U.S. FOOD & DRUG ADMINISTRATION

FDA PERSPECTIVE

Emergency Use Authorization Assessment – Final Report

Introduction

During the prior six declared public health emergencies under section 564 of the Federal Food, Drug, and Cosmetic Act, the FDA has used its emergency use authorization (EUA) authority to authorize diagnostic tests developed by commercial manufacturers and laboratories. The EUA process provides critical flexibility and expedites access to tests during emergencies. The EUA process enabled COVID-19 tests to be developed, validated, authorized, and deployed in weeks rather than months to years, as may be the case of the more rigorous evidentiary standard required outside of a public health emergency. To date, the FDA has authorized approximately 400 tests and home collection kits and granted emergency use authorization or full marketing authorization for over 1,700 medical devices, including tests, PPE, ventilators, and other devices for diagnosing, preventing, or treating COVID-19.

Background
In March 2021, Booz Allen Hamilton was selected by the FDA to conduct an independent assessment of the FDA's Coronavirus Disease 2019 (COVID-19) Emergency Use Authorization (EUA) response. Booz Allen Hamilton reviewed primary documents and conducted internal and external stakeholder interviews to evaluate the FDA's response and develop recommendations for improvement.

To further address current and future public health needs, the FDA's Center for Devices and Radiological Health (CDRH) is sharing Booz Allen Hamilton's independent assessment. For an overview of the recommendations from the independent assessment, along with CDRH's perspectives and steps we have taken or plan to take to address the feedback, see Emergency Use Authorization of COVID-19 Tests: Independent Assessment of the FDA's Response.

The FDA agrees with the three priority recommendations identified by Booz Allen Hamilton that are presented in the independent assessment. Booz Allen Hamilton recommends that the FDA:

- Optimize the IT system to account for EUA processes
- Develop a systematic approach (a strategy and plan) for allocation and tracking of staff during public health emergencies (PHE)
- Develop a framework for how to conduct validation of diagnostic tests for emerging pathogens in the setting of a declared PHE

Priority Recommendations to Support the EUA Process

Recommendation: Consider ways to optimize the IT system to account for EUA processes

- From March 2020 to present, CDRH took several steps to identify IT system needs to improve tracking of EUA requests. In parallel CDRH has been working to streamline EUA processes.
- Further, CDRH initiated a Digital Transformation Initiative, launched in Fiscal Year (FY) 2016, which is ongoing. This initiative is focused on providing better IT infrastructures, technology solutions, and data to help both internal and external stakeholders across all regulatory programs**.** The Digital Transformation Initiative:

- Will improve tracking and data for several program areas, including EUAs, over the next two to three years.
- Will help CDRH be more agile and address pressing IT challenges and stakeholder needs during a public health emergency.
- Is made possible by funding first received from Congress in FY 2019 to support CDRH's Digital Transformation Initiative.

Recommendation: Consider developing a systematic approach (a strategy and plan) for allocation and tracking of staff during public health emergencies (PHEs).
CDRH is undertaking efforts to proactively prepare for future situations by focusing on how to identify staffing needs and deploy staff to the "right place at the right time" by:

- Outlining a blueprint for an Emergency Response Process that will provide guidelines for information sharing, staff mobilization, and operational flexibility with the goal of engaging the right people at the right time in future emergencies.
- Starting a process improvement effort to address how 'Surge Capacity' is defined and managed in a standardized way across the Center.
- Using a resource pool of qualified contractors to support various activities, including EUA review activities on an 'as-needed' basis to address the demands of the PHE.

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 review 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. The Center will continue to develop strategies to improve its ability to increase capacity for future PHEs.

Recommendation: Consider developing a framework for how to conduct validation of diagnostic tests for emerging pathogens in the setting of a declared PHE.

CDRH's experience with COVID-19 tests highlights the need for a common legislative framework to help ensure that all tests are accurate and reliable, regardless of whether they are developed in a laboratory or by a commercial manufacturer and regardless of whether there is an emergency. CDRH plans to:

- Engage with test developers to speed the availability of future *in vitro* diagnostic (IVD) devices, including establishing:
  - Generic templates for commonly anticipated pathogens that may be adapted for potential future outbreaks.
  - A framework for conducting appropriate validation under different circumstances.
- Continue strengthening communication strategies and tools that have proved effective during the COVID-19 PHE.

Further, CDRH suggests that the U.S. government consider:
- Working with international partners to establish a plan for sharing clinical specimens as soon as a public health threat emerges.
- Establishing the capacity to independently evaluate test performance before outbreaks occur so that independent evaluation can be performed quickly during an outbreak.

For more information:
- Emergency Use Authorization of COVID-19 Tests: Independent Assessment of the FDA's Response

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Emergency Use Authorization Assessment - Final Report

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EXECUTIVE SUMMARY

In March 2021, Booz Allen was selected by the U.S. Food and Drug Administration (FDA) to conduct an independent assessment of the Agency's Coronavirus Disease 2019 (COVID-19) Emergency Use Authorization (EUA) response. Booz Allen reviewed primary documents and interviewed internal and external stakeholder to evaluate FDA's response and develop recommendations for improvement. FDA has played a critical role in our nation's response to the COVID-19 public health emergency (PHE). As medical devices, particularly diagnostic tests, are the first line of defense against an emerging outbreak, the Center for Devices and Radiological Health (CDRH) was the first FDA Center to review EUA requests that were authorized under the Agency's authority to issue EUAs in this PHE. The number of device EUA requests granted by FDA were well above the total number of EUAs granted for all previous PHEs combined. The current pandemic has driven a need for medical devices, including tests and more, that has far exceeded what was experienced in prior PHEs.

This assessment focuses on the EUA process for COVID-19 tests, how the Agency prioritized processing of EUA requests, review times, accuracy/reliability of the COVID-19 tests, a comparison of FDA's response to prior PHEs, and requestors' perspectives. Throughout the course of the PHE, FDA modified the EUA process to respond to the increased volume of submissions. The findings outlined in the report identify key actions FDA took in their response to COVID-19, including the following:

- **Requestor Support:** Published three guidance documents and developed ten submission templates, and continuously updated these to maximize development of and facilitate access to COVID-19 tests with flexible policies.
- **Review Prioritization:** Established factors to prioritize review of EUA requests, including test capacity, accessibility, and supply chain considerations, to focus review time on the most impactful requests based on the state of the pandemic.
- **Process Improvements:** Developed and implemented process improvements to operationalize prioritization factors and improve review efficiency, including a front-end triage, content screen, and deprioritization process.
- **Review Volume:** Reviewed and closed out over 2,000 EUA-related submissions, including Original EUAs and Supplements as well as over 1,000 Pre-EUAs as of April 2021.
- **Authorization:** Authorized a total of 360 Original EUA requests and 452 EUA Supplements for *in vitro* diagnostics (IVD) as of April 12, 2021.
- **Real-World Evidence (RWE) Generation:** Established collaborations focused on gathering and analyzing Real-World Data (RWD)/RWE to enable data sharing, harmonized data standards, reporting, and data collection.
- **Communications and Outreach:** Hosted over 50 Town Hall sessions and webinars; posted over 300 Frequently Asked Questions (FAQ); stood-up a 24/7 hotline; created a central mailbox to help requestors accelerate submissions by providing frequent feedback; and developed educational testing resources for health care providers.
- **Test Performance Transparency:** Created three informational websites addressing test performance (molecular reference panel website, serology test performance website, and viral mutations impacts website); sent out Warning Letters and Safety Communications; and collaborated with the National Cancer Institute (NCI) for independent evaluation of certain performance characteristics of serology tests.

The recommendations presented in this report incorporate lessons learned and stakeholder perspectives and serve as a summary of actions for the Agency to consider as they continue to serve on the frontline in response to current and future public health needs.

1. ASSESSMENT BACKGROUND AND OBJECTIVES

Booz Allen evaluated the Center for Devices and Radiological Health's (CDRH) Emergency Use Authorization (EUA) process for Coronavirus Disease 2019 (COVID-19) tests. Specifically, we performed a comprehensive analysis of how the Agency prioritized the processing of the EUA requests, review times, accuracy/reliability of the COVID-19 tests, a comparison of the U.S. Food and Drug Administration's (FDA) response to prior public health emergencies (PHE), and requestors' perspectives.

FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. On January 31, 2020, the Secretary of the Department of Health and Human Services (HHS) declared a PHE related to COVID-19. On February 4, 2020, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Secretary of HHS provided FDA with the authority to grant EUAs for *in vitro* diagnostics (IVD) to detect and/or diagnose COVID-19. EUA authority helps strengthen the nation's public health protections by facilitating the availability and use of unauthorized medical products, or unapproved uses of approved medical products, during PHEs. An EUA request for a test can be issued when, among other things, FDA determines based on the totality of scientific evidence, that there is a reasonable belief that the test may be effective in diagnosing patients, and the known and potential benefits outweigh the known and potential risks, rather than waiting to grant full marketing authorization when it has reasonable assurance that the product is safe and effective.

FDA recognized the need to quickly detect the spread of COVID-19, and the first EUAs issued were for COVID-19 tests in February 2020,[1,2] allowing them to be deployed much quicker than under traditional premarket pathways. FDA faced criticism over public perceptions that surrounded COVID-19 testing ranging from the amount of time to development and availability, to the validity of tests. However, there were underlying reasons for these challenges including supply chain shortages of materials needed to develop and perform tests, unprecedented EUA volume, and inexperienced test developers.

Prior to the declaration of the PHE, FDA took actions to advance development of diagnostic tests to control the emergence and spread of COVID-19. To support early engagement with EUA requestors, FDA began proactively coordinating EUA-related activities including the development of voluntary EUA review templates, interactive review with requestors, policy development, initiating the development of reference materials, and external communications. Such initial efforts required internal coordination across the Center and were made possible by policies and procedures put in place during prior PHEs. In January 2020, FDA reached out to requestors with previous EUA experience to solicit interest in development of a COVID-19 test. In addition, FDA reached out to requestors with existing authorized tests for similar viruses to ask that they conduct analyses to determine whether their tests could be used to detect COVID-19. Figure 1-1 outlines the key actions FDA took to provide guidance and flexibility to test developers, communicate regularly with EUA requestors, implement prioritization and efficiency efforts, and develop tools and templates.

[1] The U.S. Centers for Disease Control and Prevention's 2019-nCoV Real-Time RT-PCR Diagnostic Panel was authorized on February 4, 2020 https://www.fda.gov/media/134919/download -- accessed 6/11/2021

[2] The New York State Department of Public Health's SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel was authorized on February 29, 2020 https://www.fda.gov/media/135661/download -- accessed 6/11/2021

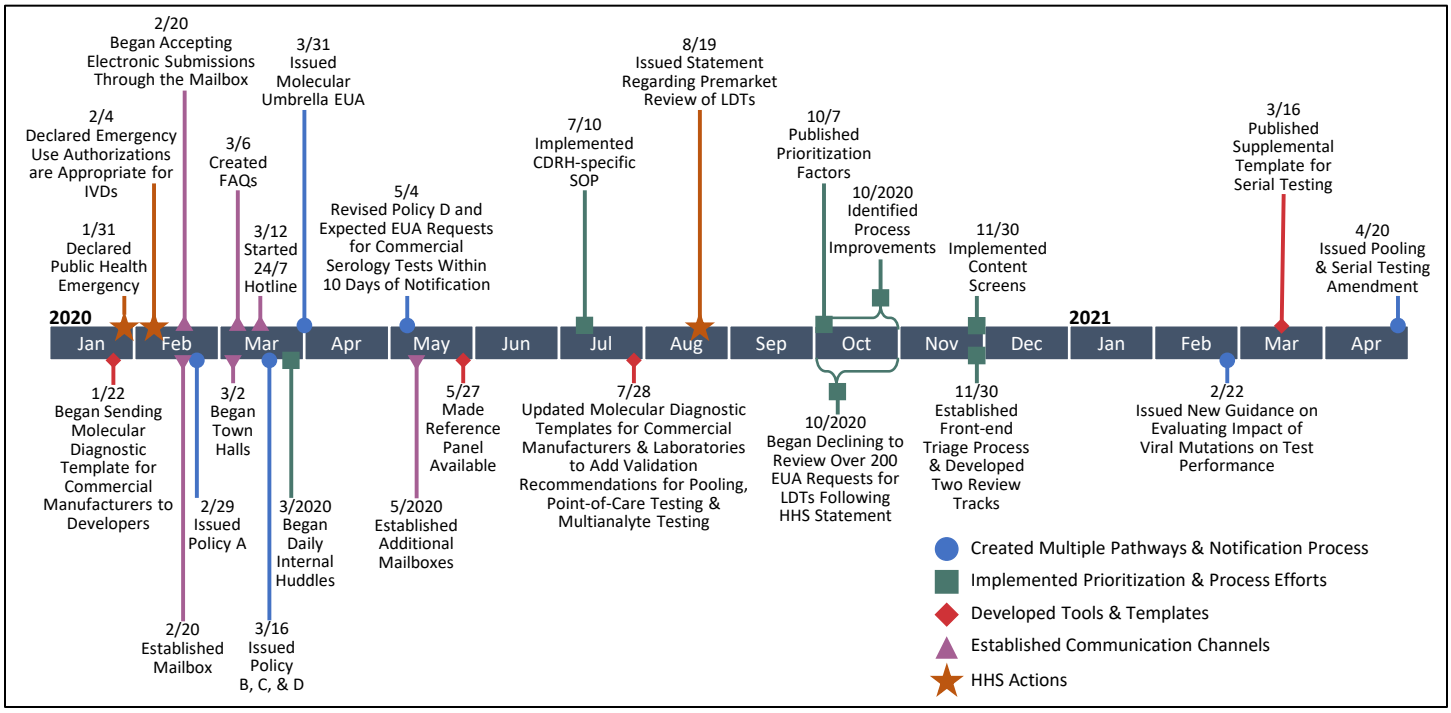

Figure 1-1. Key Actions in FDA's Response to Development and Authorization of COVID-19 Tests

* FDA first posted notice of template availability on its website on 1/27/2020. See Figure 3-1 for additional EUA template milestones.

** Policies A through D are outlined in FDA's "Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency." See Table 3-1 for descriptions of each policy.

2. METHODOLOGY

In this assessment, Booz Allen used quantitative and qualitative data analysis, as well as stakeholder interviews, to evaluate CDRH's response to COVID-19.

This independent assessment focused on the EUA process for COVID-19 diagnostic tests and how the Agency prioritized the processing of the EUA requests, review times, accuracy and reliability of the COVID-19 tests, a comparison to prior PHEs, and requestors' perspectives as outlined in Table 2-1. There are a variety of different types of tests (i.e., molecular, antigen, and serology) and each are used for different purposes. Molecular tests are preferred for diagnosis and are the primary focus of this report.

The goal of the assessment is to evaluate FDA's response, better understand challenges, and propose potential recommendations for consideration. Booz Allen gathered quantitative and qualitative data from CDRH points of contact, internal and public-facing documentation, and stakeholder interviews. These data were used to develop the findings and recommendations in this report.

Table 2-1. Assessment Objectives

Assessment Objective	Description
Prioritization	Evaluate how the Agency prioritized the processing of EUA requests and actions taken to facilitate the development, validation, and authorization of COVID–19 diagnostic tests, including: • Modified processes and policies including postmarket monitoring • Communications and interactions with EUA requestors • Triage process • Process improvements
Review Times	Evaluate Agency review times for EUAs over the course of the pandemic and assess causes and challenges
Accuracy and Reliability	Report on the accuracy and reliability of diagnostic tests, particularly real-world, postmarket performance

Assessment Objective	Description
Comparative Response	Evaluate how the Agency's response to EUAs for COVID-19 tests compares to prior PHEs
Requestor Perspectives	Evaluate EUA requestor perspectives of what has worked well compared to previous PHEs and what can be improved

3. ASSESSMENT FINDINGS

Booz Allen evaluated CDRH's COVID-19 response, including actions to facilitate the development, validation, and authorization of COVID-19 diagnostics. For each report section, we describe the approach taken by CDRH, how these actions compare to those during previous PHEs, and challenges and successes noted by stakeholders.

3.1 Approach to development, review, and authorization of COVID-19 tests

POLICY DEVELOPED TO ADDRESS COVID-SPECIFIC CHALLENGES

Created Notification Process to Provide Flexibility

To help accelerate the development and availability of COVID-19 tests, CDRH issued guidance[3] on February 29, 2020. This guidance described a policy for diagnostic tests developed by Laboratories certified to perform high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA), Policy A, shown in Table 3-1. The guidance described a unique notification policy to address the urgent need for diagnostic tests by allowing developers to offer certain tests prior to submitting their EUA request and while their EUA request was under review. The notification process established in February called for laboratory developers to: validate their test, notify FDA of their intent to offer tests, include a statement in the test report that the test was not reviewed by FDA, submit an EUA request containing test performance data within a reasonable period of time (e.g., 15 days), and confirm results for the first five positive and first five negative clinical specimens with an authorized test. Where this notification process is used, FDA explained it did not intend to object to the use of these tests.

Through an update on March 16, 2020, CDRH developed more policies to provide flexibility for additional circumstances, types of developers, and types of tests, shown in Table 3-1. Policy B allowed state authorities to take responsibility for authorizing tests developed by Laboratories certified under CLIA that meet the CLIA regulatory requirements to perform high complexity testing in their state; Policy C extended the notification process to Commercial Manufacturers of diagnostic tests, including antigen tests, and recommended that manufacturers publish performance characteristics of their test on their website; and Policy D outlined FDA's intent not to object to marketing of serology tests from Commercial Manufacturers or Laboratories who validate their test, notify FDA of the intent to offer the test, and include statements in the test report indicating the test has not been reviewed by FDA and should not be used to diagnose or exclude severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2[4]) infection. The March 16, 2020 update also broadened flexibility to modifications of authorized tests. Under this update, FDA stated that it did not intend to object to High Complexity Laboratories using a modified version of an already authorized test without a new or amended EUA request, provided that the modification was validated with a bridging study.[5] In addition, FDA did not object to immediate implementation of modifications to EUA-authorized tests from any manufacturer where validation data supporting the modification had been submitted to FDA while FDA conducted its review.

Policy D was intended to accelerate the availability of serology tests to advance the scientific community's study and understanding of COVID-19, but a concerning number of notified serology tests demonstrated poor performance and some tests were marketed with misleading claims. In response, CDRH updated their policy on May 4, 2020 to reflect that

[3] "Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised)," FDA https://www.fda.gov/media/135659/download -- accessed 5/28/2021

[4] SARS-CoV-2 is the name given to the virus responsible for COVID-19.

[5] High Complexity Laboratories could perform a bridging study to establish equivalent performance between parallel testing of the same specimens with the new and original components.

EUA requests were expected for serology tests from Commercial Manufacturers within 10 days of notification to ensure that claims and performance were independently assessed. CDRH established a notification list following the initial publication of the guidance[6] and published a public removal list[7] to provide transparency and address questions on the status of tests following the May 4th update. If the requestor does not submit an EUA request within a reasonable period of time, or CDRH identifies significant problems with a test, CDRH would intend to remove the test from the notification list and take additional actions, as necessary.

Table 3-1. Overview of Policies Outlined in Guidance to Expand Access to for COVID-19 Tests

Policy	Date Introduced	Date Updated	Developer	Test Type*	Key Point
Policy A	February 29, 2020	N/A	High Complexity Laboratories	Molecular	Notification process created EUA request expected within 15 days
Policy B	March 16, 2020	N/A	High Complexity Laboratories	Tests for COVID-19	States could take responsibility for authorizing tests from High Complexity Laboratories EUA not expected
Policy C	March 16, 2020	N/A	Commercial Manufacturers	Molecular and Antigen	EUA request expected within 15 days Notification process was extended to Commercial Manufacturers
Policy D	March 16, 2020	May 4, 2020	Commercial Manufacturers and High Complexity Laboratories	Serology	Following May 2020 revision, EUA request became expected within 10 days for Commercial Manufacturers but not for High Complexity Laboratories

*Excluding at-home testing and specimen collection

On March 31, 2020, CDRH used another novel mechanism created earlier in the pandemic, the Umbrella EUA, to further streamline the authorization process for certain tests, shown in Table 3-2. This mechanism creates efficiency by allowing FDA to quickly authorize multiple similar devices under pre-specified conditions of use. By using the same Letter of Authorization and fact sheets, CDRH can eliminate layers of review while maintaining the same standards for authorization as the individual device. The first Umbrella EUA for tests allows FDA to authorize multiple molecular-based tests developed and performed by Laboratories certified under CLIA to perform high complexity tests under a single EUA.

Table 3-2. Overview of Umbrella EUAs for COVID-19 Tests

Date Introduced	Date Updated	Developer	Test Type	Key Point
March 31, 2020	N/A	High Complexity Laboratories	Molecular	Eligible tests may be added to the Appendix of the Umbrella EUA
April 28, 2020	Revoked July 21, 2020	Commercial Manufacturers	Serology	Eligible tests that have been independently validated may be added to the Appendix of the Umbrella EUA[8]
April 20, 2021	N/A	Developers of Certain Authorized Molecular Diagnostic Tests	Molecular	Amends the authorization of certain previously authorized tests to include pooling and serial screening (i.e., pooled specimens for screening asymptomatic individuals when used as part of a serial testing program)

[6] "Notifications and Emergency Use Authorizations: FAQs on Testing for SARS-CoV-2," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/notifications-and-emergency-use-authorizations-faqs-testing-sars-cov-2 -- accessed 5/28/2021

[7] "Removal Lists of Tests that Should No Longer Be Used and/or Distributed for COVID-19: FAQs on Testing for SARS-CoV-2," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/removal-lists-tests-should-no-longer-be-used-andor-distributed-covid-19-faqs-testing-sars-cov-2 -- accessed 5/28/2021

[8] No devices were authorized under the Umbrella EUA for independently validated serology tests prior to its revocation. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-serology-and-other-adaptive-immune-response-tests-sars-cov-2#umbrella-serological -- accessed 6/30/2021

Table 3-3 illustrates the number of requestors with tests authorized in an Umbrella EUA as of May 21, 2021. FDA authorized 38 molecular Laboratory Developed Tests (LDT) under this mechanism, representing approximately 14% (38/281) of all authorized molecular tests. On April 28, 2020, less than a month after creating the Umbrella EUA for molecular LDTs, CDRH subsequently issued an Umbrella EUA for serology tests. The Umbrella EUA for serology tests was revoked on July 21, 2020 given concerns that the scope of the Umbrella EUA was too restrictive of the test performance and claims. Instead, FDA authorized Individual EUAs for these tests since this allowed for broader indications and scopes of authorization, individualized conditions of authorization to address any issue unique to a specific test, and more streamlined EUA amendments such as additional uses that would not fall under the Umbrella EUA.

Table 3-3. Use of Individual and Umbrella EUAs

Test Type	EUA Type	Number of EUAs Issued*
Molecular test	Individual	243
Molecular test	Umbrella	38[9]
Antigen test	Individual	25
Serology test	Individual	79

**As of May 21, 2021*

Continued to Update Policy to Address Evolving Needs

CDRH continues to adjust authorization policies and make updates when appropriate. For example, on March 16, 2021, CDRH published a new supplemental template that outlined a streamlined path to authorization for COVID-19 tests for screening with serial testing. Approximately two weeks later, FDA issued the first five authorizations for serial screening tests, including non-prescription tests for fully at-home use. In April 2021, FDA issued a pooling and serial testing umbrella amendment[10] that streamlined the approach to adding pooling and serial screening claims to certain authorized tests.

An emerging need identified by requestors was guidance on transitioning an EUA-authorized test to a full marketing authorization under traditional pathways (e.g., De Novo, 510(k)). FDA discussed this topic and lessons learned from past PHEs at a February 2020 workshop hosted by the Medical Device Innovation Consortium (MDIC)[11] and announced plans in November 2020 to develop a draft guidance on transitioning COVID-19 tests authorized under EUA. On March 17, 2021, one test received a full marketing authorization via the De Novo pathway, which established special controls and opened the 510(k) pathway for other COVID-19 molecular tests.

Developed Templates to Streamline Submission Process

CDRH developed voluntary templates to support developers with EUA requests, as was done in prior PHEs (e.g., Zika virus). Ten EUA templates were developed to support various test types and developers, shown in Figure 3-1. The templates help organize the EUA request and outline recommendations for the submission package. In addition, the templates provide specific recommendations on analytical and clinical validation (e.g., number of clinical specimens recommended for evaluation). These templates also form the basis for CDRH's internal review memos, streamlining the review process as well as the submission process.

The templates were initially available upon request, which allowed CDRH to track who was developing tests and provide this information to government partners such as the Biomedical Advanced Research and Development Authority (BARDA). On February 29, 2020, the same day that FDA issued guidance, FDA made the template available on its website to support its new notification policy. As CDRH gained experience with reviewing EUA requests for specific test types and noticed certain information was commonly missing in submissions, they revised the templates to include more specific details about test validation. Templates were revised a total of 11 times as of April 12, 2021. These templates also expanded over time to address different testing scenarios that increased access and availability of testing.

[9] In total, 38 tests were authorized under the Umbrella EUA for LDTs. Some tests subsequently received individual Authorizations after the test was modified. There are currently 32 tests authorized under the Umbrella EUA as of May 21, 2021.

[10] "Letter to Developers of Molecular-Based Diagnostic Tests Authorized for Emergency Use for Coronavirus Disease 2019 (COVID-19 as of Today's Date," FDA https://www.fda.gov/media/147737/download -- accessed 5/28/2021

[11] "Advancing EUA IVD Products Toward Full Marketing Status," MDIC https://mdic.org/event/advancing-eua-ivd-products-toward-full-marketing-status/ -- accessed 5/28/2021

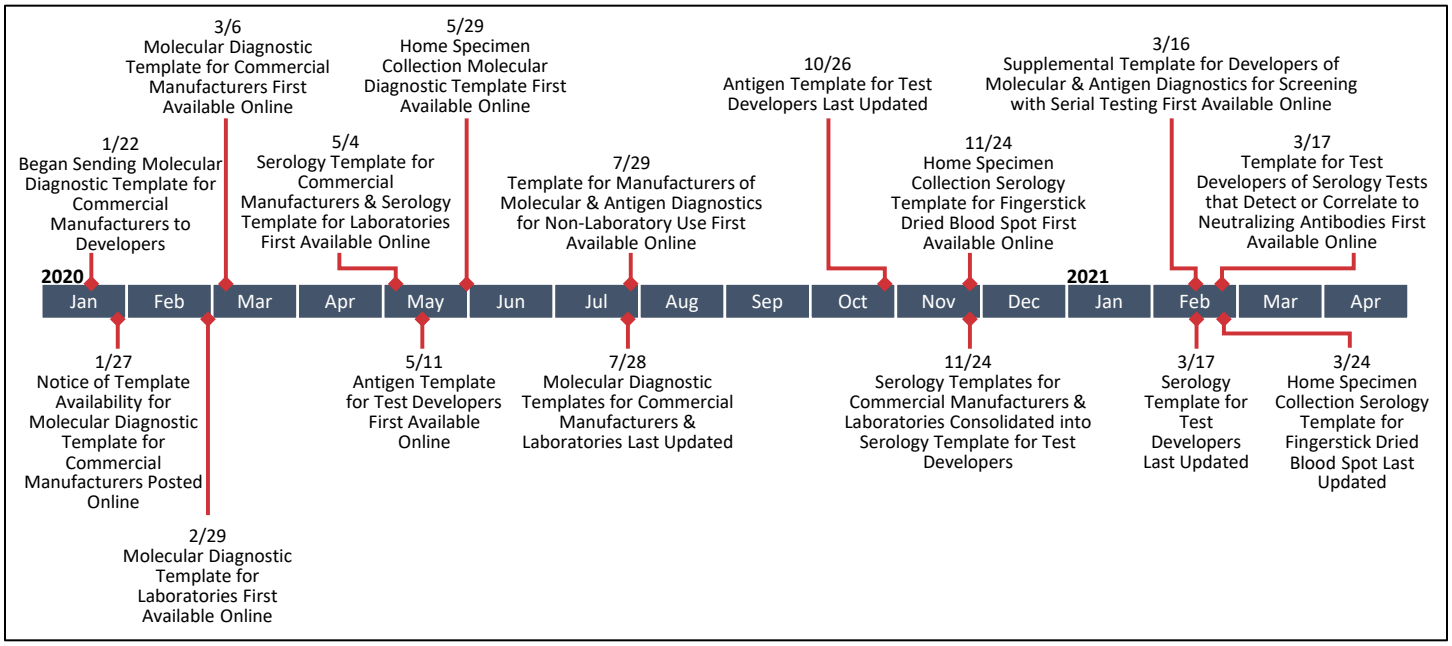

Figure 3-1. Submission Templates Published

STAKEHOLDER PERSPECTIVES AND LESSONS LEARNED

To help inform current and future public health needs, Table 3-4 outlines stakeholder perspectives and lessons learned on the approach to development, review, and authorization of COVID-19 tests. Stakeholders included a mix of experienced/inexperienced firms, small and large companies, multiple technologies and Laboratories as well as Commercial Manufacturers, and developers with varied previous EUA experience.

Table 3-4. Stakeholder Perspective on the Approach to Development, Review, and Authorization of COVID-19 Tests

Focus Areas	Key Takeaway and Lessons Learned
Policy	• All stakeholders noted that the templates were helpful resources and often requested additional ones for different test types and developers. • Stakeholders appreciated FDA's efforts to gather feedback on the templates. • Some stakeholders noted changes in the guidances were hard to follow. For example, there was confusion regarding some of the nuanced CLIA laboratory certifications and the state-based authorization processes listed in Policy B. • Stakeholders identified the need for guidance on transitioning an EUA-authorized test to full marketing applications (e.g., De Novo, 510(k)). • Stakeholders provided input on ways to communicate and incorporate continuous improvements to the templates. For example, stakeholders indicated that definitions (e.g., low positive sample, high sensitivity) were not the same across the templates, causing some stakeholders to refer to multiple templates to determine all information needed.

3.2 Approach to process improvements and review times

IMPLEMENTED PROCESS CHANGES TO KEEP PACE WITH EVOLVING NEEDS AND INCREASING SUBMISSION VOLUME

Developed CDRH-specific Standard Operating Procedure to Define Roles and Enhance Review Efficiency

Prior to the COVID-19 pandemic, the FDA had in place an Agency-wide Standard Operating Procedure (SOP) for EUAs used during previous PHEs. CDRH has followed this SOP from the beginning of the outbreak. As part of CDRH's 2018-2020 strategic priorities, CDRH had engaged in a process improvement effort for all major business processes, including for CDRH's portion of the EUA process. These efforts were still ongoing when the pandemic began and did not take into consideration a scenario in which the volume of EUA requests approached that seen during the COVID-19 pandemic. In

the Spring of 2020, CDRH determined that a more detailed Center-level SOP was needed to manage COVID-19 EUA requests due to the higher volume of EUA requests compared to prior PHEs and to reflect CDRH-specific processes put in place during the COVID-19 PHE (e.g., electronic submissions through the public inbox). Taking into consideration the lessons learned from the 2019 business process improvement effort and experience with EUA requests in the COVID-19 pandemic, CDRH implemented a CDRH EUA Pilot Process SOP on July 10, 2020 to more clearly outline CDRH staff roles and responsibilities and consistent processes to follow for EUA review in CDRH.

Developed Prioritization Factors and Implemented Processes to Address Growing Backlog

At the beginning of the pandemic when there were relatively few diagnostic tests authorized, the Center's priority was to rapidly increase the availability of tests, which meant that every test was a priority. CDRH staff were able to interact closely with most developers, including requestors who submitted incomplete requests and those who had little to no prior experience with EUAs or FDA. As the number of tests available and in development increased and the state of the pandemic changed, the early levels of interaction were unsustainable and necessitated the development of prioritization factors shown in Table 3-5 to best utilize the available CDRH resources for the public health need. Prioritization factors were implemented internally and discussed at weekly Town Halls in Spring 2020. In the context of tests offered through the notification policies described above, FDA focused on tests for which an initial review identified performance or safety concerns. In such cases, FDA made it a priority to work with the developer to address the concerns or stop testing. In early October 2020, factors FDA considers in prioritizing review of EUA requests were posted on FDA's website[12] through Frequently Asked Questions (FAQ) and further discussed during the weekly Town Hall sessions. CDRH identified a series of process improvements to support prioritization and efficiency, which are described below in the next sections.

Table 3-5. COVID-19 Test Prioritization Factors

Factors	Description
Increases Testing Capacity	Tests for which there is a capacity for large-scale manufacturing, distribution, or processing (e.g., high-throughput tests, high product volume tests), or that reduce reliance on limited testing supplies (e.g., saliva-based tests)
Expands Test Accessibility	Tests with increased availability or convenience because of where they can be performed (e.g., Point-of-care (POC) tests, home collection devices, at-home tests)
Reduces Real-World Performance Concerns	Tests that were being offered under a notification policy and for which FDA identified performance concerns

Implemented Process Changes

In Fall 2020, CDRH introduced a number of process changes to try to address the growing backlog of EUA requests and help focus Center resources. These changes included alignment with the structure of CDRH's standard review processes for other regulatory submissions. In addition, updates to the pilot SOP enabled reviewers to more efficiently deal with incomplete submissions (i.e., close files with requests for information), allowing them to focus on submissions with complete information that could move quickly through the authorization process. If files were closed with requests for information, requestors could provide the requested information in response for FDA to review.

Front-End Triage

Beginning in Fall 2020, CDRH instituted a front-end triage and prioritization process for all EUA requests to help focus Center resources on tests that were deemed to have a significant impact on the PHE, such as those that would increase testing accessibility or capacity. Staff use this process for all Pre-EUA and EUA requests soon after they are logged into CDRH's IT systems and assigned a Lead Reviewer. Given the substantially higher submission volume received during this pandemic compared to prior PHEs, having a formal set of prioritization factors was necessary to evaluate the potential scope and urgency of each request.

Deprioritization Processes

To complement the front-end triage process, CDRH introduced streamlined mechanisms to quickly Decline to Issue tests that had significant validation problems and Decline to Review low-priority files such as those that were highly manual, low-volume tests. Prior to implementation, CDRH processed all negative decisions for tests as Denials, which were issued by the FDA Chief Scientist. These deprioritization processes (i.e., Decline to Issue and Decline to Review), introduced in

[12] "COVID-19 Test Development and Review: FAQs on Testing for SARS-CoV-2," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-development-and-review-faqs-testing-sars-cov-2 -- accessed 6/11/2021

Spring 2020 and streamlined for IVDs beginning in October 2020,[13] was designed to allow CDRH to more easily process these files when requests were not a priority (or were deemed to not have an impact on the PHE), did not have sufficient information to evaluate whether they met the EUA criteria, or had validation or performance issues (and were not being offered under a notification policy). In the case of low-priority tests (e.g., because they were low throughput or low manufacturing capacity), CDRH would Decline to Review the file and close it, communicating the decision and reason why to the requestor. Alternatively, for priority tests with critical deficiencies (e.g., inadequate or missing performance data) that the requestor was unable to resolve in a reasonable period of time, CDRH would Decline to Issue the EUA, notifying the requestor and providing them with a list of deficiencies that had been identified. Requestors could choose to address the outstanding concerns in a follow up to the submission. Both options provided a mechanism for reviewers to focus on relatively high-priority (i.e., high-impact) and comparatively complete EUA requests that were going to make an impact on the PHE.

Following HHS's August 2020 statement[14] announcing its updated policy that FDA would no longer require premarket review of any LDTs (including those for COVID-19) absent rulemaking, CDRH Declined to Review over 200 LDT EUA requests in October. Given that LDTs could be marketed without an EUA and also the high volume of other EUA requests, this action allowed CDRH to focus valuable resources on priority tests that could not be offered without FDA review and authorization (e.g., home collection tests, POC tests, multi-analyte panels).

Supply Chain Monitoring

Beginning early in the pandemic, global manufacturing and distribution supply chains experienced strain, especially in response to demand increases, which had a substantial impact on certain medical devices. Recognizing this, FDA proactively reached out to medical device companies in February 2020 to monitor the supply chain for signs of shortages. Provisions in the Coronavirus Aid, Relief, and Economic Security (CARES) Act (enacted March 2020) further strengthened the Agency's early response by providing FDA with new statutory authority to require manufacturers to notify FDA about changes in the production of certain devices to mitigate public health impacts of shortages. In addition, CDRH established a Medical Devices Shortages Mailbox for manufacturers to report interruptions, shortages, and discontinuances of devices critical to the pandemic, and additionally conducted outreach to other U.S. government agencies, trade groups, hospital systems, and non-profit organizations to determine supply and demand issues. Leveraging this network, FDA identified 11 shortages related to testing, which are published on their website.[15]

As the pandemic progressed, CDRH began to operationalize the information gathered from its monitoring network. Supply chain issues were discussed during daily huddles to inform current review priorities. The CDRH Office of Strategic Partnerships and Technology Innovation (OST) also played a key role in supply chain activities by initially providing analysis of products flagged by review teams as possibly experiencing a supply shortage. Eventually, both the analytical process and the output data from it were formally incorporated into CDRH's overall EUA review process in the form of a consult service (part of the front-end triage process) and internal shortage dashboard, complementing the public-facing shortage list, enabling CDRH to prioritize submissions experiencing supply chain issues. For example, information obtained by OST informed CDRH's response to nasal swab shortages, allowing CDRH to pivot and prioritize tests that used saliva specimens.

Review Tracks

In Fall 2020, CDRH developed two review tracks for EUA requests: an Express Track and Standard Track. Tests eligible for the Express Track included those for which there was a critical need (e.g., no alternatives available, including other EUA-authorized devices) or the subject device is significantly better in terms of improved performance or safety compared with the alternatives. This allowed the most impactful devices to be reviewed not only first, but more quickly as each track had its own review milestone goals. Generally, files on the Express Track are not closed with requests for information but instead information is requested interactively. The goal is for the review team to make recommendations within 30 days. Files on the Standard Track follow a similar review process, although these submissions are lower in the queue, may be closed with requests for information if additional information is needed that cannot be provided in a timely manner, and

[13] CDRH initially used the prioritization process in Spring 2020 for IVDs to determine which tests would be assigned to a lead reviewer and which tests would be placed in a queue for later review. CDRH did not begin implementing the Decline to Review process, issuing a letter prior to substantive review, until October 2020, after over 250 EUAs had been authorized for tests and collection devices.

[14] "HHS Announcement on FDA Premarket Review of LDTs," Congressional Research Service https://crsreports.congress.gov/product/pdf/IN/IN11548 -- accessed 5/20/2021

[15] "Medical Device Shortages During the COVID-19 Public Health Emergency," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/medical-device-shortages-during-covid-19-public-health-emergency -- accessed on 6/4/2021

have a longer final recommendation goal (i.e., 60 days). Regardless of the review track, recommendations from the Office of Health Technology 7 (OHT7) for authorization or denial are sent to the Office of the Chief Counsel (OCC) and the Office of Counterterrorism and Emerging Threats (OCET) for review, and OCET provides the final sign off on such decisions. Decisions to Decline to Issue an EUA are signed off by OHT7.

Content Screen and Closing with Requests for Information

CDRH observed that some EUA requests frequently lacked information that was recommended in publicly available documents (e.g., EUA guidance or templates). As a result, the Center implemented a content screen in Fall 2020. Occurring after the front-end triage and prioritization process, these screens follow a checklist to determine if various criteria are met, including administrative (e.g., the submission is written in English and a description of the product and its intended use) and technical requirements such as the inclusion of a device description and performance data (e.g., evaluation using clinical specimens). These screens were implemented to identify EUA requests with sufficient information for review that could quickly move through the EUA process as well as requests with major issues that could not be addressed quickly. In such cases, FDA closed the files with requests for information, which the requestor could provide in an amended submission. By reducing the need for lengthy back-and-forth interactive review of submissions missing basic information, this provided staff with the opportunity to focus their time reviewing high-impact devices with complete submissions. Of the Original IVD EUA requests CDRH received since implementing the content screen, about two-fifths (144/357) of the files did not pass the content screen (as of April 23, 2021). Ultimately, CDRH intends to use the results of these content screens, noting specifically which information is most frequently being missed or requirements not followed, to inform an update to the interactive review templates, emphasizing and clarifying CDRH's expectations.

VARIOUS FACTORS IMPACTED REVIEW TIMES OVER THE COURSE OF THE PUBLIC HEALTH EMERGENCY

Allocation of Staff to Support COVID-19 Response

As the PHE progressed, CDRH continued to receive a high volume of EUA requests, regular workload continued to accrue, and inexperienced EUA requestors required extensive support from FDA. These challenges led FDA to develop processes to refocus resources from lower impact EUA requests to higher impact EUA requests. Additional reviewers were allocated to help address the COVID workload and support the response. Some came from within OHT7, but CDRH also leveraged reviewers from other offices and hired term employees. The specialized nature of IVD scientific expertise and regulatory experience limits how quickly a large volume of staff can be quickly or easily trained in this area. Training of reallocated staff requires time from the IVD specialists which pulls them away from review work.

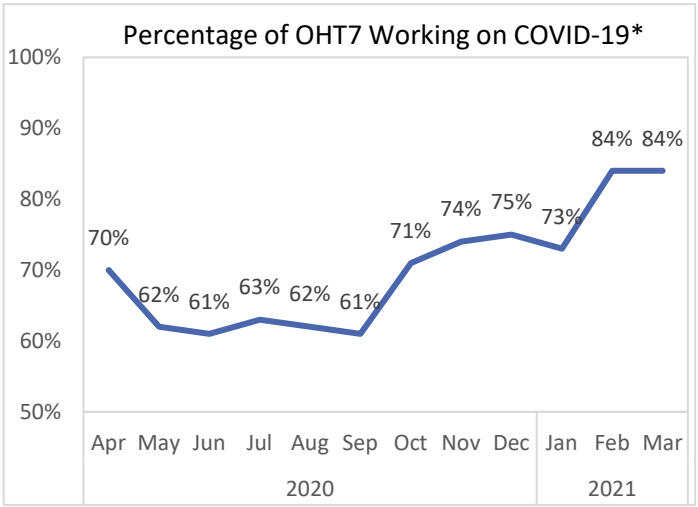

Figure 3-2. Percentage of OHT7 Working on COVID-19
*excludes Division of Radiological Health and Division of Mammography Quality Standards

The number of staff conducting review of COVID-19 tests fluctuated throughout the pandemic. In Spring 2020, CDRH directed some reviewers of other medical devices from other offices to focus on COVID-19 work. In Fall 2020, additional IVD reviewers performing non-COVID-19 work were shifted to focus on review of COVID-19 tests. Figure 3-2 shows a representative piece of the larger picture, showing the percentage of OHT7 staff (excluding the Division of Radiological Health and Division of Mammography Quality Standards) working on the COVID-19 response.[16] These data include review and non-review work, but they do not indicate the percentage of a *person's time* dedicated to COVID-19. Data were not available for contractors or staff from other Offices of Health Technology (OHTs) or Centers who provided OHT7 with assistance in the review of COVID-19 tests.

Reallocating staff and resources from product areas less impacted to those with increased submission volume presents a trade-off in meeting other priorities, even with others picking up extra non-COVID-19 work to support the response. This

[16] A new system, Insight Time Reporting (ITR), was implemented in March 2020 and uptake of the system impacted the ability to accurately report on allocation, which could have led to underreporting of COVID work.

has resulted in review delays for non-COVID-19 work, and CDRH is declining to review IVD pre-submissions that are not related to COVID-19, companion diagnostics, a breakthrough designation, or significant public health impact.[17]

Submission Volume Surpassed All Prior PHEs

As of April 2021, CDRH reviewed and closed out over 2,000 EUA requests, including Original EUAs and Supplements (i.e., requests for revisions to previously authorized tests), Authorizing or Acknowledging 812 requests as of April 12, 2021. Acknowledged decisions reflect files where CDRH concurs with changes in Supplements or Amendments that do not require an update to the Letter of Authorization (e.g., addition of a new laboratory instrument, extraction method, or sample type). Supplements that result in changes to the Letter of Authorization are reauthorized by OCET and include changes that commonly involve new indications such as home collection or screening. The number of Original Authorized EUA requests (360) dwarfs the number of tests authorized during all previous PHEs combined (Figure 3-3). Figure 3-4 shows the trends in authorization by month. In addition to these authorized tests, several tests had submitted notification to FDA and were marketing their tests while FDA reviewed their EUA requests. This substantially increased the volume of available tests, particularly in Spring 2020.

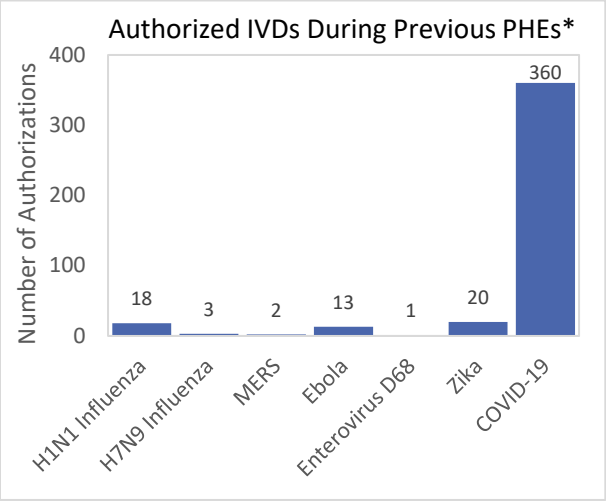

Figure 3-3. Authorized IVDs During Previous PHEs

*IVDs includes serology, molecular, and antigen tests. Prior PHE values represent authorized devices. COVID-19 value represents authorized Original EUAs. Data as of April 12, 2021.

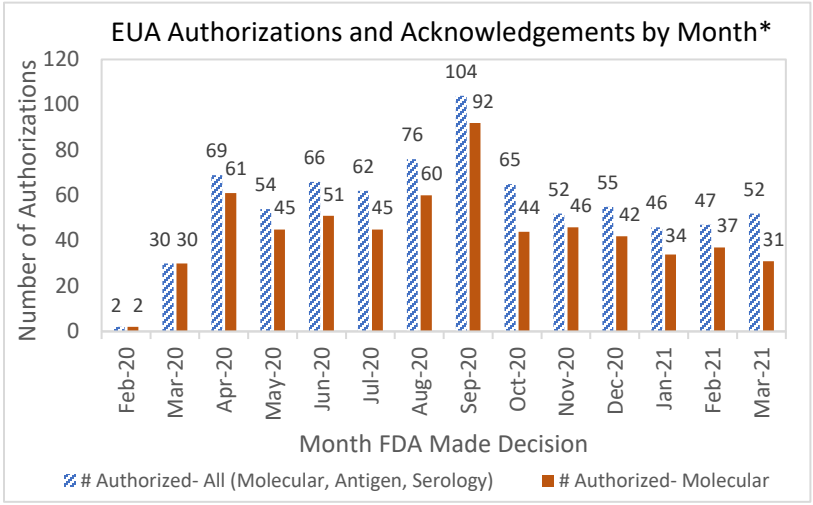

Figure 3-4. EUA Authorizations and Acknowledgements by Month

*Includes authorized Original EUAs and Supplements. Time is month FDA made decision, not month submitted. Data as of April 12, 2021.

Table 3-6 shows a breakdown of decisions made on EUA requests, both for all COVID-19 test types (i.e., including molecular, serology, and antigen) as well as molecular diagnostics in particular since they represented the majority of CDRH's files reviewed. As of April 12, 2021, 2,133 EUA requests were closed out. Of these, 61% (1,294) were molecular diagnostic tests, 29% (623) were serology and 9% (199) were antigen tests. Molecular IVD EUA requests were split evenly between Commercial Manufacturers and Laboratories, with more Original requests than Supplements. Overall, molecular tests were Authorized or Acknowledged more and Denied/Declined, Withdrawn, or Closed with Requests for Information slightly less frequently than all tests combined. While only a small percentage of molecular tests were either Denied or Declined to Issue due to concerns with the EUA request (e.g., regarding test validation), CDRH Declined to Review a larger proportion of low-priority files (e.g., low-volume tests) that were deemed to have a smaller impact on the PHE. Withdrawn files were done so at the request of the requestor for a variety of reasons (e.g., after receiving deficiencies from FDA or utilizing the flexible policy that does not require an EUA when bridging to an authorized test).

[17] "A Year Into the Pandemic: How FDA's Center for Devices and Radiological Health is Prioritizing its Workload and Looking Ahead," FDA https://www.fda.gov/news-events/fda-voices/year-pandemic-how-fdas-center-devices-and-radiological-health-prioritizing-its-workload-and-looking -- accessed 5/28/2021

Table 3-6. COVID-19 Test EUA Breakdown by Decision

Decision	Description	All EUA Requests for COVID-19 Tests n (% of Column Total)	Molecular EUA Requests n (% of Column Total)
Authorized or Acknowledged	• Action taken to authorize Original EUA requests and Supplements for changes requiring reissuance of the Letter of Authorization (reauthorization) • Action taken to acknowledge EUA Supplements for changes that do not require changes to the Letter of Authorization	812 (38%)	642 (50%)
Closed with Requests for Information	• Action taken to close an EUA request when additional information is needed to support authorization, but it is not readily available; the EUA request may be reopened at a later date if the requestor submits the additional information	233 (11%)	109 (8%)
Declined to Issue or Denied	• Action taken to close an EUA request with critical deficiencies that the requestor is unable to resolve in a reasonable period of time	280 (13%)	83 (6%)
Declined to Review	• Action taken to close EUA requests that are a low priority without complete review	460 (22%)	315 (24%)
Withdrawn	• Action taken to close EUA requests when the requestor voluntarily withdraws their request	348 (16%)	145 (11%)
Total*		2,133	1,294

**Data as of April 12, 2021*

Figure 3-5 shows the trend of all files submitted in that month, including Original EUA requests and Supplements, as well as 1,070 Pre-EUA requests. This includes all files received each month between March 2020 and March 2021, including those that have been closed and those that remain under review, and represents the total number (3,672) of COVID-19 IVD submissions for CDRH to review. This demonstrates a large influx in the early months of the pandemic with sustained numbers throughout the Summer, then leveling out in the Winter. As submission volume grew, CDRH pivoted to focus efforts on authorizing tests that would make the largest impact on public health, as described in Section 3.2.

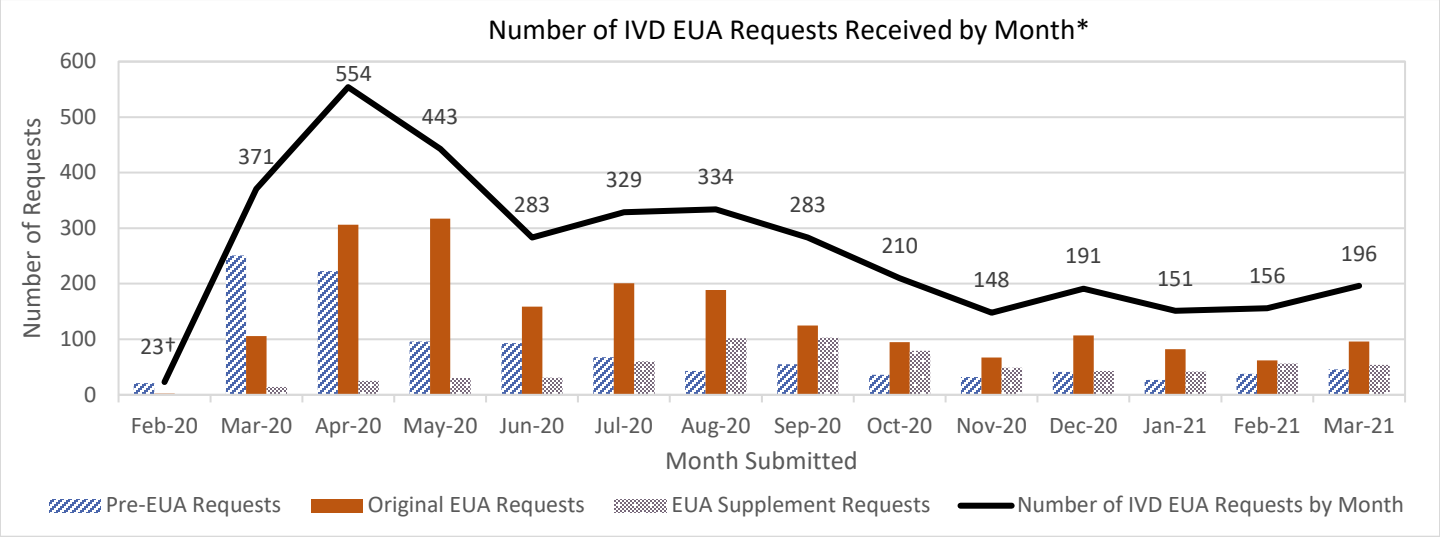

Figure 3-5. Number of IVD EUA Requests Received by Month

* These include Pre-EUA requests as well as requests for Original EUAs and Supplements: all test types and all developers. Time is the month submitted, not the month FDA began active review. Data as of June 9, 2021.

† In February 2020, there were 21 Pre-EUA requests and two Original EUA requests received.

Trends in Review Time

As shown in Figure 3-6, review times for denied EUA requests were initially much higher than for authorized EUAs, which reflects the many layers of review in the denial process. CDRH implemented its Decline to Review and streamlined Decline to Issue processes for IVD EUAs in October 2020 (as described above), which deprioritized a large volume of low-priority

tests and tests with validation or performance concerns, reducing burden on staff and allowing them to focus on high-impact submissions. Review times for authorized tests steadily increased during the Fall months, corresponding to the high volume of requests received. In addition, EUA requests for tests available through the notification process were not as highly prioritized as others which were not already in use, unless the triage revealed performance or safety concerns. Review times for authorized tests ultimately decreased and then remained steady throughout the Winter as process improvements were implemented (e.g., content screen, closing incomplete files with requests for information), Center staff were reallocated, and the number of new requests submitted each month began to decrease. Median review times may increase as more files are closed out.

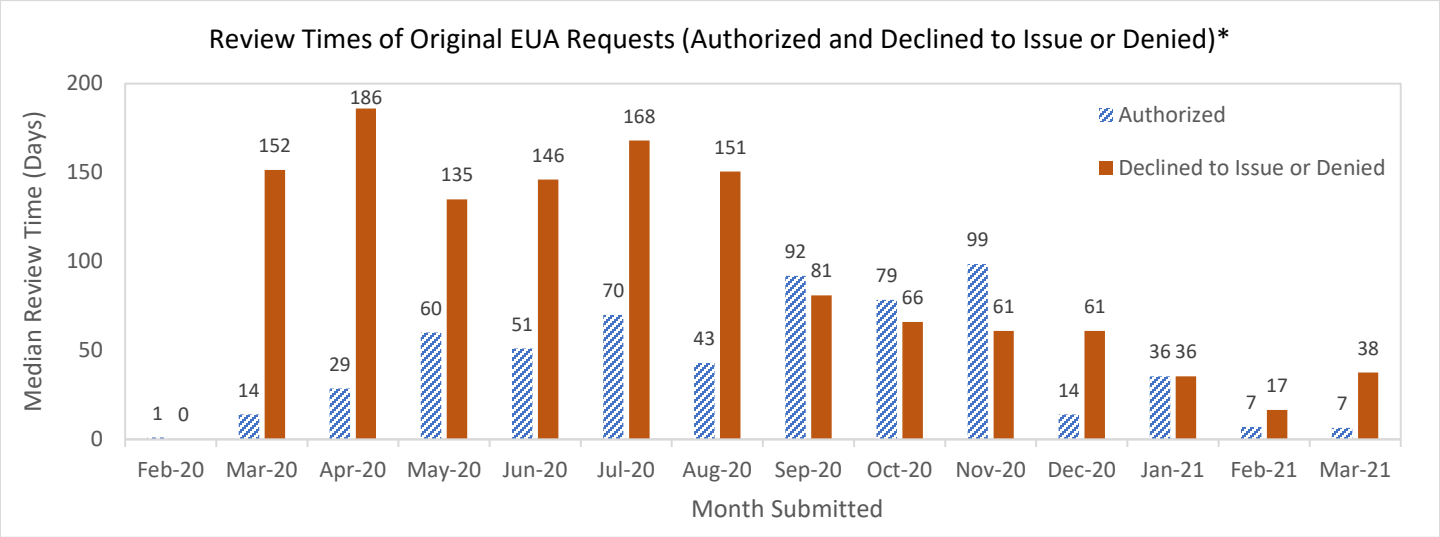

Figure 3-6. Review Times of Original EUA Requests (Authorized and Declined to Issue or Denied)

*These are EUA Originals: all test types and all developers. Time is the month submitted, not the month FDA began active review. Data as of April 12, 2021.

Review times for authorization/acknowledgement of Supplements compared to Originals were relatively fast in the early months of the pandemic, during which there were relatively fewer Supplements received. As developers began to modify their tests (e.g., using saliva as a specimen type, seeking authorization for at-home collection or POC settings for use in asymptomatic patients), review times for both types increased. Although Supplements made up only one-third of EUA requests reviewed for COVID-19 tests, Figure 3-7 shows that Supplements can take as long (if not longer) to review than Original EUA requests. While some Supplements included changes in the device use (e.g., at-home collection or POC settings), others included changes to add instruments, extraction methods, or indications for sample pooling and screening. Validating these changes can involve new clinical and analytical studies, similar to or beyond that of the Original Authorization. Many of these changes were implemented immediately upon submission of validation data to FDA under CDRH's modification policy. As a result, many Supplements were not high priorities for review.

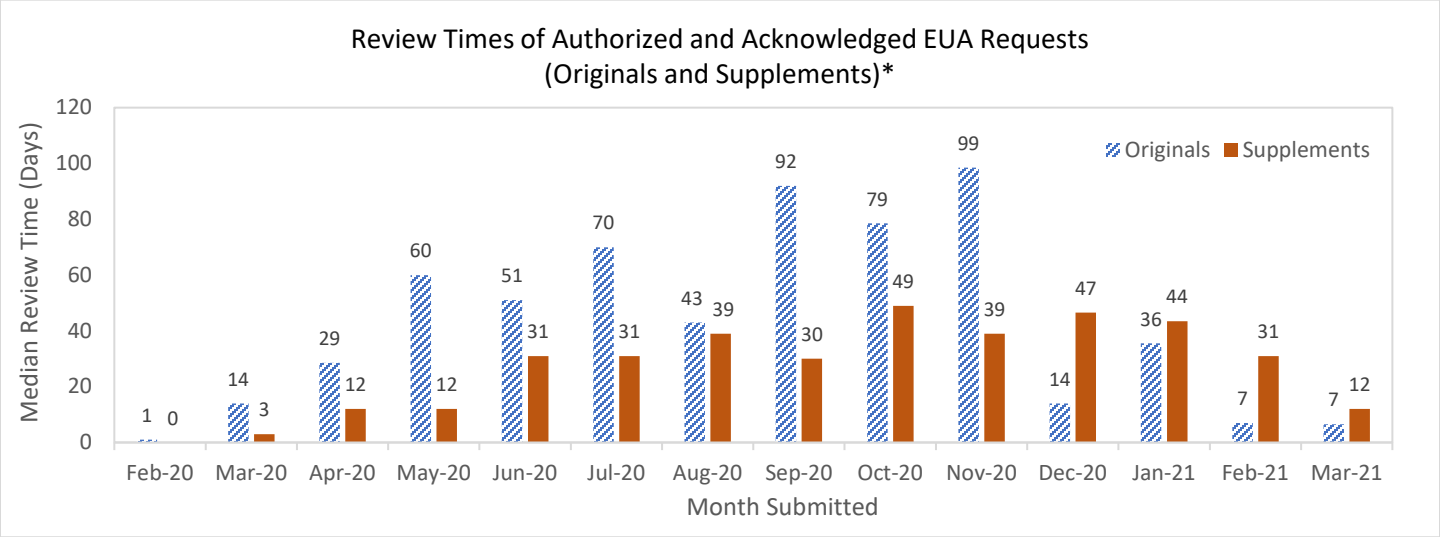

Figure 3-7. Review Times of Authorized and Acknowledged EUA Requests (Originals and Supplements)

*These are EUA Originals and Supplements: all test types and all developers. Time is the month submitted, not the month FDA began active review. Data as of April 12, 2021.

Figure 3-8 and Figure 3-9 show how review times for Original molecular EUA requests varied by month, broken down by decision and manufacturer type. Similar to observations presented in Figure 3-6, denials initially took much longer than authorizations for both Laboratories and Commercial Manufacturers, although review times for requests from Commercial Manufacturers tended to be longer compared to those from Laboratories, except during the Summer months. The decrease in review times for tests approaching Fall 2020 highlights the impact the streamlined Decline to Issue process had on review times.This could possibly be explained by the higher number of tests from Laboratories submitted early in the pandemic and certain Laboratories' relative inexperience in preparing EUA requests. Review times for authorized tests were initially longer for tests from Laboratories than those from Commerical Manufacturers, although they began to converge in the Summer and then the trend reversed in the Fall and Winter months.

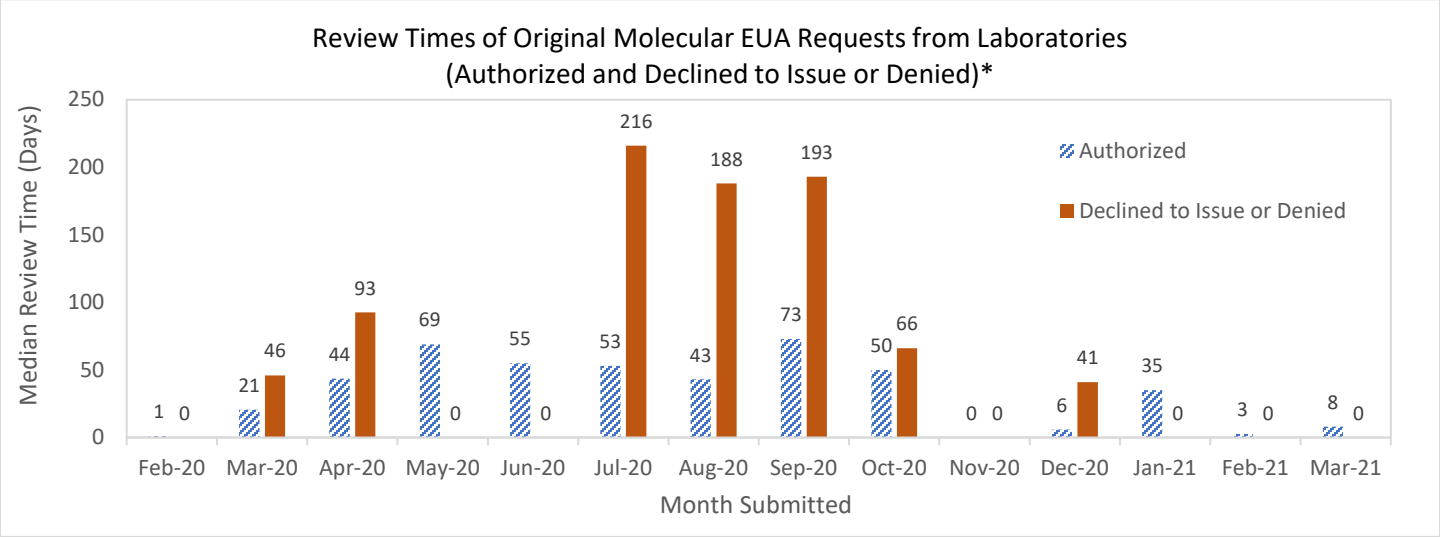

Figure 3-8. Review Times of Original Molecular EUA Requests from Laboratories (Authorized and Declined to Issue or Denied)

*These are EUA Originals: Molecular tests from Laboratories. Time is the month submitted, not the month FDA began active review. Data as of April 12, 2021.

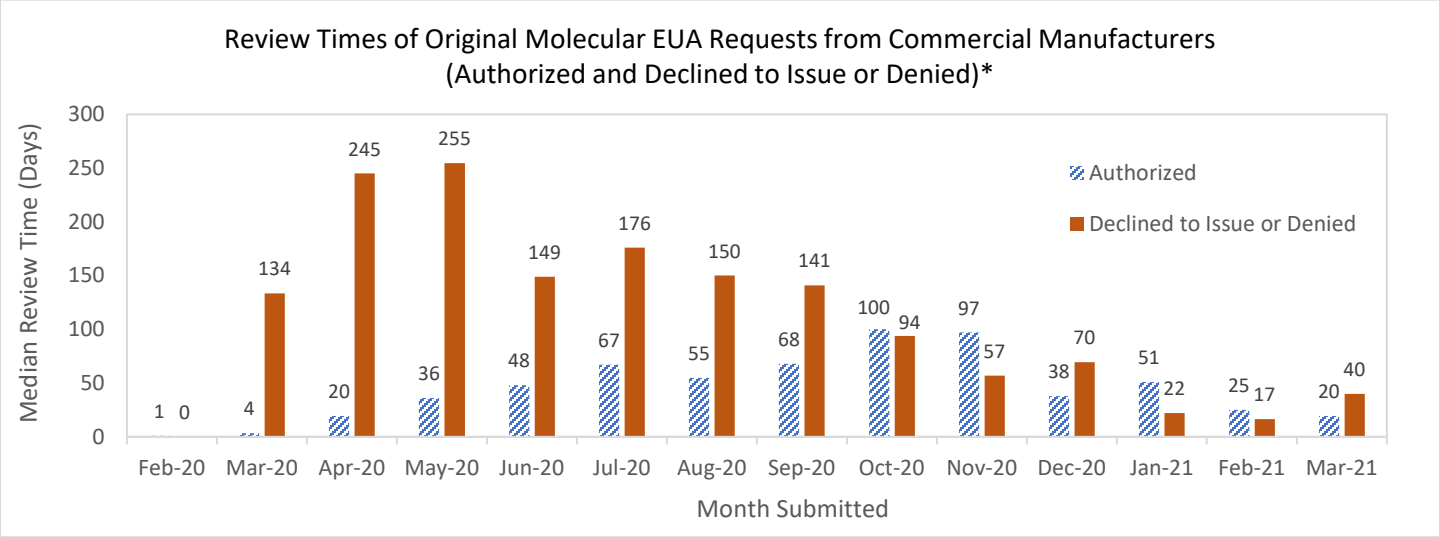

Figure 3-9. Review Times of Original Molecular EUA Requests from Commercial Manufacturers (Authorized and Declined to Issue or Denied)

*These are EUA Originals: Molecular tests from Commercial Manufacturers. Time is the month submitted, not the month FDA began active review. Data as of April 12, 2021.

Figure 3-10 shows a subset of the graph above, comparing review times of Original EUA requests from Commercial Manufacturers and Laboratories that were authorized while overlaying the number of submissions (regardless of test type or decision) submitted in each month. The figure demonstrates the large number of new submissions received each month, particularly at the beginning of the pandemic. The number of EUA requests submitted peaked at over 550 in April, declining into the early Summer, and then becoming relatively stable in October.

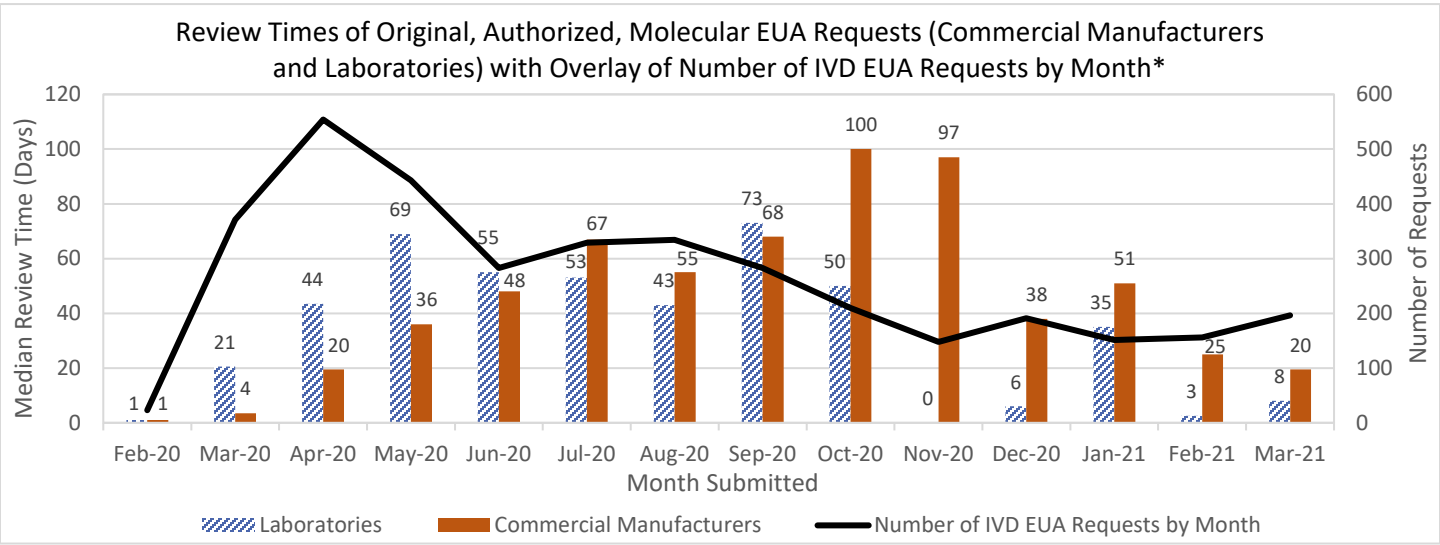

Figure 3-10. Review Times of Original, Authorized, Molecular EUA Requests (Commercial Manufacturers and Laboratories) with Overlay of Number of IVD EUA Requests by Month

*Review Time bars are EUA Originals: Molecular tests. Volume line includes Pre-EUAs as well as EUA Originals and Supplements: all test types and all developers. Time is the month submitted, not the month FDA began active review. Data as of April 12, 2021.

Figure 3-11 shows that a greater percentage of Original EUA requests from Commercial Manufacturers were authorized (37%) compared to those from Laboratories (25%). In addition, requests from Commercial Manufacturers were Declined to Issue or Denied (15%) at a higher rate than those from Laboratories (3%). The Decline to Review rate for Laboratories (48%) is higher compared to Commercial Manufacturers (22%) because as the pandemic progressed, LDTs were deprioritized in October 2020 following HHS' statement on LDTs.

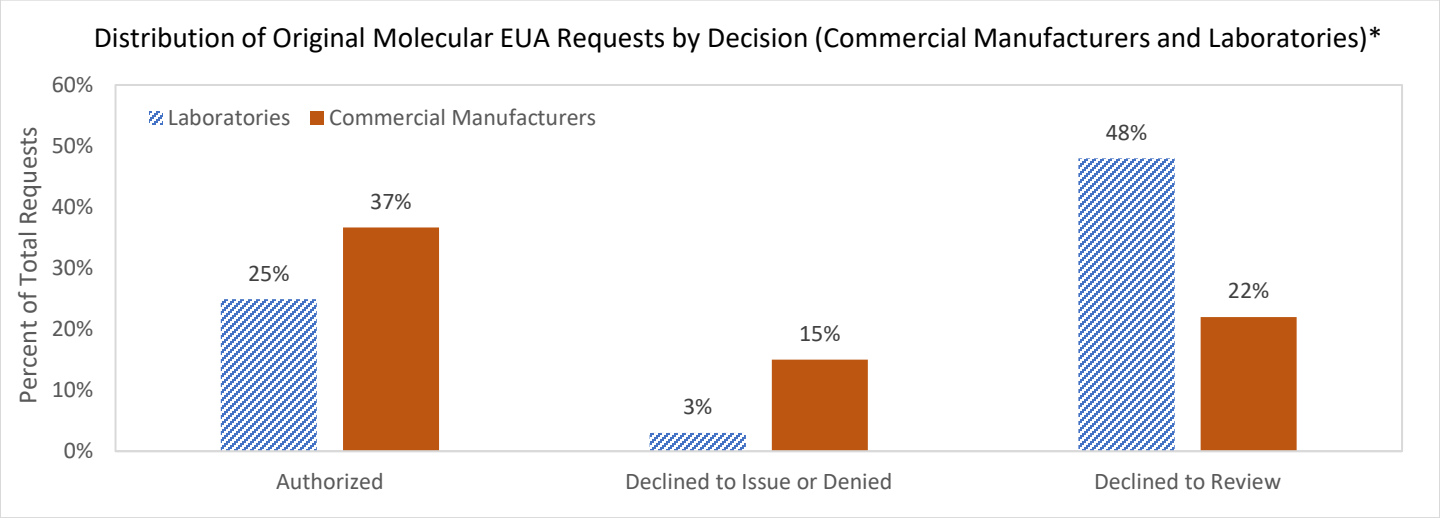

Figure 3-11. Distribution of Original Molecular EUA Requests by Decision (Commercial Manufacturers and Laboratories)

*These are EUA Originals: Molecular tests. Data as of April 12, 2021.

STAKEHOLDER PERSPECTIVES AND LESSONS LEARNED

To help inform current and future public health needs, Table 3-7 outlines stakeholder perspectives and lessons learned on the approach to process improvements and review times.

Table 3-7. Stakeholder Perspective on the Approach to Process Improvements and Review Times

Focus Areas	Key Takeaway and Lessons Learned
Process and Review Times	• Stakeholders shared positive feedback about interactions with review teams and their dedication to providing support throughout the EUA process. • Stakeholders relied on direct communications with review teams for updates. Stakeholders shared that they frequently asked about timelines for follow up with reviewers, information on review times, and contacted other groups at FDA (e.g., EUA mailboxes) if they did not hear back from them. • Stakeholders noted that response times were faster in the beginning and as volume increased, interactions became less frequent. • Stakeholders asked frequently about prioritization factors, which FDA later posted on their website and discussed during the weekly Town Hall sessions.

3.3 Approach to test validation, postmarket actions, and evaluation of real-world test performance

VALIDATION AND USE OF REFERENCE PANEL TO DEMONSTRATE PERFORMANCE

Developed Flexible Validation Process to Establish Performance

During preparation of EUA requests, requestors must validate their test by conducting a series of studies that demonstrate the product may be effective. These include both analytical studies, for example determining the smallest concentration of virus the test can detect and differentiating between other pathogens, and clinical evaluations, focusing on the real-world ability of the test to detect the virus in human samples. CDRH provides recommendations for these studies in guidance, which incorporates each of the ten EUA templates, although developers may propose alternative study designs as long as they adequately demonstrate that the test is accurate and reliable.

Based on experience with prior PHEs, CDRH anticipated some challenges related to test validation. For example, understanding that clinical specimens are difficult to find early in an outbreak, the January 2020 template provided flexibility to validate tests with contrived specimens instead. Contrived specimens can be made with either genetic

material taken from the virus itself or from synthetic genetic material matching the virus. FDA later saw that validation with certain types of contrived specimens masked performance issues for some tests.

FDA coordinated (with other U.S. government agencies) shipment of viral material (produced by culturing the virus in a laboratory) to developers working on tests in February 2020.[18] Subsequently, FDA authorized 59 COVID-19 diagnostic tests based on validation data using contrived samples between February and May.[19] However, validation with contrived samples is not as robust a validation study as those performed with clinical specimens; as availability of both standardized commercial samples and natural clinical specimens increased, CDRH recommended in a May 11, 2020 policy update that developers obtain and use these for validation.

Developed Reference Panel to Assess Comparative Performance

Recognizing the limitations of the type of validation that can reasonably be accomplished early in an outbreak, CDRH has developed reference panels for this and prior PHEs. Reference panels are composed of common, independent, and well-characterized reference material that allow for a more precise comparison of the analytical performance of different molecular IVDs.[20] CDRH began collaborating with the Center for Biologics Evaluation and Research (CBER) on development of a reference panel for SARS-CoV-2 molecular diagnostic tests in January 2020. The team obtained viral material when it became available in February 2020. The reference panels and accompanying protocol for evaluation by test developers became available on May 27, 2020. More than 1,000 reference panels were produced for SARS-CoV-2 compared to approximately 80 produced for Zika virus, reflecting the difference in scale between the PHEs.

Starting with the first authorization in February 2020, CDRH established conditions of authorization requiring requestors of all authorized EUAs to submit their test's performance data on FDA-recommended reference materials. Once the reference panel was available, FDA contacted all developers with EUAs to request they evaluate the reference panel per the established condition of authorization. Results were submitted as EUA Supplements and are made available on FDA's website, allowing comparisons across tests. Once final results were released by CDRH, requestors updated their labeling information with the new performance data and the Supplements were closed. Results were first posted on FDA's website on September 15, 2020 and last updated in December 2020 (Table 3-8). As of this date, three-quarters of developers either had data currently under review or published on FDA's website[21] (147/195); just under one-fourth (48/195) had either not provided shipping information or returned data, or had presented uninterpretable data, although no EUAs have been revoked for these reasons.

Table 3-8. Molecular Diagnostic Reference Panel Results

Reference Panel Results Status	Number of Tests*
No shipping information	17
Data not returned	26
Data uninterpretable	5
Under interactive review	21
Data published	126
Total	195

**All data as of December 2020 update*

Development of the molecular reference panel differed from the approach to the evaluation of serology tests, which involved a collaboration beginning in April 2020 with the National Institutes of Health's (NIH) National Cancer Institute (NCI). One difference in approach was that developers ran the molecular reference panel themselves, but serology tests were sent to NCI so the government could conduct its own evaluation against a standard set of samples. Similar to the molecular reference panel approach, results from the NCI evaluation of serology tests and underlying validation data are made publicly available on FDA's website[22] and openFDA,[23] which allows test developers to compare their in-house data to the validated results of other developers' tests, provides additional information to clinicians, and promotes increased transparency to the public. The partnership with NCI represents a collaborative model that could streamline data analysis and improve the response to future PHEs.

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[18] "Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency: Immediately in Effect Guidance," FDA https://www.fda.gov/media/135707/download -- accessed 5/21/2021

[19] "SARS-CoV-2 Reference Panel Comparative Data," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data -- accessed 5/21/2021

[20] Ibid.

[21] "SARS-CoV-2 Reference Panel Comparative Data," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data -- accessed 6/11/2021

[22] "EUA Authorized Serology Test Performance," FDA https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance -- accessed 5/28/2021

[23] "Independent Evaluations of COVID-19 Serology Tests," FDA/HHS https://open.fda.gov/apis/device/covid19serology/ -- accessed 5/28/2021

USING REAL-WORLD EVIDENCE TO CONFIRM TEST PERFORMANCE

Established Postmarket Reporting Requirements to Support Monitoring

CDRH has had to strike a balance between timely access to tests and assurance of real-world test performance. The EUA process allows FDA to authorize tests with less data than typical review pathways, which underscores the importance of postmarket monitoring. Allowing for this type of process underscores the need for reporting mechanisms. The primary way CDRH is able to monitor trends in performance is through the established postmarket reporting requirements communicated to requestors under conditions of authorization in the Letters of Authorization. Requestors are required to have appropriate processes in place and, pursuant to Code of Federal Regulations Title 21 Part 803 and the conditions of authorization, to track and report to FDA adverse events (AEs), including any occurrence of false results (i.e., false positives, false negatives) or any significant deviations from established performance characteristics. Many of the requestors already had and used existing mechanisms in place to report results, which is standard practice for medical devices.

It is unclear how well EUA requestors and their authorized Laboratories are complying with the reporting requirements at this time. For example, authorized Laboratories are required to collect information on test performance and report it to FDA through the designated email inbox CDRH-EUA-Reporting@fda.hhs.gov. As this is a non-traditional reporting mechanism, not all Laboratories have processes in place to do this reporting.

EUA requestors are also required to comply with labeling requirements under FDA regulations, and document where and how many tests have been distributed. In some instances, CDRH required postmarket studies as a condition of authorization in an attempt to provide requestors with some flexibility with their pre-authorization data package (e.g., requiring prospective clinical study when contrived samples were used for validation). The additional data and study requests, which include performing the reference panels as outlined in the previous section, are included in the Letter of Authorization and in some cases also outlined in the EUA templates.

Conducted Postmarket Surveillance and Enforcement Activities

Device manufacturers, including those of diagnostic tests, must follow certain conditions of authorization once their products are marketed such as reporting malfunctions and AEs. Surveillance allows FDA to monitor these incoming data and determine what actions, if any, need to be taken in assessing tests' real-world test performance by reviewing information submitted to identify network signals, evaluate potential risks to the public, and conduct follow up investigations when necessary. These reports contain data from a variety of sources including: (1) Medical Device Reports (MDRs), mandatory AE and device malfunction reports from manufacturers; (2) MedWatch, FDA's voluntary device safety reporting program for health care providers and consumers; (3) Medical Product Safety Network (MedSun), CDRH's mandatory AE reporting system for hospitals and other health care facilities; and (4) publicly available reporting mailboxes (e.g., CDRH-EUA-Reporting@fda.hhs.gov). As of May 2021, over 6,000 MDRs have been reported for COVID-19 tests, each including information about the device, who reported it, and the problem experienced (e.g., false positive/negative). CDRH reads incoming reports daily and conducts weekly analysis to identify potential trends or emerging safety issues. As more COVID-19 tests were authorized, CDRH observed a steady increase in report submission starting in Summer 2020 (between 650 and 1,050 reports per month); to handle the increase in volume, the Center reallocated resources from other areas and implemented process improvements (e.g., automating part of the data entry process to summarize MDRs).

Surveillance efforts can lead to postmarket actions (e.g., EUA revocation, removal from the notification list, Warning Letters issued). Many of these postmarket activities pertain to serology tests and were informed by real-world performance identified by CDRH's surveillance activities. A breakdown of all the actions and communications taken by CDRH as of June 11, 2021 during the PHE are summarized in Table 3-9.

Table 3-9. EUA Postmarket Actions

Postmarket Action/Communication	Description	Number[24]
EUA Revoked	The criteria for issuance are no longer met or other circumstances make such revocation appropriate to protect the public health or safety.	3[25]
Notification Removal List – Laboratories with Diagnostic Tests	Diagnostic tests developed by Laboratories and offered under the notification policy that may have significant problems that cannot be addressed in a timely manner and should no longer be used.	2
Notification Removal List – Commercial Manufacturers with Diagnostic Tests	Diagnostic tests developed by Commercial Manufacturers and offered under the notification policy that may have significant problems that cannot be addressed in a timely manner and should no longer be used.	18
Notification Removal List – Commercial Manufacturers with Serology Tests	Serology tests developed by Commercial Manufacturers and offered under the notification policy that may have significant problems that cannot be addressed in a timely manner and should no longer be used.	266
Warning Letters	Letters sent to developers that have adulterated or misbranded products related to COVID-19.	36
Letters to Health Care Providers	Letters sent to health care providers about safety concerns and recommendations for medical devices used in health care facilities.	7
Safety Communications	FDA posts Medical Device Safety Communications to describe FDA's current analysis of an issue and contain specific regulatory approaches and clinical recommendations for patient management.	4

One of the postmarket actions taken is the revocation of an EUA. This has resulted primarily due to the criteria for issuance of authorization no longer being met (e.g., the known and potential benefits of the product no longer outweigh the known and potential risks, such as due to poor performance) or the availability of adequate approved alternatives (e.g., as a result of subsequent premarket authorization through 510(k) clearance, De Novo classification, or PMA approval). For example, two EUAs for serology tests for COVID-19 have been revoked. CDRH notified the requestors of poor performance issues between the NCI evaluation of serology tests and the clinical and analytical data submitted with their applications. The requestors were provided an opportunity to provide information to refute FDA's findings. Once a decision was made to revoke the EUA, the requestor was notified via letter and notice of the revocation was published in the Federal Register. This process thereby removes the ability of the test to be legally marketed and further informs the public of FDA's intent to take strong action against poor-performing tests. The previous PHEs also had a small number of tests revoked due to performance issues: one antigen test for Ebola and one molecular test for Zika virus.[26]

Collaborated on Real-World Evidence Generation

CDRH participated in various collaborations focused on gathering and analyzing real-world data (RWD) and real-world evidence (RWE) to help inform its COVID-19 response. Table 3-10 describes ongoing collaborations with stakeholders from the medical device industry, academia, non-profit organizations, and other U.S. government agencies that seek to better understand how to use data to improve testing quality and incorporate data into evaluation of COVID-19 diagnostic and antibody tests to better inform population testing strategies and understand patterns of disease transmission.

Table 3-10. Collaborations to Evaluate the Potential Application of RWE During a PHE

Collaboration	Partners	Research Objectives	Anticipated Outcomes
Systematic Harmonization and Interoperability Enhancement of Lab Data (SHIELD)	Federal agencies, industry, Laboratories, Electronic Health Record vendors, standards developers, academia	Promote harmonized application and implementation of diagnostic data standards	Enable rapid data sharing between different data sources to facilitate evaluation of RWD/RWE

[24] As of June 11, 2021

[25] FDA has issued a De Novo classification order for one COVID-19 diagnostic test, and accordingly revoked the EUA. Two additional individual EUAs were revoked due to performance issues. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information -- accessed 6/11/2021

[26] "Emergency Use Authorization--Archived Information," FDA https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information -- accessed 6/11/2021

Collaboration	Partners	Research Objectives	Anticipated Outcomes
Diagnostic Evidence Accelerator	Reagan Udall Foundation, Friends of Cancer Research	Encourage collaboration and development of data linkages within the research community, critically discuss findings from different data sources, and develop key research questions that multiple teams can address simultaneously	Provide actionable information on specific populations and highlight individual risk factors for patients, improve the understanding of disease to tailor public health interventions and strategies to mitigate risk, identify supply chain issues, and provide RWE of test performance
Informatics-driven real-world analysis of SARS-CoV-2 serologic response and IVD accuracy	Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation	Correlate diagnostic test results with clinical disease using RWD to better understand serologic results	Address questions about the COVID-19 immune response, including how long patients remain infected, the accuracy of serology test methods over time, formation of antibodies, and how long an individual may be immune after infection[27]

STAKEHOLDER PERSPECTIVES AND LESSONS LEARNED

To help inform current and future public health needs, Table 3-11 outlines stakeholder perspectives and lessons learned on the approach to test validation, postmarket actions, and evaluation of real-world test performance.

Table 3-11. Stakeholder Perspective on the Approach to Test Validation, Postmarket Actions, and Evaluation of Real-world Test Performance

Focus Areas	Key Takeaway and Lessons Learned
Postmarket Performance	• Stakeholders had questions regarding expectations for test validation and the degree of flexibility in the validation recommendations. • Stakeholders noted it was helpful to talk through validation study options with reviewers during the Pre-EUA process. • Stakeholders had many questions around Supplements and Amendments, with common themes including asymptomatic testing, pooling, and at-home/POC validation expectations. • Stakeholders noted that molecular reference panel was a helpful tool; however, some had technical issues running the panel. Commercial Manufacturers expressed concerns about not having a reference panel until May 2020. International EUA requestors indicated challenges receiving the reference panel. • Experienced stakeholders leveraged postmarketing reporting processes they already had in place.

3.4 Approach to communication with requestors, clinical community, and the public

ESTABLISHED MULTIPLE COMMUNICATION CHANNELS

Established Weekly Town Halls for EUA Requestors

In March 2020, CDRH started to host weekly, hour-long Town Hall meetings as an opportunity for OHT7 Leadership, including the OHT7 Director, to provide updates and answer questions for test developers. By the end of April 2021, CDRH had hosted 53 Town Halls that have been well attended (>40,000 attendees to date). Transcripts, slides, and recordings of the Town Halls are posted to the FDA's website, typically within one week after being recorded. The Town Halls are ongoing and provide an opportunity for test developers to have an open dialogue on EUA policies and guidance, tools and resources (e.g., Templates, FAQs, CDRH mailboxes), validation and postmarket performance procedures, test development recommendations, review time expectations and prioritizations. For example, when new policies and policy updates have been announced, such as new or updated guidance documents and EUA templates, FDA has responded to stakeholder questions and concerns about policy implementation. OHT7 Leadership provides specific feedback and directs requestors to reach out to the EUA template mailbox or their reviewer for details on highly technical questions. For

[27] "Yale University-Mayo Clinic CERSI: Current Projects" Yale School of Medicine https://medicine.yale.edu/core/current_projects/cersi/research/ -- accessed 6/30/2021

example, in response to requestor questions on validation, OHT7 Leadership provides insight into analytical and clinical validation expectations including the number of positive samples developers are expected to evaluate while explaining that these expectations may be dependent on specific details of the test, which may not all be apparent in the brief discussion on the Town Hall. In addition, OHT7 uses the Town Halls as a platform to provide information on CDRH's review and prioritization processes and test development recommendations. For example, FDA began to encourage development of POC and at-home tests in Summer 2020, and also encouraged the development of multi-analyte panels to prepare for the upcoming flu season. Similarly, OHT7 Leadership has discussed in the Town Halls the significance and limitations of serology tests, and the focus on different types of tests at different stages in the pandemic.

Created Central Mailbox for Inquiries

CDRH developed a public-facing email inbox to collect questions from EUA requestors and requests for submission templates, which provided CDRH an opportunity to track the pipeline of interested requestors. In addition, EUA requestors could submit electronic submissions through the mailbox, COVID19DX@fda.hhs.gov, starting February 20, 2020 as opposed to mailing physical submission packages to the Document Control Center. Mailboxes are also a primary way of obtaining feedback from requestors, enabling CDRH to identify communication or expectation gaps and informing future Town Hall topics and template revisions. Between March and May 2020, CDRH received over 120,000 emails to the COVID19DX@fda.hhs.gov inbox. By October 2020, there were over 170,000 inquiries. CDRH deployed two dedicated full-time employees and other part-time staff to triage and respond to inquiries, process submissions, and filter submissions to the appropriate contact. The questions received related to how to submit an EUA request, specific data requirements, and how enforcement policies outlined in guidance apply to a specific test. CDRH quickly established additional mailboxes enabling more specialized information to be quickly directed to various stakeholders. By May 2020, CDRH had an EUA template mailbox for Pre-EUA questions, template inquires and general questions about COVID-19 tests, a fraud mailbox to report false labeling, and a SHIELD mailbox for insight into data harmonization and the SHIELD program. As with prior emergencies, CDRH also used mailboxes for external stakeholders (e.g., hospitals, group purchasing organizations) to report shortages in diagnostic test supplies and other supply disruptions.

Developed FAQs and 24/7 Hotline

CDRH established several additional mechanisms for communicating with EUA requestors, including a 24/7 phone hotline to communicate expectations for test developers, information related to shortages and alternative supplies, and issues related to safety and test performance. In addition, CDRH posted FAQs on the FDA website to educate EUA requestors on the development and performance of COVID-19 tests. Over 300 FAQs have been posted so far across nine websites (i.e., Notifications and Emergency Use Authorizations, Removal Lists of Tests that Should No Longer Be Used and/or Distributed for COVID-19, Test Development and Review, Test Settings, Test Uses, Test Supplies, 3D Printed Swabs, COVID-19 Related Test Data and Reporting, and Serology/Antigen Tests). The FAQs are updated as needed and include other resources for test developers. For example, FDA has published an interactive Testing Supply Substitution Strategies resource that includes validated supply alternatives that Laboratories can use to continue performing testing when there is a supply issue with some components of a molecular test. As information needs evolved, FDA added websites to cover topics including scientifically valid alternative testing supplies during shortages[28] and pooling strategies.[29]

Communicated Surveillance Information to Developers and Health Care Providers Through Multiple Channels

In addition to using surveillance efforts to inform postmarket actions, FDA also communicates information about tests and test performance in a variety of ways. These communications convey information on tests' real-world performance trends to EUA developers, the clinical community, and the general public. FDA communicated this information through Letters to Health Care Providers, Safety Communications, other press releases, weekly Town Halls, and updates to FDA's website.

Letters to Health Care Providers and Safety Communications are similar communication mechanisms used to provide information about test issues, potential impacts on performance, and recommendations on how these tests should be used. Seven Letters to Health Care Providers have been issued as of June 11, 2021. The first Letter to Health Care Providers was published on April 17, 2020 on the use of serology tests. These letters are posted to the FDA website in addition to being sent to the health care community. Each one provides background information, recommendations, FDA actions taken, mechanisms for reporting additional problems, and additional information such as linking to the EUA, appropriate

[28] "Testing Supply Substitution Strategies," FDA https://www.fda.gov/media/138548/download --accessed 6/18/2021

[29] "Pooled Sample Testing and Screening Testing for COVID-19," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/pooled-sample-testing-and-screening-testing-covid-19 -- accessed 6/18/2021

FDA websites, and updates on instructions. Safety Communications are similar but are targeted at the general public. Four have been issued as of June 11, 2021. Both Letters to Health Care Providers and Safety Communications are intended to inform the appropriate audiences on trends to watch for and instruction updates.

FDA has closely tracked the potential impact of emerging viral mutations on COVID-19 test performance by routinely comparing the genetic sequences of each new mutation to the target sequences of currently marketed tests. FDA has publicly posted the tests whose performance could be impacted by SARS-CoV-2 viral mutations, along with general information for clinical laboratory staff and health care providers on the potential for false negatives. As of June 11, 2021, FDA has identified four molecular diagnostic tests for COVID-19 potentially impacted by SARS-CoV-2 mutations.[30] FDA has also issued guidance for test developers to evaluate the potential impact of emerging and future viral mutations on COVID-19 tests for the duration of the COVID-19 PHE.[31]

There are a variety of examples where CDRH's surveillance efforts have detected trends using real-world performance and communicated accordingly. For example, CDRH quickly determined there were inaccuracies with the Abbott ID Now POC tests based on the AE reports received. As a result, CDRH was able to alert the public through a press release and the clinical community through a Letter for Health Care Providers, and to work with Abbott to update the Instructions for Use, all within a month of the test's Original Authorization. Another example involves Becton, Dickinson and Co (BD) SARS-CoV-2 Reagents for the BD Max System test, which was granted authorization in April 2020. Analysis of real-world performance data showed a false positive rate of about 3%. CDRH worked with BD to identify the issue and address it through updates to labeling and the Factsheet for Health Care Providers. CDRH also issued a Letter to Health Care Providers on July 7, 2020 alerting them of the potential for false positives and recommending positive results be confirmed with an alternate authorized test.[32]

FDA maintains lists on their website of previously notified tests that should no longer be used and that have been removed from the lists of notified tests. A test may be placed on the removal list for a variety of reasons: (1) failure to submit an EUA request in a reasonable amount of time as outlined in guidance; (2) poor test performance or inadequate validation; and (3) voluntary withdrawal of the EUA request by the requestor. FDA expects that tests on this list will not be distributed unless and until an EUA is issued for the test. This process may also facilitate the withdrawal of poor-performing tests from the market. The vast majority of tests on the removal lists are serology tests, which may be a reflection of serology developers taking advantage of the notification policy to a greater extent than commercial developers of diagnostic tests (i.e., antigen and molecular).

To address an influx of firms marketing fraudulent tests with false or misleading claims, FDA issued Warning Letters to companies for adulterated and misbranded products related to COVID-19. Warning Letters are issued when FDA finds that a manufacturer has violated FDA regulations (e.g., poor manufacturing practices, unsubstantiated claims). These Warning Letters are published on FDA's website and provide information on the tests and the company that produced it.[33] These companies are provided 48 hours to explain how they have addressed their violations. The first Warning Letter for a COVID-19 test was issued on June 10, 2020, and a total of 36 Warning Letters have been issued, as of June 21, 2021, for firms offering violative COVID-19 tests.[34] 19 of the firms that were issued Warning Letters have ceased marketing of their violative COVID-19 tests. The public is encouraged to submit tips of potential fraud through the appropriate channels like

[30] "SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests -- accessed 6/11/2021

[31] "Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests," FDA https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-evaluating-impact-viral-mutations-covid-19-tests -- accessed 6/11/2021

[32] "False Positive Results with BD SARS-CoV-2 Reagents for the BD Max System - Letter to Clinical Laboratory Staff and Health Care Providers," FDA https://www.fda.gov/medical-devices/letters-health-care-providers/false-positive-results-bd-sars-cov-2-reagents-bd-max-system-letter-clinical-laboratory-staff-and -- accessed 5/28/2021

[33] "Warning Letters," FDA https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters -- accessed 5/28/2021

[34] "Fraudulent Coronavirus Disease 2019 (COVID-19) Products," FDA https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products -- accessed 6/30/2021

the Fraud Email and Office of Criminal Investigations. FDA stated that it has provided companies with regulatory flexibility but would not tolerate fraud or conduct that puts the health of Americans at risk.[35]

Communicated with the Public Through Various Mechanisms

FDA used a variety of communications to increase transparency and understanding of the EUA process. Since January 27, 2020, FDA has issued press releases,[36] often daily, with the latest information on COVID-19. These releases cover topics such as key authorizations, descriptions of policy decisions, safety concerns, and guidances. In addition to these press releases, FDA has provided updates through other communication channels. For example, Dr. Jeff Shuren, Director of CDRH, published an article[37] on the "FDA Voices" page on July 21, 2020, describing FDA's ongoing work to support diagnostic test accuracy and availability. Similarly, FDA published three medical device consumer updates related to COVID-19,[38] translated into five other languages, which describe regulatory terminology, potential for fraudulent products, and testing basics. FDA has supplemented these resources with videos and infographics to further clarify information.

FDA has developed communications to promote transparency of real-world test performance to further bolster confidence in the EUA process for COVID-19 diagnostic tests. CDRH publicly posts reference panel results for COVID-19 molecular diagnostic tests on FDA's website,[39] allowing for direct comparison of available tests' performance for the public. Similarly, results from NCI's validation studies on serology tests were made public,[40] which provides the opportunity to see the objective performance of each test. FDA also shared lessons learned with the public through multiple avenues, including peer-reviewed publications on molecular diagnostic tests[41] and antibody tests,[42] blog posts of expert opinions on CDRH's strategy to facilitate COVID-19 test development and authorization,[43,44] and a report of FDA's analysis of South Korea's COVID-19 response.[45]

STAKEHOLDER PERSPECTIVES AND LESSONS LEARNED

To help inform current and future public health needs, Table 3-12 outlines stakeholder perspectives and lessons learned on the approach to development, review, and authorization of COVID-19 tests.

[35] "Coronavirus (COVID-19) Update: FDA Issues Warning Letters to Companies Inappropriately Marketing Antibody Tests, Potentially Placing Public Health at Risk," FDA https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-warning-letters-companies-inappropriately-marketing-antibody -- accessed 6/25/2021

[36] "Coronavirus Disease 2019 (COVID-19)," FDA https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19 -- accessed 6/11/2021

[37] "FDA's Ongoing Work to Support and Advance COVID-19 Diagnostic Test Accuracy and Availability," FDA https://www.fda.gov/news-events/fda-voices/fdas-ongoing-work-support-and-advance-covid-19-diagnostic-test-accuracy-and-availability -- accessed 6/11/2021

[38] "Medical Devices," FDA https://www.fda.gov/consumers/consumer-updates/medical-devices -- accessed 6/11/2021

[39] "SARS-CoV-2 Reference Panel Comparative Data," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data -- accessed 6/11/2021

[40] "Independent Evaluations of COVID-19 Serological Tests," FDA https://open.fda.gov/apis/device/covid19serology/ -- accessed 6/11/2021

[41] Shuren, J and T Stenzel, 2020, Covid-19 Molecular Diagnostic Testing - Lessons Learned, N Engl J Med, 383(17):e97. doi: 10.1056/NEJMp2023830

[42] Shuren, J and T Stenzel, 2021, The FDA's Experience with Covid-19 Antibody Tests, N Engl J Med, 384(7):592-594. doi: 10.1056/NEJMp2033687

[43] "Bending The Arc Of COVID-19 Test Development To Increase Access And Ensure Reliability—Now And In The Future," Health Affairs https://www.healthaffairs.org/do/10.1377/hblog20210318.9094/full/ -- accessed 6/11/2021

[44] "FDA: We're constantly working on COVID testing options," FDA https://thehill.com/opinion/healthcare/515628-fda-were-constantly-working-on-covid-testing-options -- accessed 6/25/2021

[45] "South Korea's Response to COVID-19," FDA https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/south-koreas-response-covid-19 -- accessed 6/11/2021

Table 3-12. Stakeholder Perspective on the Approach to Communication with Requestors, Clinical Community, and the Public

Focus Areas	Key Takeaway and Lessons Learned
Communications	• Stakeholders shared that frequent communications were beneficial. Specifically, stakeholders found the Town Halls very informative, appreciated the opportunity to ask questions, and often had representation at the meetings to bring back information to their teams. • Stakeholders leveraged the FAQs and other FDA websites often, many of the EUA requestors kept them bookmarked to frequently check for updates. • Stakeholders appreciated the convenience of electronic EUA requests and hoped that electronic submissions would be implemented permanently. • Some stakeholders noted technical issues with file type and size constraints when submitting their EUA request electronically. • Stakeholders indicated the need for greater clarity on certain issues, specifically: (1) when a change to the test requires filing an EUA Supplement; (2) how to get authorized; and (3) updates to templates since it likely impacts development programs.

4. BEST PRACTICES AND PRIORITY RECOMMENDATIONS

Booz Allen identified areas where CDRH could build on lessons learned and successful improvements as well as priority recommendations to further strengthen the EUA process.

We observed best practices, outlined in Table 4-1, that CDRH should continue to leverage as well as areas for additional improvement to further strengthen and optimize the EUA process.

Table 4-1. Best Practices Identified by Booz Allen to Support the EUA Process

	Focus Area
Best Practices	• Rapid updates to guidance and policy regarding different test types and developers, allowing CDRH to strike a balance between urgent need for tests and assurance of test performance • Use of publicly available templates to provide guidance on the EUA requests and continue to gather feedback from stakeholders on the templates • Factors to prioritize submission review, including test capacity, accessibility, novelty, and supply chain considerations, to focus review resources on the most impactful requests • Development and required use of a reference panel for assurance of performance • Collaboration on validation and performance testing; generation and evaluation of RWD; and supply chain monitoring • Hosting Town Halls to communicate interactively and frequently • Electronic submission to facilitate the process for EUA requestors

Table 4-2. outlines priority recommendations that would allow FDA to capitalize on its previous success, enhance current processes and procedures, and facilitate the next steps to strengthen FDA's public health infrastructure to respond to future PHEs.

Table 4-2. Priority Recommendations Identified by Booz Allen to Support the EUA Process

Key Observation	Priority Recommendation	Intended Impact
Precise tracking of new review metrics was encumbered by the IT system, which is not optimized to account for updated EUA processes	Consider ways to optimize the IT system to account for EUA processes	Fully automate submission and tracking of EUA requests (e.g., linking Pre-EUA to EUA; lags while awaiting additional information from requestors; lags due to backlog or priority designation) to provide more comprehensive picture of review time from EUA submission to decision for review efficiency, performance monitoring, prioritization, process improvements, and workload management

Key Observation	Priority Recommendation	Intended Impact
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	Consider developing a systematic approach (i.e., strategy and plan) for allocation and tracking of staff during PHE	Quick determination of staffing needs and deployment of the right staff to the right place at the right time to maximize review efficiency. Identification of most likely areas for future PHEs (e.g., emerging infectious diseases) and development of process for cross-training to prepare a subset of staff in those areas in the event of a PHE
There was limited understanding in the test developer community on how to appropriately validate a diagnostic test	Consider developing a framework for how to conduct validation of diagnostic tests for emerging pathogens in the setting of a declared PHE	Earlier access to appropriate, effective diagnostic tests

5. APPENDIX

5.1 Glossary

Table 5-1. Glossary of Abbreviations and Acronyms

Abbreviation or Acronym	Definition
AE	Adverse Event
BARDA	Biomedical Advanced Research and Development Authority
BD	Becton Dickinson
CBER	Center for Biologics Evaluation and Research
CARES	Coronavirus Aid, Relief, and Economic Security
CDRH	Center for Devices and Radiological Health
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
FAQ	Frequently Asked Question
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
HHS	Health and Human Services
IDE	Investigational Device Exemption
IO	Immediate Office
IVD	*In Vitro* Diagnostic
LDT	Laboratory Developed Test
MDIC	Medical Device Innovation Consortium
MDR	Medical Device Report
MedSun	Medical Product Safety Network
NCI	National Cancer Institute
NIH	National Institutes of Health
OCC	Office of the Chief Counsel
OCET	Office of Counterterrorism and Emerging Threats
OHT	Offices of Health Technology
OHT7	Office of Health Technology 7 - In Vitro Diagnostics and Radiological Health
OPEQ	Office of Product Evaluation and Quality
OST	Office of Strategic Partnerships and Technology Innovation
PHE	Public Health Emergency
POC	Point of Care
RWD	Real-World Data
RWE	Real-World Evidence
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SHIELD	Systematic Harmonization and Interoperability Enhancement of Lab Data
SOP	Standard Operating Procedure

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