Contains Nonbinding Recommendations

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

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

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For questions about this document, contact OHT7 at 301-796-7692 or OHT7/Division of Microbiology Devices at 301-348-1778 or 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 for novel coronavirus (COVID-19) molecular diagnostics tests developed and used in laboratories certified to perform high-complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) prior to issuance of emergency use authorizations (EUA) for such tests.

On February 4, 2020, the Secretary of Health and Human Services 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 an accelerated policy enabling laboratories to use tests they develop faster in order to achieve more rapid testing capacity in the United States.

[1] https://www.fda.gov/media/135010/download.

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& 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.

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 and which has now been detected in 50 locations 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 rapidly spread, 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 effectively respond 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 available testing capabilities in healthcare settings, and reference and commercial laboratories.

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 EUA on February 4, 2020.[2] Since authorizing CDC's EUA, FDA has been actively working with other SARS-CoV-2 diagnostic 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 allow unapproved medical products or unapproved uses of approved medical products to be used in

[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.

[3] Nothing in this guidance supersedes CDC's recommendations regarding which patients should be tested for COVID-19.

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.

FDA understands that some laboratories certified to perform high-complexity testing under CLIA are developing diagnostic tests to detect theSARS-CoV-2 virus and pursue EUA authorization for those tests. 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 tests for specimen testing, as described below. FDA believes 15 days is a reasonable period of time to prepare an EUA submission for test that has already been validated.

This guidance is intended to help rapidly expand testing capacity by facilitating the development of molecular SARS-CoV-2 diagnostic assays. The accelerated approach discussed below should be considered for initial testing of patient specimens, with subsequent confirmatory testing performed as appropriate.

III. Scope

The policy described in this guidance applies to laboratories certified to perform high-complexity testing under CLIA, that comply with CLIA requirements, that have developed and are using their own validated diagnostic test, and are pursuing an EUA.

IV. Policy

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.

A. Validation

All clinical tests should be validated prior to use; however, 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. Below, FDA has provided recommendations regarding the minimum testing to be performed to ensure analytical and clinical validity of these tests, and FDA encourages laboratories to discuss any alternative testing with FDA that they would like to conduct.

(1) Limit of Detection

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., 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. 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, nasophayngeal (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. Twenty of the contrived clinical specimens should be spiked at a concentration of 1x-2x LoD, with the remainder of specimens spanning the assay testing range. 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 an 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. 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 should follow recognized laboratory procedures in the context of the sample types intended for testing for any additional cross-reactivity testing.

B. 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]

C. 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] ~~See FDA's Guidance, Emergency U~~se 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.

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

D. EUA Request

The COVID-19 specific EUA template can be obtained by contacting FDA (CDRH-EUA-Templates@fda.hhs.gov), or downloading the template available on the FDA website.[5] FDA will communicate any questions or concerns regarding the completed EUA request or EUA template to the clinical laboratory. FDA will also work collaboratively to address any potential concerns or safety considerations raised in the request and will contact the laboratory regarding a final determination on the EUA request.

If FDA is not able to authorize an EUA, FDA will notify the laboratory. FDA believes it would be important for the laboratory to terminate testing patient specimens and issue a corrected test report that indicates the prior test result may not be valid.

E. 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.

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[5] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization