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February 12, 2019

# Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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February 12, 2019

# Outline

- Background
  - Types of Devices
  - Important Regulations, Timelines, and Guidance
- FDA Review of Traditional Drug and Device Submissions
- Concerns: Time Lag Between Drug Approval and Antimicrobial Susceptibility Test  Availability
- Coordinated Development Activities
- FDA Initiatives to Streamline the Process
- Highlights

# Objectives

- To familiarize stakeholders with the history of the Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices and the regulatory review process for timely availability of devices

- To provide an update on the FDA Guidance for coordinated development and the various supportive activities

# Definitions — Antimicrobial Susceptibility Test Device

- **Antimicrobial Susceptibility Test Device**
  - An antimicrobial susceptibility test is a device that incorporates concentrations of antimicrobial agents into a system for the purpose of determining *in vitro* susceptibility of bacterial pathogens isolated from clinical specimens. Test results obtained after incubation are used to determine the antimicrobial agent of choice to treat bacterial diseases.

  - The FDA regulates these devices under different regulations and uses multiple product codes depending on the type of devices.

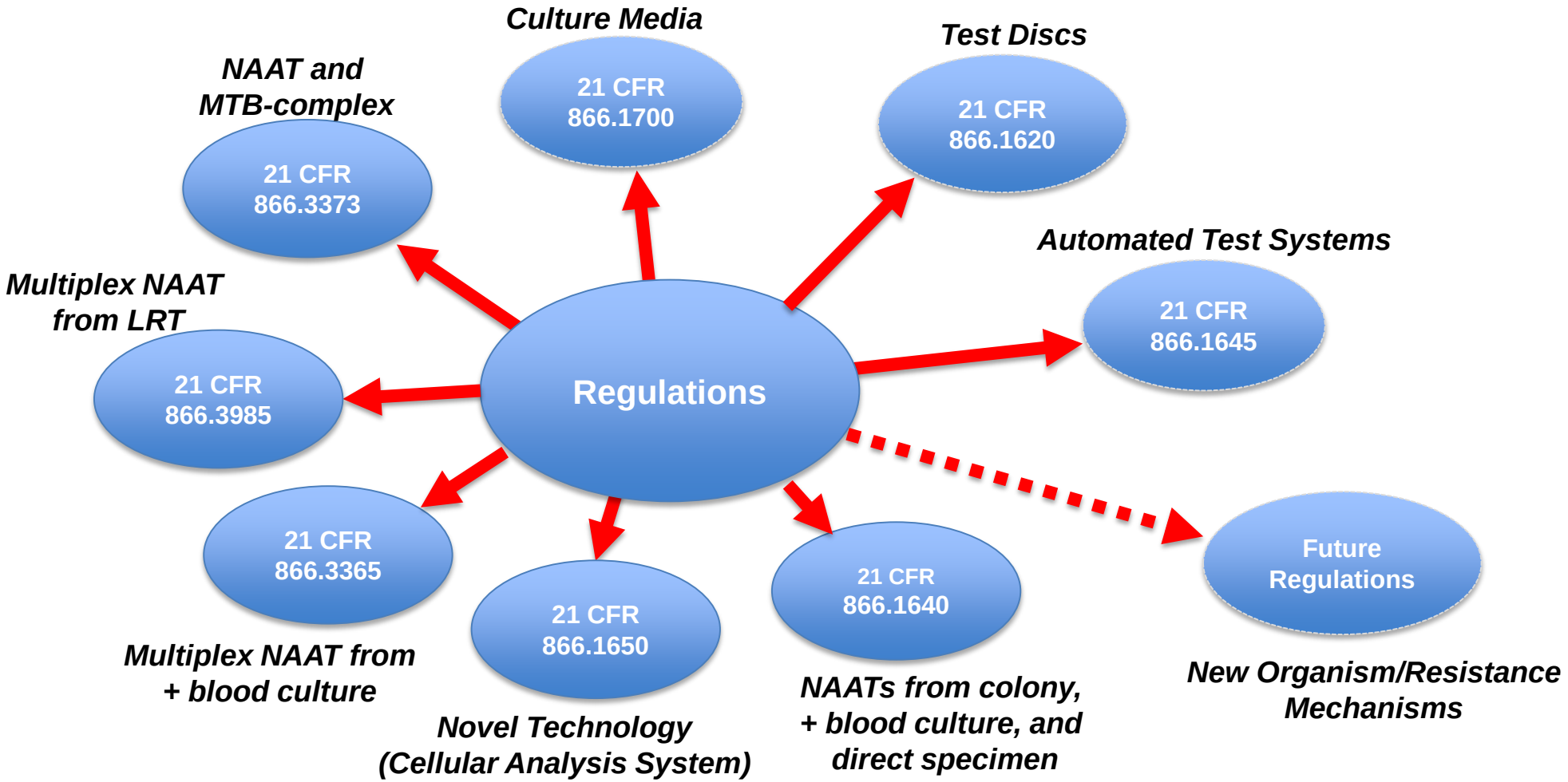
# Types of Antimicrobial Susceptibility Test Devices

- Disk Diffusion-Based Devices (Zone Diameter)
- Dilution-Based Devices (Minimum Inhibitory Concentration)
  - Agar Gradient Diffusion
  - Visually (Manually)-Read Panels
  - Instrument-Read Panels (Automated), Algorithm-Driven Devices
    - From colonies or Positive Blood Cultures
- Variations in Testing Methods Can Include:
  - Specific Media
  - Inoculation Methods
  - Complex Software/Instrumentation

# Relevant Antimicrobial Susceptibility Test Device Review Timelines, Regulations, and Guidances

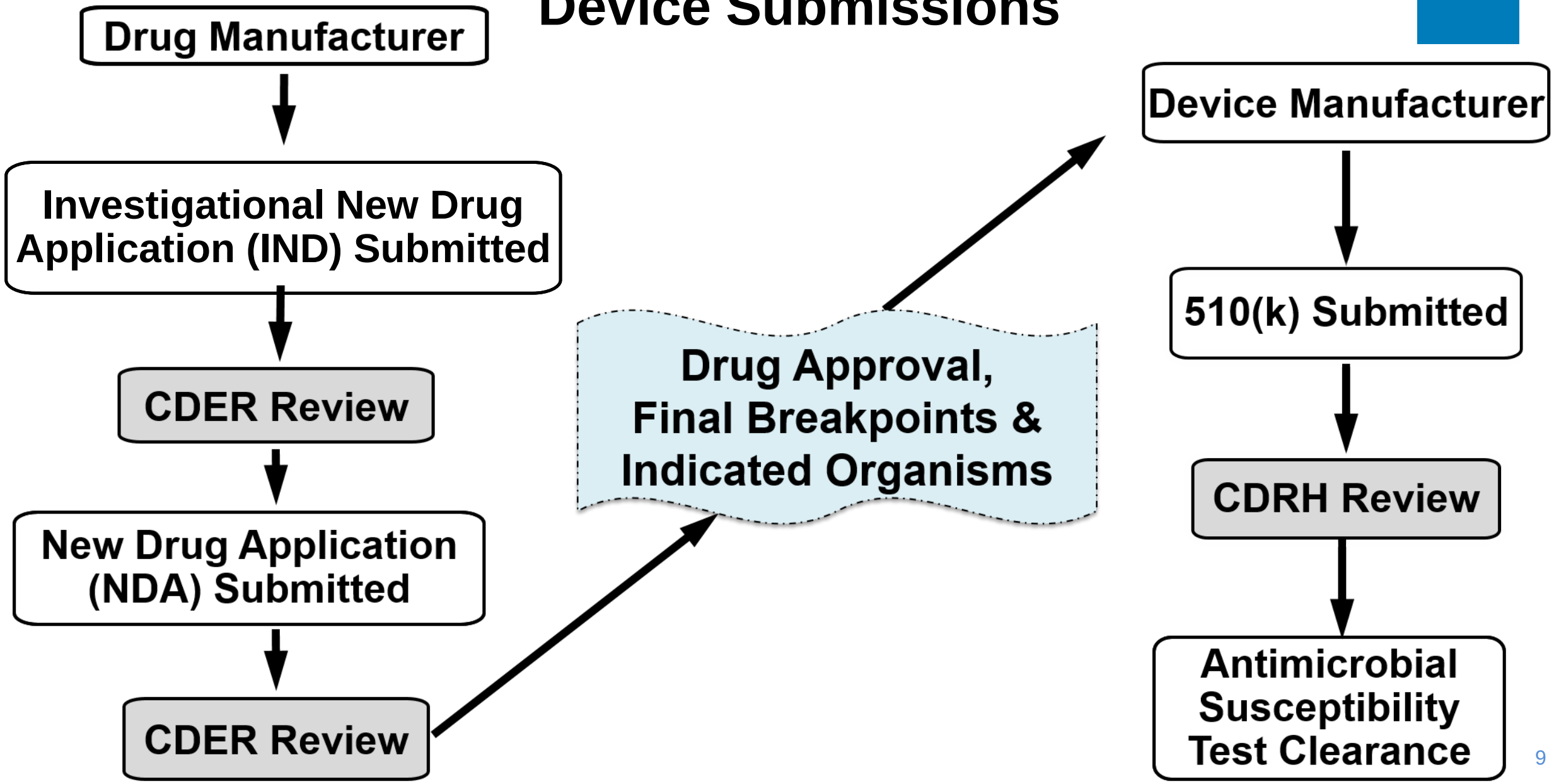
- Class II, require a 510(k) premarket notification (that is, non-exempt)
- Subject to **90 day** review cycle
- Regulations (21 CFR):
  - Colonies (depending on device type):866.1640, 866.1645, 866.1620
  - Positive Blood Culture: 866.1650
- The Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) guidances that outline:
  - Types of Studies
  - Data Requirements
  - Evaluation Criteria
- FDA-recognized guidelines and standards (for example, Clinical and Laboratory Standards Institute)

# Diversity of Regulations for Antimicrobial Susceptibility Test Device and Antimicrobial Resistance Markers

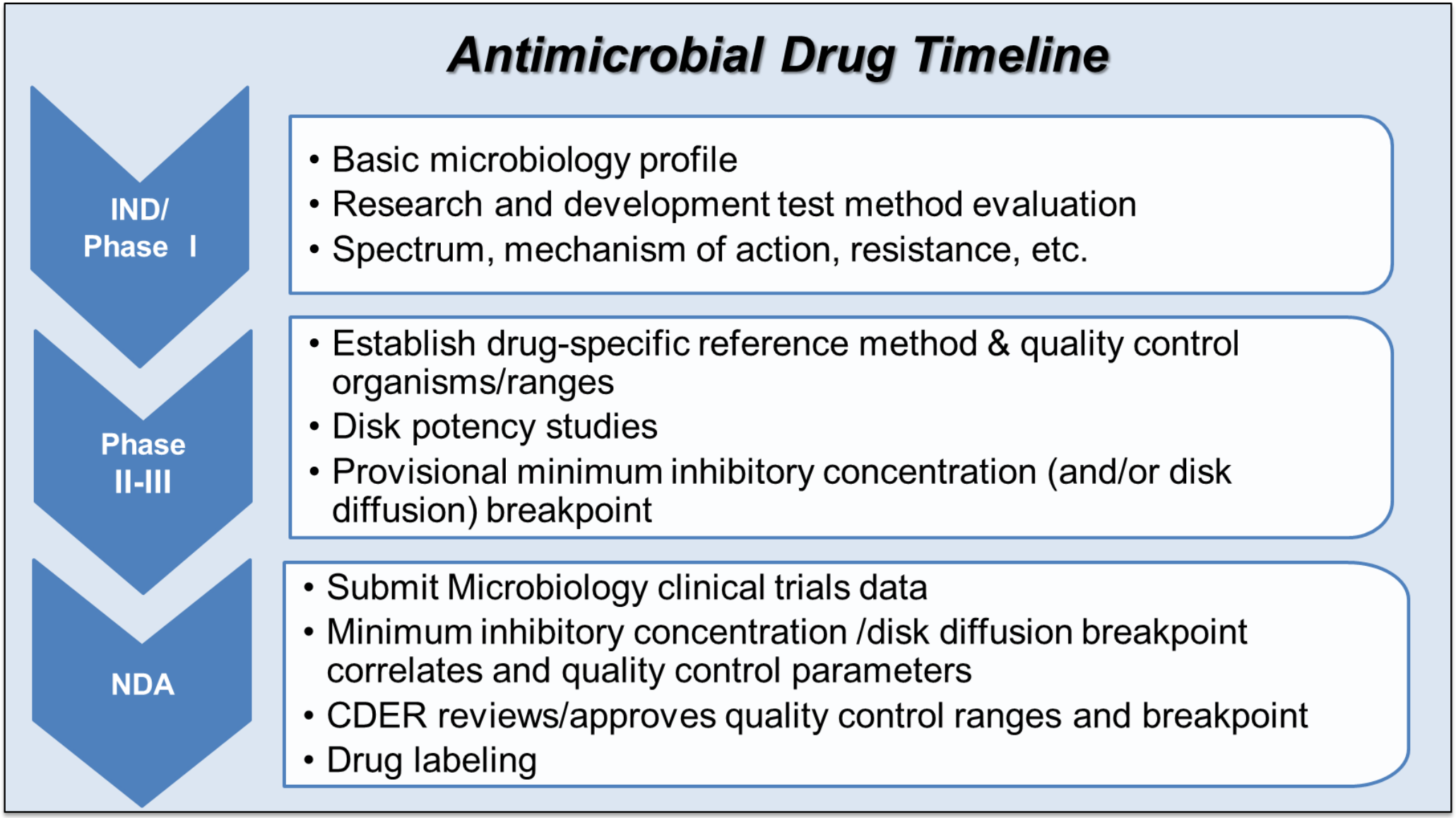



- Nucleic Acid Amplification Test (NAAT)
- Mycobacterium tuberculosis (MTB)
- Lower Respiratory Tract (LRT)

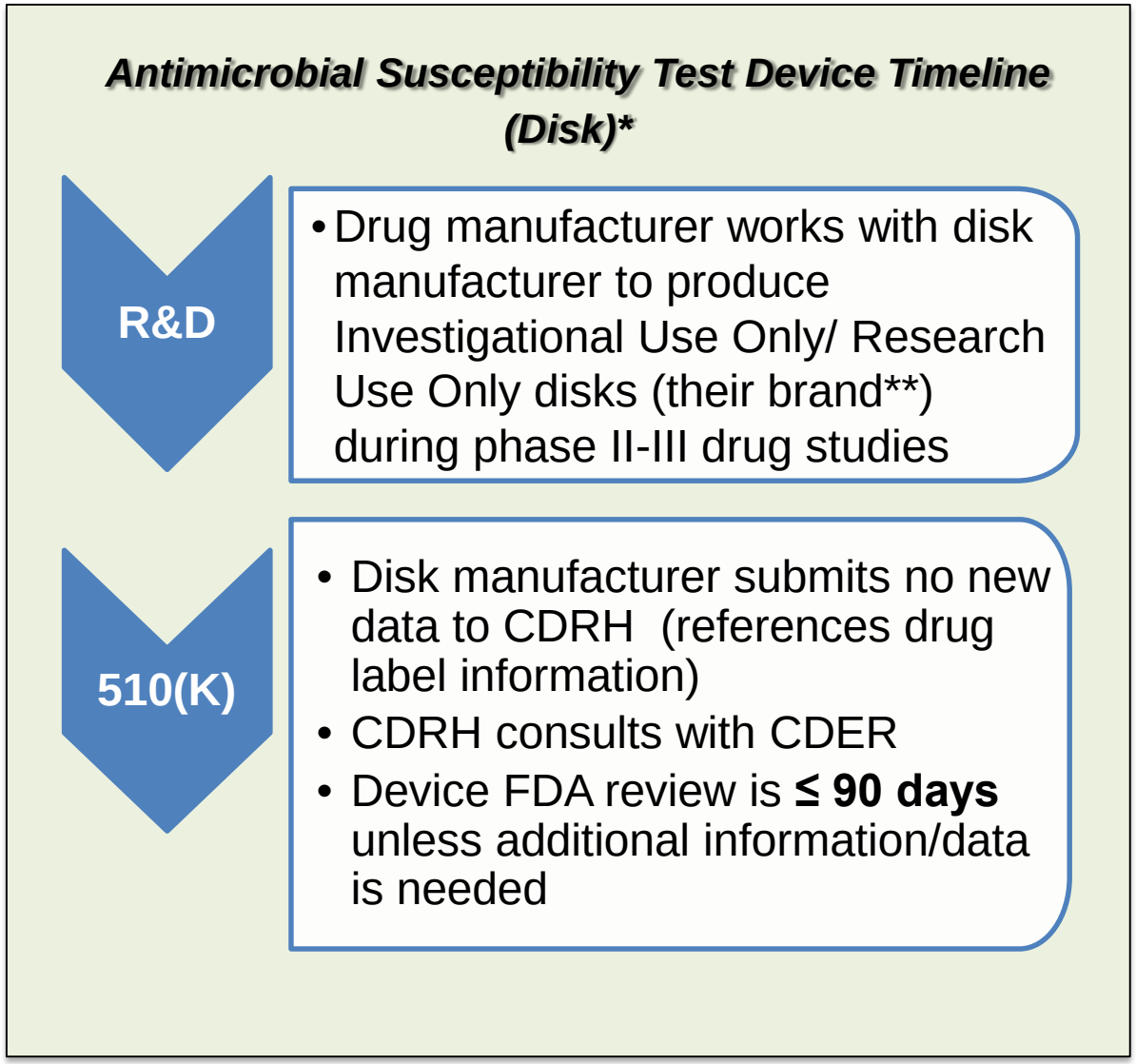
# FDA Review of Traditional Drug and Device Submissions



# Microbiology Information: Drug



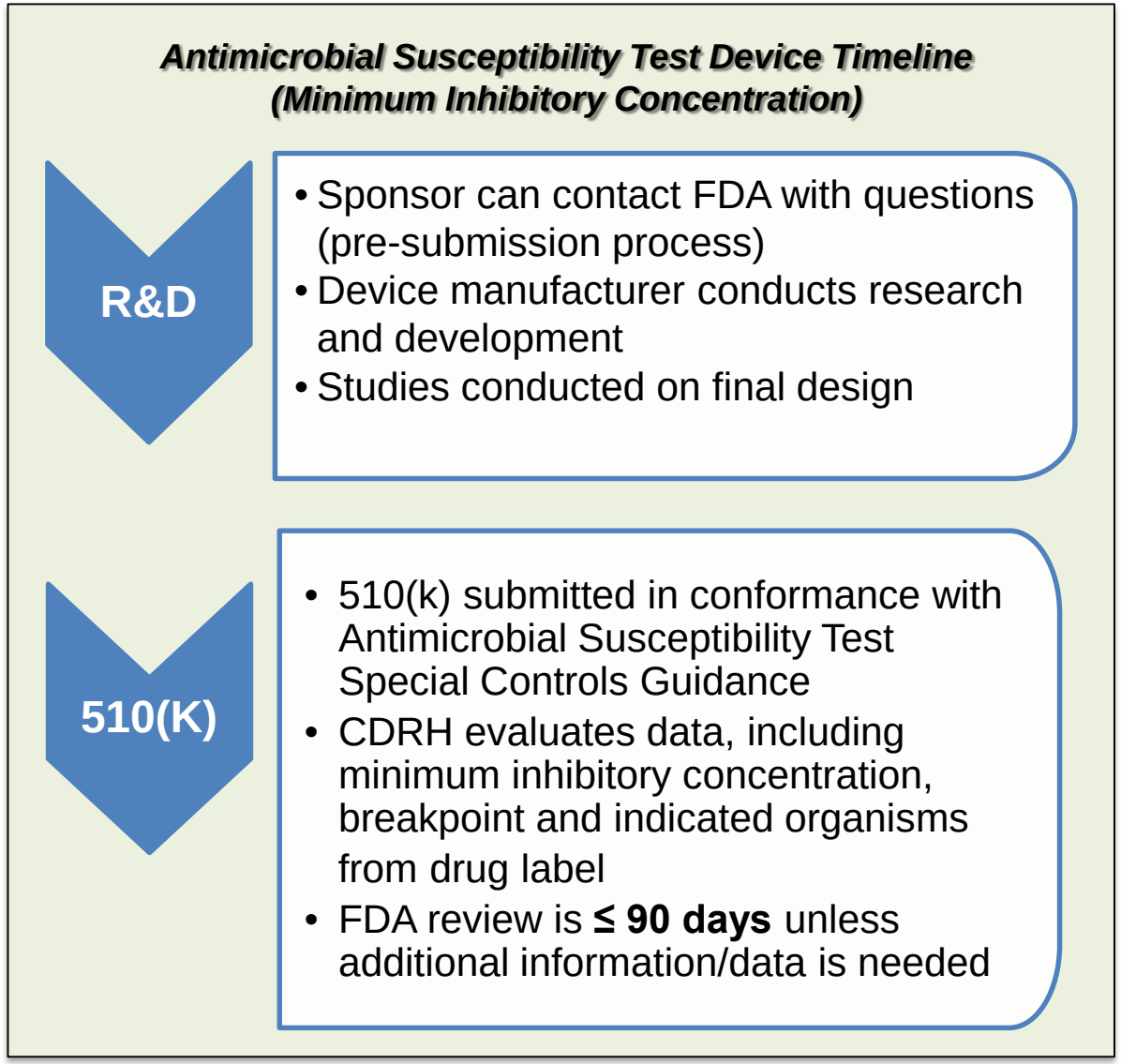
# Microbiology Information: Antimicrobial Susceptibility Test Device




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

***For brands not evaluated through this pathway, separate studies are needed to support a 510(k)*

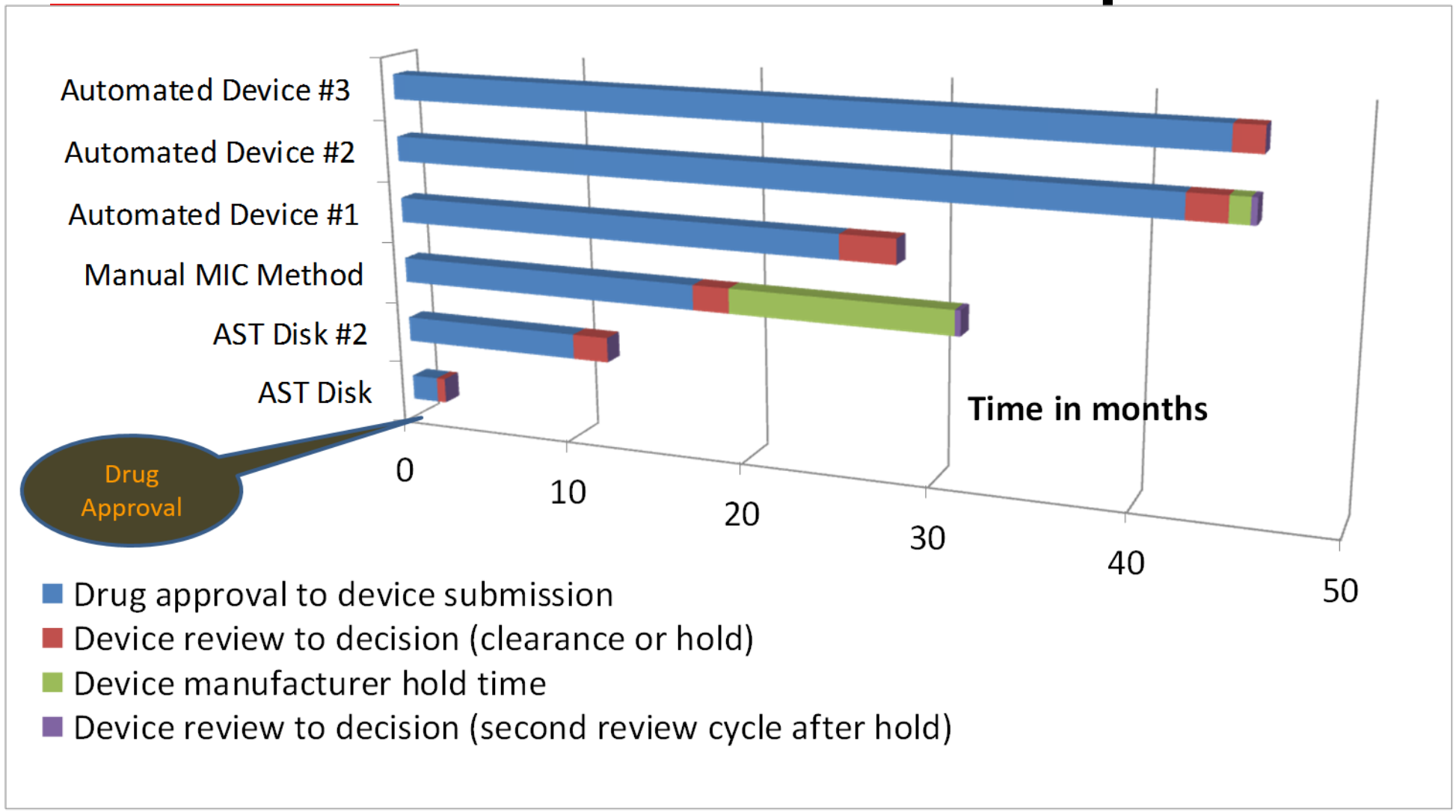
# Microbiology Information: Antimicrobial Susceptibility Test Device




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

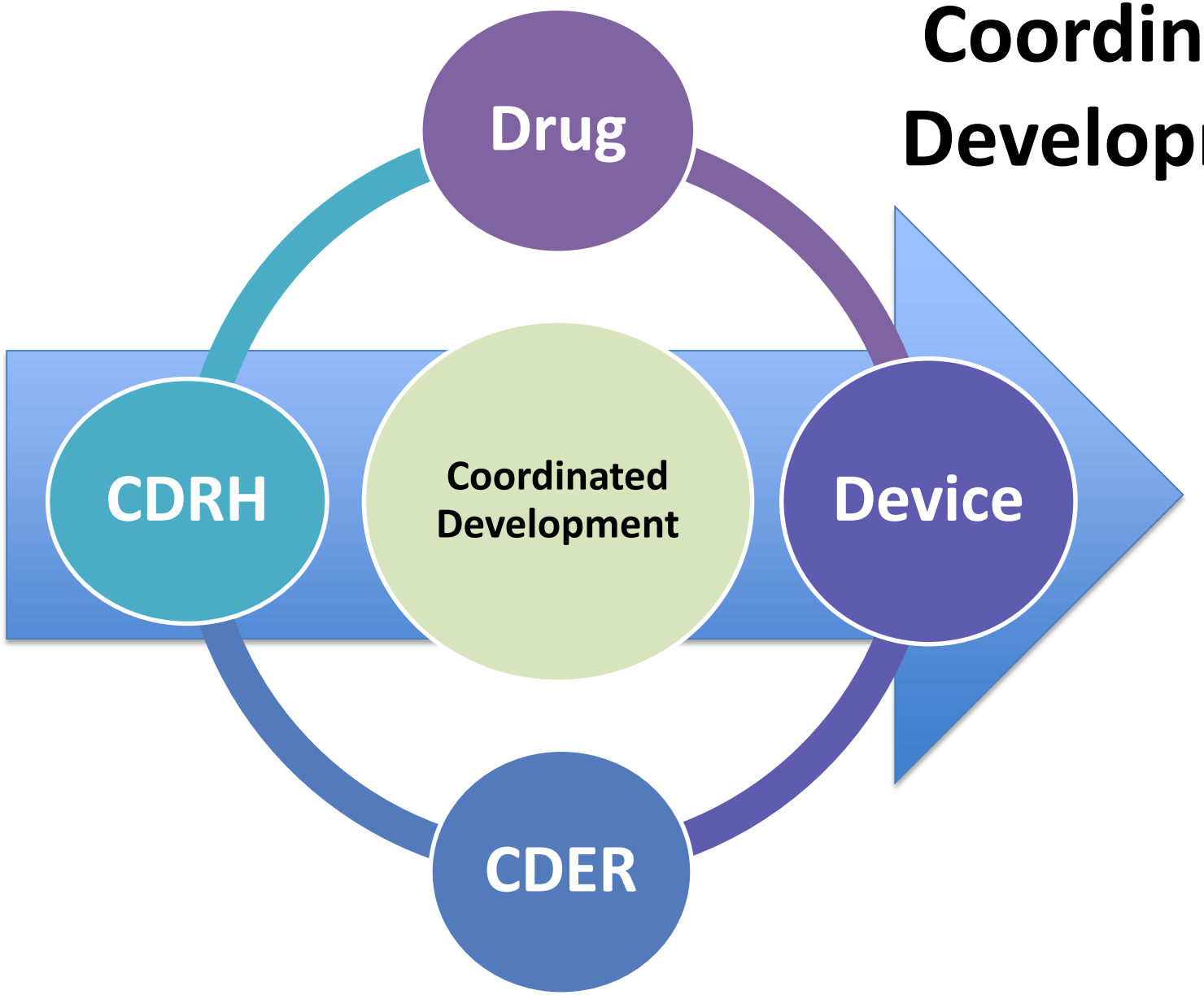
***For brands not evaluated through this pathway, separate studies are needed to support a 510(k)*

# BEFORE Coordinated Development




*New Drug Approval to Antimicrobial Susceptibility Test  Device Clearance: Elapsed Time (Months)*

# Coordinated Development




*Improved Patient Care*

# Coordinated Development Workshop and Draft Guidance

## September 29, 2016, Silver Spring, MD


- Overview of antimicrobial susceptibility test devices landscape from different perspectives (agenda topics covered)
  - ❖Clinician—New drugs and susceptibility test results/updated breakpoints
  - ❖Laboratory—Routine drug susceptibility testing, drug/organism combinations, and quality control /training
  - ❖Drug Sponsors—Agreements between sponsors, breakpoints, research use only testing, and complexity of development process
  - ❖Diagnostic Device Manufacturers—Susceptibility Test Manufacturer's Association, development cycle, FDA review, and breakpoint revisions
- How American Society for Microbiology and Clinical and Laboratory Standards Institute can help with the process
- Two panel sessions were held to clarify questions from audience

# Comments to the Docket

- **54** Comments Received from Stakeholders
  - Industry (**36**), Professional Societies (**11**), Trade Associations (**7**)

- **4** Comment Types
  - Policy (**10**), Editorial (**9**), Procedural (**19**), Technical (**16**)

***Substantive changes to the content of the draft guidance were made based on comments to the docket***

# Scope

- Intended to assist drug sponsors and device manufacturers who are planning to develop new antimicrobial drugs and antimicrobial susceptibility test devices

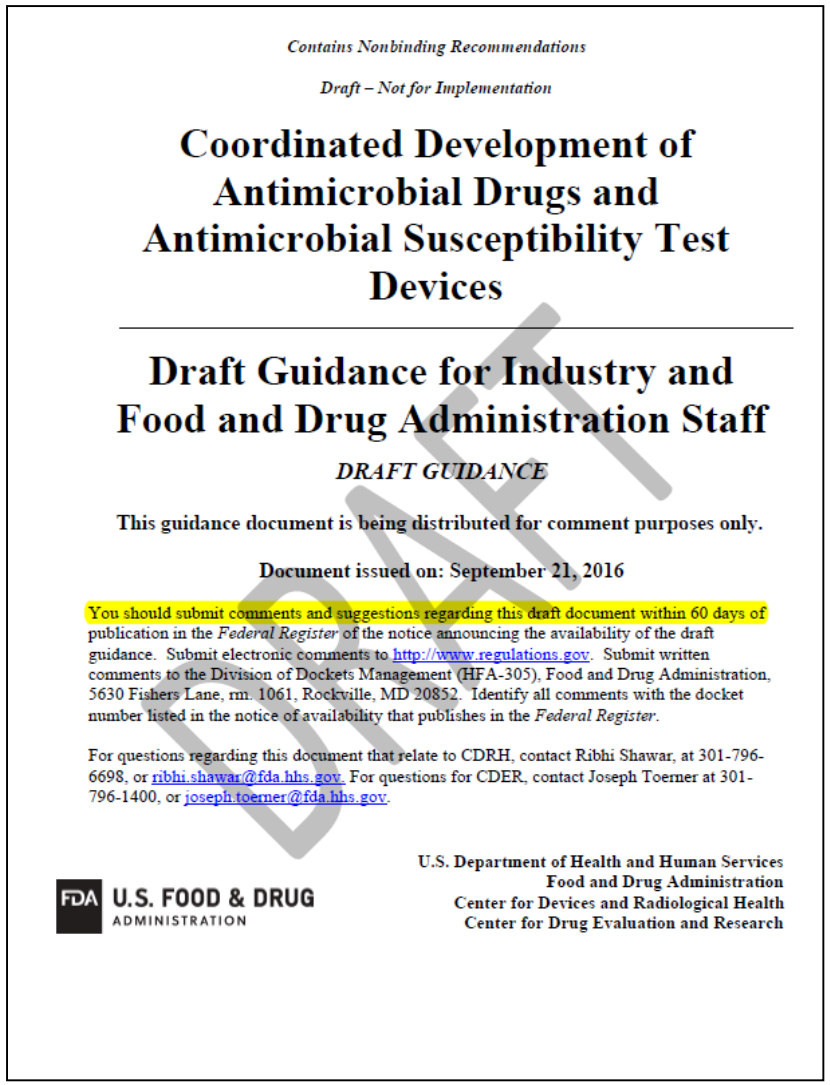
- Specifically, the guidance intends to accomplish the following:
  - Describe interactions between drug sponsors and device manufacturers for coordinated development of a new antimicrobial drug and an antimicrobial susceptibility test device;
  - Explain the considerations for submitting separate applications to CDER (drug) and CDRH (device) when seeking clearance of an antimicrobial susceptibility test device to coincide with, or soon following, antimicrobial drug approval; and
  - Clarify that the review of the new antimicrobial drug product and antimicrobial susceptibility test device(s) will remain independent.

# Goals of the Guidance

- **Provide recommendations** to the medical device and drug industries on how to work together to facilitate timely clearance of antimicrobial susceptibility test devices by the FDA

- **Minimize time** between the approval of new antimicrobial drugs and clearance of antimicrobial susceptibility tests used to determine the potential effectiveness of those drugs

# Final Guidance Published January 17, 2019



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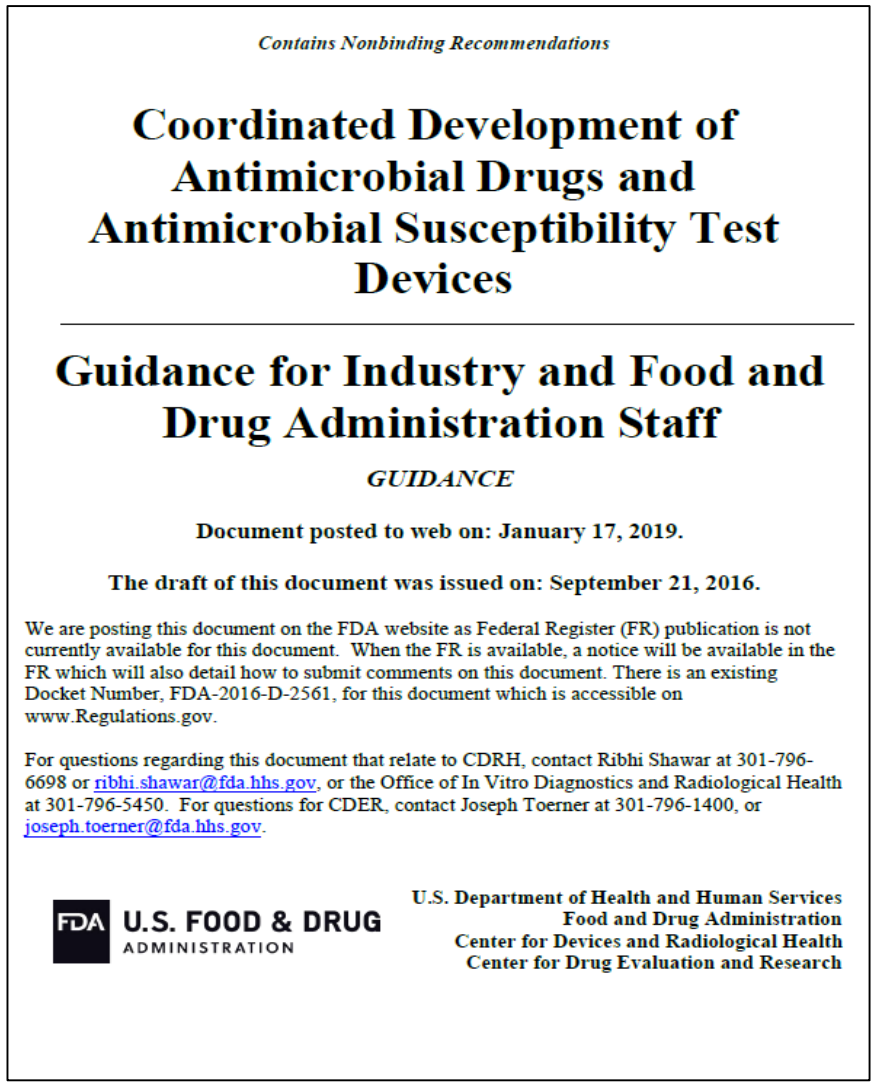
**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**
**Center for Drug Evaluation and Research**



*Contains Nonbinding Recommendations*

## Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

## Guidance for Industry and Food and Drug Administration Staff

*GUIDANCE*

**Document posted to web on: January 17, 2019.**

**The draft of this document was issued on: September 21, 2016.**

We are posting this document on the FDA website as Federal Register (FR) publication is not currently available for this document. When the FR is available, a notice will be available in the FR which will also detail how to submit comments on this document. There is an existing Docket Number, FDA-2016-D-2561, for this document which is accessible on www.Regulations.gov.

For questions regarding this document that relate to CDRH, contact Ribhi Shawar at 301-796-6698 or ribhi.shawar@fda.hhs.gov, or the Office of In Vitro Diagnostics and Radiological Health at 301-796-5450. 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**

# From Draft to Final: Summary of Changes

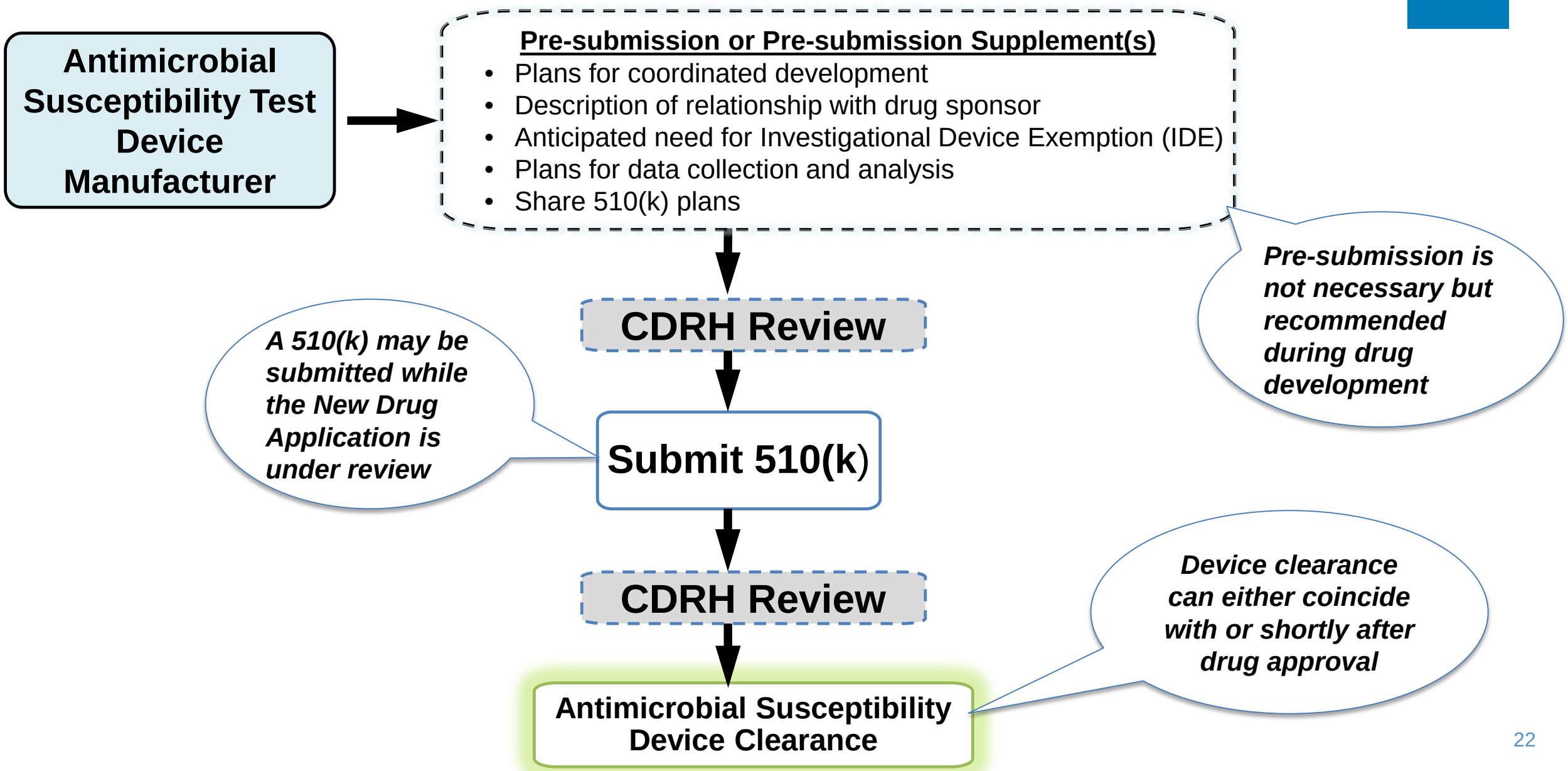
- **Process for coordinated development:**
  - Clarified process and timeline for coordinated development of antimicrobial drugs and antimicrobial susceptibility test devices.
  - Added a flowchart depicting the recommended interactions between drug and device manufacturers, CDER, and CDRH to facilitate coordinated development.
- **Applicability of the guidance to molecular devices:**
  - Revised to indicate that the processes of coordinated development outlined in the document are applicable to molecular devices for the detection of antimicrobial resistance markers that infer drug resistance and to traditional growth-based microbiological devices.

# Changes to Final Guidance Based on Comments to the Docket

Clarification of the:

- Need for improved coordination between drug and device development
- Process for coordinated development
- Types of antimicrobial susceptibility test devices to include molecular devices
- Recommended timing for submission of antimicrobial susceptibility test devices to CDRH in relation to submission of the new drug application to CDER
- Process for coordinated development in without a pre-submission
- Content of a pre-submission, if utilized

# Coordinated Development-Drug & Device Manufacturers



# Functions of Coordinated Development

## Does

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

## Does Not

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

# Pre-Submission Interaction Topics (1)

**General:**

- Outline of studies that will have been or will be performed
- Provisional breakpoints and indicated organisms
- Expected timeline
- Assessment of Broth Microdilution variability for the drug
- Description of any specific Broth Microdilution modifications to standardize drug testing
- Anticipated procurement of resistant or on-scale strains
- Information regarding Drug/Device agreements
- Specific questions to allow better FDA feedback

# Pre-Submission Interactions Topics (2)

**Specific for Antimicrobial Susceptibility Test  Device Evaluation Studies**

- Isolates can be provided by the drug manufacturer
- Organisms from drug evaluation studies **can** be used as challenge/stock isolates for device evaluation
- Broth Microdilution devices should test a wide range of dilutions to allow flexibility for breakpoint changes (and avoid truncated minimum inhibitory concentration values)
- Disk brands not included during drug trials will require separate studies to support a 510(k) for their brand
- Any additional information specific to the drug
  - Specific resistance mechanisms
  - Special reporting instructions (resistance mechanisms, media, etc)

# Activities to Date

## 2016

- Workshop
- Draft Guidance
- 1 Pre-submission

*Timeline*: Drug Approval to Device Clearance

Could be up to **40 months**

## 2017

- (6) Pre-submissions
- (9) 510(k)s

**New Drugs/New Devices**

- Delafloxacin
- Meropenem/Vaborbactam

*Timeline:* Drug Approval to Device Clearance

Some Shortened to **1-2 months**

## 2018

- (6) Pre-submissions
- (4) 510(k)s

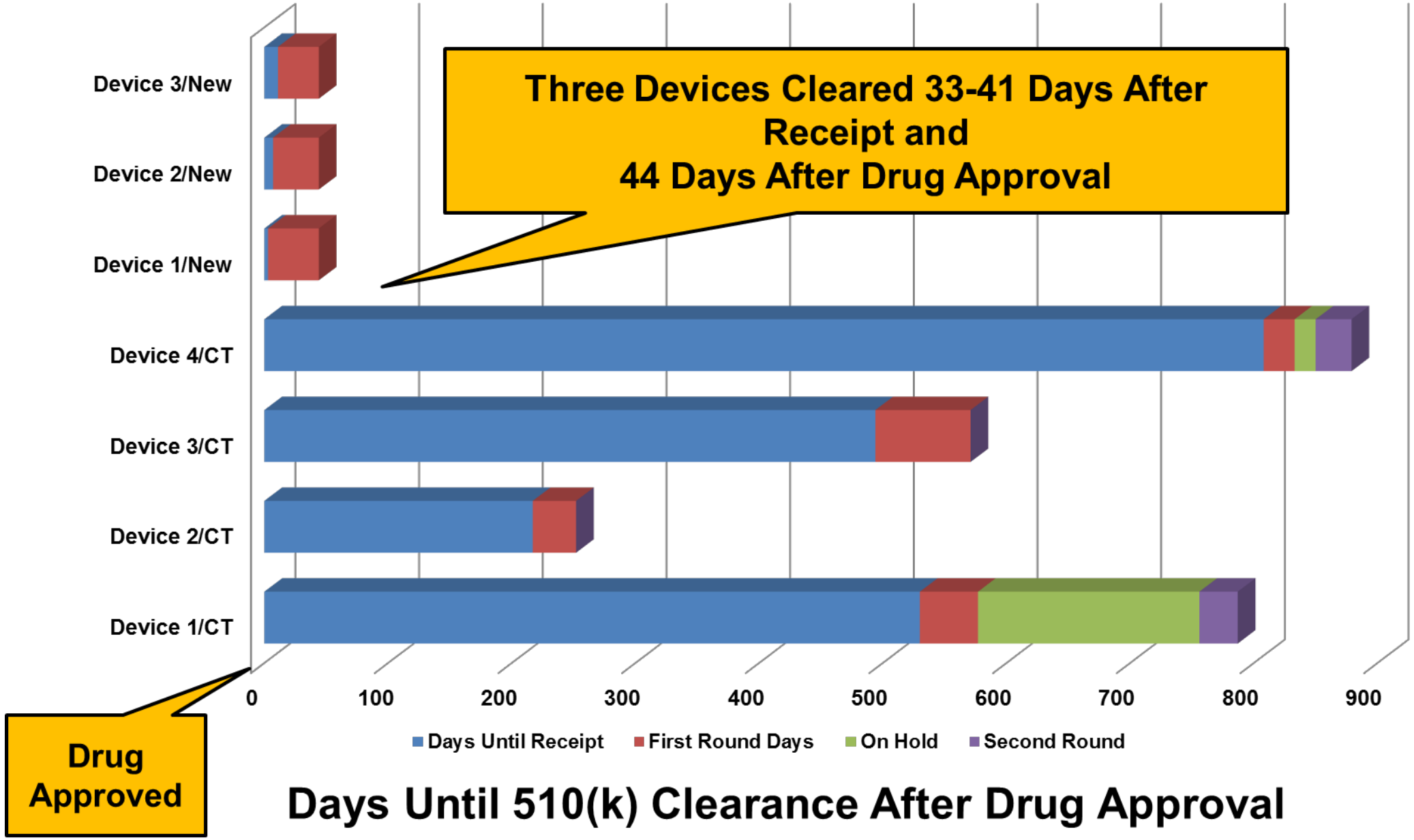
**New Drugs/New Devices**

- Plazomycin
- Omadacycline
- Eravacycline

*Timeline:* Drug Approval to Device Clearance

Some Shortened to **1-2 months**

# AFTER Coordinated Development



# Additional Advancements

- **The Centers for Disease Control and Prevention (CDC) & FDA Antimicrobial Resistant Isolate Bank**

*Isolates from the AR Isolate Bank can be used to support in vitro diagnostic device premarket submissions. To date, it has contributed to 13 clearances/approvals for Antimicrobial Susceptibility Test and other infectious disease test submissions since its launch in 2015.*

- **21st Century Cures**

# Benefits to Public Health

- Earlier availability of a diversity of antimicrobial susceptibility test diagnostics for improved patient care
- Contributes to antimicrobial stewardship
- Improved ability to monitor emergence of antimicrobial resistant strains

**With 21st Century Cures**

- Flexibility in drug testing and reporting
- Streamlined device updates and labeling

# Resources

- **AST Special Controls Guidance**

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm388961.pdf

- **Coordinated Development Guidance**

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM521421.pdf

- **Coordinated Development Guidance Docket**
  https://www.federalregister.gov/documents/2019/02/01/2019-00569/coordinated-development-of-antimicrobial-drugs-and-antimicrobial-susceptibility-test-devices

- **CDC & FDA Antimicrobial Resistant Isolate Bank**

https://www.cdc.gov/drugresistance/resistance-bank/index.html

- **FDA and 21st Century Cures**

https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm

# Questions?

Division of Industry and Consumer Education:
DICE@fda.hhs.gov

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http://www.fda.gov/training/cdrhlearn

Under Heading: Specialty Technical Topics; Subheading: In Vitro Diagnostics

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