Considerations from the College of American Pathologists for Implementation of an Assay for SARS-CoV-2 Testing after a Change in Regulatory Status

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ABSTRACT The U.S. Food & Drug Administration (FDA) regulates the marketing of manufacturers' *in vitro* diagnostic tests (IVDs), including assays for the detection of SARS-CoV-2. The U.S. government's Clinical Laboratory Improvement Amendments (CLIA) of 1988 regulates the studies that a clinical diagnostic laboratory needs to perform for an IVD before placing it into use. Until recently, the FDA has authorized the marketing of SARS-CoV-2 IVDs exclusively through the Emergency Use Authorization (EUA) pathway. The regulatory landscape continues to evolve, and IVDs will eventually be required to pass through conventional non-EUA FDA review pathways once the emergency declaration is terminated, in order to continue to be marketed as an IVD in the United States. When FDA regulatory status of an IVD changes or is anticipated to change, the laboratory should review manufacturer information and previously performed internal verification studies to determine what, if any, additional studies are needed before implementing the non-EUA version of the IVD in accordance with CLIA regulations. Herein, the College of American Pathologists' Microbiology Committee provides guidance for how to approach regulatory considerations when an IVD is converted from EUA to non-EUA status.

The College of American Pathologists (CAP) has deemed status in the Clinical Laboratory Improvement Amendments (CLIA) of 1988 for the inspection of clinical diagnostic laboratories, and the CAP inspects clinical laboratories to ensure that these laboratories adhere to CLIA regulations. The CAP has received numerous questions from laboratories about the implications of a change in the U.S. Food & Drug Administration (FDA) regulatory status of tests detecting the presence of SARS-CoV-2, the causative agent of COVID-19.

Until recently, all tests for SARS-CoV-2 reviewed by the FDA were evaluated under the Emergency Use Authorization (EUA) pathway. This pathway is distinct from other FDA

Citation Peaper DR, Rhoads DD, Sullivan KV, Couturier MR, Humphries RM, Martin IW, Nolte FS, Rowlinson M-C, She RC, Simner PJ, Theel ES, Wojewoda CM. 2021. Considerations from the College of American Pathologists for implementation of an assay for SARS-CoV-2 testing after a change in regulatory status. *J Clin Microbiol* 59:e01167-21. <https://doi.org/10.1128/JCM.01167-21>.

Editor Alexander J. McAdam, Boston Children's Hospital

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Accepted manuscript posted online 14 July 2021

Published 20 September 2021

review pathways, including Pre-Market Authorization, 510(K), and the recently developed *De Novo* classification process. A test for SARS-CoV-2 RNA that had previously obtained EUA was recently granted marketing authorization through the *De Novo* classification process, and other assays may follow through this or other non-EUA pathways (<https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-sars-cov-2-diagnostic-test-using-traditional-premarket-review-process>).

When an *in vitro* diagnostic test (IVD) changes FDA regulatory status from EUA to non-EUA, there are several assay-specific factors that should be considered by a laboratory when determining what, if any, additional studies are needed before implementing the updated version of the test based on FDA regulatory status (Table 1). This table may also provide a framework for discussions with front-line clinical services if any changes in clinical operations may be needed to maintain regulatory compliance.

For the purposes of this Commentary we are considering assay verification from the CLIA perspective, that is, a one-time process to establish the appropriate performance of an assay in your laboratory regardless of whether the method is FDA-approved/cleared/authorized or a laboratory-developed test (LDT). We recognize this differs from the CAP definition, which differentiates verification and validation based on assay regulatory status. Additionally, “bridging study” refers to a formal analysis performed by a laboratory to establish equivalent performance of specimens, instruments, and/or reagents contained in the instructions for use of an EUA assay to those that may be substituted by a laboratory.

The laboratory should request documentation from the manufacturer to determine if any aspects of the assay (e.g., primer and probe design, detection method, reagents, procedure, specimen types, interpretive criteria, interpretive software, etc.) differ between the EUA assay version currently in use by the laboratory and the assay version receiving a traditional classification status by the FDA.

1. If there are material changes between the EUA and non-EUA assay versions, then a full verification study of the new assay should be performed.
2. If the manufacturer indicates there are no changes to the assay other than the labeling, then the laboratory may use the original verification study of the EUA version of the assay to meet some or all of the performance verification requirements. The laboratory director should review the original verification study to confirm if it meets CLIA requirements and any internal policies for assay verification.
3. If clear documentation from the manufacturer stating the similarity or difference of the EUA and non-EUA assays is unavailable, then the laboratory should assume the newly labeled assay is different from the previous EUA assay. In this case, the laboratory should perform a full verification study of the newly labeled IVD.

The requirements for the verification of a test granted marketing authorization under a non-EUA pathway by the FDA have been reviewed previously (1). This review discusses laboratory-developed tests (LDT), and it provides a comprehensive overview of the background and definitions for establishing test performance, including non-LDT methods. Consideration of requirements for LDT verification may be needed following termination of the emergency declaration, especially if bridging studies were performed to allow the use of alternative reagents and/or instrumentation that are not included in the non-EUA assay. Specific guidelines for verification studies are available in laboratory accreditation documents, such as the inspection checklists from the CAP (2). A more general description of these requirements is contained within CLIA regulations themselves (3). A description of recommendations for verification of EUA assays has also been published, including one approach for a limited verification study for multilaboratory health systems (4).

The transition of an IVD from EUA to non-EUA status is a good opportunity to review the initial verification study to confirm it meets the CLIA regulations, internal policies describing the components of verification studies, and accreditation requirements. Table 2 provides one approach to such a review. This is especially important

TABLE 1 Factors to consider when comparing Emergency Use Authorized (EUA) assay versions to the corresponding non-EUA assay

Issues to consider	Questions to ask
Manufacturer Information	Has the manufacturer provided a letter stating that there are no differences between the EUA and non-EUA assay versions?
Specimen types	Is the non-EUA assay authorized for the specimen types you wish to test (e.g. nasopharyngeal, anterior nares, oropharyngeal, serum, plasma, etc.?)
Transport media	Is the non-EUA assay authorized for the transport media you wish to accept (e.g. viral transport media, saline, liquid Amies, etc.?)
Assay design and interpretation	Does the non-EUA assay use the same viral targets as the EUA assay? Are the interpretive criteria the same between assays including cut-off values or generation of invalid or inconclusive results?
Test procedure	Are there differences in any of steps for assay performance? Is the instrumentation required the same for the EUA and non-EUA assays?
Results reporting	Are reported results the same (e.g. "positive" versus "detected") between assay versions? Is the content of comments appended to results appropriate for the change in regulatory status?

since verification studies performed earlier in the pandemic may have been abbreviated due to shortages of any of the following: supplies, staff, positive specimens, and time. If the laboratory identifies any gaps in the initial verification studies of the EUA assay, then the laboratory should perform additional studies to fill these gaps before implementing the non-EUA IVD. The same rigor should be applied to the verification needs of off-label specimen types and other target analytes if the SARS-CoV-2 target is part of a multiplex panel. If appropriate, testing data obtained in the interim between initial EUA implementation and evaluation of verification adequacy outlined in Table 2 could potentially be used to demonstrate satisfactory assay performance. Such testing data could include results of quality control testing, proficiency testing, instrument comparison studies, and/or clinical testing confirmed by secondary methods. For example, if the initial accuracy study was limited in scope due to reagent or sample availability, results of proficiency testing performed during the pandemic could be used to supplement the initial verification study.

If additional work is needed to complete a full verification study, the source of all data used should be indicated in a verification summary. The exact composition of this verification study is at the discretion of the laboratory director, but it should meet all CLIA requirements and follow institutional policies and procedures. If no additional verification work is required when transitioning from the EUA IVD to the non-EUA IVD, this conclusion and the justification thereof should be formally documented by the laboratory. Also, the date of transition from EUA to non-EUA reagents by the laboratory should be identifiable in case of query, audit, or inspection.

Special consideration should be given by laboratories that performed bridging studies to expand the spectrum of specimens, transport media, reagents, and/or instruments used by EUA assays. Depending on the nature of the bridging study, the changes made to the EUA assay may necessitate additional verification studies when applied to a non-EUA assay. Some changes previously supported by bridging studies may be considered a modification to the assay if they are not included in the approved non-EUA assay manufacturer's instructions, even if there is no material change in the assay (e.g., use of an alternative nucleic acid extraction method). These modifications require verification and may impact the CLIA complexity of the test.

Finally, it is important for the laboratory to update its operating procedures and any requisite regulatory verbiage or interpretative comments that may appear on their reports to accurately reflect the regulatory status of the method used. The specific requirements for reporting EUA assays differ from those for non-EUA versions.

The determination of a public health emergency and declaration of circumstances justifying the emergency authorization of IVDs is a formal process. While the emergency declaration remains in effect, manufacturers can elect to submit their assays for authorization through non-EUA pathways. However, at some point in the future, the public health emergency or the circumstances justifying the use of the EUA pathway

TABLE 2 Factors to consider when assessing the adequacy of initial verification studies for Emergency Use Authorized (EUA) assay versions prior to implementing a non-EUA version of the same assay

Issues to consider	Questions to ask
Specimen types	Did we adequately verify all the specimen types that we currently accept or plan to accept?
Transport media	Did we adequately verify all the types of transport media types that we currently accept or plan to accept?
Verification study design: types of samples	Did we include an appropriate combination of contrived and clinical specimens in our original verification study?
Verification study design: no. of samples	Did we include an appropriate no. of positive and negative samples in our original verification study for determination of accuracy?
	Did we include an appropriate no. of positive and negative samples in our original verification study for determination of precision?
	Did we test an appropriate no. of inter- and intra-run samples for determination of precision?
Bridging studies	Was a bridging study used to verify any modifications to an EUA assay?
	Are the verification data from bridging study adequate for the continued use of that modification in a non-EUA assay?

may end, and IVDs currently authorized through the EUA pathway will be unable to be marketed. However, before the justification for emergency authorization ends, there will be appropriate advance notice allowing laboratories and manufacturers to prepare for changes in test availability. Importantly, currently authorized methods that do not undergo review through non-EUA pathways may no longer be marketed, and some of these may be considered LDTs and subject to more complete verification studies.

We are encouraged that device manufacturers are submitting SARS-CoV-2 assays for marketing review through FDA non-EUA pathways, and we expect the number of such assays to increase with time. While the first SARS-CoV-2 assay to be reviewed outside of the EUA pathway was a molecular test, other assay types, including antigen and antibody assays, will likely be reviewed by conventional pathways in the future. It will be important for laboratories to maintain awareness of the regulatory status and requirements of the assays they are using for SARS-CoV-2 testing.

ACKNOWLEDGEMENTS

D.R.P. reports stock options from Tangen Biosciences. D.D.R. reports an advisory board role for Luminex and Talis Biomedical and research funding from BD, BioFire Diagnostics, Cepheid, Cleveland Diagnostics, Hologic, Luminex, Qiagen, Q-Linea, Roche, and Specific Diagnostics. K.V.S. reports no disclosures. M.R.C. reports research reagents from Apacor and Techcyte, household income from BioFire Diagnostics, and stock in bioMérieux. R.M.H. reports consultancy from ThermoFisher, Accelerate Diagnostics, GI Scientific, and Qpex Pharmaceuticals, and stock in Accelerate Diagnostics. I.W.M. reports no disclosures. F.S.N. reports consultancies from Clear Labs, Karius, and Medscape, and lectures from Abbott Molecular. M.-C.R. reports no disclosures. R.C.S. reports consultancy from Accelerate and Speakers Bureau from bioMérieux. P.J.S. reports grants and personal fees from Accelerate Diagnostics, OpGen Inc. and BD Diagnostics, grants from bioMérieux, Inc., Affinity Biosensors, and Hardy Diagnostics, and personal fees from Roche Diagnostics, Shionogi, Inc., and GeneCapture. E.S.T. reports board membership for Roche. C.M.W. reports no disclosures.

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