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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

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Agenda

• Background

• Summary of Immediately In Effect Guidance

• Questions and Answers
Objective

• Explain policy for molecular diagnostics testing in high-complexity Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories prior to emergency use authorization for coronavirus disease-2019 (COVID-19) during the public health emergency.
• Guidance issued February 29, 2020 describes a policy regarding certain laboratories immediately using tests they developed and validated in order to achieve more rapid testing capacity in the U.S.

• To address the COVID-19 public health emergency, the FDA has determined that prior public participation for this guidance is not feasible or appropriate and issued this guidance without prior public comment.

• This guidance document is immediately in effect, but it remains subject to comment in accordance with the FDA's good guidance practices.
Scope

• The new policy is limited to:
  – Laboratories certified to perform high complexity testing, consistent with the requirements under the Clinical Laboratory Improvement Amendments (CLIA)
  – Molecular diagnostics for SARS-CoV-2

• The new policy does NOT impact:
  – Requirements under the Clinical Laboratory Improvement Amendments
  – CDC recommendations for who should be tested
The guidance includes recommendations regarding:

- Validating newly developed SARS-CoV-2 tests prior to clinical use
- Notifying FDA when clinical use of a validated test begins
- Confirming the first 5 positive and negative samples with an EUA authorized test
- Indicating in test reports that the test has been validated but independent review by FDA is not yet complete
- Submitting an EUA within 15 days of initiating testing
- Steps to take if any specimens fail confirmatory testing or if FDA is unable to authorize the EUA
Test Validation

• The guidance includes recommendations regarding the minimal testing to be performed for validation:
  – Limit of Detection (LoD)
  – Clinical Evaluation
  – Inclusivity
  – Cross-Reactivity

• Limited viral materials are available
  – FDA, BARDA, and CDC prioritize and coordinate shipments to labs when ready to validate
Limit of Detection

• Defined as the lowest concentration at which 19/20 replicates are positive

• Methods:
  – Recommend testing dilution series with 3 replicates per concentration (range finding) and
  – confirming final concentration with 20 replicates (around initially identified LoD only)

• Samples:
  – pooled negative clinical samples or artificial matrix
  – if multiple specimen types are intended, most challenging should be evaluated (e.g., sputum)
Clinical Evaluation

- Recommend testing at least 30 contrived reactive specimens and 30 non-reactive specimens
  - Contrived reactive specimens can be created by spiking viral RNA or inactivated virus into leftover clinical specimens
  - Twenty (20) of the contrived specimens should be spiked at a concentration of 1x-2x LoD, with the remainder of specimens spanning the assay testing range.

- Acceptable performance:
  - 95% agreement at 1x-2x LoD and
  - 100% agreement at all other concentrations and for negative specimens
Inclusivity

• Recommend conducting an *in silico* analysis of the percent identity matches against publicly available SARS-CoV-2 sequences that can be detected by the proposed molecular assay.

• 100% of published SARS-CoV-2 sequences should be detectable with the selected primers and probes
Cross-Reactivity

• Recommend conducting an *in silico* analysis of the assay primer and probes compared to common respiratory flora and other viral pathogens

• There should be >80% homology between one of the primers/probes and any sequence present in the targeted microorganism

• Recommend following recognized laboratory procedures for any additional cross-reactivity testing in the context of the sample types intended for testing
Status of EUA Tests

- CDC EUA authorization Feb 4, 2020
  - Covers CDC-qualified IDT 2019-nCoV Kit Lot#0000500383
  - Additional IDT lots undergoing qualification by CDC

- NYS Wadsworth Center EUA Authorization Feb 29, 2020

- CDC, FDA and BARDA are working with multiple IVD manufacturers and laboratories to enable additional EUA authorizations as soon as possible; monitor at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019
Submissions to FDA

• **Notification** of clinical use of a validated test should be directed to CDRH-EUA-Templates@fda.hhs.gov and should include:
  – name of the laboratory
  – name of the lab director
  – address
  – contact person

• **EUA** should be submitted within 15 days of initiating clinical testing to OIR-Operations@fda.hhs.gov and should include:
  – Form 3514 available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf
  – Completed EUA template available at: https://www.fda.gov/media/135658/download
Resources


• General EUA Guidance Document: https://www.fda.gov/media/97321/download

Questions?

For questions on the guidance and accelerated EUA template, or if you wish to consider use an alternative specimen type, contact the Division of Microbiology devices at (301) 348-1778 or: CDRH-EUA-Templates@fda.hhs.gov.

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Under Heading: Special Technical Topics; Subheading: In Vitro Diagnostics

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