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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.

Background

- 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

Policy

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

- COVID-19 Guidance Document: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-diagnostics-testing-laboratories-certified-perform-high-complexity-testing-under-clia-prior

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

- FDA's Novel Coronavirus (COVID – 19) webpage: https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-covid-19

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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