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Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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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
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 \textit{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

- **21 CFR 866.1650**
- **21 CFR 866.3365**
- **21 CFR 866.3373**

**Culture Media**
- **21 CFR 866.1700**

**Test Discs**
- **21 CFR 866.1620**

**Automated Test Systems**
- **21 CFR 866.1645**

**Future Regulations**

**New Organism/Resistance Mechanisms**
- Nucleic Acid Amplification Test (NAAT)
- Mycobacterium tuberculosis (MTB)
- Lower Respiratory Tract (LRT)

**Multiplex NAAT**
- from LRT
- from colony, + blood culture, and direct specimen
- + blood culture

**Novel Technology**
- (Cellular Analysis System)
FDA Review of Traditional Drug and Device Submissions

Drug Manufacturer

- Investigational New Drug Application (IND) Submitted
  - CDER Review
  - New Drug Application (NDA) Submitted
    - CDER Review

Drug Approval, Final Breakpoints & Indicated Organisms

Device Manufacturer

- 510(k) Submitted
  - CDRRH Review
  - Antimicrobial Susceptibility Test Clearance
Microbiology Information: Drug

**Antimicrobial Drug Timeline**

- **IND/Phase I**
  - Basic microbiology profile
  - Research and development test method evaluation
  - Spectrum, mechanism of action, resistance, etc.

- **Phase II-III**
  - Establish drug-specific reference method & quality control organisms/ranges
  - Disk potency studies
  - Provisional minimum inhibitory concentration (and/or disk diffusion) breakpoint

- **NDA**
  - Submit Microbiology clinical trials data
  - Minimum inhibitory concentration /disk diffusion breakpoint correlates and quality control parameters
  - CDER reviews/approves quality control ranges and breakpoint
  - Drug labeling
**Microbiology Information: Antimicrobial Susceptibility Test Device**

**Antimicrobial Susceptibility Test Device Timeline (Disk)**

1. **R&D**
   - Drug manufacturer works with disk manufacturer to produce Investigational Use Only/ Research Use Only disks (their brand**) during phase II-III drug studies

2. **510(K)**
   - Disk manufacturer submits no new data to CDRH (references drug label information)
   - CDRH consults with CDER
   - Device FDA review is \( \leq 90 \text{ days} \) unless additional information/data is needed

*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

**Antimicrobial Susceptibility Test Device Timeline**

*(Minimum Inhibitory Concentration)*

**R&D**

- Sponsor can contact FDA with questions (pre-submission process)
- Device manufacturer conducts research and development
- Studies conducted on final design

**510(K)**

- 510(k) submitted in conformance with Antimicrobial Susceptibility Test Special Controls Guidance
- CDRH evaluates data, including minimum inhibitory concentration, breakpoint and indicated organisms from drug label
- FDA review is \( \leq 90 \text{ days} \) unless additional information/data is needed

*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)

- Drug approval to device submission
- Device review to decision (clearance or hold)
- Device manufacturer hold time
- Device review to decision (second review cycle after hold)
Coordinated Development

Improved Patient Care
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
  o Industry (**36**), Professional Societies (**11**), Trade Associations (**7**)  

• **4** Comment Types
  o 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**
• 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
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.
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
Antimicrobial Susceptibility Test Device Manufacturer

Pre-submission or Pre-submission Supplement(s)
- Plans for coordinated development
- Description of relationship with drug sponsor
- Anticipated need for Investigational Device Exemption (IDE)
- Plans for data collection and analysis
- Share 510(k) plans

A 510(k) may be submitted while the New Drug Application is under review

Pre-submission is not necessary but recommended during drug development

Device clearance can either coincide with or shortly after drug approval

Antimicrobial Susceptibility Device Clearance
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
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
- Omadacyclline
- Eravacycline

Timeline: Drug Approval to Device Clearance
Some Shortened to 1-2 months
AFTER Coordinated Development

Three Devices Cleared 33-41 Days After Receipt and 44 Days After Drug Approval

Days Until 510(k) Clearance After Drug Approval
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.

• 21\textsuperscript{st} 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

• Coordinated Development Guidance

• Coordinated Development Guidance Docket

• CDC & FDA Antimicrobial Resistant Isolate Bank
  https://www.cdc.gov/drugresistance/resistance-bank/index.html

• FDA and 21st Century Cures
Questions?

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Slide Presentation, Transcript and Webinar Recording will be available at:
http://www.fda.gov/training/cdrhlearn
Under Heading: Specialty Technical Topics; Subheading: In Vitro Diagnostics

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