REGULATORY FOCUS

COVID-19 diagnostics: Moving from laboratory to home-based testing

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The US Food and Drug Administration (FDA) has worked closely with diagnostics developers during the past year to facilitate access to COVID-19 testing and accelerate development of home-based tests. By creating a flexible regulatory framework, the agency has enabled authorization of nearly one COVID-19 diagnostic per day, including at-home tests that have a critical role in the ongoing response to SARS-CoV-2.

Introduction

The emergence of the COVID-19 pandemic created significant opportunities for diagnostics developers who moved quickly to bring SARS-CoV-2 detection tests to market under the emergency use authorization (EUA) policy. To get these tests into the hands of healthcare providers as quickly as possible, the FDA was under pressure to be adaptable and offer regulatory flexibility under unprecedented circumstances. This article will review the FDA response to COVID-19, trace the shift from healthcare setting to home-based collection and testing, and explore the regulatory challenges and successes in the transition to at-home diagnostics.

Current state of COVID-19 diagnostics

Since the start of the pandemic, the FDA has authorized an average of nearly one COVID-19 diagnostic test a day.[1] As of 1 June 2021, more than 350 tests and sample collection devices had received EUAs, comprising:[2]

- More than 250 molecular tests and sample collection devices, including 37 tests using samples collected at home and 1 prescription at-home test;
- 25 antigen tests, including 2 prescription at-home tests and 4 over-the-counter (OTC) at-home tests; and
- 80 antibody tests.

On 1 March 2021, the FDA issued an EUA for the second prescription at-home antigen test. In a related press release, Jeff Shuren, MD, JD, director of the FDA's Center for Devices and Radiological Health, indicated the agency would continue prioritizing the availability of at-home testing options for COVID-19.[3] In addition, during FDA townhalls, the agency continues to indicate priority of reviews based on home collection, home testing, point-of-care, and high-throughput laboratory tests.

On 17 March 2021, FDA granted the first de novo to Biofire Diagnostics for a molecular respiratory panel, establishing a new regulation and paving the way for the submission of 510(k)s using Biofire as a predicate device (DEN200031).[4]

Initial FDA response to the pandemic

On 2 February 2020, the acting secretary of the Department of Health and Human Services (HHS) declared that public health circumstances justified the authorization of emergency use of in vitro diagnostics for the detection and/or diagnosis of COVID-19. EUAs allow the FDA to facilitate availability of unapproved medical products or unapproved uses of approved medical products during public health emergencies.[5] FDA guidance on EUAs was originally finalized in January 2017.[5]

On 29 February 2020, the agency issued, with immediate effect, guidance on administering COVID-19 tests during the public health emergency to speed up availability of novel COVID-19 tests. This guidance was subsequently updated on 16 March 2020, 4 May 2020, and 11 May 2020.[6]

On 24 March 2020, the acting HHS secretary broadened the previous month's declaration to include emergency use of alternative products used as medical devices, including home collection kits and interleukin-6 (IL-6) tests.[7]

The FDA has developed a range of templates to facilitate the preparation, submission, and authorization of EUAs (**Table**).[6,7] Developers interested in pursuing an EUA are encouraged to submit a pre-EUA to initiate discussions with the agency.

Table. Available templates for EUA submissions[8]

Molecular diagnostic template for commercial manufacturers
Molecular diagnostic template for laboratories
Antigen template for test developers
Serology template for test developers
Home specimen collection molecular diagnostic template
Home specimen collection serology template for fingerstick dried blood spot
Template for manufacturers of molecular and antigen diagnostic COVID-19 tests for nonlaboratory use
Supplemental template for developers of molecular and antigen diagnostic COVID-19 tests for screening with serial testing
Template for test developers of serology tests that detect or correlate to neutralizing antibodies

The agency also established a SARs-CoV-2 Reference Panel as a tool for assessing and comparing the performance of molecular tests. This panel is available to developers of SARS-CoV-2 nucleic acid-based amplification tests.[9]

Keeping up with an evolving regulatory landscape

Throughout the public health emergency, the FDA has demonstrated a commitment to providing timely guidance to support COVID-19 response efforts. It has held weekly virtual town hall meetings for test developers since 25 March 2020 to address technical questions about the development and validation of tests for SARS-CoV-2. The presentations and transcripts of each of these meetings are available online.[10]

The agency also publishes a monthly update summary on its COVID-19 response efforts,[2] which includes an overview of facts and supporting figures. The FDA also continues to monitor all authorized tests and emerging scientific evidence and may revise or revoke EUAs. In addition, the agency provides continuous updates on its comprehensive FAQs on Testing for SARS-CoV-2 page.[11]

On 22 February 2021, the FDA issued a suite of guidances for medical product developers to address the emergence and potential emergence of SARS-CoV-2 variants.[12] Among those guidances, the agency's Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests provides information on evaluating the potential impact of viral genetic mutations on test design, performance, and monitoring.[13]

A failed experiment in regulatory flexibility

In the early days of the pandemic, the FDA was overwhelmed with evaluating new molecular diagnostics for active coronavirus infections and allowed antibody tests to be distributed without review if manufacturers validated the tests themselves and did not advertise them as a standalone method of COVID-19 diagnosis.[14] Antibody tests flooded the market in March and April 2020 and were purchased by the millions, even though it was not yet known which types of antibodies and what titer thresholds would correlate with immunity.[1] Unverified claims, falsified data, and illegitimate tests abounded and, in May

2020, the FDA increased its oversight of COVID-19 tests, removing hundreds from its website and issuing at least 15 warning letters.[15]

In a recent editorial The New England Journal of Medicine, Shuren and Stenzel discussed the flaws of the initial open-door policy, underscoring "the importance of authorizing medical products independently, on the basis of sound science, and not permitting market entry of tests without authorization."[14] They also called for public-private research collaborations that would enable rapid, independent assessment of molecular, antigen, and antibody assays, and expedite the availability of accurate tests.[14]

From hospital- to home-based collection and testing

Diagnostics for SARS-CoV-2 and COVID-19 fall into 3 broad categories:[8]

- Diagnostic tests, which detect components or fragments of the SARS-CoV-2 virus and can be used to diagnose infection. Molecular tests and antigen tests fall into this category.
- Serology/antibody tests and other immune response assays that detect antibodies or measure immune responses to SARS-CoV-2 but cannot be used to diagnose infection.
- Tests for management of patients with confirmed COVID-19, which comprise assays used to inform decisions about patient management and treatment.

In the months after declaration of the public health emergency, diagnostics for SARS-CoV-2 and COVID-19 evolved quickly from hospital-based tests to point-of-care (PoC) platforms. PoC platforms allow for more rapid decision-making and expand access by enabling specimen collection and testing in settings ranging from physician offices and pharmacies to school health clinics; long-term care facilities; and even temporary locations, such as drive-through sites.[16]

Each EUA includes the settings in which the test is authorized for use. Generally, facilities that administer COVID-19 testing must be certified under the Clinical Laboratory Improvement Amendments (CLIA). Authorized settings include:[17]

- H, which limits use to CLIA-certified laboratories that meet the requirements to administer high-complexity tests;
- M, which refers to laboratories certified under CLIA that meet the requirements to administer moderate complexity tests; and
- W, which denotes tests that have been CLIA-waived for use in patient care settings with a CLIA certificate of waiver.

Given the restrictions of the pandemic, the ability to collect specimens at home is an opportunity to limit exposure and reduce test-related burden on both patients and healthcare providers. The FDA has been supportive of at-home self-collection and has authorized multiple molecular diagnostics that allow self-collected specimens to be mailed to a laboratory for processing. At-home self-collection must be specifically authorized in the EUA.

In recent months, the agency has issued EUAs for a number of fully at-home diagnostic tests, although most of them are specimen collection kits and not

true home-based tests. The FDA has stated it has always been a major priority for the agency to have a test that can be fully administered entirely outside of a laboratory or healthcare setting.[18]

Challenges in developing tests

The FDA's revised document of policies for COVID-19 tests during the pandemic specifically states that the policies do not apply to at-home testing, including home collection of specimens, because of additional considerations that would require FDA review.[6] Specimen collection in the home versus a healthcare setting presents different risks and raises issues, such as:[6]

- Whether the everyday user can safely and properly collect the specimen;
- Whether the components of the transport media are safe for use in the home environment;
- How to ensure proper shipment and adequate stability of the specimen during the time between collection and testing, for specimens that are sent to a laboratory for analysis; and
- How to ensure the ability of the everyday user to collect a specimen, administer the test, and interpret the results accurately, for fully at-home tests.

On 29 July 2020, the FDA provided a template to facilitate the preparation, submission, and authorization of EUA requests for at-home and OTC diagnostic tests. The template includes recommendations on the analytic and clinical evaluation required to validate these tests and the expected performance metrics. Performance evaluation must include flex studies, which assess the robustness of the assay performed with the device in its final design, and should be conducted by testing a negative sample and a low-positive sample. These studies should evaluate the most common or likely sources of error based on the test procedure and the anticipated locations of use.[19]

The template also provides guidance on how to demonstrate the ability of everyday users to administer the test correctly. Usability testing should include a minimum of 100 participants for OTC tests and 30 participants for prescription-only tests and should take place in an actual-use environment or an environment that simulates actual use. For OTC tests, the FDA recommends splitting the usability study into two sections – 50 participants testing themselves, and 50 participants testing another person who is part of the intended use population. The agency further encourages developers to submit their usability study protocols and participant questions for FDA review before conducting the study. Although it may be possible to combine usability with clinical evaluation, developers should be aware that this study design involves more risk because issues with the instructions for use could result in a failed clinical evaluation.

EUA submissions for at-home and OTC tests must include a description of how the developer will ensure all users of the test can report all test results to the relevant public health authorities and/or other authorities, in accordance with local, state, and federal requirements. Of note, when comparing the

performance requirements for OTC tests, which must include both symptomatic and asymptomatic users, with those for prescription home-use tests designed for symptomatic patients only, the FDA has a higher threshold of performance for positive and negative percentage agreement for OTC tests.

On 16 March 2021, in response to a more urgent need for broad screening of individuals to facilitate back-to-work and school initiatives, the FDA released a supplemental template for molecular and antigen tests. In this template, the agency provides an alternative clinical approach for achieving a claim for "individuals without symptoms or other epidemiological reasons to suspect COVID-19 infection, when tested twice over two (or three) days," which allows for use of clinical trial data from serial samples collected from symptomatic patients to support initial market entry in point-of-care, at-home, and OTC for screening in the absence of having data from asymptomatic subjects. This could reduce the time between sample collection and EUA authorization, enabling broader use in the nontraditional laboratory settings.[20]

Regulatory professionals supporting products moving from PoC to at-home diagnostics need to have a solid understanding of the differences between home collection and home collection and testing and between prescription home use and OTC use and, more important, the studies required for successful authorization by FDA.

Below are three examples of tests that received emergency use authorization for at-home use, but with differences in how the samples are collected and the tests administered and reported.

- On 17 November 2020, the FDA issued an EUA for the Lucira COVID-19 All-In-One Test Kit, making it the first diagnostic authorized for full self-administration, available by prescription. To enable tracking and monitoring of results, the EUA notes that healthcare providers prescribing the test are required to report all test results to their relevant public health authorities in accordance with local, state, and federal requirements.[21]

- On 15 December 2020, the FDA issued an EUA for the Ellume COVID-19 Home Test, the first OTC, fully at-home diagnostic test for COVID-19.[22] The difference between Ellume and Lucira are that Ellume was authorized as OTC and uses an analyzer that connects with a smartphone mobile application to help users administer the test and interpret the results. In this example, the smartphone mobile application includes software that enables reporting to appropriate public health authorities to monitor disease prevalence.

- Just one day later, on 16 December 2020, the FDA issued an EUA for the BinaxNOW COVID-19 Ag Card Home Test. Like Lucira, the BinaxNOW is available by prescription. However, it is offered in partnership with a telehealth provider who will also be responsible for reporting all test results to relevant public health authorities.[23]

Regulatory strategies for keeping up with change

As already noted, the regulatory processes associated with responding to the pandemic are challenging and can change daily. Regulatory professionals, therefore, need to be flexible and knowledgeable to stay current with the changes and inform both diagnostic developers and senior leadership of changes as they arise. The conventional regulatory toolbox for use of presubmissions and interactive conversations with FDA have become limited as FDA resources have been refocused on prioritizing certain kinds of COVID-19 test reviews. For example, the agency recently stated it will prioritize at-home, PoC, and high-throughput assays for EUA issuance over more traditional, moderately or high complexity tests.

Similarly, the usual process for reviewing decision summaries and guidance documents for previously cleared devices to inform our teams during the test development process is limited under the EUA process. For example, while the templates provide guidance on what to do, when reading the actual authorizations posted for products, often FDA has allowed for authorization with less than complete data, while including post-EUA commitments. An additional tool available to regulatory professionals to help navigate this ambiguity are the FDA townhalls held weekly with FDA. Questions can be submitted in advance as well as asked during the meeting itself. Often FDA provides additional guidance and direction that goes beyond what can be read from the templates or EUA authorization letters.

Conclusion

Diagnostic testing remains a cornerstone of the response to COVID-19. With the emergence of viral variants, it is expected that SARS-CoV-2 will be an ongoing concern after the public health emergency comes to an end and COVID-19 becomes an endemic disease. Throughout the pandemic, the FDA has worked with test developers to expand access to COVID-19 testing and support the development of fully at-home tests. Understanding the evolving regulatory landscape – and the nuances of market access – can help developers bring accurate, easy-to-use tests to market more quickly.

Abbreviations

CLIA, Clinical Laboratory Improvement Amendments; **COVID-19,** Coronavirus disease 2019; **EUA,** emergency use authorization; **FDA,** [US] Food and Drug Administration; **HHS,** Health and Human Services; **OTC,** over the counter; **PoC,** point of care; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2.

About the author

Karen L. Richards, RAC, is senior vice president of IVD regulatory and quality consulting at Precision for Medicine. She has worked in the in vitro diagnostics regulatory, quality, clinical trial, and compliance areas for more than 35 years. In that time, she has been responsible for multiple regulatory submissions and approvals in the US, EU, and rest of world for in vitro diagnostic products and biological in vitro diagnostic assays for use in blood screening. She has also been responsible for approval of laboratory tests in all US states requiring a license, including New York State, as well as certification to College of American Pathologists (CAP). She has implemented from the ground up quality systems for diagnostic products to meet the requirements of the FDA, ISO 9001, ISO 13485, CLIA, and CAP. She has also developed and implemented clinical trials for multiple products that were used to generate data for regulatory submissions. Richards has served as the compliance officer for three companies, covering both traditional diagnostic

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