Selection Process for CLIA-Waived Testing for SARS-CoV-2, Respiratory Syncytial Virus, and Influenza Viruses

White Paper
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Introduction

The diagnostic testing landscape for respiratory diseases has evolved rapidly because of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Because of this increase in testing, the number of testing facilities has increased substantially. Some of these facilities are operating outside a central laboratory and are closer to the patient to ensure timely and actionable results affecting clinical management of patients. The overlap in clinical symptoms for respiratory pathogens makes it difficult to distinguish the pathogen without an accurate diagnosis; thus, very few health care providers are diagnosing empirically. Diagnosing respiratory infections based on symptoms alone is difficult and typically has poor diagnostic accuracy.[1] Additionally, there are several use cases that require asymptomatic testing or screening. This white paper provides guidance on selecting tests that can be used at the point of care (POC) under a Clinical Laboratory Improvement Amendments of 1988 (CLIA) waiver to detect SARS-CoV-2, respiratory syncytial virus (RSV), and influenza A and B viruses. There are two common testing modalities: rapid antigen tests and rapid molecular tests. Considerations based on testing location, patient population, and appropriate use of tests are discussed.

POCT18 includes information on different testing platforms, interpreting the manufacturer's stated performance, and choosing the best test for the user's needs. An explanation of emergency use authorization (EUA) is included. The intended users may lack specific laboratory training to perform tests in outpatient settings such as physician offices, urgent care facilities, and pharmacies.

The following topics are not discussed in detail:

- Specific information related to appropriate coding of laboratory tests
- Verification of performance specifications (accuracy and precision) for instruments or tests for SARS-CoV-2, RSV, or influenza viruses
- Specimen pooling strategies for testing
- Reporting laboratory test results and data to public health agencies
- Cost and reimbursement considerations
- Patient self-testing (at home or in other locations)
- Patient education
- Immune response testing
- Antibody tests for detecting past SARS-CoV-2 infections

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Quick and accurate identification of the agent responsible for a viral respiratory infection is essential for effective treatment of disease and ongoing clinical management of the infected person. Rapid tests used at the POC and in laboratories or other facilities under a CLIA Certificate of Waiver can provide increased access to testing and care, especially in community settings with persons that may not readily have access to traditional health care or laboratory facilities.[2,3] The coronavirus disease 2019 (COVID-19) pandemic has highlighted the need for rapid CLIA-waived tests for SARS-CoV-2 to identify or rule out cases of infection in both symptomatic and asymptomatic individuals, properly treat patients who test positive, guide appropriate isolation or quarantine, expedite reporting to public health, and ultimately assist in reducing transmission of the virus. Because of the overlap in clinical symptoms with many respiratory pathogens, rapid CLIA-waived tests for other common respiratory viruses, such as RSV and influenza viruses, offer similar advantages.

This white paper is intended to provide information to guide the selection and implementation of CLIA-waived tests for SARS-CoV-2, RSV, and influenza viruses in point-of-care testing (POCT) sites, such as physician offices, urgent care centers, clinics, pharmacies, and other nontraditional health care facilities. Although specific reference is made to the US Food and Drug Administration (FDA) and CLIA regulations, POCT18 also serves as a useful resource for an international audience.

Although POCT is not synonymous with CLIA-waived testing, many waived tests are used in POCT sites that have a CLIA Certificate of Waiver. In addition, CLIA-waived tests can also be used in laboratories with other CLIA certificate types, including a Certificate for Provider-Performed Microscopy Procedures, a Certificate of Compliance, or a Certificate of Accreditation. Except in times of a public health emergency (PHE), tests for SARS-CoV-2, RSV, and influenza viruses can be CLIA waived if they are cleared by the FDA for home use or approved for waiver by the FDA under the CLIA criteria. Certain tests for SARS-CoV-2 have been granted EUA by the FDA for use at the POC. As discussed in FDA guidance, when the FDA issues such an EUA, tests are deemed CLIA-waived tests. Accordingly, for the duration of the emergency declaration, such tests can be performed in a POC setting under one of the CLIA certificates listed above.[4] The only CLIA requirements for performing waived testing, whether authorized by the FDA through an EUA or approved for waiver by meeting CLIA criteria, are that the POCT site must have a CLIA certificate and must follow the manufacturer's instructions for use (IFU) without modification.[3]

On 31 January 2020, the Secretary of the US Department of Health and Human Services declared a nationwide PHE as a result of confirmed SARS-CoV-2 cases (known as 2019 Novel Coronavirus or 2019-nCoV at the time of the declaration).[5] Subsequently, on 4 February 2020, the Secretary determined that the PHE has "a significant potential to affect national security or the health and security of United States citizens living abroad." The Secretary also determined that circumstances justified the authorization of emergency use (ie, EUA declaration) of *in vitro* diagnostic (IVD) tests for detection or diagnosis of SARS-CoV-2.[6] The FDA authorized the first EUA on 4 February 2020, for a real-time PCR molecular diagnostic test developed by the Centers for Disease Control and Prevention (CDC).[7] Since then, the FDA has authorized emergency use for multiple molecular and antigen diagnostic tests, as well as serology, antibody, and other adaptive immune response tests. Several multiplex molecular tests can detect various pathogens simultaneously in one sample (ie, SARS-CoV-2, RSV, and influenza A and B viruses). Some of these molecular tests are designed for on-demand testing with rapid results, suitable for use at the POC (compared with others that batch tests on instrument systems).

An EUA authorizes emergency use of an unapproved IVD test or an unapproved use of an approved test that "may be effective" at diagnosing infection, such as SARS-CoV-2, for the duration of the PHE (see figure). When the circumstances justifying authorization of emergency use no longer exist, the EUA declaration is terminated, and an EUA(s) issued based on that declaration is also no longer effective; thus,

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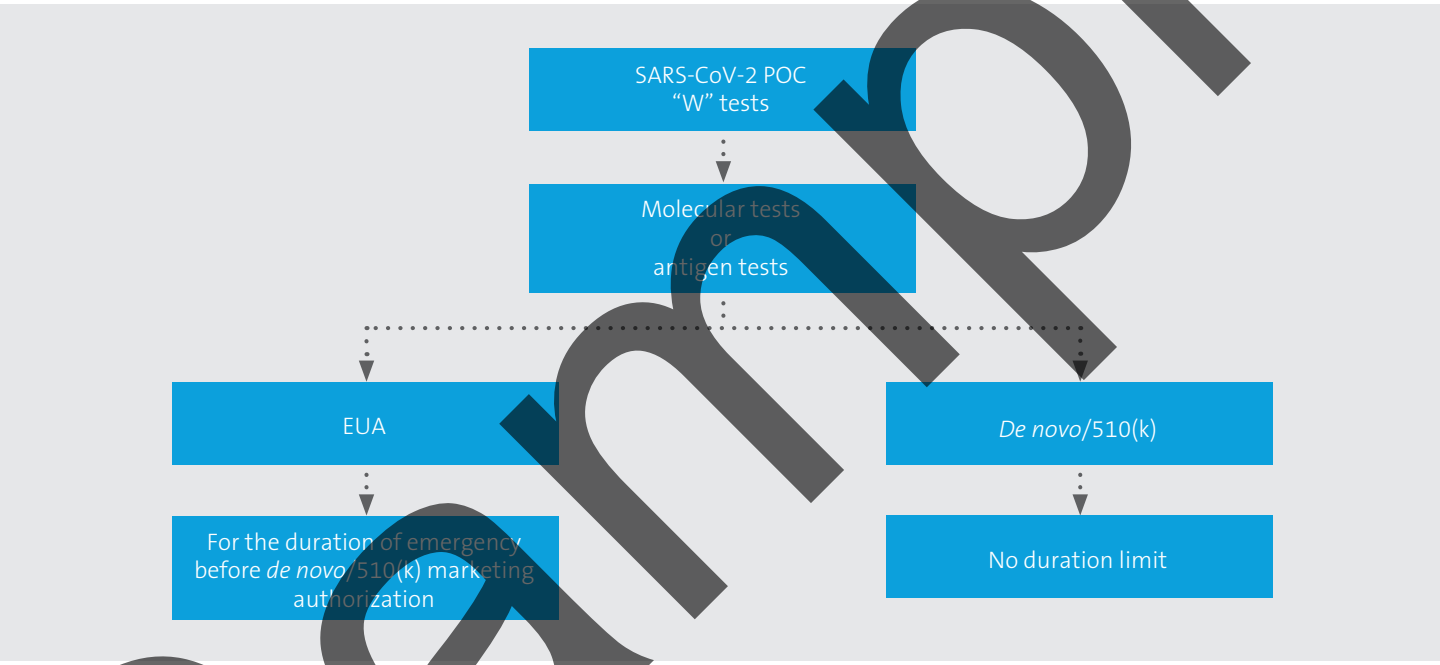
testing can no longer be completed with methods authorized by the EUA. An EUA could also be revoked if circumstances make revocation appropriate to protect public health or safety. This revocation may include a determination by the FDA that the test no longer meets the criteria for authorization because revocation is requested by the EUA holder, such as when the EUA holder is no longer offering the test, or when a test receives full marketing authorization from the FDA, such as through a *de novo* or 510(k) review pathway. Although termination of the EUA declaration affects all EUAs issued under that declaration, revocation of a specific EUA does not revoke EUAs for other, similar tests. A *de novo*, reclassified, or 510(k)-cleared test does not depend on an EUA declaration and may continue to be marketed after the EUA declaration is terminated. A *de novo* reclassification or 510(k) clearance provides reasonable assurance of the safety or effectiveness of a test for its intended use. On 30 January 2023, the US government announced its plans to end the national COVID-19 PHE on 11 May 2023, pursuant to Section 319 of the Public Health Service Act. IVD products on the market under an EUA will remain on the market until the separate EUA declaration (Section 564) is over. The FDA issued a draft guidance on the transition in December 2021 but has not finalized the document. The PHE is not tied to the EUA declaration expiration.



Abbreviations: CLIA, Clinical Laboratory Improvement Amendments of 1988; EUA, emergency use authorization; IVD, *in vitro* diagnostic; POC, point of care; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Comparison of Duration of EUA With *De Novo* Reclassification Order or 510(k) Clearance. The SARS-CoV-2 tests authorized for emergency use that are designated by a "W" in the Authorized Settings column of the EUA tables on the IVD EUA Web page[8] are CLIA waived for use in patient care settings operating under a CLIA Certificate of Waiver.

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