Q&A column, 7/17

Editor: Frederick L. Kiechle, MD, PhD

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Submit a Question

We devote the full column this month to a question about Emergency Use Authorization tests and specifically a test issued under EUA for detecting Zika virus infection.

Q. A laboratory is considering the implementation of a laboratory test for the diagnosis of Zika virus infection. This test is currently labeled as a test under the issuance of an Emergency Use Authorization. What specific regulations regarding the use of this test, quality control, and proficiency testing apply when performing this test on patient specimens?

A. To answer this question, I will first discuss the Emergency Use Authorization (EUA) process in general and provide background on how the Food and Drug Administration uses it. I will then discuss the specific regulations and requirements for implementing a test issued under EUA for detection of Zika virus infection in patient specimens.
EUA process. The EUA is a legal mechanism under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by which the FDA can allow the following:

- use of an *unapproved medical product* (e.g. diagnostic device, drug, or vaccine) or

- the *unapproved use of an approved medical product* during an emergency for the diagnosis, treatment, or prevention of a serious, life-threatening illness caused by chemical, biological, radiological, and nuclear (CBRN) agents, including emerging infectious diseases.

In the situation described above, a Zika virus test is an unapproved medical product for detection of Zika virus RNA in clinical specimens such as serum and urine. With the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) of 2013, amendments to the EUA authority enabled the FDA to further help strengthen the nation's public health protections against CBRN threats by facilitating the availability of medical countermeasures (e.g. drugs, vaccines, and diagnostic devices) during public health emergencies.

Of note, the use of a medical product under the EUA authority is, however, distinctly different from the use of a medical product under an investigational application, such as an Investigational New Drug Application or Investigational Device Exemption, for which different regulations apply. The objective of the IDE/IND is to assess efficacy and safety of the investigational medical product while ensuring the protection of the human subjects during the research of such product. Institutional Review Board (IRB) approval; written, signed, and witnessed informed consent; adverse event monitoring and reporting; and protocol training of all study personnel are required components of IDE/IND protocols. However, for Emergency Use Authorizations, IRB approval, informed consent, and specific protocol training are typically not required.

Situations in which FDA issues an EUA. The FDA's issuance of an EUA is predicated on the declaration of an emergency by the secretary of the Department of Health and Human Services that justifies the authorization of emergency use for a medical product. Such declaration is based on one of four scenarios:

- determination of the existence of or the potential for a domestic emergency by the secretary of the Department of Homeland Security;

- determination of the existence of or the potential for a military emergency by the secretary of the Department of Defense;
- determination of the existence of or the potential for a public health emergency by the secretary of the Department of Health and Human Services; or
- identification by the secretary of the Department of Homeland Security of the existence of a significant threat to the national security and/or the health and security of U.S. citizens living abroad.

Based on the declaration of one of these four scenarios, and after additional consultation by the Office of the Assistant Secretary for Preparedness and Response, the director of the National Institutes of Health, and the director of the Centers for Disease Control and Prevention, the commissioner of the FDA may issue an EUA. Ebola virus and H1N1 (2009) Influenza A are examples of significant infectious threats that have resulted in the issuance of an EUA.

At the point of declaration of a significant emergency or threat, the issuance of an EUA also requires that the following four statutory criteria have been met:

- the CBRN agents identified in the declaration must cause a serious and/or life-threatening illness;
- the medical product considered under the EUA "may be effective" to diagnose, treat, or prevent the serious illness;
- some evidence exists to support a risk-benefit analysis for the intended use of the medical device; and
- there are no adequate, approved, and/or alternative medical products to the candidate product.

As stated under the categories of products section of the guidance document for EUA, medical products for EUA consideration also include approved medical products for unapproved use. One example is the substitution of a critical reagent of an approved in vitro diagnostic test with another reagent that has not (yet) been cleared for the specific use with this particular device.

The FDA can issue an EUA not only during an ongoing medical emergency stemming from CBRN agents but also in advance based on the potential for an emerging threat, therefore allowing for a more rapid availability of the medical product/device during the actual emergency. The corresponding sections of the FD&C Act and PAHPRA provide further information and recommendations for the submission of requests for issuance of an EUA for a medical product. Manufacturer submissions for EUA must include a description of the product and its intended use, a need analysis, and data regarding safety and effectiveness of the product. However, data from clinical trials is *not* required. Instead, general clinical experience or data derived solely from bench testing may be sufficient. In the case of IVDs, this would include performance data (e.g. analytical sensitivity and specificity) to support the intended use that may be derived from testing of fresh, contrived, or archived specimens. While Current Good Manufacturing Practice requirements (e.g. proper storage or handling requirements of the medical product) apply to EUAs, the FDA may waive such requirements under specific circumstances of the emergency. In addition, the FDA may also waive the Risk Evaluation and Mitigation Strategies requirements.

Under section 564(m) of the FD&C Act and PAHPRA, the FDA is authorized to categorize the complexity of an in

vitro diagnostic device and specifically to determine whether the test can be performed in a point-of-care setting, or only in a laboratory capable of handling moderate-complexity and/or high-complexity testing. The FDA may also establish appropriate conditions and requirements for the performance of the test. Such requirements are included in the actual EUA document for the particular IVD. The complexity categorization determined by the FDA is effective for the same period as the EUA itself; it is independent of, and may differ from, the categorization made under the Clinical Laboratory Improvement Amendments regulations.

Implementing a test under EUA—Zika virus. The following are key components the performing laboratory must consider for each test it wishes to implement:

1. Does the laboratory meet general facility and staffing requirements for performing the test based on the FDA categorization of complexity?
2. Have in-lab verification studies including evaluation of accuracy and precision been performed, and do they demonstrate acceptable performance within the testing laboratory as determined by the laboratory director?
3. Does the laboratory have a plan to monitor the performance of the assay over time? Laboratories using an IVD under EUA are not required to perform proficiency testing for this particular IVD, since generally PT materials are not (yet) available.
4. Can the laboratory adhere to the specific requirements for testing as determined by the FDA? Laboratories are *not* allowed to modify tests provided under EUA and must adhere to the information and requirements listed in the letter of authorization, the fact sheet for health care providers, and the fact sheet for patients, and any additional information on labeling and storage. The fact sheet for health care providers contains specific directions on the use of the IVD, requirements for test implementation and verification, instructions for quality control and quality assurance, as well as data monitoring and reporting of adverse events. EUAs pertaining to Zika virus and various Zika virus IVDs can be found at www.bit.ly/EUAZika.
5. Does the laboratory have systems in place for event monitoring and reporting? In general, IRB approval, informed consent, and specific protocol training are not required for use of EUA devices.

However, adverse event monitoring and reporting as well as detailed record keeping are required for use of medical products under EUA. The FDA specifically requires MedWatch and VAERS reporting for all EUA products in use.

Finally, the laboratory must also understand what happens when the EUA is revoked or terminated. The FDA periodically reviews the appropriateness of a previously issued EUA; such review includes the overall circumstances that warranted the issuance of the initial EUA. The FDA specifies the effective date of the EUA under section 564 of the FD&C Act, and in general the EUA will remain in effect for the duration of the EUA declaration

under which it has been issued. The FDA, from time to time, will then make revisions to EUAs as additional and/or new data become available on the need, performance, efficacy, and/or safety of the medical product subject to the EUA. The FDA may revise or revoke the EUA altogether if the circumstances justifying its issuance no longer exist, the criteria for the original issuance are no longer met, or other circumstances require revisions.

Upon revocation or termination of the EUA, *the medical product will become unapproved and must be disposed of* pursuant to the corresponding sections of the FD&C Act. Disposal of all unapproved medical product must be documented and the documentation made available for review by the regulatory authorities upon request. (An exception to this rule pertains to the use of medical products for treatment of patients in whom therapy with the medical product was begun prior to termination of the EUA under which treatment was authorized. In such circumstances, treatment with the unapproved medical product shall continue to the extent found necessary by the patient's attending physician.)

The review process of an EUA also includes regular assessments based on additional information about clinical performance, efficacy, and safety, with respect to the FDA's subsequent potential approval of the medical product. In that respect, information provided by the manufacturer of the medical product regarding status of licensure and approval/clearance of the unapproved product is critical to the assessment of the EUA status. Should the FDA revoke the EUA because a medical product has become approved and/or licensed, all standard regulatory requirements regarding such (newly) approved medical product must be followed and met, irrespective of prior exemptions under the EUA. Current EUA declarations can be viewed on the FDA website at www.bit.ly/EUAinfo.

It is the responsibility of the health care provider, including a laboratory director, who is using a medical product under EUA regulation to regularly assess the validity of the EUA declaration in order to maintain compliance with the standards and regulations governing use of medical products under EUA declarations.

1. U.S. Department of Health and Human Services, et al. Emergency use authorization of medical products and related authorities: guidance for industry and other stakeholders. www.bit.ly/EUAguidance. Published January 2017. Accessed May 22, 2017.
2. Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) Medical Countermeasure (MCM) Authorities: FDA questions and answers for Public Health Preparedness and Response stakeholders. www.bit.ly/PAHPRAqa. Published January 2014. Accessed May 23, 2017.
3. Landry ML, St George K. Laboratory diagnosis of Zika virus infection. *Arch Pathol Lab Med.* 2017;141(1):60–67.
4. U.S. Food and Drug Administration. Emergency Use Authorizations website. www.bit.ly/EUAZika.
5. Zika virus detection by RT-PCR test, letter of authorization from the FDA to ARUP Laboratories; Sept. 28, 2016. www.bit.ly/FDAZikaletter.

Stefan Riedel, MD, PhD, D(ABMM), Associate Professor, Pathology, Harvard Medical School
Associate Medical Director, Clinical Microbiology Laboratories
Department of Pathology, Beth Israel Deaconess Medical Center, Boston

Member, CAP Microbiology, Resource Committee

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Dr. Kiechle is a consultant, clinical pathology, Cooper City, Fla. Use the reader service card to submit your inquiries, or address them to Sherrie Rice, CAP TODAY, 325 Waukegan Road, Northfield, IL 60093; srice@cap.org. Those questions that are of general interest will be answered.