Overview of AST Device Clearance Process: CDRH Perspective

CDER/CDRH Workshop:
Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices
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Outline

- Overview of the AST landscape and FDA review process
  - Disk diffusion and MIC-based tests
- Discuss concerns and relate to FDA data and experiences
  - Show examples of timelines, particularly focusing on the lag in availability of ASTs for new drugs
- FDA initiatives and resources to address challenges, advance the field and facilitate the process
  - Key messages from the “Coordinated Development Guidance”
  - FDA/CDC Antimicrobial Resistant Isolates Bank and other resources
  - Adapting to innovative technological advances by offering solutions

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.
  - Future…..
- Resistance Detection
  - Growth-Based, Culture Media
  - Culture-independent, Resistance Markers, molecular (w/wo ID)
  - Future……

Regulations, Guidance and Review Timelines

- AST devices
  - All are Class II, require review and 510(k) premarket notification (i.e., non-exempt)
  - Subject to 90 day review cycle
  - Regulations: 21 CFR 866.1640 and 21 CFR 866.1645 depending on device type
  - Studies, data requirements and evaluation criteria
    - Several CDER and CDRH guidance documents

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 is cleared **in 90 days, but usually in less time**

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

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NDA-Approval

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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 is cleared in **90 days or less unless additional information/data is needed**

AST for MIC Based Assay

Studies for 510(k) Application	Comparison to Reference	Purpose/Rationale
Clinical Fresh, Stock 3 Clinical sites (1 internal)	EA, CA, (> 89.9 %.), Error Rates	• Robust evaluation of real life performance • Recent/Contemporary isolates • Geographic diversity • Evaluate discrepancies and trending by organism • 50% can be stock isolates to facilitate development • Data analyzed to identify needed warnings or limitations
Challenge, Internal study	EA, CA, Error Rates	• Compensate for insufficient resistant isolates, unique or rare organisms
Reproducibility 3 sites, each panel/instruments	Reproducibility ≥95% agreement	• Demonstrate acceptable performance/ability to produce equivalent results under varying conditions
QC 3 Clinical sites	Within range 95% of the time	• Confirms experience observed for QC ranges that were established by reference method

AST Devices: Time to Market Availability

The Players:

- FDA (CDER/CDRH), drug manufacturers, device manufacturers (illustrated on the next slides)

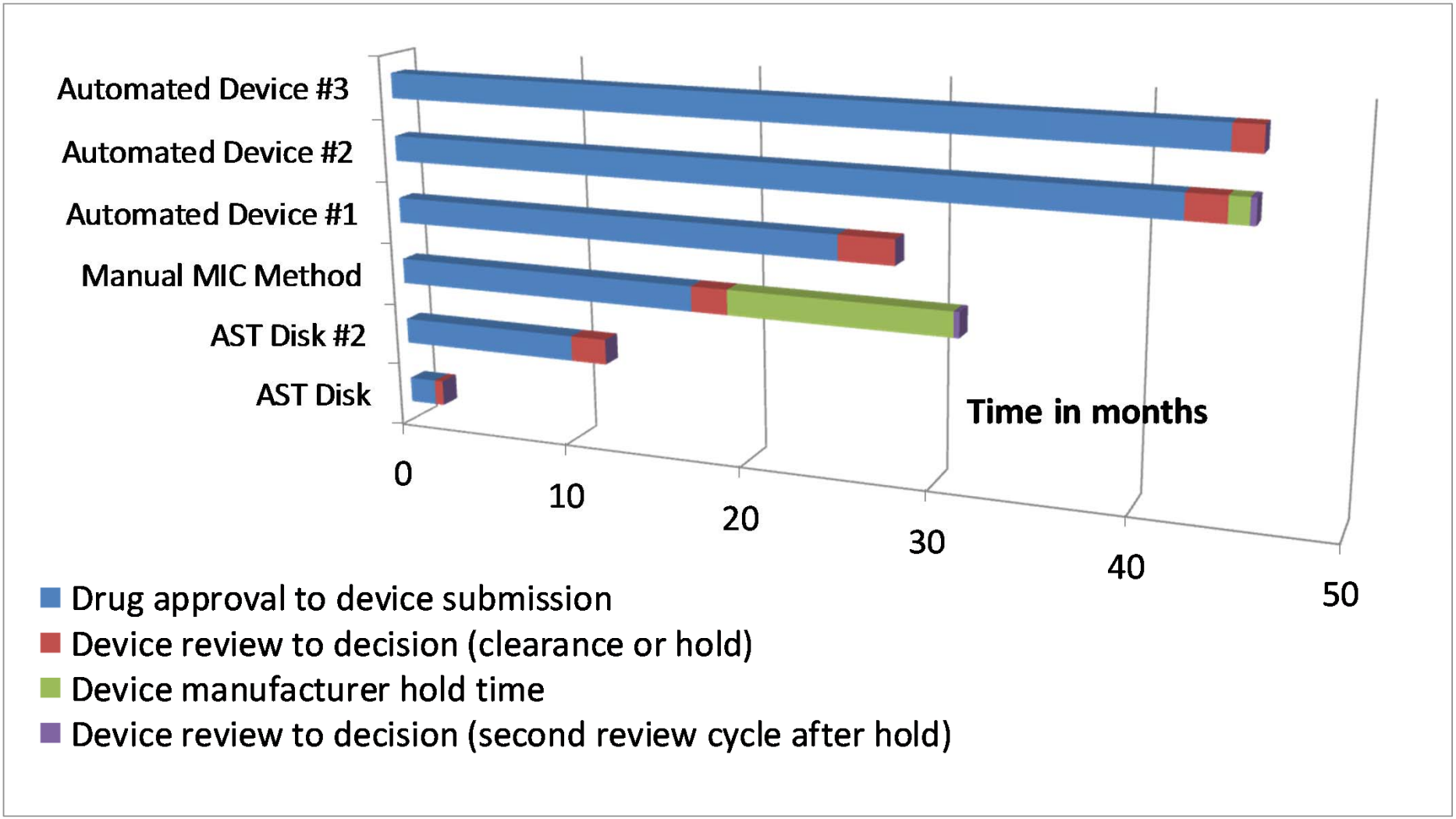
Old Drug: breakpoint change:

- CDRH is mandated to consider clearance only when breakpoint changes make it into the drug label
- Delay between breakpoint changes for a drug and availability of AST device/labeling with the updated changes
- **FDA is exploring options for AST device manufacturers to use up-to-date breakpoint information in their device labeling in a more timely manner.**

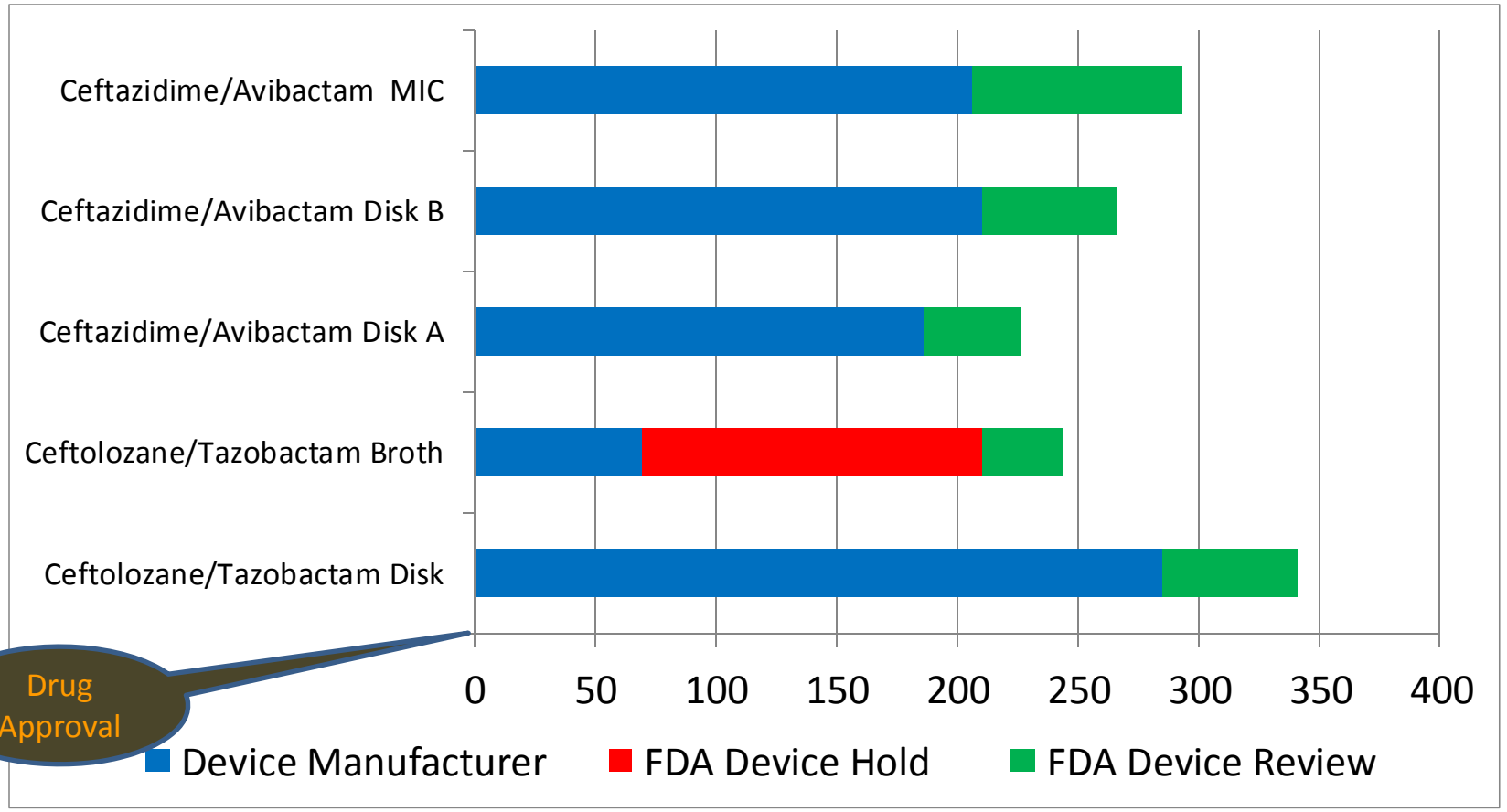
New Drug:

- Delay between drug approval and availability of an AST device

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



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



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.

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Comment By: November 21, 2016

How Can FDA 'Facilitate' Coordinated Development?

- Highlights:
  - Draft Guidance is intended to be a general guide and not prescriptive
  - Drug applications and AST device applications remain separate
  - Review timelines for separate products will not be influenced by each other
  - Encourages early interactions among antibacterial drug and AST device companies and FDA. For example,
    - Engage ALL parties early in CDER and CDRH meetings/ discussions
    - Identify coordinated development strategies (and synergies where possible)

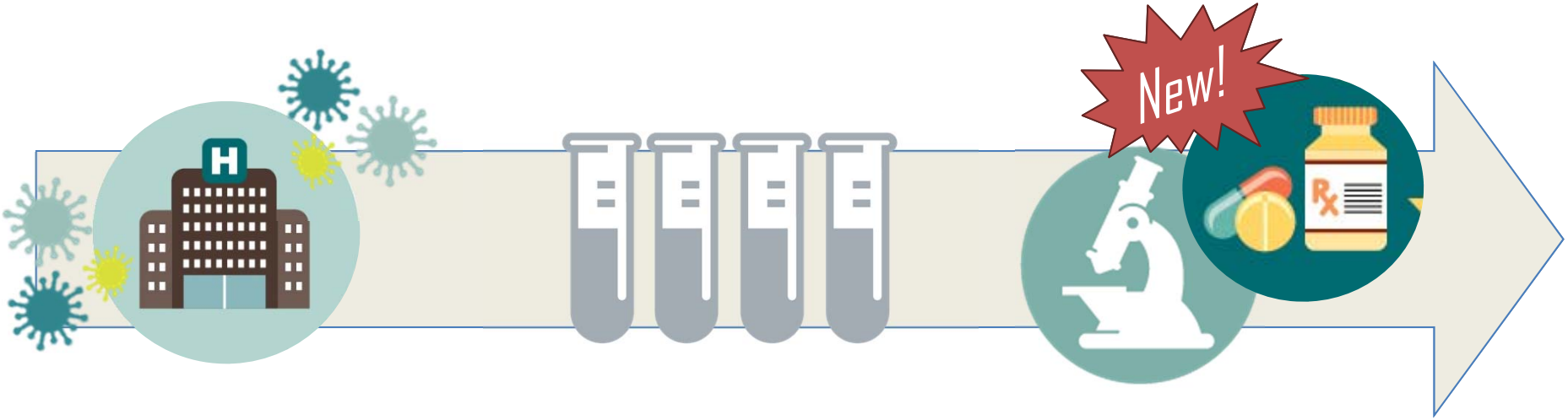
How Can FDA 'Facilitate' Coordinated Development?

- Highlights:
  - Emphasizes FDA's belief that better coordination of development (not Co-development) of drugs and AST devices offers benefits to patients, clinical labs, healthcare providers and industry.
  - Provides a flexible mechanism to allow for concurrent review of drug and device
  - NOT Companion Diagnostics: Emphasizes that AST systems should not be confused with *in vitro* companion diagnostic devices, outlined in In Vitro Companion Diagnostic Devices issued August 6, 2014

How Can FDA "Facilitate" Coordinated Development?

- Some Practical Points:
  - Respective companies can submit their coordinated development plans to CDER and CDRH for review and comment
    - pre-IND/IND for CDER, and Q-Sub for CDRH
  - Respective companies can request a joint meeting (drug sponsor, device manufacturer, CDER and CDRH)
  - The device manufacturer should, in its 510(k) submission, provide appropriate permissions to FDA from the drug sponsor to cross-reference drug sponsor's NDA to facilitate AST device review.
    - CDRH will consult with CDER to maximize the likelihood that AST device clearance can occur either coincident with or shortly after drug approval.
    - The AST device 510(k) submission should be submitted early enough to allow sufficient time for FDA to complete its review

The FDA-CDC AR Isolate Bank



CDC gathers resistant bacteria through surveillance/ sentinel networks/ outbreak investigations and other sources

CDC analyzes the resistance & shares with researchers, assay developers and device manufacturers.

New diagnostic tests & antibiotic drugs can be developed using these isolates and data.

Project officially started on August 1, 2014

www.cdc.gov/DrugResistance/Resistance-Bank

Summary

- Reviewed concerns and provided insight into FDA experiences
- Illustrated the impact of timelines, particularly focusing on the lag in availability of ASTs for new drugs
- Provided an overview of FDA initiatives and resources to address challenges and facilitate the review process

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

"It Takes a Village"

FDA Guidance Documents

- 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
- CDRH: Review Criteria for Assessment of Antimicrobial Susceptibility Test Discs-Issued October 30, 1996
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM094102.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?