Implementing a Laboratory Test Under Emergency Use Conditions

White Paper
EP43-Ed1

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- Expiration of authorization unless renewed or rescinded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

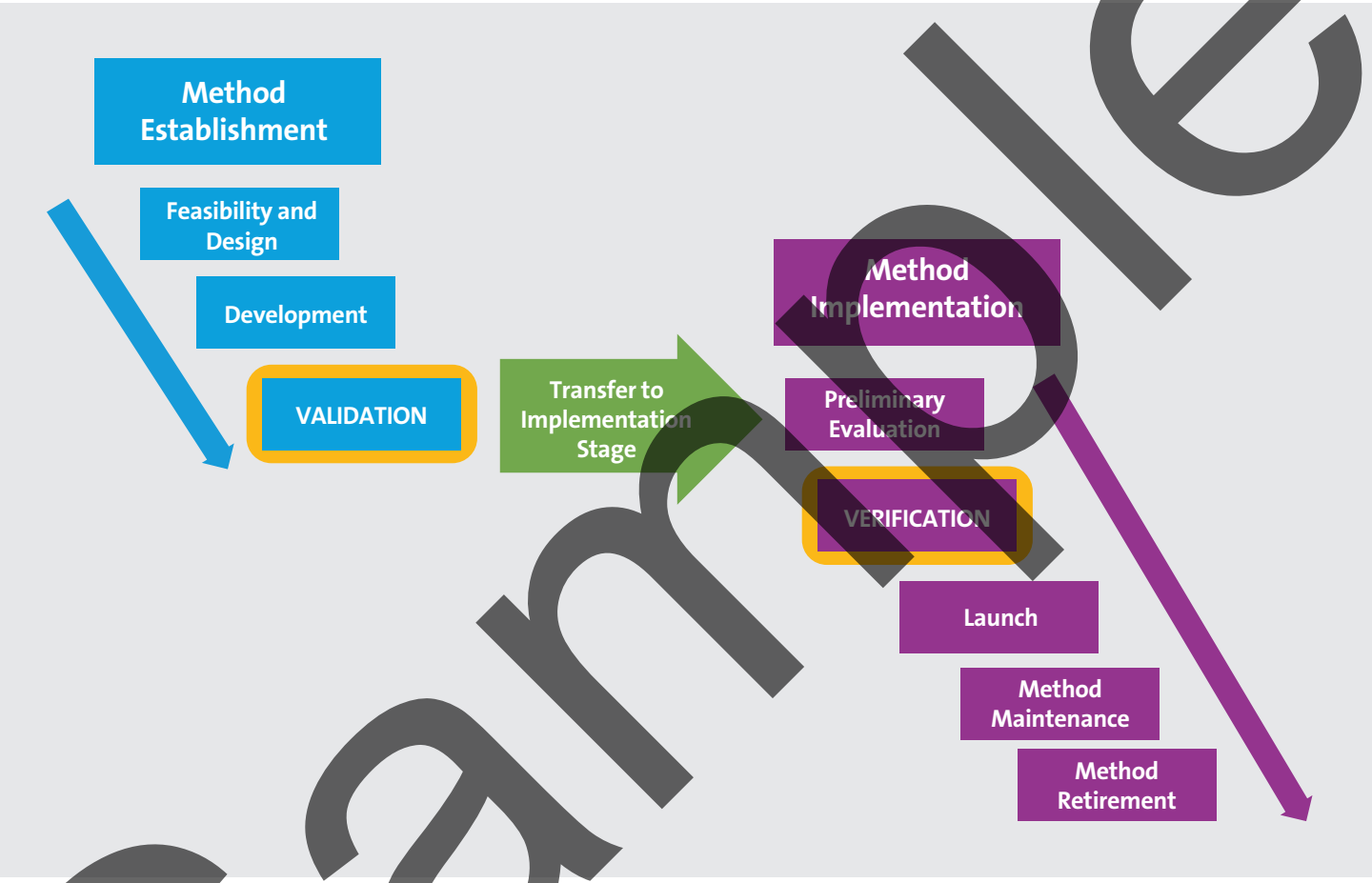
Guidance from various public health entities may refer to EUAs during a PHE. However, regulatory authorities are responsible for the EUA's unique regulatory parameters. The characteristics listed above make EUA tests effective for meeting rapidly evolving testing needs during a PHE, but they may also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

EUAs are normally implemented only when a PHE has been declared and the jurisdictional authorities deem that existing conditions warrant use of an extraordinary process to expedite access to laboratory tests, drugs, personal protective equipment, and/or other medical devices. The appendix compares two PHEs that have prompted EUAs: the 2014 Ebola crisis and the SARS-CoV-2 pandemic.

Establishment and Implementation of Emergency Use Authorization Tests

CLSI document EP19[3] introduces the concept of the Test Life Phases Model[a] shown in the figure below.



This model extends from the initial concept (ie, conceptualization of a test to measure a biomarker) through retirement of the test by the end user. This framework is extremely useful for manufacturers considering establishment of an EUA test or for end users considering implementation, and it informs the structure of this white paper. EP43 focuses on end users who intend to implement EUA-authorized tests in their laboratories.

The Test Life Phases Model is divided into two main parts—establishment and implementation. Each part involves sequential phases that progress when the preceding evaluation acceptance criteria are successfully met. CLSI document EP19[3] provides an overview of the complete Test Life Phases Model, including references to many CLSI documents that are useful in each phase of the process, and can serve as the guide for establishing or implementing an EUA.

[a] To maintain figure consistency across related CLSI documents, "method" was retained in this model. The main text of EP43 uses "test" in place of "method."

The following example underscores the importance of preliminary evaluation.

The Importance of Preliminary Evaluation: Ebola vs SARS-CoV-2

Ebola: During the 2014 Ebola crisis, hospitals in the United States were on alert for travelers and health care workers from West Africa who met criteria for ruling out Ebola infection. Diagnostic testing for Ebola was mainly achieved by FDA-authorized nucleic acid or antigen testing performed at public health laboratories or the CDC. At that time, there were no antibody tests that were FDA authorized. One rule-out test episode per patient was the expected norm. Molecular and serologic assays[b] for detection of antibodies to Ebola were part of patient specimen testing. After transporting specimens for Ebola testing, medical laboratories were challenged with determining whether, and how, to support patients with Ebola by offering tests for non-Ebola diagnostics (eg, malaria, influenza, sepsis) and for supportive medical care, considering the hazards of specimen handling and protocol modifications required to mitigate biosafety concerns. While some laboratories had to restrict non-Ebola testing to a few assays, others were able to offer a larger testing menu (eg, blood cultures, molecular respiratory pathogen testing, Gram stains and body fluid smear analysis, cell counts, chemistries, blood gases, and metabolic panels).[14] However, testing often necessitated dedicated Ebola and non-Ebola laboratory teams to accommodate routine and special segregated testing workflows. At the time, there were many concerns about the potential for instrument contamination. Thus, preliminary evaluation of how the laboratory could best support patients with Ebola was an important part of planning for implementation.

SARS-CoV-2: In contrast with Ebola, the SARS-CoV-2 pandemic impelled many hospital medical laboratories to implement both diagnostic SARS-CoV-2 EUA testing and routine testing for support and therapeutic management. As the pandemic persisted, the norm evolved to include multiple SARS-CoV-2 testing events per patient over an indeterminate timeframe in addition to extending supportive testing for inpatients. The unique nature of SARS-CoV-2 transmission also necessitated testing asymptomatic and presymptomatic individuals. Laboratory testing options evolved to include assays for viral antigens and SARS CoV-2–specific antibodies in addition to molecular diagnostics. For SARS-CoV-2, compartmentalization of specimen handling and testing was not inherently as problematic compared with the Ebola crisis. However, non–SARS-CoV-2 supportive testing caused a notable increase in testing volumes (eg, coagulation and inflammatory marker testing; hepatic, cardiac, and renal function testing).[15] As of this white paper's publication, agreement on the most appropriate way laboratories can support the various testing needs, including the desire to screen asymptomatic patients, and clinicians' preference for an indirect indicator of viral load, such as C_T, remains unresolved.

[b] The generic term "serologic assay" may refer to the detection of agent antigens or agent-specific antibodies.