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Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency

Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff

Document issued on the web on March 16, 2020.

This document supersedes “Policy for Diagnostics Testing in Laboratories Certified to Perform High-Complexity Testing under Clinical Laboratory Improvement Amendments (CLIA) prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency” issued February 29, 2020.

For questions about this document, contact CDRH-EUA-Templates@fda.hhs.gov.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2020-D-0987. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 20010 and complete title of the guidance in the request.

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

I. Introduction

The Food and Drug Administration (FDA or Agency) is issuing this guidance to provide a policy to help accelerate the availability of novel coronavirus (COVID-19) diagnostic tests developed by laboratories and commercial manufacturers during the public health emergency.

On February 4, 2020, the Secretary of Health and Human Services (HHS) determined that there is a public health emergency and that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the novel coronavirus (2019-nCoV).¹ Rapid detection of COVID-19 cases in the United States requires wide availability of diagnostic testing to control the emergence of this rapidly spreading, severe illness. This guidance describes a policy for laboratories and commercial manufacturers to help accelerate the use of tests they develop in order to achieve more rapid and widespread testing capacity in the United States.

In light of this public health emergency, this guidance is being implemented without prior public comment because the FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is immediately in effect, but it remains subject to comment in accordance with the Agency's good guidance practices.

¹ <https://www.fda.gov/media/135010/download>

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus that was first detected in Wuhan City, Hubei Province, China, which has now been designated a pandemic by the World Health Organization (WHO) and which has been detected internationally, including cases in the United States. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). SARS-CoV-2 has demonstrated the capability to spread rapidly, leading to significant impacts on healthcare systems and causing societal disruption. The potential public health threat posed by COVID-19 is high, both globally and to the United States. To respond effectively to the COVID-19 outbreak, rapid detection of cases and contacts, appropriate clinical management and infection control, and implementation of community mitigation efforts are critical. FDA believes the policy set forth in this guidance will help address these urgent public health concerns by helping to expand the number and variety of diagnostic tests, as well as available testing capabilities in reference and commercial laboratories and healthcare settings.

The Centers for Disease Control and Prevention (CDC) laboratories have supported the COVID-19 response, including development of a diagnostic assay that was issued an Emergency Use Authorization (EUA) on February 4, 2020.² Since authorizing CDC's EUA, FDA has been actively working with other SARS-CoV-2 diagnostic test developers to help accelerate development programs and respond to requests for in vitro diagnostic EUAs. However, the severity and scope of the current COVID-19 situation around the globe necessitates greater testing capacity for the virus than is currently available.³

The EUA authorities allow FDA to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear (CBRN) threats by facilitating the availability and use of medical countermeasures initiatives (MCMs) needed during certain public health emergencies. Under section 564 of the FD&C Act, the FDA Commissioner may authorize the use of unapproved medical products, or unapproved uses of approved medical products, in certain emergency circumstances, after the HHS Secretary has made a declaration of emergency or threat justifying authorization of emergency use, to diagnose, treat, or prevent serious or life-threatening disease or conditions caused by CBRN threat agents when certain criteria are met.

² See FDA's February 4, 2020, letter authorizing CDC's 2019-nCoV (RT)-PCR Diagnostic Panel for the presumptive qualitative detection of nucleic acid from the 2019-nCoV in upper and lower respiratory specimens, available at <https://www.fda.gov/media/134919/download>. This EUA was re-issued in its entirety on March 15, 2020 to reflect a number of amendments including changes to the intended use and primer and probe materials.

³ Nothing in this guidance is intended to impact or supersede CDC's recommendations regarding which patients should be tested for COVID-19.

III. Scope

The policies described in this guidance for accelerated availability of testing for COVID-19 applies to certain laboratories and commercial manufacturers developing SARS-CoV-2 diagnostic tests during the public health emergency, as described below.

IV. Policy

This guidance describes policies intended to help rapidly expand testing capacity by facilitating the development and use of SARS-CoV-2 diagnostic tests during the public health emergency.

This guidance describes two policies for accelerating the development of certain laboratory tests for COVID-19 – one leading to an EUA submission to FDA, and the other not leading to an EUA submission when the test is developed under the authorities of the State in which the lab resides and the State takes responsibility for COVID-19 testing by laboratories in its State. The policy leading to an EUA remains unchanged from the initial publication of this guidance on February 29, 2020.

In addition, this guidance describes a policy for commercial manufacturers to more rapidly distribute their SARS-CoV-2 diagnostics to laboratories for specimen testing after validation while an EUA is being prepared for submission to FDA.

This guidance also describes a policy regarding the use of serological testing without an EUA.

In the context of a public health emergency involving pandemic infectious disease, it is critically important that tests are validated as false results can have broad public health impact beyond that to the individual patient. In this guidance, FDA provides recommendations regarding validation of COVID-19 tests. FDA encourages test developers to discuss any alternative approaches to validation with FDA.

A. Laboratories Certified under CLIA that Meet the CLIA Regulatory Requirements to Perform High-Complexity Testing Using Their Validated Tests Prior to EUA Submission

The policy described in this subsection applies to laboratories certified under Clinical Laboratory Improvement Amendments (CLIA) that meet the CLIA regulatory requirements to perform high-complexity testing and that seek to develop and perform diagnostic tests to detect the SARS-CoV-2 virus and pursue EUA authorization from FDA for those tests.

FDA anticipates that clinical laboratories may need to design and manufacture the individual test kit components (e.g., primers, probes, etc.), or to purchase research use only (RUO) components from third party manufacturers, for the development of their assays.

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In light of the increasing numbers of COVID-19 cases throughout the country and the urgent need to expand the nation's capacity for COVID-19 testing during the public health emergency, for a reasonable period of time after validation and while they are preparing their EUA requests, FDA does not intend to object to the use of these SARS-CoV-2 tests for specimen testing, as described below. FDA believes that 15 business days is a reasonable period of time to prepare an EUA submission for a test that has already been validated.

1. Validation

All clinical tests should be validated prior to use. In the context of a public health emergency, it is especially important that tests are validated as false results can have broad public health impact beyond that to the individual patient. FDA has provided recommendations regarding the minimum testing that should be performed to ensure analytical and clinical validity in section V below. FDA encourages laboratories to discuss any alternative testing with FDA that they would like to conduct.

2. FDA Notification

Following completion of assay validation, laboratories should notify FDA (e.g., e-mail to CDRH-EUA-Templates@FDA.HHS.GOV) that their assay has been validated. This notification should include the name of the laboratory, name of the lab director, address, and contact person in this email. FDA will acknowledge receipt of this notification via auto-reply. As noted above, FDA recommends that laboratories submit a completed EUA request within 15 business days of the initial communication to FDA that the assay has been successfully validated.⁴

It would be helpful to FDA if laboratories provide information on testing capacity. This information will help the Agency and Department monitor the landscape as we work to ensure adequate testing capacity across the country.

3. Reporting of Results

In order to provide transparency, FDA recommends that test reports include a general statement that the test has been validated but FDA's independent review of this validation is pending.

Additionally, reporting of results from serological testing under this policy should include the limitations outlined in section D below unless and until data is submitted and an EUA is authorized for any claims outside those described in section D below.

Laboratories should immediately notify appropriate Federal, State, and local public health agencies of all positive results.

⁴ See FDA's Guidance, Emergency Use Authorization of Medical Products and Related Authorities, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>.

4. EUA Request

FDA has made available, through download from our website, a template that laboratories may choose to use to facilitate the preparation, submission, and authorization of an EUA.⁵

Laboratories that intend to use alternative approaches should consider seeking FDA's feedback or advice to help them through the pre-EUA and EUA process. FDA encourages laboratories to discuss any alternative technological approaches with FDA through CDRH-EUA-Templates@FDA.HHS.GOV.

Soon after receiving the EUA request, FDA intends to perform a preliminary review to identify if there are any problems with the performance data. If a problem is identified, FDA intends to work with the laboratory to address the problem (e.g., through labeling or bench testing). If any problems are significant and cannot be addressed in a timely manner, FDA would expect the laboratory to stop testing and issue corrected test reports indicating prior results may not be accurate.

If FDA is not able to authorize an EUA, FDA will notify the laboratory. FDA would expect the laboratory to stop testing and issue corrected test reports indicating prior test results may not be accurate. FDA does not intend to object to the use of a test, without a new or amended EUA, where the test is validated using a bridging study to an EUA-authorized test. One way to bridge to a new component is to establish equivalent performance between parallel testing of the same specimens with the new and original components. We recommend testing 3-fold serial dilutions of SARS-CoV-2 viral materials (e.g., whole genomic viral RNA or inactivated virus, etc.) in pooled respiratory sample matrix in triplicate.

FDA would like to see your validation data informally through an email to CDRH-EUA-Templates@FDA.HHS.GOV. If FDA's review of validation data indicates that it could be applicable to modifications of other tests with an authorized EUA, and the laboratory agrees to FDA sharing that information on our website for use by other laboratories, FDA intends to update our FAQs so other laboratories can refer to the validation for their testing, without conducting their own bridging study for the same modification.

5. Clinical Testing

While awaiting FDA determination on the EUA request, FDA recommends that clinical laboratories obtain confirmation of the first five positive and the first five negative clinical specimens using an EUA-authorized assay, which may involve sending these ten specimens to another laboratory for confirmation. If any of these results cannot be confirmed, the laboratory should notify FDA at CDRH-EUA-Templates@FDA.HHS.GOV, and take other appropriate actions such as terminating testing patient specimens, and issuing a corrected test report that indicates the prior test result may not be valid.

⁵ <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019>

B. State Authorization of Laboratories Certified under CLIA that Meet the CLIA Regulatory Requirements to Perform High-Complexity Testing

On March 12, 2020, FDA issued enforcement discretion and stated that it was not objecting to the Wadsworth Center authorizing certain laboratories in the State of New York to begin patient testing under certain circumstances to increase availability of COVID-19 testing in response to a request from the Wadsworth Center of the New York State Department of Health (Wadsworth). Wadsworth had informed FDA that it would be willing to have clinical laboratories that currently hold a New York State Department of Health clinical laboratory permit to notify Wadsworth that they have validated a test for COVID-19, and to submit validation studies to Wadsworth. Wadsworth likewise said it would notify the laboratory if it identified any concerns, and request that the laboratory terminate testing patient specimens and issue a corrected test report that indicates the prior test result might not be valid.

On March 13, 2020, the President issued a “Memorandum on Expanding State-Approved Diagnostic Tests” (Memorandum), which refers to the flexibility that FDA allowed New York State and states as follows:

“Should additional States request flexibility to authorize laboratories within the State to develop and perform tests used to detect COVID-19, the Secretary shall take appropriate action, consistent with law, to facilitate the request.”

In accordance with the Memorandum, FDA describes below its policy regarding States and territories that authorize laboratories within their State or territory to develop their own COVID-19 tests and perform specimen testing, where the notification of SARS-CoV-2 test validation is not submitted to FDA and the laboratory does not submit an EUA request to FDA.

A State or territory choosing to authorize laboratories within that State or territory to develop and perform a test for COVID-19 would do so under authority of its own State law, and under a process that it establishes. FDA does not intend to object to the use of such tests for specimen testing where the notification of SARS-CoV-2 test validation is not submitted to FDA and the laboratory does not submit an EUA request to FDA, and where instead the State or territory takes responsibility for COVID-19 testing by laboratories in its State during the COVID-19 outbreak.

FDA requests that the State or territory notify us if they choose to use this flexibility to expedite COVID-19 testing. FDA will not be reviewing the process adopted by the State or territory, which we understand may be different than the process adopted by New York State. FDA expects that such states as part of their oversight process will require laboratories developing SARS-CoV-2 tests to validate those tests prior to use. FDA encourages laboratories that develop and perform a test for COVID-19 under this policy to notify FDA that they have started clinical testing by sending an email to that effect to CDRH-EUA-Templates@FDA.HHS.GOV. It would be helpful to FDA if laboratories provide information on testing capacity. This information will help the Agency and Department monitor the landscape as we work to ensure adequate testing capacity across the country.

C. Commercial Manufacturer Development and Distribution of Tests Prior to EUA Submission

The policy described in this subsection applies to commercial manufacturers that seek to develop and distribute diagnostic test kits to detect the SARS-CoV-2 virus to clinical laboratories or to healthcare workers for point-of-care testing. This policy does not apply to at home testing.

In light of the increasing numbers of COVID-19 cases throughout the country and the urgent need to expand the nation's capacity for COVID-19 testing during the public health emergency, FDA does not intend to object to a commercial manufacturer's development and distribution of SARS-CoV-2 test kits for specimen testing for a reasonable period of time after the manufacturer's validation of the test and while the manufacturer is preparing its EUA request where the manufacturer provides instructions for use of the test and posts data about the test's performance characteristics on the manufacturer's website. Transparency can help mitigate potential adverse impacts from a poorly designed test by facilitating better informed decisions by potential purchasers and users.

FDA believes that 15 business days is a reasonable period of time to prepare an EUA submission for a test whose performance characteristics have already been validated. Soon after receiving the EUA request, FDA will perform a preliminary review to identify if there are any problems with the performance data. If a problem is identified, FDA intends to work with the manufacturer to address the problem (e.g., through labeling or bench testing). If the problem is significant and cannot be addressed in a timely manner, and the manufacturer has already distributed the device, FDA would expect the manufacturer to suspend distribution and conduct a recall of the test.

1. Validation

All clinical tests should be validated prior to use. In the context of a public health emergency, it is especially important that tests are validated as false results can have broad public health impact beyond that to the individual patient. FDA has provided recommendations regarding the minimum testing that should be performed to ensure analytical and clinical validity in section V below. FDA encourages laboratories to discuss any alternative testing with FDA that they would like to conduct.

2. FDA Notification

Following completion of assay validation, manufacturers should notify FDA (e.g., e-mail to CDRH-EUA-Templates@FDA.HHS.GOV) that their assay has been validated and they intend to begin distribution. This notification should include the name of the manufacturer, address, contact person, and a copy of the instructions for use including summary of assay performance. FDA will acknowledge receipt of this notification via auto-reply. As noted above, FDA

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recommends that manufacturers submit a completed EUA request within 15 business days of the initial communication to FDA that the assay has been successfully validated.⁶

It would be helpful to FDA if manufacturers provide information on testing capacity, as well as the number of laboratories in the U.S. with the required platforms installed. This information will help the Agency and Department monitor the landscape as we work to ensure adequate testing capacity across the country.

3. Reporting of Results

In order to provide transparency, FDA recommends that test reports include a general statement that the test has been validated but FDA's independent review of this validation is pending.

4. EUA Request

FDA has made available, through download from our website, a template for test kit manufacturers that is intended to facilitate the preparation, submission and authorization of an EUA.⁷ Manufacturers can use alternative approaches. Manufacturers who intend to use alternative approaches should consider seeking FDA's feedback or advice to help them through the pre-EUA and EUA process. FDA encourages manufacturers to discuss any alternative technological approaches with FDA through CDRH-EUA-Templates@FDA.HHS.GOV.

FDA will communicate any questions or concerns regarding the completed EUA request or EUA template to the manufacturer. FDA will also work collaboratively to address any potential concerns or safety considerations raised in the request and will contact the manufacturer regarding a final determination on the EUA request.

If FDA is not able to authorize an EUA, FDA intends to notify the manufacturer. FDA would expect the manufacturer to suspend distribution and conduct a recall of the test.

Modifications to a manufacturer's EUA-authorized test are submitted as an amendment to the EUA. Where validation data supporting the modification has been submitted in the amendment, FDA does not intend to object to implementation of the modification while FDA conducts its review.

5. Clinical Testing

While awaiting FDA determination on the EUA request, FDA recommends that manufacturers make publicly available on their website the instructions for use, including a summary of assay performance.

⁶ See FDA's Guidance, Emergency Use Authorization of Medical Products and Related Authorities, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>.

⁷ <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019>

D. Commercial Manufacturer Development and Distribution and Laboratory Development and Use of Serology Tests Without an EUA

The policy described in this subsection applies to developers of serology tests that identify antibodies (e.g., IgM, IgG) to SARS-CoV-2 from clinical specimens. This policy is limited to such testing in laboratories or by healthcare workers at the point-of-care. This policy does not apply to at home testing.

Considering that serology tests are less complex than molecular tests and are solely used to identify antibodies to the virus, FDA does not intend to object to the development and distribution by commercial manufacturers or development and use by laboratories of serology tests to identify antibodies to SARS-CoV-2, where the test has been validated, notification is provided to FDA, and information along the lines of the following is included in the test reports:

- This test has not been reviewed by the FDA.
- Negative results do not rule out SARS-CoV-2 infection, particularly in those who have been in contact with the virus. Follow-up testing with a molecular diagnostic should be considered to rule out infection in these individuals.
- Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.
- Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E.

FDA recommends that developers planning to submit an EUA for serological testing as the sole basis to diagnose or inform infection status, include information along the lines of the statements above in their test reports until data is submitted and an EUA is authorized for additional uses.

V. Validation Study Recommendations Based on the Technological Principles of Diagnostic Tests

In this section, FDA provides recommendations for developers regarding the minimum testing that should be performed for SARS-CoV-2 diagnostics based upon the underlying technological principles of the test. Depending on the characteristics of your test, additional validation studies may be recommended. FDA encourages test developers to discuss any alternative technological approaches with FDA through CDRH-EUA-templates@FDA.HHS.GOV.

A. Molecular Diagnostics

FDA defines SARS-CoV-2 molecular diagnostic tests as tests that detect SARS-CoV-2 nucleic acids from human specimens. FDA recommends that the following validation studies be conducted for a molecular SARS-CoV-2 diagnostic:

(1) Limit of Detection

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FDA recommends that laboratories document the limit of detection (LoD) of their SARS-CoV-2 assay. FDA generally does not have concerns with spiking RNA or inactivated virus into artificial or real clinical matrix (e.g., Bronchoalveolar lavage [BAL] fluid, sputum, etc.) for LoD determination.

FDA recommends that laboratories test a dilution series of three replicates per concentration, and then confirm the final concentration with 20 replicates. For this guidance, FDA defines LoD as the lowest concentration at which 19/20 replicates are positive. If multiple clinical matrices are intended for clinical testing, FDA recommends that laboratories submit in their EUA requests the results from the most challenging clinical matrix to FDA. For example, if testing respiratory specimens (e.g., sputum, BAL, nasopharyngeal (NP) swabs, etc.), laboratories should include only results from sputum in their EUA request.

(2) Clinical Evaluation

In the absence of known positive samples for testing, FDA recommends that laboratories confirm performance of their assay with a series of contrived clinical specimens by testing a minimum of 30 contrived reactive specimens and 30 non-reactive specimens. Contrived reactive specimens can be created by spiking RNA or inactivated virus into leftover clinical specimens, of which the majority can be leftover upper respiratory specimens such as NP swabs, or lower respiratory tract specimens such as sputum, etc. We recommend that twenty of the contrived clinical specimens be spiked at a concentration of 1x-2x LoD, with the remainder of specimens spanning the assay testing range. For this guidance, FDA defines the acceptance criteria for the performance as 95% agreement at 1x-2x LoD, and 100% agreement at all other concentrations and for negative specimens.

(3) Inclusivity

Laboratories should document the results of an *in silico* analysis indicating the percent identity matches against publicly available SARS-CoV-2 sequences that can be detected by the proposed molecular assay. FDA anticipates that 100% of published SARS-CoV-2 sequences will be detectable with the selected primers and probes.

(4) Cross-reactivity

At a minimum, FDA believes an *in silico* analysis of the assay primer and probes compared to common respiratory flora and other viral pathogens is sufficient for initial clinical use. 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 addition, FDA recommends that laboratories follow recognized laboratory procedures in the context of the sample types intended for testing for any additional cross-reactivity testing.

Additional information for the validation of molecular diagnostics is included in the manufacturer and laboratory EUA templates available for download on our website.

B. Antigen Detection Diagnostics

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FDA defines SARS-CoV-2 antigen diagnostic tests as those that detect SARS-CoV-2 antigens directly from clinical specimens. FDA recommends that the following validation studies be conducted for a SARS-CoV-2 antigen test:

- Limit of Detection/Analytical Sensitivity
- Cross-reactivity/Analytical Specificity
- Microbial Interference
- Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. FDA believes that clinical agreement should be established on human specimens, preferably leftover specimens from patients with or without SARS-CoV-2 infection. If SARS-CoV-2 positive clinical specimens cannot be obtained, it is acceptable to spike leftover specimens with SARS-CoV-2 materials. For devices claiming multiple clinical matrices, the most challenging matrix should be used in your validation studies.

C. Serological Diagnostics

FDA defines SARS-CoV-2 serological diagnostic tests as tests that identify antibodies (e.g., IgM, IgG) to SARS-CoV-2 from clinical specimens. FDA recommends that the following validation studies be conducted for a SARS-CoV-2 serological assay:

- Cross-reactivity/Analytical Specificity
- Class Specificity
- Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. FDA recommends that clinical accuracy should be established on human specimens from patients with microbiologically confirmed COVID-19 infection.