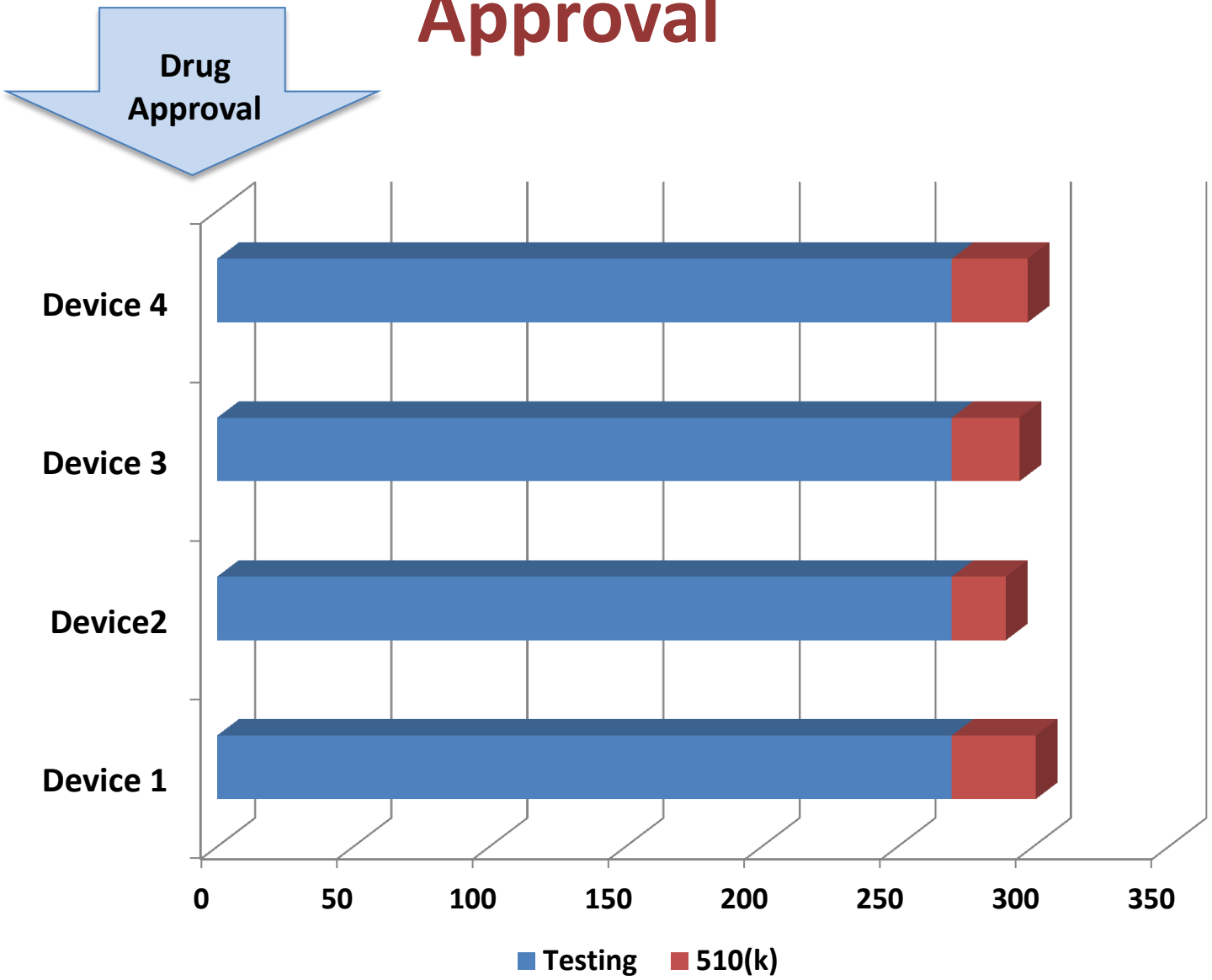
AST Device Evaluation Studies

- BMD reference method should be performed as recommended by CLSI
- Clinical evaluation – at least 3 clinical sites
- New device should be tested at sites representative of the clinical lab end user (i.e., CLIA-certified labs)
- Device evaluation should be totally independent of drug evaluation – but can take place concurrently

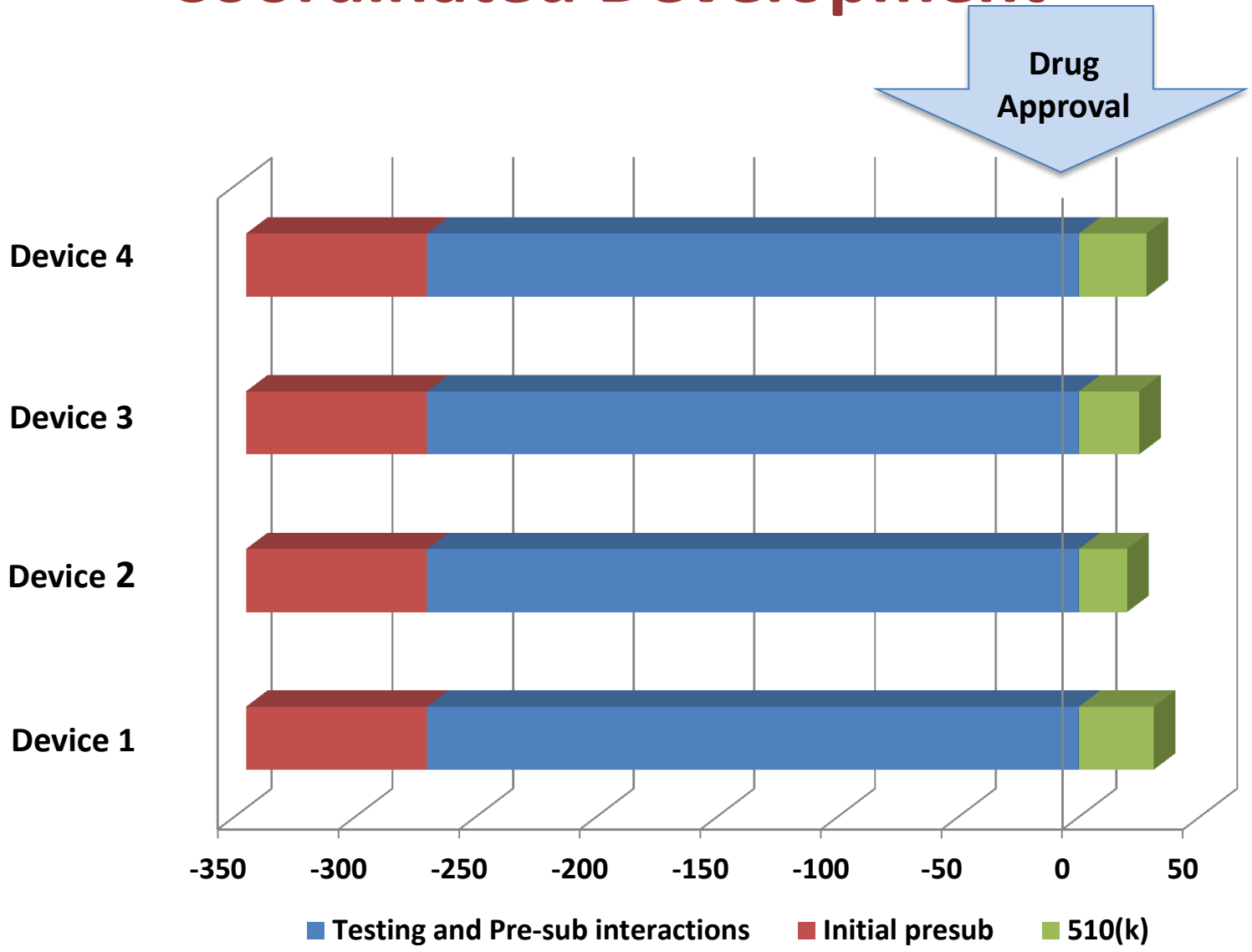
AST Device Evaluation Studies (Cont.)

- Isolates can be provided by the drug manufacturer
- Organisms used for drug evaluation **can** be used as challenge/stock isolates for device evaluation
- Test resistant isolates if possible – obtain isolates from the FDA/CDC AR Bank
- Broth microdilution devices should test a wide range of dilutions to allow flexibility for breakpoint changes

Time to Clearance After Drug Approval



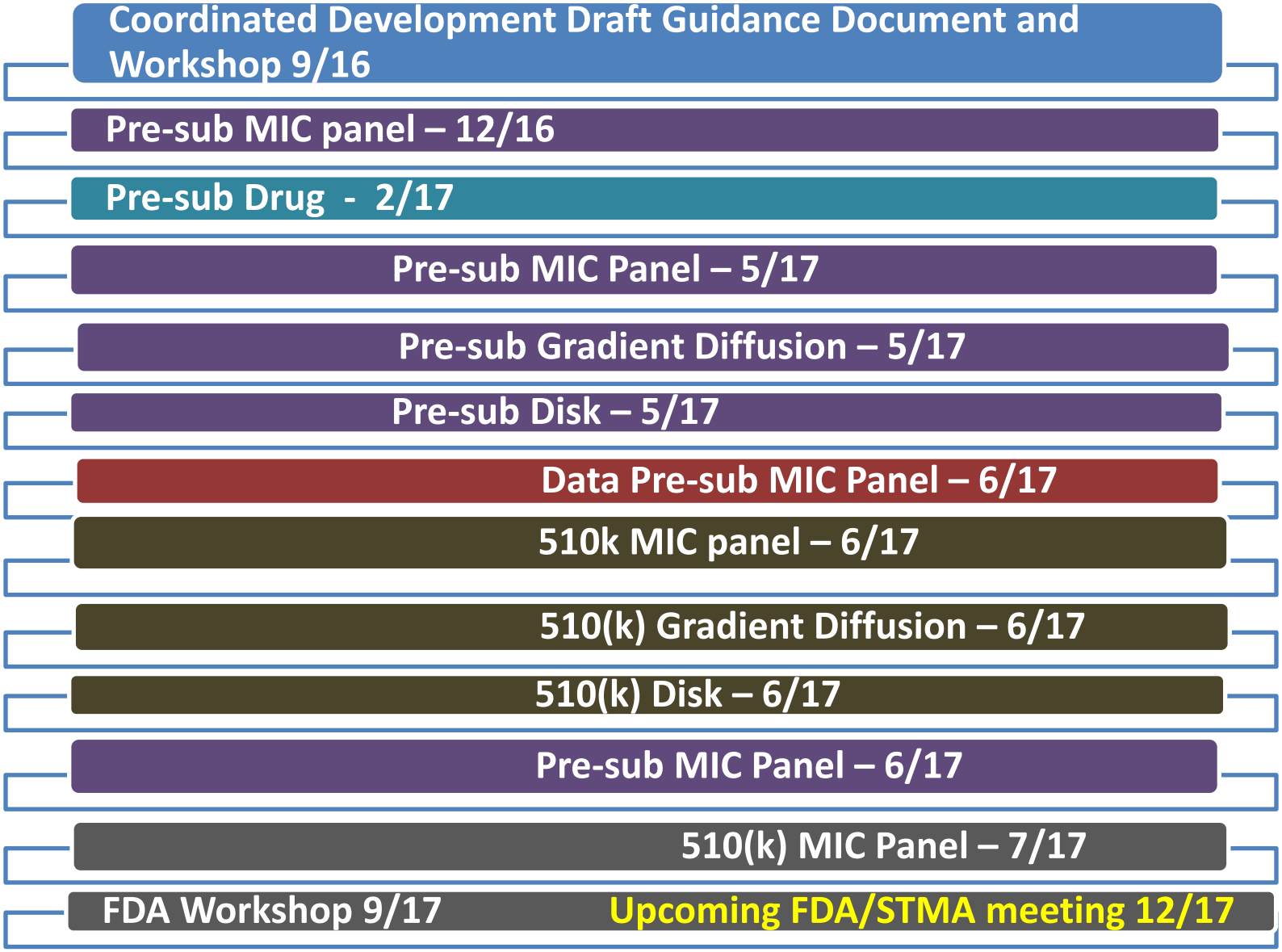
Time to Clearance
Coordinated Development



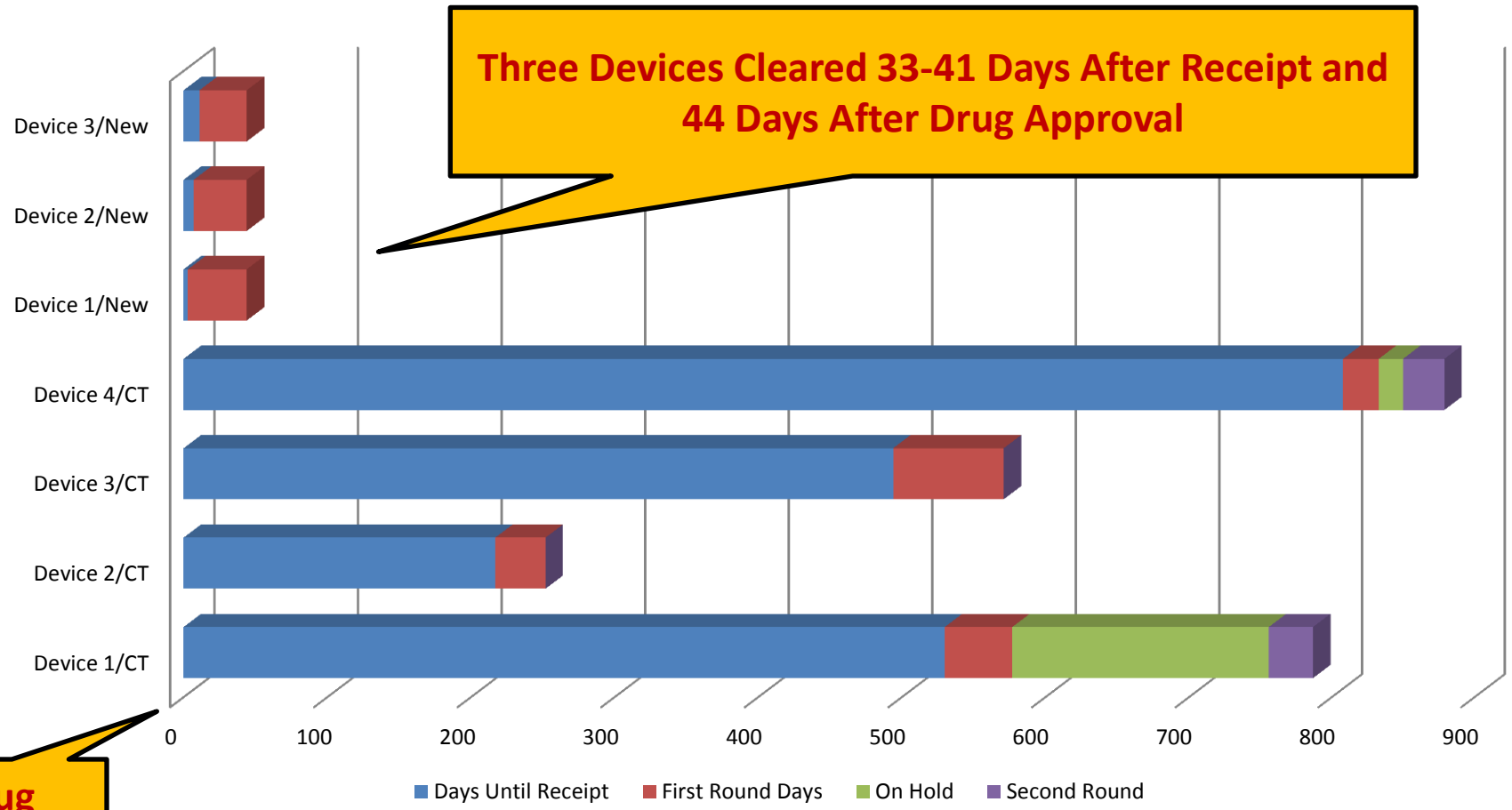
Assessment of Variability of the Broth Microdilution Method (BMD)

- BMD has been shown to provide variable results for some drug/organism combinations
- Assessment of the variability of the reference method is an important consideration when planning a new AST device evaluation for clearance
  - BMD variability should be included in discussions between drug developers and device manufacturers
- Reproducibility of the BMD reference method is addressed in CLSI M23 document

Activities: September 2016 to Date



Days Until 510(k) Clearance After Drug Approval



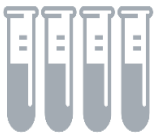
FDA Data On File

FDA-CDC AR Isolate Bank

- Presidential Order 13676 on September 23, 2014
- National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) in March 2015.
- FDA/CDRH identified a need for a well-curated repository to support development of diagnostics and antimicrobials.
- Effort funded by FDA as an inter-agency agreement with CDC
- AR Bank "opened" officially in July 2015 (CDC home page)
  - Currently contains a 14 panels, ~500 unique bacterial isolates with clinically-important R mechanisms.
  - New panels are added as this project continues to be supported through funding and scientific support from both FDA and CDC.
  - This resource was recently highlighted in a recent publication in the Journal of Clinical Microbiology (November 8, 2017).

AR Isolate Bank-How It Works

CDC uses bacteria samples (isolates) from health departments, labs, and outbreak and surveillance activities.



Susceptibility/resistance profile available for each isolate (phenotype/genotype and sequence information)

Stakeholders make a request and upon approval, CDC fulfils the request

Researchers/Developers can use the bacteria and data to challenge, develop and validate new diagnostic tests and antibiotics.

Laboratorians can use bacteria to validate tests to improve patient care.

BY THE NUMBERS

CDC curated 14 panels from its 450,000+ isolate collection

55,000 isolates sent to stakeholders since July 2015

571 unique customers

637 orders processed

AR Isolate Bank Customers

Clinical & Commercial Labs (52%)
Validating lab testing, treatment to improve patient care

Researchers & Developers (41%)
Improving diagnostics, pharmaceuticals to improve patient care

"The isolates helped us challenge our diagnostic tests to ensure they can detect a variety of resistance targets. We also used the panels to validate automated sensitivity instruments when we adopted new breakpoints."

– Diagnostic Developer

Federal Agencies (7%)

Summary

- Reviewed AST landscape and provided insight into FDA experiences
- Illustrated the concerns focusing on the lag in availability of ASTs for new drugs
- Provided an overview of FDA initiatives on coordinated development and streamlining the process
- Provided a glimpse of interactions and promising early experiences with coordinated development

Goal: Benefit to patients, clinical labs, healthcare providers and industry

Resources and FDA Guidance Documents

- FDA-CDC Antimicrobial Resistance Isolate Bank
  - https://www.cdc.gov/drugresistance/resistance-bank/index.html
- CDRH: Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems-Issued on: August 28, 2009 (update to March 5, 2007)
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM388961.pdf
- CDER/CDRH: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices-Issued on: June 2009
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM169359.pdf
- CDER/CDRH: Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Testing Devices-Issued: September 21, 2016
  - http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm521421.pdf
- CDER: Microbiology Data for Systemic Antibacterial Drugs: Development, Analysis, and Presentation- Issued August 2016
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm182288.pdf

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Thank you!

Questions?