FDA Executive Summary

Prepared for the September 8, 2023 meeting
of the Microbiology Devices Panel of the Medical Devices Advisory Committee
to discuss in vitro diagnostic devices used in pandemic preparedness and response

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I. Introduction

This document is the U.S. Food and Drug Administration (FDA or the "Agency") Executive Summary for the Microbiology Devices Panel of the Medical Devices Advisory Committee Meeting session to be held on September 8, 2023 discussing in vitro diagnostic (IVDs) devices used in pandemic preparedness and response.

The sessions on September 7, 2023 will be reserved for discussion on the potential future reclassification of certain Hepatitis B virus (HBV), Parvovirus, and Tuberculosis (TB) devices. The Executive Summary for those sessions will be provided separately. The panel meetings will be held in a virtual format over the course of two days and includes time for FDA presentations, open public comment, questions by the panel, and panel deliberation.

FDA plays a central role in the nation's response to pandemics and protecting the public health. FDA continues to prepare to combat future threats and ensure access to safe and effective medical products in response to those threats. A critical element in pandemic preparedness and response is ensuring IVDs are available or can be made readily available in a timely fashion, as IVDs generally are used to identify the presence of an emerging disease threat. Further, testing is vital to diagnose infected individuals and understand spread of an emerging disease in preparation for and during a pandemic.

Within FDA, the Center for Devices and Radiological Health (CDRH) regulates IVDs and is responsible for assessing the safety and effectiveness of IVDs which may be used in response to an emerging infectious disease in an effort to combat pandemic threats. The purpose of the session on September 8, 2023, is to discuss prospective actions and identify opportunities to strengthen and improve the Agency's preparedness and response to future pandemics with respect to IVDs. This session is also consistent with the requirements under section 3302 of the Food and Drug Omnibus Reform Act of 2022, which was signed into law as part of the Consolidated Appropriations Act, 2023 (Pub. L. 117-328).

II. Background Information

Accurate and reliable IVDs (also referred to as tests) are critical to the detection, tracking, treatment, and suppression of transmission during outbreaks of infectious disease and other actual or potential emergencies. The global COVID-19 pandemic was a public health crisis of unprecedented scale and severity. Numerous assessments have been performed either on behalf of the FDA or by other parts of the U.S. government to assess FDA's response to the demands for COVID-19 testing as well as provide recommendations for future challenges and

pandemics.[1, 2, 3] CDRH is actively working to implement recommendations provided in these reports to proactively prepare for and respond to future pandemics. The input provided during this session will assist FDA in building the Agency's resilience to prepare and respond to future pandemics.

FDA plays a critical role in a pandemic response. The Agency has specific statutory authorities for use in an actual or potential emergency and FDA's pandemic and all-hazards preparedness framework provides a foundation for much of the Agency's response.[4] CDRH continues to learn from our experiences with past pandemics and continues to identify new opportunities to strengthen our pandemic preparedness. CDRH believes that we gained valuable insight based on our recent experience with the COVID-19 pandemic from which we can generate a summary of options for the Agency to consider in future pandemic preparedness and response and is an ideal starting point for Panel discussion, serving to identify opportunities to strengthen our future pandemic responses.

Accordingly, CDRH believes it might be helpful to provide some examples of CDRH's COVID-19 response strategies and approaches to serve as the basis for discussion and continued learning beyond the COVID-19 pandemic. Examples of CDRH's COVID-19 response activities included the following:

- Reviewed over 6000 emergency use authorization (EUA) requests and pre-EUA requests and issued over 400 EUAs for COVID-19 tests in addition to early engagement with commercial and laboratory test developers (hereafter referred to collectively as "test developers") about potential EUAs through pre-EUAs;

- Published COVID-19 Test Policy guidances that announced CDRH's review priorities and enforcement policies for tests;

- Published several templates for EUA submissions, which outlined key information test developers should develop and submit to support EUA requests for a variety of test types;

- Regularly engaged with industry, healthcare providers, policy makers, federal partners, and other external stakeholders, including the American public; and

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[1] See the Office of Inspector General (OIG) report titled "FDA Repeatedly Adapted Emergency Use Authorization Policies To Address the Need for COVID-19 Test" available at https://oig.hhs.gov/oei/reports/OEI-01-20-00380.pdf.
[2] See the US Government Accountability Office (GAO) report titled "FDA Took Steps to Make Tests Available for Future Public Health Emergencies Needed" available at https://www.gao.gov/assets/gao-22-104266.pdf.
[3] See the Booz Allen Hamilton report titled "Emergency Use Authorization Assessment – Final Report" available at https://www.fda.gov/media/152992/download.
[4] FDA Pandemic and all-hazards preparedness reauthorization Act of 2013 (PAHPRA).

- Engaged with manufacturers and other members of industry to support supply chain stability and mitigate potential test shortages.

IVD Emergency Use Authorizations (EUAs)

Under section 319[5] of the Public Health Service (PHS) Act, the U.S. Department of Health and Human Services (HHS) Secretary can issue a determination (also referred to as a "declaration") that a "public health emergency" (PHE) exists. Separately, under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the HHS Secretary can issue a determination that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a chemical, biological, radiological, or nuclear (CBRN) agent or agents, or a disease or condition that may be attributable to such agent or agents. Based on such a determination under section 564 of the FD&C Act, the HHS Secretary may declare that circumstances exist justifying the authorization of emergency use of medical products.

Subject to the provisions of section 564, the FDA Commissioner may then authorize the introduction into interstate commerce of a drug, device, or biological product intended for use in an actual or potential emergency (EUAs).[6] EUAs can be issued for unapproved medical products, or unapproved uses of approved medical products, when certain statutory criteria are met including when the Commissioner concludes it is reasonable to believe that the product "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions that can be caused by the CBRN agent(s) identified in the HHS Secretary's determination that there is a public health emergency, or a significant potential for a public health emergency, under section 564(b). The "may be effective" standard for EUAs provides for a lower level of evidence than the "reasonable assurance of effectiveness" standard that governs traditional device authorizations (e.g., traditional IVD marketing submissions such as a premarket approval application (PMA) or premarket notification submissions (510(k)). The EUA authorities allow FDA to help strengthen the nation's public health protections against CBRN agents and diseases or conditions that may be attributable to such agents by facilitating the availability and use of medical countermeasures when there is a public health emergency or a significant potential for a public health emergency. An EUA for a test can be issued when, among other things, FDA concludes that, based on the totality of scientific evidence available to it, it is reasonable to believe that the test may be effective in diagnosing in patients the relevant disease or condition, and the known and potential benefits of the test, when used to diagnose such disease or condition, outweigh the known and potential risks of the test. FDA's guidance "Emergency Use Authorization of Medical Products and Related Authorities" explains FDA's general

[5] Available at https://www.congress.gov/109/plaws/publ417/PLAW-109publ417.htm.
[6] As provided in section 1003 of the FD&C Act and existing delegations of authority (found in the FDA Staff Manual Guide 1410.10), the Secretary of Health and Human Services (HHS Secretary or Secretary of HHS) has delegated most of the authorities under sections 564 to the Commissioner of FDA (Commissioner).

recommendations and procedures applicable to the authorization of the emergency use of certain medical products under section 564, including IVDs.[7]

FDA has exercised its EUA authority to authorize IVDs in actual or potential emergencies for emerging infectious diseases for influenza A H1N1 (2009), avian influenza A H7N9 (2013), MERS-CoV (2013), Ebola (2014), Enterovirus D68 (2015), Zika (2016), COVID-19 (2020), and mpox (2022).[8] Generally, when FDA reviews an EUA request for an IVD the Agency is reviewing analytical and clinical validation studies of the device to determine whether an EUA authorization is appropriate. Past examples of EUA-authorized IVDs can be found on FDA's website.[9] In the context of an actual or potential emergency involving pandemic infectious disease, it is critically important that tests are validated because false results not only can negatively impact the individual patient but also can have a broad public health impact.

Upon issuance of an EUA, test developers become EUA holders and receive a letter of authorization from FDA. This letter of authorization includes a number of conditions of authorization that are requirements for the EUA holder, and in some instances, requirements for associated entities involved in the distribution or use of the EUA-authorized test (e.g., authorized distributors). In past pandemics, these conditions of authorization have included requirements to monitor for impacts of microorganism mutations, complete testing with an FDA recommended reference material, include certain labeling information, certain requirements for postmarket reporting of adverse events to CDRH, and when to request additional authorization from CDRH.

To help prepare for potential emergencies, CDRH can also work with test developers to prepare pre-EUA packages, when appropriate.[10] A pre-EUA package contains data and information about the safety, effectiveness and quality of the product, its intended use under a future or current EUA, and information about the emergency or potential emergency situation. The pre-EUA process allows FDA scientific and technical subject matter experts to begin a review of information and assist in the development of conditions of authorization, fact sheets, and other documentation that would be needed for an EUA in advance of an actual or potential emergency and also helps to facilitate complete EUA requests while a section 564 declaration is in effect. Please note that since FDA cannot authorize EUAs unless there is an applicable section 564 declaration, Pre-EUAs cannot be transitioned to EUAs until such time.

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[7] Available at https://www.fda.gov/media/97321/download.
[8] For a list of current EUAs see FDA's website available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.
[9] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.
[10] Pre-EUA information for manufacturers of IVD tests is available on FDA's website at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/how-submit-pre-eua-in-vitro-diagnostics-fda.

EUA-related Guidances and EUA Templates

The issuance of an EUA is discretionary and FDA's decision to review and process an EUA request, and ultimately issue an EUA if the relevant statutory criteria are met, is based on a determination, on a case-by-case basis, that such action is necessary to protect the public health.[11] FDA may issue an EUA only if FDA concludes that the statutory criteria for issuance have been met.
More information on the statutory criteria for issuance of an EUA under section 564 of the FD&C Act and additional FDA authorities is available in FDA's guidance "Emergency Use Authorization of Medical Products and Related Authorities."[12]

FDA's review of requests to issue an EUA is based on a number of factors including the availability and adequacy of the information concerning the likelihood that the product may be safe and effective in preventing, treating, or diagnosing the condition, whether the request is from (or supported by) a government stakeholder, and the extent to which the product would serve a significant unmet medical need.[13]

As part of the Agency's response to the COVID-19 pandemic, FDA published and reissued a guidance document on our website that provided FDA's review priorities for IVDs used in response to the pandemic. [14] During the COVID-19 pandemic, CDRH authorized two general types of tests. The first were diagnostic tests, either molecular or antigen tests, intended to identify active infection with COVID-19. These tests may be intended for use in various settings including in a CLIA-certified laboratory, at the point of care at a site covered by a laboratory's CLIA certificate, or at home. Screening tests, which are intended for use in testing individuals without symptoms or other reasons to suspect COVID-19, are a subset of diagnostic tests. The second type of test authorized by CDRH during the COVID-19 pandemic was serology tests. Serology tests (or antibody tests) are generally used to refer to tests that are intended to detect antibodies to the SARS-CoV-2 virus. Because the antibodies are part of the body's immune response to exposure and not the virus itself, such testing cannot be used for diagnosis of acute infection.

Prioritization of certain IVD EUA requests allowed FDA to best allocate limited resources, which became critical as FDA faced an ever increasing and unprecedented number of EUA IVD

[11] Section 564(a)(1) of the FD&C Act states, in relevant part, "subject to the provisions of this section, the Secretary may authorize the introduction into interstate commerce…of a drug, device, or biological product intended for use in an actual or potential emergency."
[12] https://www.fda.gov/media/97321/download
[13] Additional factors FDA considers in prioritization of requests are discussed in FDA's guidance "Emergency Use Authorization of Medical Products and Related Authorities" available at https://www.fda.gov/media/97321/download.
[14] The current version of FDA's guidance "Policy for Coronavirus Disease-2019 Test (Revised)" issued on January 12, 2023 is available at https://www.fda.gov/media/135659/download. This version is the seventh edition of this guidance, which originally issued on February 29, 2020, and was subsequently revised on March 16, May 4, May 11, 2020, November 15, 2021, and September 27, 2022.

submissions. By the end of fiscal year 2021, CDRH received more than 3,000 EUA requests from COVID-19 test developers and CDRH prioritized the review of certain EUA requests to manage its resources in light of the record-number of EUA submissions. For example, at certain stages of the COVID-19 pandemic there was a need for rapid, more accessible COVID-19 diagnostic tests, such as over-the-counter diagnostic tests, and CDRH prioritized the review of EUA requests for over-the-counter COVID-19 diagnostic tests over many other types of COVID-19 tests. In addition, between January 2020 and September 2021, CDRH received 1,275 pre-EUA requests for COVID-19 tests to obtain the Agency's feedback on what might be needed for a successful EUA.

As described in FDA guidance documents for COVID-19 tests, FDA made available on our website EUA templates (which are part of the *Policy for Coronavirus Disease-2019 Tests (Revised)* guidance) that reflect the FDA's current thinking on the data and information that test developers should submit to facilitate the EUA process.[15] FDA followed a similar approach for mpox[16] tests during the mpox outbreak.[17] The COVID-19 test policy guidance and EUA templates were updated by FDA throughout the pandemic in response to the changing landscape and to reflect the needs of the pandemic at that stage in time. For example, in a prior version of FDA's Policy for Coronavirus Disease-2019 Tests issued on November 15, 2021, CDRH announced that at that stage of the COVID-19 pandemic, the Agency generally intended to focus its review on certain EUA requests including those requests for at-home and point-of-care (POC) diagnostic tests for use with or without a prescription and that can be manufactured in high volumes. FDA's review priorities for EUA requests for mpox IVDs during the mpox declaration followed a different approach given a different set of circumstances and generally FDA prioritized the review of EUA requests for high-throughput diagnostic tests, tests with home specimen collection, or rapid diagnostic tests, all from experienced developers with high manufacturing capacity.[18]

In addition to announcing FDA's review priorities, earlier versions of FDA's Policy for Coronavirus Disease-2019 Tests guidance described enforcement policies regarding the distribution and offering of certain SARS-CoV-2 diagnostic tests for clinical use prior to or without an EUA. These policies were issued to help quickly increase availability of tests in the early stages of the COVID-19 pandemic. For example, during the early stages of the COVID-19 pandemic, FDA did not object to certain commercial manufacturers development and distribution of SARS-CoV-2 diagnostic test kits to clinical laboratories or to healthcare workers for point-of-care testing prior to an EUA for a reasonable period of time, where the test had been

[15] See e.g., FDA's EUA templates for COVID-19 tests available on FDA's website at https://www.fda.gov/medical-devices/covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdtemplates.
[16] As explained on FDA's website (https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/fda-mpox-response), on November 28, 2022 the World Health Organization announced the name "mpox" to replace what was previously referred to as monkeypox. This document reflects this change, however, some material created prior to this change may still reflect the old name.

[18] FDA's guidance "Policy for Monkeypox Tests to Address the Public Health Emergency" is available at https://www.fda.gov/media/161443/download/.

validated and while the developer was preparing their EUA request, and where the developer provided notification of validation to FDA, among other things. Note that these policies have since been updated by FDA in response to the changing landscape of the pandemic and FDA is generally continuing those updated policies as discussed in FDA's Policy for Coronavirus Disease-2019 Tests (Revised) issued on January 12, 2023.[19]

Unless and until an EUA was issued that authorized additional testing environments for a specific test, under the Clinical Laboratory Improvement Amendments (CLIA), use of that test was limited to laboratories certified to perform high complexity testing, including testing at the point-of-care when the site was covered by the laboratory's CLIA certificate for high-complexity testing. However, these policies did not apply to at-home tests or tests with home specimen collection. As described in that guidance, FDA believed that 15 business days was a reasonable time period to prepare an EUA submission for a SARS-CoV-2 diagnostic test that had already been validated. Soon after receiving the EUA request, FDA performed a preliminary review to identify if there are any problems with the performance data. If a problem was identified, FDA worked with the manufacturer to address the problem (e.g., through labeling or bench testing). If the problem was significant and couldn't be addressed in a timely manner, and the manufacturer had already distributed the device, FDA expected the manufacturer to suspend distribution and conduct a recall of the test.

Also, as outlined in FDA's Policy for Coronavirus Disease-2019 Tests guidance issued on March 16, 2020, FDA generally did not intend to object to serology test developers distributing and offering certain tests without an EUA as long as the test was validated, the FDA was notified, and test reports included important information about limitations, including statements indicating that the test had not been reviewed by the FDA and that results could not be used to diagnose or exclude infection. The policy included additional considerations that limited the use of those serology tests to laboratories certified by the Centers for Medicare and Medicaid Services to perform high-complexity testing under CLIA. Developers of serology tests intended for use in homes or at the point of care, such as in physicians' offices (unless they were covered by a laboratory's CLIA certificate), still had to submit an EUA application and have their tests authorized by the FDA. Following the issuance of this policy, the U.S. market saw a significant increase in serology tests, some of which performed poorly and many of which were marketed in a manner that conflicted with the FDA policy; and based on these concerns, the Agency issued a Letter to Healthcare Providers on April 17, 2020.[20, 21]

These concerns indicated that greater FDA oversight of commercial serology tests was important to protect the public health and in response to these concerns, on May 4, 2020, CDRH revised its

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[19] See e.g., Section IV.C of FDA's Policy for Coronavirus Disease-2019 Tests (Revised) issued on January 12, 2023 available at https://www.fda.gov/media/135659/download.

[20] For more information, see "The FDA's Experience with COVID-19 Antibody Tests" available at https://www.nejm.org/doi/full/10.1056/NEJMp2033687.

[21] https://www.fda.gov/medical-devices/letters-health-care-providers/important-information-use-serological-antibody-tests-covid-19-letter-health-care-providers

policy so that we could evaluate all commercially distributed serology tests and assess claims of validity.[22] In addition, the Agency worked with the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), and the Biomedical Advanced Research and Development Authority (BARDA) to help establish a capability at the National Cancer Institute (NCI) for the U.S. Government to independently validate certain antibody tests.[23] The NCI assembled evaluation panels consisting of 30 frozen SARS-CoV-2 antibody–positive serum samples and 80 frozen antibody-negative serum and anticoagulant citrate dextrose solution formula A plasma samples. The panel size and composition were chosen to enable laboratory-based evaluation and provide reasonable estimates and confidence intervals for test performance given limited sample availability. This effort marked the first time the federal government evaluated tests itself to inform FDA authorizations.

The FDA used the NCI data to inform our decision making, such as whether to authorize the test, guide us in engaging the test developer for additional information to support its test remaining on the market, or take other action regarding tests that do not perform adequately, including to stop their marketing in the U.S. In addition, FDA publicly posted that test performance data on its website.[24] This marked the first time the federal government evaluated tests itself to inform FDA authorizations and this experience informed future collaborations including the RADx (Rapid Acceleration of Diagnostics) initiative[25] and NIH's Independent Test Assessment Program (ITAP).[26] Throughout the COVID-19 pandemic, CDRH met regularly with RADx participants to answer questions and provide feedback on validation plans. These efforts contributed to the EUA authorization for over 30 COVID-19 tests including over-the-counter at-home tests, point-of-care tests, high throughput molecular tests, and multiplex tests that detect multiple viruses (e.g., tests authorized for the simultaneous qualitative detection and differentiation of SARS-CoV-2, Influenza A, and Influenza B viral RNA).[27]

Based in part on the Agency's experience during the COVID-19 pandemic, FDA took a different approach with respect to the enforcement policy for mpox as described in FDA's guidance Policy for Monkeypox Tests To Address the Public Health Emergency. During the early stages of the mpox outbreak, there was an urgent need to continue to expand the nation's capacity for mpox testing. Under FDA's enforcement policy for mpox tests, FDA generally did not intend to object to the offering of diagnostic PCR tests using lesion swabs developed and performed in laboratories certified to perform high complexity testing under CLIA after the laboratory validated the test and provided notification of validation to the FDA within five business days of offering the test as described in FDA's guidance Policy for Monkeypox Tests To Address the

[22] https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy
[23] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-publicly-shares-antibody-test-performance-data-kits-part-validation
[24] https://open.fda.gov/apis/device/covid19serology/
[25] https://www.nih.gov/research-training/medical-research-initiatives/radx
[26] https://www.nibib.nih.gov/covid-19/radx-tech-program/ITAP
[27] https://www.nibib.nih.gov/covid-19/radx-tech-program/authorized-tests

Public Health Emergency. As part of this policy, the FDA provided recommendations regarding test reports for those tests; specifically, the FDA recommended that test reports should prominently disclose that the test has not been reviewed by the FDA. This policy did not apply to tests with home specimen collection or at-home tests or to tests using specimen types other than lesion swabs or technologies other than PCR. Lastly, under the policy, FDA intended to accept notifications for only 30 days after publication of the notice of availability of the guidance in the Federal Register, with a note that the FDA will continue to monitor the situation and may adjust, including shortening or lengthening this time period, as appropriate.

As discussed further below, some assessments of FDA's response to the COVID-19 pandemic recommended outlining an enforcement policy that might apply during the early stages of a future pandemic. CDRH is interested in obtaining the Panel's input on a potential enforcement policy for a future pandemic and what conditions might be included in such a policy.

External Engagement and Communications

During the COVID-19 pandemic, CDRH regularly engaged with test developers, healthcare providers, policy makers and other external stakeholders, including the American public. CDRH hosted a weekly virtual town-hall series to answer technical questions about the development and validation of COVID-19 tests. CDRH also provided frequent updates on its website to keep external stakeholders, including the American public, informed of any COVID-19 related updates. CDRH published and maintained a FAQ on Testing for SARS-CoV-2 on its website to address frequently asked questions related to COVID-19 tests and the EUA process. CDRH also maintains a list of all EUA-authorized COVID-19 tests on its website; in addition to the letter of EUA-authorization, it includes the healthcare provider and patient fact sheets and the Manufacture Instructions/Package Insert (abbreviated to IFU).[28] In addition, as discussed further above, CDRH collaborated with and worked across the US government as part of the Agency's response to the COVID-19 pandemic to accelerate regulatory review and promote the availability of safe and effective diagnostic tests.[29]

CDRH also communicated with respect to certain tests and their performance in the post-market setting and following EUA authorization, for example, the possible impact on certain test performance due to new SARS-CoV-2 variants.[30] In response to emerging new variants of SARS-CoV-2, CDRH monitored global databases for emerging variants and CDRH conducted in silico analyses of the target sequences for all authorized molecular tests. The Agency conducted

[28] See e.g., the list of authorized molecular diagnostic tests for SARS-CoV-2 available at https://www.fda.gov/medical-devices/covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-molecular-diagnostic-tests-sars-cov-2.

[29] FDA collaborated with the National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) on its Independent Test Assessment Program (ITAP) and to facilitate the authorization of at-home COVID-19 tests. See FDA's website at https://www.fda.gov/medical-devices/diagnostic-data-program/digital-diagnostics-over-counter-otc-and-point-care-poc for more information on CDRH's collaboration with ITAP and RADx.

[30] https://www.fda.gov/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2

in silico analyses of target sequences for all authorized molecular tests in addition to recommending that test developers conduct their own surveillance and analyses as well. CDRH communicated with the public, as appropriate, when FDA identified potential performance impacts due to genetic mutations.[31, 32] The Agency collaborated with the NIH and the University of Massachusetts Chan Medical School in a study including more than 7,000 participants to assess at-home COVID-19 antigen test performance.[33] Based in part on the data generated from this study, the FDA revised the EUAs for all the COVID-19 antigen tests that were authorized at that time to require updates to the labeling regarding repeat testing after a negative COVID-19 test result.[34]

Additional examples of external collaborations included a collaboration with RADx and a study performed by Emory University and Children's Healthcare of Atlanta,[35] in which the FDA reviewed data on the adequacy of pediatric self-swabbing for COVID-19 testing. Working with the Emory University and Children's Healthcare of Atlanta, this data was submitted to CDRH with a broad right of reference which allowed any entity seeking an EUA for a COVID-19 diagnostic device for use with self-sampling (under adult supervision) of anterior nares samples in pediatric populations (ages 4-14 years old) to leverage the data and protocols from the study, in conjunction with other data from the developer. This process helped shorten the time needed to prepare and submit an EUA as well as shorten CDRH's review time of a new EUA request as new developers could leverage that existing data which had previously been reviewed by CDRH through the right of reference.

CDRH's experience during the COVID-19 pandemic demonstrated the need for CDRH to communicate to the clinical community through clear, standardized, and comprehensible information for tests in order to enhance physicians' understanding of test performance, selection, interpretation, and clinical usefulness. CDRH is interested in obtaining feedback from the Panel on how CDRH can strengthen communications with the clinical community during a future pandemic to ensure that the clinical community understands test performance and how to use that information in patient care.

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[31] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests

[32] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests?utm_medium=email&utm_source=govdelivery#general

[33] https://www.fda.gov/medical-devices/safety-communications/home-covid-19-antigen-tests-take-steps-reduce-your-risk-false-negative-results-fda-safety

[34] https://www.fda.gov/medical-devices/covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2#SerialTesting

[35] https://jamanetwork.com/journals/jama/fullarticle/2795837?guestAccessKey=d98d9357-ab4b-477a-b97c-ae5c9382870c&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=082622

Supply Chain Stability and Shortages

The COVID-19 pandemic put unprecedented pressures on the IVD supply chain as demand for COVID-19 tests surged and put them at risk of shortage. In addition, certain testing components commonly found in COVID-19 test kits, such as swabs, viral transport media, and general-purpose reagents, were also subject to supply chain vulnerabilities. Many of these IVD kits and components were manufactured in foreign countries and subject to supply chain limitations.

CDRH worked with other government entities to advise and coordinate procuring these supplies and actively sought and promoted different solutions in response to shortage concerns. For example, CDRH worked with the Department of Defense (DoD) and the Federal Emergency Management Agency (FEMA), to advise and coordinate procuring COVID-19 testing supplies such as nasal swabs.

In addition to external collaborations, FDA published a number of guidance documents in response to availability concerns during the COVID-19 pandemic including the "Enforcement Policy for Viral Transport Media During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised)" to help expand the availability of transport media, which are critical to SARS-CoV-2 tests.[36] In addition, the "Modifications to FDA-Cleared Molecular Influenza and RSV Tests During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency" helped expand access to molecular assays intended for detection and identification of influenza (flu) viruses, including those molecular influenza assays that also detect and identify respiratory syncytial viruses (RSV), during the influenza season.[37]

Lastly, starting on March 3, 2020, and continuing throughout the COVID-19 pandemic CDRH held over 100 virtual IVD town halls for thousands of participants. During these virtual IVD town halls, test developers could ask for CDRH feedback on technical questions regarding their test development. In addition to providing general Agency announcements and responding to general questions from test developers, CDRH served as a clearinghouse for testing supply alternatives during the early stage of the COVID-19 pandemic providing suggestions on where test developers might be able to obtain certain test materials (e.g., swabs and transport media) when those test materials may have been difficult to obtain and when test developers might have needed to obtain alternatives.

[36] https://www.fda.gov/media/140300/download
[37] https://www.fda.gov/media/142933/download

III. Recommendations to Prepare for and Respond To Future Pandemics

As previously discussed, as part of the systemic review of the FDA's COVID-19 pandemic response, three separate assessments have been performed either on behalf of the FDA or other parts of the U.S. government to evaluate the use of EUAs during the COVID-19 pandemic and provide recommendations for future pandemic preparedness and response. As described in more detail below, CDRH is interested in obtaining feedback and recommendations at this session from the Panel on how CDRH might proactively address and implement some of the recommendations discussed in these reports in a future pandemic.

Booz Allen Hamilton Emergency Use Authorization Assessment

In March 2021, Booz Allen Hamilton (BAH) was selected by the FDA to conduct an independent assessment of the FDA's COVID-19 EUA response. BAH reviewed primary documents and conducted internal and external stakeholder interviews to evaluate the FDA's response and develop recommendations for improvement. A copy of the BAH independent assessment is available on FDA's website.[38] Provided below are key observations from the BAH assessment that CDRH would like to raise for discussion and input at the upcoming session. This is not an all-inclusive list but rather the recommendations which CDRH believes would benefit the most from the Panel's discussion.

1) BAH Key Observation: The approach to staff allocation was difficult to systematically quantify and analyze, making it difficult to determine what events or criteria triggered shifts in staff and how shifts were coordinated to address the triggering event or criteria.

   BAH recommended that CDRH consider developing a systematic approach (that is, a strategy and plan) for allocation and tracking of staff during PHEs. CDRH agrees with this recommendation and in addition to identifying ways to manage resource needs, CDRH is exploring ways to simplify and streamline the EUA process. For example, the use of EUA templates reduced the number of manufacturer submission pages and focused on what was the most important data to submit to the FDA. This helped FDA review staff work more efficiently given the staffing challenges and simplified and streamlined the submission of data and information in the EUA review process. In addition, to better allocate Agency resources in preparation or response to a future pandemic, CDRH is interested in obtaining any feedback from the Panel on how the Agency should prioritize EUAs for certain tests or developers during the early stage of a future pandemic.

2) BAH Key Observation: There was limited understanding in the test developer community on how to appropriately validate a diagnostic test.

[38] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/emergency-use-authorization-covid-19-tests-independent-assessment-fdas-response

BAH recommended that CDRH consider developing a framework for how to conduct validation of diagnostic tests for emerging pathogens in the setting of a declared PHE. CDRH agrees with this recommendation and is interested in obtaining feedback from the Panel on a framework for conducting appropriate validation under different circumstances, to speed the availability of future IVDs and common approaches to validating test design. Notably, in the early stages of a future pandemic for a novel pathogen, the science and knowledge about the microorganism and disease can be limited and our understanding of the disease is likely to progress over time. For example, during the COVID-19 pandemic the SARS-CoV-2 virus mutated over time and resulted in genetic variation in the population of circulating viral strains in patient samples which can potentially impact test performance.[39]

CDRH is interested in any feedback from the Panel on how the Agency can strengthen communication strategies and tools that were found to be generally effective during the COVID-19 pandemic in the early stages of a future pandemic. Possible options include IVD town halls, a telephone hotline and email boxes for stakeholder inquiries, templates, a website FAQ, and interactions with professional and trade organizations.

Government Accountability Office (GAO) Report

On May 12, 2022, the GAO published its report "COVID-19: FDA Took Steps to Help Make Tests Available; Policy for Future Public Health Emergencies Needed" following the GAO's review of FDA's oversight of COVID-19 tests. The report examined 1) the actions FDA took to help make COVID-19 tests available for use, 2) the number of tests FDA authorized and those for which it exercised an enforcement policy, and 3) FDA's monitoring of these tests after they were available for use. The GAO report also included stakeholder views on those actions. The GAO recommended that FDA develop a policy for the use of enforcement discretion regarding unauthorized tests in future PHEs and that this policy include the conditions under which FDA would begin and end the use of such discretion.

FDA agrees with this recommendation.[40]

Based on lessons learned during the COVID-19 pandemic, FDA believes it is generally more effective for public health to authorize a small number of high-capacity tests, rather than diffuse resources for the authorization of many lower capacity tests.[41] This approach would necessarily include pre-planning to have relationships in place with contract manufacturers, commercial

[39] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests
[40] See FDA/HHS's response to the GAO report available at https://www.gao.gov/products/gao-22-104266#:~:text=What%20GAO%20Found,of%202021%20(see%20figure).
[41] For more information, see "Covid-19 Molecular Diagnostic Testing — Lessons Learned" available at https://www.nejm.org/doi/full/10.1056/NEJMp2023830.

manufacturers, and laboratories as well as a collaborative development of validation protocols for commonly anticipated pathogens and sample types before an outbreak. CDRH is interested in obtaining feedback from the Panel on any recommendations on this advanced preparation approach to enable faster authorization of tests in the future or to ensure test availability. Potential approaches may include collaboration with certain instrument manufacturers or test manufacturers in preparation for a future pandemic response.

HHS Office of Inspector General (OIG) Report

On September 21, 2022, HHS's OIG published its report "FDA Repeatedly Adapted Emergency Use Authorization Policies To Address the Need for COVID-19 Testing" in which the OIG reviewed how FDA used its EUA authority to authorize COVID-19 tests during the crucial first months of the pandemic.[42] The review focused on the early months of the COVID-19 pandemic (January 1 through May 31, 2020) and included surveys and responses from 237 test developers that engaged with FDA about their COVID-19 tests. The OIG report found that FDA made calculated decisions to increase availability of COVID-19 testing at a potential cost to test quality. In addition, the OIG report found that FDA's decision to accept all EUA requests for COVID-19 tests resulted in a record number of submissions – often low-quality and from developers lacking experience with FDA's processes.

The OIG report included a number of recommendations, based on insights from FDA's early experiences with the COVID-19 pandemic, for FDA to consider for future infectious disease emergencies to better balance testing availability and quality. FDA concurred with the recommendations, which included:

- Assess and, as appropriate, revise guidance for test EUA submissions
- Develop a suite of EUA templates for future emergencies involving novel pathogens
- Expand the FDA Center for Devices and Radiological Health's existing device-tracking platform to facilitate EUA submission and monitoring
- Expand and improve resources for test developers on the EUA process
- Establish formal communication channels between FDA and the lab community, to be used in emergencies that require testing
- Work with Federal partners to implement lessons learned about a national testing strategy that go beyond the EUA process

[42] HHS's OIG Report is available at https://oig.hhs.gov/oei/reports/OEI-01-20-00380.asp.

At the upcoming session, CDRH is interested in obtaining feedback from the Panel on how the Agency might implement these recommendations. In particular, CDRH is interested in any Panel input on expanding and improving resources for test developers on the EUA process and steps the Agency can take to establish formal communication channels between FDA and the lab community during emerging pandemics. CDRH believes that collaboration with key stakeholders, such as the laboratory community, is critical to proactively preparing for future pandemics and ensuring preparedness and response for any future outbreaks.

IV. Questions for Panel Discussion

As explained in the discussion above, CDRH is seeking input from the Microbiology Devices Panel of the Medical Devices Advisory Committee on tests used in preparedness for and in response to future pandemics. Specifically, CDRH is seeking input on the following discussion points:

1. How can test developers (including both commercial manufacturers and laboratory test developers) best interact with CDRH when preparing for a future pandemic? What steps can CDRH take to strengthen its communication strategies in future pandemics with test developers, laboratories performing tests, and other stakeholders such as patients and clinicians? Were any methods of communication (town halls, telephone hotline, website FAQ, email boxes for stakeholders, EUA templates) more advantageous than others and what might CDRH consider doing differently in future pandemics?

2. What types of educational resources or communications from CDRH would be most valuable to aid test developers with respect to test development in preparation for a future pandemic?

3. Are there certain types of instrument manufacturers or test component manufacturers with whom CDRH should collaborate with in preparation for a future pandemic response to ensure test availability in a future pandemic. For example, would earlier engagement from CDRH to work with manufacturers of high throughput systems help ensure that well-designed, high-throughput tests can be made available at an appropriate volume to meet the needs of any future outbreak?

4. Are there certain types of tests or developers that should be prioritized for review in the early stages of a future pandemic? Examples include certain test types (e.g., diagnostic and high throughput), test protocol development for sharing with any laboratory, manufacturing capacity, or experienced test developers

5. What are key features of tests or are there certain test designs that would be helpful in a future pandemic?

6. What other lessons from the recent COVID-19 pandemic and mpox outbreak might CDRH take into consideration in preparing for future pandemics?