Implementing a Laboratory Test Under Emergency Use Conditions

White Paper
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Introduction

This white paper covers public health emergencies (PHEs) in general, the ways in which emergency use authorizations (EUAs) may be used, and the ramifications of EUAs for medical laboratories and other testing sites. EP43 uses the terminology of US processes (eg, PHE, EUA); however, similar processes exist in many jurisdictions, and the information in this white paper is globally applicable. EP43 focuses on the current PHE for coronavirus disease 2019 (COVID-19) and *in vitro* diagnostic (IVD) laboratory tests that were authorized for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing as a good example of the variable nature of PHEs, the options available when they are in effect, the changeable nature of the health system's response to an emerging pathogen, and the steps for implementation required by laboratories. Unlike viruses with well-understood pathophysiology, the lack of basic knowledge of SARS-CoV-2 (eg, infection, viral burden, transmission) and variations in its clinical course, specifically with respect to clearance of the virus and the antibody response, make it a good example of the difficulties manufacturers and laboratories face with pandemics when developing and using tests that are made available under EUAs.

Ordinarily, commercially available tests are thoroughly reviewed by the jurisdictional regulatory authorities and either "approved," "cleared," or in some cases "registered," based on their performance being shown as safe and effective or substantially equivalent to a previously marketed test. In addition, laboratories may also develop their own tests (laboratory-developed tests [LDTs]) in some jurisdictions. During PHEs, alternative pathways such as EUA may be defined to facilitate development and validation of novel tests to meet the needs of the PHE.

Because EUA tests are infrequently used, it can be difficult and confusing for end-user laboratories to know what they are allowed or required to do. Unique regulatory characteristics of EUAs include:

- Limitation to use during a declared PHE
- Expiration of authorization unless renewed or rescinded
- Regulatory flexibility to focus on the specific PHE and to define requirements for test developers and end users

Guidance from various public health entities may refer to EUAs during a PHE. However, regulatory authorities are responsible for the EUA's unique regulatory parameters. The characteristics listed above make EUA tests effective for meeting rapidly evolving testing needs during a PHE, but they may also cause confusion for laboratories.

Each PHE is different, and the array of tests available may evolve, especially when the PHE covers an extensive time period. For example, manufacturers could develop new approaches to test additional kinds of specimens, as has been the case for SARS-CoV-2. The regulatory approach is likely to evolve, especially for novel pathogens, as scientific understanding progresses and diagnostic tests improve. For example, over time, an appreciation of the need to use testing differently (eg, based on a patient's symptomatology

or local disease prevalence) may prevail. The laboratory should be aware of these issues through current sources of information from regulatory and public health authorities. For example, the US Food and Drug Administration (FDA) provides COVID-19 EUA information.[1]

One common problem typical of the early stages of a PHE involving a newly emerged pathogen is the difficulty in obtaining patient or surrogate samples for testing. In this type of a PHE, there is often a lack of well-characterized, standardized specimens that contain the pathogen. In addition, when there is no reference test or primary materials, and consensus has not been established for molecular assays' cycle thresholds (C_T), viral antigens, or antibody concentrations to establish a positive viral load or seroconversion, there will likely be variable clinical sensitivities, specificities, and lower limits of detection (LLoDs) for newly developed tests. When there are myriad tests available by EUA, as has been true for SARS-CoV-2 testing, medical laboratories are frequently asked to advise clinicians concerning apparently contradictory results. Because the EUA process typically is accelerated, with fewer clinical data available to validate clinical performance and establish performance expectations, the medical laboratory (and the manufacturer that supports it) might struggle to answer clinicians' questions.

Scope

This white paper is intended to help laboratories and manufacturers anticipate and prepare for using EUA tests under the challenging conditions described above. It provides general advice on points to consider and resources that may be available to help medical laboratories select and implement a suitable EUA test. Specifically excluded from this paper are general considerations of emergency preparedness (see CLSI document GP36[2]).

EP43 follows the Test Life Phases Model introduced in CLSI document EP19,[3] which describes how CLSI documents can be useful for a manufacturer that develops and validates a test, as well as the end-user laboratory that implements a test. For all tests, including those covered under an EUA, the performing laboratory is required to verify performance claims as part of implementation. This white paper focuses on ways laboratories can stay abreast of rapidly emerging information and how they can implement tests issued under an EUA.

EP43 does not focus on what manufacturers should consider in creating, developing, or validating a test intended for EUA. In the United States, the FDA provides information for test developers in EUA templates posted on the FDA's website.[1] The regulatory requirements for manufacturers developing EUAs, and potentially for laboratories developing and using LDTs, vary depending on the jurisdiction and are therefore beyond the scope of this white paper. Test developers (both manufacturers and laboratories) should seek regulatory information directly from the pertinent regulatory authorities.

NOTE: This white paper is not intended to replace guidance from regulatory authorities for manufacturers or test developers for developing EUA tests. Changes in the EUA regulatory process may occur, and it is the test developer's responsibility to be aware of such changes.

Background

Since 1995, PHEs have been declared in the United States in response to many naturally occurring disasters caused by earthquakes, hurricanes, typhoons, floods, and wildfires, in addition to those caused by transmissible infectious diseases with actual (COVID-19, H1N1 influenza) or potential (Zika virus) pandemic spread. Lists of past[4] and current[5] EUAs in the United States are available.