NAVIGATING THE FDA’S EUA PROCESS FOR DIAGNOSTICS IN THE PRESENT AND FUTURE:

A STAKEHOLDER PANEL DISCUSSION

A 360Dx Roundtable, sponsored by PerkinElmer NOVEMBER 2020
This 360Dx report is based on a virtual roundtable that discussed the US Food and Drug Administration’s Emergency Use Authorization (EUA) authority, including trends, challenges, and possible future developments.

As cases of COVID-19 continued to grow this spring and summer in the US, so too did the number of EUAs from the FDA for clinical diagnostic tests aimed at detecting current and past infections. The agency’s policies for granting EUAs for both molecular and antibody tests evolved over time as more was learned about SARS-CoV-2 and its spread, and diagnostics firms and labs needed to adapt to these changes.

In October, 360Dx convened a panel of expert stakeholders from the regulatory, diagnostic development, and clinical lab communities to discuss this evolution of the FDA’s EUA process and what it means for the diagnostic community going forward.

### MODERATOR:

| Ed Winnick | Editor-in-Chief, 360Dx |

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BACKGROUND ON THE FDA’S EUA PROCESS

Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs at the US Food and Drug Administration’s Center for Devices and Radiological Health, set the stage for the discussion with a review of the history of EUA and the current setting.

She explained that in 2004, the Project Bioshield Act granted authority to the secretary of health and human services (HHS) to declare a public health emergency. Such a declaration triggers the FDA to authorize diagnostic tests for this emergency. The first application of EUA was with H1N1 in 2009.

The bar for securing EUA is very different from the bar for getting medical products approved in the normal setting, Hillebrenner said. For EUA, the submitter must show that the proposed product may be effective to diagnose, treat, or prevent the emergency; that the known and potential benefits outweigh the known and potential risks; and that there are no approved alternatives. Much less data is required to show that a product may be effective compared to showing actual effectiveness for full approval, she explained.

The EUA process kicks into gear for a suspected outbreak with the Centers for Disease Control (CDC) in Atlanta evaluating a patient specimen. The CDC begins to develop an assay that can ultimately be manufactured and distributed to its public health lab network. In parallel, the specimen is shared with other US government groups to grow up the virus, extract the RNA, and develop material that other labs outside of the CDC can use to develop and validate their own tests. This creates separate parallel tracks and ensures that there is greater testing capacity for the pathogen.
The CDC is typically the first to develop a test and conducts a rolling review of the validation data as it generates it. Hillebrenner noted that the FDA is in touch with the CDC several times a day and uses what it learns from those interactions to create an EUA template for other developers. This template outlines the type of validation the FDA would need to see specifically for that particular pathogen.

Hillebrenner explained that the COVID-19 outbreak has been “unprecedented” in its scale and, as such, the FDA has had to adopt and respond differently. The agency was running the parallel tracks starting in January, working on one hand with CDC, and on the other hand with what grew to more than a hundred developers. Early on in the COVID-19 pandemic, she said, the FDA was able to authorize many EUA tests within 24 hours of completion of the data.

February 4 was the rollout of the CDC test to the public lab network, but there were problems that had stemmed from manufacturing. Hillebrenner said that the FDA continued to work with the CDC on contingency plans and the CDC ultimately chose a contract manufacturer. This helped ensure that there were enough kits by early March to deploy to nonpublic health labs, she said.

Development work was proceeding on the parallel track, but the scarcity of viral material was a huge challenge. It takes time to grow it up and to extract the RNA, aliquot it, and make it available to other developers, Hillebrenner pointed out. Labs could not validate their tests without sufficient material.

As time went on, some labs asked for more flexibility in the submission process. This coincided with the realization that the virus was spreading faster than in prior outbreaks in the US. Consequently, the FDA published a first-of-its kind policy on February 29 for the COVID-19 pandemic that gave more flexibility to labs. “We said, ‘Tell us that you’re about to start testing and go ahead and start,’” Hillebrenner said. Under this policy, follow-up with the EUA is required within three weeks.

Hillebrenner said that by late February, there were about 45 lab-developed tests (LDTs) being run and a handful of authorized tests, noting that this was not enough capacity to meet the country’s needs. Therefore, in the middle of March, the FDA updated the guidance to cover commercial manufacturers as well. Hillebrenner noted that the agency had received inquiries from states interested in overseeing LDTs within their jurisdictions and wrote that flexibility into this guidance.

SEROLOGY

Hillebrenner explained that as the pandemic unfolded, the FDA started to think more about antibodies and immunity. The agency felt the best way to get some answers was to make antibody tests more readily available. None were available with EUA at the time. The FDA wrote a policy that allowed any lab or commercial developer to introduce an antibody test without an EUA, provided they validated it, informed the agency, and included certain limitations. Because antibody tests can’t be used to diagnose or exclude infection, the risk is low, she said, adding that the agency saw the potential for these tests to be useful in an understanding of the effectiveness of therapeutics and vaccines.
Unfortunately, Hillebrenner noted, many across the country began to rely on serology tests for uses that were unsupported by the science and inconsistent with the limitations that the FDA had laid out. The tests were being used to diagnose infection or determine immunity and received public support as a way to open up the economy. The marketplace was flooded with serology tests, some of which did not work at all and some of which were simply used inappropriately.

Based on this misuse, the FDA issued a letter to healthcare providers explaining these tests. The agency also collaborated with US government partners, particularly the National Cancer Institute (NCI) and CDC, to develop a capacity to evaluate serology tests in-house at the National Cancer Institute Serology Lab. By late April, the FDA had authorized about a dozen serology tests under EUA. On May 4, the FDA updated the guidance again, requesting that commercial manufacturers of serology tests submit an EUA post-market just like the agency required for diagnostics. Within two weeks of introducing the test, the manufacturer is expected to bring in an EUA so that FDA can look at the science behind the test and the claims. The FDA then introduced an EUA template for serology tests.

**LESSONS LEARNED**

Hillebrenner highlighted some important lessons that the FDA has learned from the COVID-19 pandemic:

- **Limited availability of viral material slowed initial test development and validation.** There is a need for better global coordination on this.

- **The EUA development system is inefficient.** The FDA has issued more than 275 EUAs and there are “hundreds and hundreds” sitting in the queue, Hillebrenner said. She suggested that a more organized approach at the outset could have been more helpful, where the FDA would pick a handful of developers who already have platforms installed throughout the country, focusing on getting a few tests deployed in high volumes rather than reviewing a thousand different tests.

- **There is a need for a common framework from which all stakeholders are working up front.** Hillebrenner noted that 82 of the first 125 EUA submissions had issues with design and/or validation. It would be helpful, she said, if labs were already familiar with the FDA and how it approaches validation.

- **The FDA needs to include the clinical community into its communications processes,** making sure they are clear on what tests can and can't do.
The following roundtable discussion has been lightly edited for clarity and length.

Ed Winnick: To all of our panelists, what do you think has worked well with the EUA program and what would you like to see improved?

Danelle Miller: The FDA generally did a good job of balancing the need for quick access to in vitro diagnostics (IVDs) early in the pandemic while protecting the public health. I agree with the lessons that Elizabeth spelled out, and I would also like to see greater flexibility in the use of alternatives to clinical specimens, such as surrogate samples, in silico testing, et cetera.

Robert Boorstein: I think the FDA really has to be commended, especially for its rapid response and flexibility in recognizing when things weren’t working and changing directions. I work at a commercial lab and I think this society does need to rethink whether it was helpful to restrict commercial labs from entering the space until February 29 in view of the magnitude of what was needed. Clearly, commercial labs needed to be a major part of the solution. I would estimate that in March and April, 80 to 90 percent of all testing was done on installed commercial platforms, repurposed to run commercial COVID-19 test kits as soon as they were made available by the large companies.

The flexibility was helpful to us. We work closely with one of the large manufacturers of automated equipment, so we could be one of the first to go live with the tests once reagents were made available. We were able to provide a very high volume of service very quickly.

Gail Javitt: I do think that the decision to not exercise enforcement discretion for laboratories developing COVID tests was unfortunate. A crisis often exposes the underlying weaknesses in a system, and I think that’s what we saw with LDTs. There is a long-standing controversy, going back decades, about whether FDA has or should have authority over laboratories. A pandemic is no time to discover that there’s not a clear answer to that. We are blessed in this country with very strong laboratory infrastructure. There was a missed opportunity.

Based on the magnitude of this crisis, I completely agree with the suggestions about international collaboration, and I would add to that finding other entities to help review tests, including third parties.

Jeffrey Klausner: I’m the medical director for a large COVID-19 PCR testing laboratory. We started our EUA submission mid-March and received the final EUA mid-April. At that time, the FDA was very responsive and things went well. But around mid-April it seemed that the FDA had become overwhelmed and did not have the capacity to respond to the EUA amendments and changes. It became very difficult.

Ed Winnick: The FDA said recently that it will no longer review EUAs for the COVID LDTs. What effect will this have on firms and labs that had planned to seek an EUA for their LDT, and what is the intention and expected result for FDA in making this change?

Elizabeth Hillebrenner: Tests that are run at multiple sites, such as in a lab network, and tests that are run with home-collected specimens are not considered LDTs so there is no impact on them from this statement. The change is that labs offering true LDTs, those that are designed, manufactured, and run in a single lab, do not now need an EUA. This isn’t to say that we’re not
concerned with the performance of LDTs. But because the process for reviewing these tests for EUA is so lengthy, HHS has determined this is not feasible in addressing the current health need. In the meantime, we may not be able to remove a poorly performing LDT from the market or take other necessary steps to assure that these tests for COVID-19 are accurate, safe, and reliable. We are instead focusing our resources on the tests that increase access and capacity, can be done at the point of care or for home use, are high throughput and distributed, and reduce reliance on test supplies.

Jeffrey Klausner: Another negative from my perspective was the severe regulatory barriers limiting commercial laboratories and those that have experience with LDTs from running tests. We had been working in accordance with Clinical Lab Improvement Amendments (CLIA) for years and, all of a sudden, we’re not able to do that.

Gail Javitt: One significant issue for labs that cannot get an EUA is the impact in terms of potential liability. Under the Public Readiness and Emergency Preparedness (PREP) Act, you do get immunity if you have an FDA-authorized medical product, whether it’s a drug or a device or an LDT subject to EUA. Laboratories that don’t already have an EUA will not have the benefit of PREP Act protection going forward.

The other observation I have is one of messaging. Certainly, we understand FDA’s actions given HHS’s announcement. On the other hand, from the public’s perception, from state government’s perspective, you now have a two-tier system – the LDTs that have EUAs and LDTs that don’t, which does not say anything about the quality of the tests. It’s going to be important for purchasers and users to understand that the lack of an EUA doesn’t necessarily say something about the overall quality of the test.

Robert Boorstein: This FDA viewpoint has left a lot of people in limbo. For example, if a lab running 5,000 tests a day using an EUA now wants to modify their test to do, say, two or five times that, does that become an LDT and who would regulate that? Previously, we’ve worked with a number of labs that have gotten multiple revisions of their EUAs. If existing EUAs cannot be modified, that puts someone back into the LDT category.

The other issue is that users, insurers, and payers view FDA approval as a measure of quality. Before we got the EUA document, a number of our clients said they wanted to use other suppliers because they wanted the quality assurance.

In the past, LDTs have been regulated under CLIA by the states or through accreditation programs. New York has a very aggressive program of regulating LDTs, but now they had been deferring to the FDA and allowing the EUA process to substitute for that. I think if we have to go back to an LDT process that relies on the states or accreditation agencies such as the College of American Pathologists (CAP) for oversight, we will have challenges because they don’t have the resources to do this in a timely and systematic manner.

Ed Winnick: Earlier on in the pandemic, there were questions regarding the accuracy of some of the tests that were getting EUAs. I want to ask Elizabeth in particular, how can the FDA address more quickly the issue of inaccurate tests getting EUAs?

Elizabeth Hillebrenner: There is definitely a trade-off. When we start off with a bar of “may be effective,” we’re opening the door for this to happen. When we look at less data, we may not be able to detect all the issues up front. We make that tradeoff for accessibility. It’s applying a
risk/benefit calculation to the emergency situation. But that’s why the EUA is not everlasting. This is why we follow up with post-market monitoring and the conditions of authorization for the reference panel. In some cases, we’ve even revoked EUAs. We’ve changed our policies to address the issues that have arisen with inaccurate tests. So, we’re constantly reevaluating the benefits and risks of our policies, in some cases even our decisions.

Danelle Miller: As we look at how these tests are performing in the real world, what we’re realizing is that it’s hard to get performance information. Before we face another public health emergency, we need to build the infrastructure, giving these tests codes so that we can track the real-world performance.

Ed Winnick: Some companies have complained about the length of time it takes to receive an EUA after they have filed. Elizabeth, is there a way for the FDA to speed up this timeline?

Elizabeth Hillebrenner: We have an all-hands-on-deck approach. We pulled people back from retirement, from other parts of the agency that have the expertise, other parts of the center. People are working around the clock to try to address the tremendous volume. And when issues come up with validation, we take the time to work with developers and that can slow things down.

To address concerns about the backlog, we recently posted a frequently asked questions (FAQ) to provide transparency on our priorities. We want to make sure people understand that we are focusing on things that deliver increased accessibility and capacity. Developers can speed up their work by studying our templates up front.

Gail Javitt: We have clients who submitted in May and were still waiting for an answer six months later. Frequent follow-up and troubleshooting can help, but it’s very challenging to get movement in the process.

Ed Winnick: We’ve had several attendees ask how much longer the FDA plans to grant EUAs for COVID tests, and when 510(k) clearance will be required. Elizabeth, do you have thoughts on that?

Elizabeth Hillebrenner: We are going to continue to work through the EUA process for the foreseeable future, as long as the emergency is in effect. We are thinking about what a transition plan would look like. Some of the general principles that will guide us are transparency, advance notice, and a phased-in approach. We can’t have all 4,000 of these submissions come in as de novos and 510(k)s at once.

Ed Winnick: We’ve had several questions about the link between EUA status and reimbursement. Several were specific to EUAs no longer being available for LDTs.

Robert Boorstein: I don’t think the verdict is in here yet, and I think it’s going to be a real challenge. Historically, payers have looked to FDA clearance as a mark of quality. I think some of the larger laboratories are offering both LDT-type tests and historic EUA-type tests and can migrate customers back and forth between the two. Going forward, the FDA and Center for Medicare and Medicaid Services (CMS) are going to have to clarify what their view is on new LDTs in this space that would have been covered by EUA last year or last month.
Ed Winnick: Elizabeth, what is the FDA stance on granting EUAs for testing asymptomatic patients?

Elizabeth Hillebrenner: We’ve authorized a few. A big question is, “what is the bar?” Serial testing might be helpful in this area, to increase the hit rate.

Gail Javitt: I think it’s just important that we distinguish between the FDA’s role in authorizing certain indications and the clinical community’s role in deciding how to use tests in a way that they see best for their patients. As we all know, in the non-COVID context and even in the COVID context, an off-label use of a diagnostic or medicine is not a misuse. I just want to make that clarification.

Jeffrey Klausner: That’s an excellent point. Certainly, most hospitals around the United States are using these tests to screen patients, pre-procedure or pre-surgical activity. Many are screening pre-hospitalization. So that’s an asymptomatic population, and the clinical community has determined that the benefits of testing them might outweigh the risks.

Elizabeth Hillebrenner: We recommend the use of a high-sensitivity test in those cases, as outlined in the FAQ on our website.

Robert Boorstein: The demand to use tests off-label is not just coming from doctors and health organizations. The federal government and some state governments have thrown their weight behind buying large volumes of some of these tests with the clear, observable use for circumstances that were not part of the instructions for approved use.

Ed Winnick: With the increased frequency of epidemics and potential pandemics, will the EUA program develop further, and what kind of changes might be made moving forward for pathogen detection of infectious diseases?

Elizabeth Hillebrenner: The EUA provisions have worked effectively for many outbreaks. This one has been unusual, and we are continually reevaluating where we are and applying lessons learned as we go. We also will need to do a retrospective. There’s a lot of discussion about diagnostic reform, including subjects we’ve already discussed such as coordinating internationally to get access to specimens, and we support congressional efforts in that space.