



**AdvaMed**

Advanced Medical Technology Association

701 Pennsylvania Avenue, NW  
Suite 800  
Washington, D.C. 20004-2654  
Tel: 202 783 8700  
Fax: 202 783 8750  
[www.AdvaMed.org](http://www.AdvaMed.org)

November 21, 2016

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

***Re: Docket No. FDA-2016-D-2561-0001; Draft Guidance for Industry and Food and Drug Administration Staff—Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices; Availability***

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (“FDA”) “Guidance for Industry and Food and Drug Administration Staff—Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test (“AST”) Devices (hereinafter “Coordinated Development Guidance”).

AdvaMedDx represents the world’s leading manufacturers of medical diagnostic tests, including those that are front-line tools in the fight against antibiotic resistance. Diagnostic manufacturers are developing critical tests to help reduce the threat of antibiotic resistance and will be a critical component in any strategy to help reduce the threat of antibiotic resistance. These innovative tests can be used to identify, monitor, track, treat, and prevent resistance and improve the judicious use of antibiotics.

## **GENERAL COMMENTS**

AdvaMedDx commends the FDA (or “Agency”) for the development of this guidance, which helps promote the public health and reflects FDA commitment to reducing antibiotic resistance. We also applaud the Agency’s broader efforts to speed the availability of ASTs for newly approved antibiotics or antibiotics with updated breakpoints, including FDA’s work to organize the September 29, 2016 public workshop.

We strongly agree with the statements in the Coordinated Development Guidance: “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, antimicrobial susceptibility testing used in epidemiological studies can identify the emergence of drug resistance and monitor overall population changes in antimicrobial susceptibility.”



We also appreciate that this Coordinated Development Guidance was developed in concert with the Center for Drug Evaluation and Research. Most notably, this Coordinated Development Guidance indicates the Agency's willingness to allow AST sponsors to submit a 510(k) for an AST contemporaneously with the New Drug Application (NDA). Previously, a sponsor of an AST had to wait until FDA approved the NDA to submit the 510(k). The Coordinated Development Guidance underscores the importance of early and coordinated engagement of AST developers and antimicrobial developers with FDA. We view the Coordinated Development Guidance as a helpful first step towards more comprehensive efforts to assist innovators and we laud the Agency for undertaking this effort.

However, the Coordinated Development Guidance by itself will not resolve the host of complex policy issues raised during the September 29 public workshop related to the challenges of ensuring availability of an AST either concurrently with, or soon after, approval of the drug. During the workshop, stakeholders, including drug manufacturers and clinicians, stated that there is unmet medical need for ASTs as months-to-years can elapse between when a new antimicrobial is available, and when the corresponding AST is available. This time lag is hurting high-quality patient care and public health.

For instance, several stakeholders indicated that without a cleared AST, clinicians are reluctant to use an antimicrobial, particularly a novel one. Detailing the challenges of treating a critically-ill patient in a hospital with a novel antimicrobial without an AST, one clinician stated: "You're a practicing clinician and your patient is failing therapy, is it because you're not giving enough drug? Is it because they've got a new infection, or is it because there's development of resistance on therapy? And therefore, you really need timely access to susceptibility tests." Drug manufacturers added that the availability of cleared susceptibility tests is vital to developing effective antimicrobial stewardship programs, as such tests are needed to "be able to detect the emergence of resistance, especially when a new antibiotic comes out. It is critically important to know whether there's a pattern of resistance development or not."

The September 29 public workshop demonstrated the need for a multi-pronged effort that goes beyond the current draft Coordinated Development Guidance. The Coordinated Development Guidance, for instance, does not address the important issue of incorporating new information about breakpoints of existing antimicrobials into the labeling of the AST. Currently, FDA will not consider a change to the labeling for an AST to reflect an updated breakpoint of an antimicrobial until the drug sponsor changes the drug labeling. Thus, if there is a delay in the change to the drug labeling, for whatever reason, the hands of the AST manufacturer are tied. During the workshop, FDA indicated that "FDA is currently exploring options for AST device manufacturers -- so that they can use up-to-date breakpoint information in their device labeling in a more timely manner."

FDA also indicated during the workshop that it is drafting a Frequently Asked Questions ("FAQs") document to clarify ambiguities in "Guidance for Industry and FDA, Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems" (hereinafter Special Controls Guidance). While we would appreciate clarification helpful to industry, we also think there are aspects of the Special Controls guidance where the document has a clear position, such as the expectation of Category Agreement, which should be revisited as discussed below.

We would welcome the opportunity to collaborate with FDA on the broader issues raised in the workshop, including possibly revising the Special Controls Guidance and discussing mechanisms to update labeling with new breakpoints in a more timely fashion.

In addition, while we look forward to a broader discussion in the near future, for now, we have noted areas of specific comments to the Coordinated Development Guidance. These comments are intended to support FDA key objectives to provide clarity to industry and support the optimal adoption of the guidance.

## **SPECIFIC COMMENTS**

AdvaMedDx's specific comments on the draft guidance follow, which provide more detailed recommendations and points for additional clarification in issuing final guidance. A line-numbered version of the draft guidance is also attached for your reference.

### **Addressing Changes to Breakpoints/Claimed Organisms during FDA NDA Review**

FDA should add language to the Guidance for AST developers in the event that drug breakpoints and/or claimed organisms change during the FDA review of the NDA. The Special Controls Guidance calls for Category Agreement (performance calculated using antibiotic breakpoints) for clinically relevant organisms as the criteria for clearance of AST devices. As a result, the Center for Devices and Radiological Health (CDRH) cannot grant clearance of an AST until FDA has approved the antimicrobial drug indications, specifically the clinically relevant organisms and breakpoints. The breakpoints and claimed organisms can change very late in the drug approval cycle as labeling is one of the last items in the NDA to be negotiated between the drug sponsor and FDA.

These potential changes raise great uncertainty for AST developers, and act as a disincentive for coordinated development. AST development is performed based on input from the drug company, which provides its best educated guess at the time that it submits the NDA as to what the breakpoints/claimed organisms will ultimately be. If the drug company's best guess for the breakpoints is close, but not exact, the data for the AST 510(k) submission would need to be repackaged and reanalyzed. If the drug company is "off" in its guess, then the AST developer would need to re-conduct analytical and clinical testing, wasting both time and money.

We recommend that FDA consider, among other potential options to address this issue, granting clearance to the AST based on Essential Agreement (agreement within plus or minus, one two-fold dilution of the new device under evaluation with the reference method minimal inhibitory concentration) instead of Category Agreement. As an alternative, we would recommend that the breakpoints and claimed organisms are reviewed earlier in the drug approval process. Without language to address this issue, AST developers will be concerned that development of ASTs earlier in the NDA review process will amount to a gamble that they could lose if the drug sponsor's estimate of the breakpoints and claimed organisms turns out to be incorrect.

## **Investigational Use**

While AdvaMedDx is in general concurrence with this Coordinated Development guidance, we are concerned with the potential expectation that an investigational device exemption (“IDE”) study may be needed in addition to an investigational new drug (IND) study “if the AST device under development (*e.g.*, a rapid susceptibility testing device) is to be used for clinical trial enrollment...”

We believe that an IND should be able to incorporate necessary elements so that the same clinical trial can be conducted for both products under the IND in most cases. We fully support use of one or more pre-submission meetings to help coordinate review and active involvement among the relevant Centers and assure study design that supports appropriate validation of the AST to support clearance.

We recommend that FDA explicitly allow for an IND when an AST and antimicrobial are to be studied together. We see no specific advantage in requiring an additional IDE submission in such cases, which would likely create unnecessary redundancy, tie up FDA resources, and delay the review process.

While we do not support an expectation for an IDE, any such expectation should not be imposed by FDA on early studies (*i.e.*, Phase 1 and 2). Furthermore, in the event where sponsors have opted to conduct two investigational submissions (*i.e.*, IND and IDE), FDA should provide guidance to assist with the coordination of these submissions. In that vein, FDA should add the following sentence after line 140: “To assist with coordination between the two relevant Centers in the review of an IND and IDE, the sponsor could submit a letter to both Centers.” This would support a clear process for coordinating the FDA review of these submissions.

AdvaMedDx appreciates the Agency’s development of this helpful guidance. We hope our comments are useful as FDA moves to issue final guidance and develop additional initiatives to accelerate the availability of ASTs soon after development of new antimicrobials. These collective initiatives are welcomed by industry and will play an important role in supporting the development of new AST innovations, paving the way for advancements in combatting antimicrobial resistance.

Respectfully submitted,

/s/

Jamie K. Wolszon  
Associate Vice President  
Technology and Regulatory Affairs

*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](mailto:ribhi.shawar@fda.hhs.gov). For questions for CDER, contact Joseph Toerner at 301-796-1400, or [joseph.toerner@fda.hhs.gov](mailto:joseph.toerner@fda.hhs.gov).



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*

*Draft – Not for Implementation*

## **Preface**

### **Additional Copies**

Additional copies are available from the Internet. You may also send an e-mail request to [CDRH-Guidance@fda.hhs.gov](mailto:CDRH-Guidance@fda.hhs.gov) to receive a copy of the guidance. Please use the document number 1400061 to identify the guidance you are requesting.

Additional copies of this guidance document are also available from:

Center for Drug Evaluation and Research  
Division of Drug Information  
10903 New Hampshire Ave., Bldg. 51, rm. 2201  
Silver Spring, MD 20993-0002  
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Table of Contents**

I. Introduction .....	1
II. Background .....	2
III. Interactions between Antimicrobial Drug Sponsors and AST Device Manufacturers .....	3
IV. Considerations for Coordinated Development of Antimicrobial Drugs and AST Devices	4

**DRAFT**

1 **Coordinated Development of**  
2 **Antimicrobial Drugs and**  
3 **Antimicrobial Susceptibility Test**  
4 **Devices**

---

7 **Draft Guidance for Industry and**  
8 **Food and Drug Administration Staff**  
9

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

16 **I. Introduction**  
17

18 This guidance, when finalized, is intended to assist drug sponsors and device manufacturers who  
19 are planning to develop new antimicrobial drugs and antimicrobial susceptibility test (AST)  
20 devices and who seek to coordinate development of these products such that the AST device could  
21 be cleared either at the time of new drug approval or shortly thereafter.  
22

23 Specifically, the guidance intends to accomplish the following:

- 24 • Describe interactions between drug sponsors and device manufacturers for coordinated  
25 development of a new antimicrobial drug and an AST device;
- 26 • Explain the considerations for submitting separate applications to CDER and CDRH when  
27 seeking clearance of an AST device coincident with, or soon following, antimicrobial drug  
28 approval; and
- 29 • Clarify that the review of the new antimicrobial drug product and AST device(s) will  
30 remain independent, and that coordinated development does not influence the  
31 MDUFA and PDUFA review timelines for either product.  
32

33 FDA's guidance documents, including this guidance, do not establish legally enforceable  
34 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

35 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
36 cited. The use of the word “should” in Agency guidances means that something is suggested or  
37 recommended, but not required.

## 38 **II. Background**

39  
40 Antimicrobial susceptibility testing is an important component in supporting the development of  
41 new antimicrobial drugs and the subsequent clinical use of these agents. In addition to informing  
42 the appropriate clinical use of antimicrobial drugs, antimicrobial susceptibility testing used in  
43 epidemiological studies can identify the emergence of drug resistance and monitor overall  
44 population changes in antimicrobial susceptibility.

45  
46 The development of antimicrobial drugs and AST devices that test for in vitro susceptibility of  
47 bacterial pathogens isolated from clinical specimens to antimicrobials has traditionally occurred  
48 independently, with AST device development often initiated following drug approval.  
49 Coordinated development of new antimicrobial drugs with AST devices can potentially minimize  
50 the time between the approval of a new antimicrobial drug and clearance of an AST device that  
51 tests for in vitro susceptibility of pathogens to that drug product. Coordinated development also  
52 offers possible benefits to both the drug sponsor and device manufacturer during the antimicrobial  
53 drug and AST device development processes. Drug sponsors may benefit by having access to  
54 AST device technology that may be valuable during clinical studies. AST device manufacturers  
55 may similarly benefit by having access to clinical samples and isolates obtained during the drug  
56 development that may aid in validation of the device. These benefits may be particularly  
57 applicable to molecular-based and other devices that infer antimicrobial resistance through the  
58 detection of microbial resistance markers.

59  
60 AST devices are regulated by CDRH. These devices include AST discs,<sup>1</sup> automated AST  
61 systems,<sup>2</sup> and other devices used for the testing of in vitro susceptibility of bacterial pathogens to  
62 antimicrobial drugs. In general, a premarket notification (510(k)) submission is required for an  
63 AST device being introduced into commercial distribution for the first time, or for changes or  
64 modifications to a cleared AST device, where the modifications could significantly affect the  
65 safety or effectiveness of the device. See sections 510(k), 513(f), and 513(i) of the Federal Food,  
66 Drug, and Cosmetic Act (FD&C Act); 21 CFR 807.81. For example, when seeking to add a new,  
67 approved antimicrobial drug to an existing AST panel used with an automated AST system, a  
68 510(k) submission is generally required because this could significantly affect the safety or  
69 effectiveness of the device and is a major change or modification to the intended use of the  
70 device. 510(k) submissions are typically provided to FDA for such AST devices subsequent to the  
71 approval of an NDA for a new antimicrobial drug. The time between NDA approval and  
72 submission of a 510(k) for an AST device that incorporates the new antimicrobial drug is  
73 primarily due to the time it takes manufacturers to develop and test AST devices with the new  
74 antimicrobial drug and time to prepare the necessary regulatory submission. Minimizing the time

---

<sup>1</sup> 21 CFR 866.1620.

<sup>2</sup> 21 CFR 866.1645.

## *Contains Nonbinding Recommendations*

### *Draft – Not for Implementation*

75 between approval of new NDAs and clearance of related AST devices would more quickly enable  
76 these AST devices to be accessible for clinical use in assessing in vitro pathogen susceptibility.  
77 This would also be true for molecular-based or other assays that identify genetic markers or  
78 mutations associated with phenotypic resistance as determined by traditional AST device  
79 methods.

80  
81 There are several other FDA guidances that may be of interest to developers of new antimicrobial  
82 drug products or AST devices. The guidance “Microbiological Data for Systemic Antimicrobial  
83 Drug Products — Development, Analysis, and Presentation,” available at  
84 [http://www.fda.gov/downloads/  
85 Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf), addresses the  
86 microbiological data that FDA recommends be submitted for new antimicrobial drug product  
87 development. The guidance “Class II Special Controls Guidance Document: Antimicrobial  
88 Susceptibility Test (AST) Systems,” available at: [http://www.fda.gov/medicaldevices/  
89 deviceregulationandguidance/guidancedocuments/ucm080564.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080564.htm), identifies specific risks  
90 associated with automated short-term incubation cycle AST systems and describes measures that,  
91 if followed by manufacturers and combined with the general controls, will generally address the  
92 risks associated with these AST devices prior to marketing such a device. There are also FDA  
93 guidances that address related issues, e.g., the development of molecular multiplex assays that  
94 may include the detection of resistance markers.

95  
96 Coordinated development of an antimicrobial drug and an AST device as discussed in this  
97 guidance is distinct from the discussion of in vitro companion diagnostic devices in the FDA  
98 guidance entitled “In Vitro Companion Diagnostic Devices; Guidance for Industry and Food and  
99 Drug Administration Staff,” available at:  
100 [http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/  
101 GuidanceDocuments/UCM262327.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf). As described in this guidance, FDA has traditionally not  
102 considered microbiology diagnostics to be companion diagnostic devices, i.e., “as an in vitro  
103 diagnostic device that provides information that is *essential* for the safe and effective use of a  
104 corresponding therapeutic product” (emphasis added).

### **III. Interactions between Antimicrobial Drug Sponsors and AST Device Manufacturers**

105  
106  
107  
108 FDA encourages antimicrobial drug sponsors and AST device manufacturers to discuss  
109 coordinated development opportunities during antimicrobial drug development with each  
110 other. These discussions should take place early during drug development to enable  
111 information helpful to the development of AST devices to be generated during the clinical  
112 trials for the drug product. This approach may be broadly applicable to various types of AST  
113 devices, including AST broth dilution panels, disc diffusion, or gradient diffusion devices  
114 used with antimicrobial test systems, or new or existing molecular-based devices that can  
115 identify mutations associated with decreased antimicrobial susceptibility. The nature of these  
116 interactions can take many forms and need not be restricted to a single device manufacturer.  
117 The availability of a drug to multiple device manufacturers for use during AST device

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

118 development may increase clinical laboratories' access to AST devices at the time of drug  
119 approval or shortly thereafter.

120 **IV. Considerations for Coordinated Development of**  
121 **Antimicrobial Drugs and AST Devices**  
122

123 Coordinated development of antimicrobial drugs and AST devices depends on agreements  
124 between the antimicrobial drug sponsor and AST device manufacturer. We recommend that if  
125 proceeding with coordinated development, both the drug sponsor and AST device manufacturer  
126 submit their coordinated development plans to CDER and CDRH, respectively, for review and  
127 comment.<sup>3</sup> FDA also welcomes joint meetings with the drug sponsor and device manufacturer  
128 and personnel from both CDER and CDRH to address issues that affect the coordinated  
129 development of both the drug and AST device. Usually such meetings would be requested by an  
130 AST device manufacturer through the CDRH pre-submission process, which can also be used to  
131 obtain recommendations regarding the AST device under development. The CDRH pre-  
132 submission process should be used to communicate with CDRH plans for coordinated  
133 development of antimicrobial drugs and AST devices. In addition, drug sponsors should submit  
134 such information in their investigational new drug application (IND).  
135

136 In general, an investigational device exemption (IDE) is not needed for the investigation of AST  
137 devices if the requirements and conditions of 21 CFR 812.2(c)(3) are met. However, if the AST  
138 device under development (e.g., a rapid susceptibility testing device) is to be used for clinical trial  
139 enrollment, an IDE may be needed for the device (21 CFR part 812).<sup>4</sup> This should also be  
140 discussed with CDRH through the pre-submission process.  
141

142 If coordinated development of a drug and an AST device is pursued, CDRH can communicate  
143 with CDER and review the 510(k) submission during the NDA review process, to maximize the  
144 likelihood that AST device clearance can occur either coincident with or shortly after drug  
145 approval. For device clearance to occur either coincident with or shortly after drug approval, the  
146 AST device 510(k) submission should be submitted early enough to allow sufficient time for FDA  
147 to complete its review. In the 510(k) submission, appropriate permissions to FDA from the drug  
148 sponsor to cross-reference information from the NDA should be provided in the 510(k)  
149 submission to facilitate AST device review.  
150

---

<sup>3</sup> CDRH feedback on device development can be obtained through the pre-submission program. See *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: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>. Information regarding the CDER pre-IND consultation program for the Office of Antimicrobial products is available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>.

<sup>4</sup> For IND requirements applicable to drug development, please consult IND regulations and relevant CDER materials, such as “Development & Approval Process (Drugs),” available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>.

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

151 Despite coordinated development, FDA will continue to make review decisions for the  
152 antimicrobial drug product and the AST device independently, i.e., coordinated development of  
153 the antimicrobial drug product with an AST device would have no effect on our reviews, review  
154 timelines, or approval or clearance of either product, other than facilitating clearance of the AST  
155 device coincident with or shortly after drug approval, as appropriate.

DRAFT