



FDA requirement updates for EUAs for diagnostics to support COVID-19

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This article discusses the evolution and implementation of the emergency use authorization (EUA) by the US Food and Drug Administration (FDA) for diagnostic devices during the COVID-19 pandemic in the United States. The author suggests that this limited oversight will affect future requirements for demonstrable superiority claims after the EUAs are terminated and diagnostics for the virus undergo increased scrutiny by the agency for marketing authorization. She covers the implications for the diagnosis and treatment of COVID-19 associated with variations in state and federal oversight, the authorization of diagnostics as it has evolved since late 2019, and their potential impact on future regulation of such devices. The scope of this article covers molecular diagnostics and antigen and serologic tests.

Introduction

The FDA currently does not require premarket notification or authorization for validated tests developed by laboratories in order to meet immediate, emergent need for specific and highly sensitive tests. Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA commissioner has the authority to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency.¹ This section of the FD&C Act has been amended on numerous occasions to align with prevailing public health needs.²⁻⁹ The 2013 amendment to the Pandemic and All-Hazards

Preparedness Act of 2006, allows the commissioner to facilitate expedited reviews and issue EUAs for use of medical products for risks of public health emergencies involving chemical, biological, radiological, and nuclear (CBRN) and emerging infectious disease agents.^{10,11}

This means that when the secretary of the Department of Human Health and Services (HHS) has determined significant threat to public health by CBRN agents, the FDA may issue EUAs for the development of medical counter measures. This was enacted on 4 February 2020, when the HHS secretary determined a significant public health threat in the US from the novel coronavirus, now known as COVID-19.^{12,13} To support industry and other manufacturers in the current state of public emergency, the agency issued EUAs, guidance, policy, and template documents to address current and emergent medical needs across the US.¹³ The current policy for EUAs does not address at-home test kits for COVID-19.

What is an EUA?

To address the emergent need for COVID-19 testing kits, the FDA has provided guidance on two different pathways to compliantly manufacture, distribute, and use COVID-19 tests quickly. One pathway involves submission of an EUA to the agency, and the other allows states to determine acceptance criteria for laboratory-developed diagnostics without an EUA submission. This means that tests to diagnose or detect exposure to COVID-19 may or may not undergo FDA review for an EUA.

The EUA review timeline and process is significantly less rigorous than that for a marketing authorization. The authorization lasts until such time that the HHS determines there is no longer a perceived public health risk by the emergent CBRN, or the EUA is revoked¹¹ because the circumstances justifying its issuance no longer exists.¹⁴ Conditions pertaining to potential termination of an EUA are discussed in the authorization letter issued for the diagnostic.^{15,16}

Multiple manufacturers may hold EUAs for the same type of diagnostic test, with no requirement to demonstrate superiority or equivalence to other diagnostics.¹⁷ Multiple serologic tests may be authorized under a single umbrella EUA.¹⁸ This umbrella approach differs from marketing authorization and premarket notifications for commercially available products. In those instances, the umbrella approach is generally not appropriate,¹⁹ but can be done, although it requires careful consideration in its execution. The guidance specifically calls out compliance expectations for labs certified under Clinical Laboratory Improvement Amendments (CLIA) as well as commercial manufacturers planning to use tests with or without an EUA. The FDA does not object to use of diagnostics under review for EUA as long as they have been validated and results include a statement that the test has been validated but is under review with the FDA.¹⁸

EUA application requirements

For laboratories and commercial manufacturers

FDA has provided explicit guidance for obtaining an EUA in anticipation of clinical labs having to design and manufacture test components or purchase research-use-only components for the development of on-site assays.¹⁸ Tests developed in laboratories with CLIA certification – that is, a certificate of compliance – from the HHS to perform high-complexity testing are eligible for EUA after the test has been validated. FDA does not prohibit use of the validated test before receipt of EUA. The expectation is that, upon completion of validation, the manufacturer should notify FDA by email (CDRH-EUA-Templates@fda.hhs.gov).

The EUA should take no more than 15 business days from the date of completion of validation. EUA applications should be submitted to the agency using the aforementioned email. If FDA has concerns, it will notify the applicant and work with the lab to address the issues. The agency expects the laboratory to stop testing until the issues have been addressed. In that case, new test reports would be issued to patients afterward indicating that previous results may not be accurate. FDA does not object to use of the test until a new or amended EUA is submitted.

For commercial manufacturers

The FDA does not intend to object to commercial manufacturers developing and distributing COVID-19 test kits to healthcare workers for point-of-care testing after validation of the test and before EUA submission. The anticipated timeframe for commercial manufacturers to prepare and submit an EUA is the same as for CLIA labs – 15 business days after notification of completion of validation. The agency expects validation data to be provided for review informally by email at the time of notification. It also expects the manufacturer to make the instructions for use and the performance characteristics available on the manufacturer's website while it awaits EUA determination from FDA. Any clinical testing completed during the review period should include a statement that the test is validated but that the FDA's review is pending.¹⁸

For state authorization for use of new tests

In early March 2020, the FDA issued an enforcement discretion, in response to a request from the Wadsworth Center in the New York State Department of Health, in which it did not object to the center reviewing validation test reports from local labs that held a laboratory permit from the state health department.²⁰ An ensuing Presidential Memorandum expanded this enforcement discretion to state authorities to approve use of diagnostic tests.²¹ This means that a state or territory may choose to authorize CLIA-certified laboratories within that state to develop and use COVID-19 diagnostics under a review process developed by the state. FDA will not review the validation data or have direct oversight of the processes the states implement. However, the agency recommends that:

- validation of testing should be part of the state review,
- the state notify the agency should it choose to use this flexibility in oversight to expedite COVID-19 test development,

- clinical labs confirm the first five negative and positive test results against an EUA-authorized assay while awaiting FDA determination for EUA request.¹⁸

The current policy for COVID-19 testing does not include discussion of the use of state authorization in lieu of obtaining an EUA for commercial manufactures. However, the agency has been clear about the allocation of resources to commercial manufacturers to expedite test availability. The FDA does not intend to neglect oversight of any commercially available test, regardless of the source of authorization for use. It will take appropriate necessary action with notification of tests with poor performance or of tests with misleading statements in labeling.¹⁸

FDA validation for new diagnostic tests

Validation of user needs for SARS-CoV-2 diagnostics is mandatory for each EUA submission. The laboratory or manufacturer may begin use of the test after notification via email is submitted to the FDA, as previously mentioned. The agency has specified parameters for validation to be included in EUA request.

Three types of diagnostic devices have been discussed in the FDA's policy:

- molecular tests, which detect viral genetic material,
- antigen detection tests, which detect specific proteins on the surface of the COVID-19 virus, and
- serologic tests, which are intended to detect antibodies to the virus.

Some validation principles may overlap with these categories, but each type of test requires unique performance functions to be confirmed.²²

Molecular diagnostic validation requirements

The four main validation concerns that must be addressed in the EUA application include establishing a limit of detection, clinical evaluation, inclusivity, and cross-reactivity.²²

Limit of detection. The limit of detection (LoD) is the lowest concentration of analyte, in this case COVID-19 virus, that a diagnostic can reliably detected.²³ For COVID-19 diagnostics, it is recommended that the developer perform serial dilution testing triplicate per concentration level, then confirm the final LoD with the lowest concentration detectable with 20 samples. The LoD will be the lowest concentration for which 19 of 20 samples test positive.

It is necessary to characterize the LoD to appreciate the diagnostic specificity of the test. LoD supports the validity of the test by determining how much virus someone has to have in their sputum to obtain a positive test result for COVID-19. Before measurements of LoD can be confirmed, conditions of use – including the minimum quality for diagnostic analyte (virus or RNA) and the titrant (sputum or nasal secretions) – must be determined through contrived sample evaluation.

Clinical evaluation. The FDA does not typically request prospective clinical studies for Class I and II medical devices. Examples of such devices would be a microorganism differentiation and identification diagnostic,²⁴ and diagnostic intravascular catheters,²⁵ respectively. Usually, Class III IVDs to detect infectious diseases, such as the oxidase screening test for gonorrhea,²⁶ require clinical studies to establish safety and effectiveness due to their technology²⁷ and the significant influence on the patient's plan of care based on the test results. It would stand to reason, based on the novelty of COVID-19, that the innovative technology and diagnostics being established should be held to the same standard. However, given the emergent nature of this CBRN threat to public safety and health with the lack of widely distributed reference standards, the level of clinical data required for EUA diagnostics cannot be equivalent to that required for a marketing application.

FDA has recommended that contrived clinical specimens should be used to confirm performance of an assay. In this context, contrived specimens may be leftover clinical specimens that are spiked with a known concentration of RNA or inactivated virus. In all, 30 contrived reactive specimens and 30 nonreactive specimens should be used to confirm performance of the assay. Twenty of the contrived clinical specimens should be spiked at a concentration of 1-2 times the LoD, with the remaining 10 having concentrations spanning the testing range. The agency's acceptance criteria for performance is 95% agreement with 1-2 times LoD and 100% agreement at all other concentrations and for negative specimens. This is a calculation of percentage agreement, rather than sensitivity, because there may not be a reference standard available to calculate sensitivity or specificity of new tests.²⁸

By using clinical specimens without the virus or RNA to assess the diagnostic's effectiveness, the impact of common microbiota that are inconsequential to the assessment of COVID-19 present in each sample can be established as viral concentration increases. This measurement can be used to establish noise from true, meaningful output from the assay.

Inclusivity. Inclusivity can be thought of as the percentage of target analyte (in this case, DNA or virus) that gives the correct positive result. Inclusivity is part of the characterization required to establish analytic specificity, which is the ability of the test to accurately measure the presence of COVID-19 RNA or virus in clinical specimens.²⁹ Taken together, these measurements support the diagnostic specificity of a clinical test.³⁰ In the absence of a reference standard,²⁸ inclusivity is the most reliable measure that can be presented at this juncture.

The FDA requires the applicant submit information from an in silico analysis to be performed to purport the percentage match of the samples used to establish inclusivity of the assay. In other words, the samples used to detect LoD, or any other performance characteristics of the diagnostic submitted for authorization, should be matched via computer-generated,³¹ web-based assessment of the genetic sequence for the contrived specimens to ensure that the test can detect all published genetic variants of COVID-19 in vitro. If the samples used as a "reference" to establish LoD and perform clinical evaluation include 100% of the

known genetic variants of COVID-19 as required by FDA,¹⁸ then the test will have a high level of inclusivity. The impetus for this measurement, in lieu of other more statistically meaningful measures, could be due to the notoriously unstable nature of viral genomes coupled with a lack of historical samples for COVID-19.

Ideally, people who do not have COVID-19 should test negative for COVID-19. By ensuring that available diagnostics are targeted at COVID-19 specifically (and not other, less nocuous, strains of coronavirus) and can be quantified, false positives can be avoided in clinical settings and avoid waste of limited resources to treat the growing pandemic.

Cross-reactivity. Cross-reactivity occurs when a non-COVID-19 molecule triggers an inaccurate test result. False positive test results and lead to unnecessary treatment in individuals who do not actually have the virus. Current policy recommends cross-reactivity wet testing on common respiratory flora and other viral pathogens that may be in respiratory tract secretions¹⁸ Components of molecular assays to confirm the presence of COVID-19 will include RNA primers and probes to identify genetic material from the targeted organism. It is important to confirm that the components of the assay used to target the pathogen whose presence you want to confirm will not propagate a signal due to another organism. One way to do that is confirm the amount of homology³² – matching RNA in a shared gene – between two species. Understanding this overlap with primers and probes can indicate how likely they are to interact with nontargeted species. This helps determine the precision of your selected sequencing tools used to determine if a clinical specimen has COVID-19 viral genetic material present.

FDA recommends wet lab testing at concentrations of 10^6 CFU/ml or higher for bacteria, and 10^5 pfu/ml or higher for viruses, except for SARS-Coronavirus and MERS-Coronavirus. For the latter two, in silico studies are considered sufficient for tests of cross-reactivity. The agency believes an in silico analysis of the assay primer and probes, compared with common respiratory flora and other viral pathogen genomes, can be performed. For this guidance, FDA defines in silico cross-reactivity as greater than 80% homology between one of the primers/probes and any sequence present in the targeted microorganism. In other words, if the overlap in genetic sequence greater than 80% between primers and probes intended to target COVID-19 with other organisms indicates deficient precision to target the virus for detection. FDA recommends that developers follow recognized laboratory procedures for sample types and management intended for testing for any additional cross-reactivity testing.^{18,22}

Antigen detection and serologic test validation requirements

Antigen detection studies detect proteins that are part of the COVID-19 virus in clinical specimens. There is some overlap in testing requirements for antigen detection and the molecular diagnostics described above. These submissions must include LoD, cross-reactivity, and microbial interference. In addition to this requirement, a clinical agreement study must be performed. Meaning clinical

specimens must be compared to leftover specimen with a known viral status, either positive or negative is sufficient.¹⁸

Serologic tests detect antibodies to the COVID-19 virus. In other words, instead of detecting viral RNA or protein, these tests look for the human body's response to viral exposure. Time from exposure, extent of exposure, and immunocompetence can affect detectability of antibodies. Therefore, serologic tests cannot be used for sole diagnosis. Serologic tests submissions must include cross-reactivity and clinical agreement study must be performed with microbiologically confirmed COVID-19 positive human specimens.³³ Class specificity is an additional requirement for serologic tests in order to confirm a test's ability to detect antibodies to COVID-19. This means that the manufacturer submitting for authorization must establish the degree of precision of the test's ability to detect antibodies for COVID-19 over any other organism.

Reporting results to patients

In general, the FDA recommends that all test reports from an EUA device include a statement that the test has been validated but that the agency's independent review of the validation is pending. When reporting serologic results to patients, the agency expects test reports to include statements that the test has not been reviewed by FDA; negative results do not rule out SARS-CoV-2 infection; results from antibody testing should not be used as the sole basis for diagnosis or excluding a diagnosis for SARS-CoV-2 infection; and that positive results may be due to past or present infection non-SARS-CoV-2 coronavirus strains.¹⁸ These caveats provide transparency for patients to understand that these diagnostic tools are still evolving, as is their regulation under these unprecedented circumstances.

Manufacturing EUA diagnostics

Diagnostics authorized for emergency use are not subject to the majority of the quality system regulation requirements, because the requirements have been waived for the duration of the authorization. High-complexity laboratories should perform tests in accordance with commensurate practices. The FDA has stated that compliance history will be a consideration for waiving quality system regulation requirements for a specific product authorization.¹⁸

Templates for EUAs for diagnostic tests

FDA templates for EUA submissions are located on the agency's website to expedite their preparation, submission, and authorization.³⁴ There are currently six different templates for submission to agency that target specific information needed for review for:

- molecular diagnostics developed by commercial manufacturers,
- molecular diagnostics developed by laboratories,
- serology templates for commercial manufacturers,
- serology templates for laboratories,
- an antigen template, and
- home specimen collection molecular diagnostic template.

These should be submitted to the agency by email (CDRH-EUA-Templates@fda.hhs.gov).

Once validation has been completed, the manufacturer or lab should notify the FDA by the same email address. This should include the name of the manufacturer, address, contact person, a website link, and a copy of the instructions for use, including a summary of assay performance. An automated email acknowledgment of receipt will be sent from the agency. A reasonable time afterward, 10-15 business days, the completed EUA submission should be sent to the same email address and another auto-acknowledgment will be received. Once a submission is sent to the email address above, the agency will perform a preliminary review, akin to the refuse-to-accept policy,³⁵ with the performance data demonstrating validation.¹⁸

If issues are identified, the FDA will work with the manufacturer to resolve issues. In the event these problems are significant and cannot be addressed in a timely manner, the manufacturer should stop use of the test and submit corrected reports indicating that previous results may not have been accurate. In such an event, the FDA will remove the EUA from its EUA website.³⁶

The manufacturer will be notified if the agency is not able to issue an EUA. If tests have been distributed, the agency will expect suspension of the test and notification to patients that test results may not be accurate. Any further action will be taken as the agency sees appropriate.

Modifications to the authorized test will not require submission to the agency where appropriate validation is completed using a bridging study to the EUA-authorized test. For instance, this could be using the new and the original components on the same specimen to confirm performance.

Outlook for current tests

It remains to be seen what impact of tests will have without direct evidence of sensitivity and specificity. Without reliable testing, treatment approaches can vary from center to center, inhibiting development of an evidence-based, industry-wide, accepted standard of care. Only time and hindsight will show if this approach is helpful or harmful in addressing growing concerns over the current global pandemic.

The closest historical perspective is the influenza pandemic of 1918. The epidemiologic knowledge from that pandemic meant that the world was better positioned to manage COVID-19, even if management strategies have not been evenly applied globally. The 1918 pandemic left us with knowledge of social distancing, quarantining, good hygiene, and the use of disinfectants for containing the spread of infectious agents.³⁷

The advantages of the COVID-19 pandemic will be a greatly expanded knowledge base of infectious disease containment and the molecular, antigen, and serologic impacts of the illness. The advent of vaccines has allowed us to hope for a return to pre-COVID normalcy, of going to grocery stores without

masks and social gatherings. Much will be learned from the current pandemic, and much will be stay with us and prepare us for similar, future emergencies, including the tools and treatments that deliver us from it.

Abbreviations

CBRN, chemical, biological, radiological, and nuclear; **CLIA**, Clinical Laboratory Improvement Amendments; **EUA**, emergency use authorization; **FDA**, [US] Food and Drug Administration; **FD&C**, Federal Food, Drug, and Cosmetic [Act]; **HHS**, Human Health and Services; **LoD**, limit of detection; **US**, United States

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