Contains Nonbinding Recommendations

Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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Guidance for Industry and Food and Drug Administration Staff

GUIDANCE

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2016-D-2561. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance is intended to assist drug sponsors and device manufacturers who are planning to develop new antimicrobial drugs and antimicrobial susceptibility test (AST) devices and who seek to coordinate development of these products such that the AST device could be cleared either at the time of new drug approval or shortly thereafter.

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 AST device;
- Explain the considerations for submitting separate applications to the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) when seeking clearance of an AST device coincident with, or soon following, antimicrobial drug approval; and
- Clarify that the review of the new antimicrobial drug product and AST device(s) will remain independent, and that coordinated development does not influence the Medical Device User Fee Act (MDUFA) and the Prescription Drug User Fee Act (PDUFA) review timelines for either product.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or

recommended, but not required.

II. Background

Antimicrobial susceptibility testing is an important component in supporting the development of new antimicrobial drugs and the subsequent clinical use of these agents. In addition to informing the appropriate clinical use of antimicrobial drugs for individual patients, antimicrobial susceptibility testing used in epidemiological studies can identify the emergence of drug resistance and monitor overall population changes in antimicrobial susceptibility.

This guidance applies to AST devices, including qualitative disc diffusion or elution tests,[1] manual and automated systems that provide qualitative and quantitative susceptibility information,[2] and other growth-based devices[3] used for the testing of in vitro susceptibility of bacterial pathogens to antimicrobial drugs. This guidance may also apply to molecular-based devices that infer antimicrobial resistance through the detection of microbial resistance markers.

AST devices are subject to premarket notification 510(k) requirements. Such devices are often updated to accommodate new antimicrobial drugs or other improvements. A new submission is required for modifications to a cleared AST device when the modifications could significantly affect the safety or effectiveness of the device.[4] For example, when seeking to add a new antimicrobial drug to an existing AST panel, a 510(k) submission is generally required because this could significantly affect the safety or effectiveness of the device and is a major modification to the intended use of the device. Firms manufacturing a device of a type classified under 21 CFR 866.1645 must show that the device addresses the issues of safety and effectiveness identified in the Class II Special Controls Guidance Document on AST Systems,[5] either by meeting the special controls identified in the Class II Special Controls Guidance Document on AST Systems or by some other means that provides equivalent assurances of safety and effectiveness. Although AST devices classified under other classification regulations are not subject to these special controls, we recommend the studies and performance characteristics outlined in the Class II Special Controls Guidance Document on AST Systems to support 510(k) submissions for these devices.

Historically, the development of antimicrobial drugs and AST devices that test for in vitro antibiotic susceptibility of bacterial pathogens has not been optimally coordinated, with AST device development sometimes occurring late in the drug development process or after the drug development/approval process is completed. This has contributed to delays in the availability of AST devices for newly approved drugs. FDA encourages sponsors of new antimicrobial drugs and AST devices to collaborate early in the drug development process to minimize the time between the new antimicrobial drug approval and the clearance of an AST device that tests for in

[1] 21 CFR 866.1620.
[2] 21 CFR 866.1640; 21 CFR 866.1645.
[3] 21 CFR 866.1700.
[4] See 21 CFR 807.81(a)(3) and FDA Guidance, *Deciding When to Submit a 510(k) for a Change to an Existing Device*, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf.
[5] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm388961.pdf.

vitro susceptibility of pathogens to that drug product. Drug sponsors may benefit from this collaboration by having access to AST device technology during clinical studies of the antimicrobial drug, and AST device manufacturers may benefit by having access to clinical isolates obtained during the drug development process that may aid in device validation. Patients and health care professionals benefit by the early availability of AST devices to determine susceptibility to approved antimicrobial drugs.

III. Interactions Between Antimicrobial Drug Sponsors and AST Device Manufacturers

FDA encourages antimicrobial drug sponsors and AST device manufacturers to discuss coordinated development opportunities. Ideally, these discussions would occur early during new antimicrobial drug development to enable information helpful to the development of AST devices to be generated during clinical trials for the drug product. This approach may be broadly applicable to various types of AST devices, including AST broth dilution panels, disc diffusion or elution, or gradient diffusion devices used with antimicrobial test systems, and for new or existing molecular-based devices that can identify mutations associated with decreased antimicrobial susceptibility. The nature of these interactions can take many forms and need not be restricted to a single device manufacturer. Even simple availability of a drug to multiple device manufacturers for use during AST device development may translate to earlier AST device development and the ultimate goal of having clinical laboratory access to FDA-cleared AST devices at the time of drug approval or shortly thereafter.

In the circumstance where an AST sponsor has not directly coordinated development with the drug manufacturer, most of the principles described below remain applicable. AST sponsors who seek to submit a 510(k) application (e.g., for a disc AST) but have not coordinated development with the drug manufacturer as part of a New Drug Application (NDA) may obtain feedback on device development through the Q-Submission Program at CDRH.[6] For disc diffusion tests, where (or whose) performance data is available through reference to an NDA, such data may be sufficient to support a 510(k) submission by the AST sponsor who took part in those studies with the drug manufacturer.

IV. Considerations for Coordinated Development of Antimicrobial Drugs and AST Devices

Because the goal of coordinated development is timely clearance of an AST device, the device sponsor should utilize the Q-Submission Program to obtain feedback from FDA throughout the coordinated development process, as described below.

[6] CDRH feedback on device development can be obtained through the Q-Submission Program. Please refer to FDA *Guidance for Industry and Food and Drug Administration Staff, Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

FDA recommends that the AST device manufacturer submit a coordinated development plan through the Q-Submission Program[7] to CDRH for review and comment prior to or no later than shortly after the NDA submission. The plan should include: (1) identification of the antimicrobial drug under development; and (2) letters of authorization from the device manufacturer and drug sponsor permitting FDA to reference information from any relevant IND or NDA. Please refer to Appendix A in this document for information on critical points that should be considered in the coordinated development process. CDRH intends to consult with the CDER review team for the antimicrobial drug and provide joint feedback on the coordinated development plan.

After an initial Q-Submission has been submitted, additional Q-Submission supplements may be submitted, as appropriate, following NDA submission and during NDA review to facilitate a future 510(k) submission. In particular, FDA recommends an additional Q-Submission if the AST device under development is to be used in phase 2 and/or phase 3 drug clinical trial(s). Depending on the use, an investigational device exemption (IDE) may also be required (21 CFR part 812).

FDA welcomes joint meetings with the drug sponsor, the device manufacturer, and personnel from both CDER and CDRH at any point in the coordinated development process. The AST device manufacturer or drug sponsor may request such a meeting through the CDRH Q-Submission Program. If CDER participation is requested, CDRH intends to coordinate to include CDER.

FDA recommends submission of a 510(k) for the AST device 4 to 6 weeks before anticipated drug approval. The submission may be based on provisional susceptibility test interpretive criteria (breakpoints) and updated as needed when final breakpoints are identified or recognized by CDER. If appropriate documentation has been provided giving FDA permission to share information from the NDA with the AST device sponsor, FDA can communicate to the AST device sponsor information regarding breakpoint(s) and indicated organisms that are communicated to the drug sponsor during the NDA review process and prior to approval. Alternatively, if such agreements do not exist, the final breakpoints and indicated organisms would become publicly available once the drug is approved.[8] Regardless, CDRH review of the 510(k) submission can begin during the NDA review process to maximize the likelihood that AST device clearance can occur either coincident with or shortly after drug approval.

If the device manufacturer does not wish to solicit early FDA feedback on their device performance, coordinated development may still be achieved through direct interaction between the device and drug manufacturers without a Q-Submission for the device, with the 510(k) submission occurring prior to or shortly after drug approval. However, without prior FDA interaction through the Q-Submission process, there may be a delay in availability of the

[7] The Q-submission program provides several mechanisms for feedback from FDA, including face-to-face meetings, teleconferences, or written feedback. Additional information is provided in FDA *Guidance for Industry and Food and Drug Administration Staff, Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

[8] Information regarding FDA-recognized breakpoints is available at https://www.fda.gov/STIC.

device due to a potentially longer review time and/or the need for additional information to be submitted.

FDA intends to continue to make review decisions for the antimicrobial drug product and the AST device independently. Although coordinated development of the antimicrobial drug product with an AST device does not alter performance goals associated with review timelines, or approval or clearance of either product, FDA intends to facilitate clearance of the AST device coincident with or shortly after drug approval, as appropriate.

Appendix A below provides details regarding critical points in the coordinated development process.

APPENDIX A:

Review process for coordinated development with a device Q-Submission (refer to Figure A)

Each of the following steps should be considered optional, and individual device manufacturers may use pieces of the process below as applicable to their specific needs. However, FDA emphasizes that close communication during AST development can facilitate 510(k) review and successful device clearance coincident with or soon after drug approval.

1. During the drug development process, the device manufacturer submits an initial Q-Submission to solicit preliminary FDA feedback regarding their plans for coordinated development with the drug manufacturer, including, as appropriate, any anticipated need for an IDE and proposals for data collection and analysis.
2. The device manufacturer submits a supplement to the Q-Submission for the device, the content of which should describe the anticipated 510(k) submission and information based on provisional breakpoints provided by the drug manufacturer if available. (Note: There is no change in data submitted for an AST device using coordinated development for their 510(k). The information expected to be provided is the same as that described in the "Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems."[9])
3. FDA reviews each Q-Submission or Q-Submission supplement and communicates feedback regarding a future 510(k) submission to the sponsor. The device manufacturer may then provide CDRH with any necessary additional information in a Q-Submission supplement, or the requested information may be included in the 510(k) submission without prior FDA review.
4. A 510(k) can be submitted at any time during the NDA review process; however, it is strongly encouraged that interactions occur through the Q-Submission process and that formal 510(k) submission occur close to the anticipated time of drug approval (approximately 4-6 weeks prior to anticipated drug approval). For device clearance to 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.
5. CDRH and CDER intend to communicate during the drug review process such that when changes to tentative breakpoint(s) for the drug under review and indicated organisms as determined by CDER are communicated to the drug sponsor, this information can be communicated to the device manufacturer on condition that the drug and device manufacturer have the necessary agreements in place to enable such communication. Alternatively, if such agreements do not exist, the final breakpoints and indicated organisms would become publicly available once the drug is approved.
6. Once breakpoints are finalized by CDER, if necessary, the device manufacturer should modify the 510(k) package with the final data analysis using the approved breakpoints.

[9] Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

7. Assuming all issues previously communicated to the device manufacturer have been addressed and analysis of the data in the 510(k) confirms adequate performance, CDRH should be able to arrive at a regulatory decision coincident with or shortly after drug approval.
8. If there are circumstances that suggest a need for modification of the procedures noted above, they should be communicated to CDRH through the Q-Submission process.

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Figure A

Note: The figure below is an outline of the "process" of coordinated development and is intended to show the flow of information between the AST device manufacturer, the drug manufacturer, and FDA. As a representation of the overall process, it is not intended to convey exactly what information is required, nor the exact timing of the exchanges, which may differ based on the drug, the device, and the specifics of the relationship between their respective manufacturers. For example, it is not expected that CDRH and CDER review during the development stage will occur at identical times, or that a 510(k) application will be received by FDA the same day as the NDA submission.

