FDA Perspective on Scientific Review of Novel Technologies for Detection of Resistance

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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

- Devices for Detection of Antimicrobial Resistance and FDA Experience with Submitted Applications
- Advances in Diagnostic Devices for Detection of Resistance Markers and Associated Challenges
- Resources Available to Aid in Evaluating New Technologies
- Summary
Timeline of AR Test Clearances

1976
Test Discs
Culture Media

1978
Test Cards
AST Systems

1984
DNA probe (MRSA)

1986
Phenotypic/Protein (PBP2a)

1999
Chromogenic Media

2002
Microarray Identification/Resistance (mecA, vanA/B)

2004
NAAT (MRSA)

2002
Phenotypic/Enzy. Activity (carbapenemase)

2004
NAAT (Carbapenemase genes)

2012
NGS, phage therapy

2016
Phenotypic/Enzy. Activity (carbapenemase)

2017
Novel Technology Identification/Resistance (Single Cell Analysis)

Is This a Golden Era for Developing Diagnostic Devices?
Different Regulations for ASTs

AR Regulations

Culture media
- 21 CFR 866.1700

Test Discs
- 21 CFR 866.1620

NAA and MTB-complex
- 21 CFR 866.3373

Multiplex NAA from + blood culture
- 21 CFR 866.3365

Novel Technology (Cellular Analysis System)
- 21 CFR 866.1650

NAATs from colony, + blood culture, and direct specimen
- 21 CFR 866.1640

Automated Test Systems
- 21 CFR 866.1645

Future Regulations

New Organism/Resistance Mechanisms
## Device Clearances: AST and Detection of Resistance & Markers 2011-2016*

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*Does not include pre-submissions*
The Shift in Technology is Having a Dual Effect

**SIMPLE**
- Little to No Sample Manipulation
- Limited Training To Run Device
- Reduced Workload
- "Rapid" Patient Results
- Less time on Maintenance/Calibration

**COMPLEX**
- New Technology
- Combined Device Functions
- Processing Different Specimen Types
- Detecting Multiple Targets
- Testing Multiple Drugs
- Compatibility with Other Devices

(viewpoint of Operator)
(viewpoint of Reviewer)
Challenge: Level of Evidence to Support Claims

What to Consider:
- Intended Use(s)
- Colonies versus direct from specimen
- Species (Types and Number)
- Multiple Genes
- Multiple Gene Variants
- Prevalence
- Different Resistance Mechanisms
- Balance—Wet-testing vs *in silico*
- Comparator Method *(molecular, phenotypic, Composite Reference)*
- Validation of New Comparator Methods
- Presentation of Data (Amount of Data)
- Results Interpretation /Labeling
Issues Encountered During Our Review of Molecular Submissions

- Determining an appropriate Reference Method for a molecular investigational device
- Assessing organism/resistance marker identification in the context of specimen types with known bacterial flora (colonizers vs. infection)
- Reporting of resistance markers without organism identification and what to communicate to end-users
- Presenting the detection of gene variants given the dynamic nature of antimicrobial resistance, prevalence, and new variants identified
Meeting the Challenge
(Review Teams)

1 Submission = 1 Reviewer

1 Submission = Team of Reviewers
Meeting the Challenge: Resources to Evaluate New Devices

- Collaborations
- Creativity (Innovative Study Design)
- Literature & Real-World Evidence
- Workshops
- De Novo Pathway
- Pre-submissions
- Review Teams
Meeting the Challenge  
*(Flexible Study Design)*

**Composite Reference Method (Hypothetical)**

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*Approach A*

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*Approach B*
Summary

- The number and the scope of diagnostic devices for detection of AR markers continue to increase.

- Current technologies identifying AR markers have introduced new regulatory and scientific challenges, prompting a dialogue with stakeholders.

- We will continue to discuss issues pertaining to detecting, reporting, and interpreting AR markers later in the Afternoon Panel.
Thank You!