COVID-19 Regulatory Guide for Serology Tests: Pursuing EUA While Paving the Way to 510(k)*

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SARS-CoV-2 antibody tests have been identified as playing a critical role in the fight against the COVID-19 pandemic by helping healthcare professionals identify individuals who have been exposed to and developed an immune response to SARS-CoV-2. Over the past few months, the urgency of bringing these serology tests to market has been balanced against the need to ensure the deployment of accurate tests. In recent weeks, we have seen the FDA issue warning letters to multiple companies for marketing adulterated and misbranded COVID-19 antibody tests. And we have even seen the agency revoke the Emergency Use Authorization (EUA) for one of the first antibody tests authorized due to performance concerns. As case counts continue to rise, there remains a need for safe, accurate serology tests that can be used both during this public health emergency and on an ongoing basis.

In this article, we explore the marketing pathways and regulatory requirements for SARS-CoV-2 antibody tests, as well as key considerations for transitioning from EUA to marketing authorization.

In Vitro Diagnostics Marketing Pathways

The FDA has updated its policy for commercial manufacturers of serological tests for SARS-CoV-2 antibodies, providing alternative marketing pathways. All 3 pathways require analytical validation, performance of a clinical agreement study, and appropriate labeling and disclaimers (see Figure 1). Of note, under revisions to the Policy Pathway, the FDA now requires all manufacturers of serology tests to

Figure 1. Current State of EUA Authorization Pathways for COVID-19 Serology Tests

Policy Pathway IVD Policy Revised May 11, 2020	EUA Pathway	Umbrella Pathway - Letter to Manufacturers and Stakeholders April 28, 2020

▪ Analytically validate
▪ Clinical agreement study
▪ Labeling disclaimer
  ▪ This test has not been reviewed by FDA
▪ Notify FDA and submit EUA in 10 days
▪ Limited to high complexity authorization
	▪ Analytically validate
	▪ Clinical agreement study
	▪ Labeling and disclaimers
	  – As an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection
	▪ Submit EUA and await FDA authorization
		▪ Analytically validate
		▪ Independent clinical agreement at NCI
		▪ Labeling and disclaimers
		  – As an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection
		▪ Submit EUA and await FDA authorization

To guide applicants through the process, the agency has posted EUA templates to its website.

*Current state as of June 2020

submit data for EUA. This submission can be done either before or after marketing of the first test, but must be completed within 10 days of marketing. For the Umbrella Pathway, one key difference is the submission of an independent clinical agreement study through the National Cancer Institute (NCI).

Analytical Validation Study Requirements

Regardless of the pathway to market, the assay must be analytically validated. Key studies required for the analytical validation of serology tests include:

- **Class specificity,** unless the assay detects total antibodies or does not distinguish between IgG and IgM. This study should evaluate the potential for human IgM to cross-react and produce false positive results in IgG and vice versa. It should also evaluate the potential for IgG to compete with IgM and produce false positive results.
- **Cross-reactivity or analytical specificity.** For this study, a minimum of 5 individual samples should be tested for various antibody interferants from other viruses (eg, influenza, hepatitis, rhinovirus, or other coronaviruses). It should be noted that the Umbrella Pathway does not specifically require these studies. Instead, if serology tests are validated using the NCI panel and 95% specificity is achieved, the need for additional cross-reactivity tests is waived.
- **Matrix equivalency (serum, plasma, fingerstick).** Serum and plasma can be studied analytically or as part of the clinical agreement study and should be performed using the same donor. Fingerstick validation studies, which could support the potential for home testing down the road, are best studied during the clinical agreement study unless stability of collection and transport of sufficient volume can be demonstrated.

Clinical Agreement Study Requirements

Whether a manufacturer is planning its own prospective study or leveraging the Umbrella Pathway for independent testing, marketing of the assay will require a clinical agreement study for 30 confirmed positive samples per antibody and 75 confirmed negative samples. As of June 30, 2020, EUA approval requires that results from various serology matrices be compared with results from an EUA-approved molecular test, preferably with samples collected at the same time. Performance requirements for tests including both IgG and IgM are provided below.

- Overall: 90% positive percent agreement
- Overall: 95% negative percent agreement
- IgM: 70% positive percent agreement
- IgG: 90% positive percent agreement
- No cross-reactivity to HIV

Other combinations of performance characteristics apply to total antibody tests or tests detecting only IgG or IgM.

As the FDA has seen some interference with HIV cross-reactivity, the agency is requiring that at least 10 of the negative samples come from HIV+ donors or that manufacturers demonstrate through cross-reactivity studies that HIV does not interfere.

For assays that are by design simple to use and easy to perform, clinical agreement studies should include demonstration that multiple operators can use the test using simple instructions. This will help pave the way for transitioning these tests to nonclinical environments. Serology tests are well suited for home collection and testing if validated using a sample type such as a fingerstick. In fact, the FDA has added study designs to the serology template for clinical agreement studies using fingerstick samples. As these tests move out of the laboratory, additional studies are required to support clinical agreement in point-of-care settings, such as additional flex studies. However, in order to achieve claims for home use, user studies outside the scope of the FDA's current templates would need to be performed.

Transitioning an EUA to a 510(k)

Many manufacturers may be planning a transition to 510(k) following EUA. When preparing for the transition, there are number of factors to consider.

1. **Timing.** It is important to balance the risk of being first to market under EUA and thereby subject to policy changes or additional data requirements to support a future marketing claim with the benefit of setting the standard for requirements for other manufacturers to follow. Using Zika virus as a model, Figure 2 shows a real-life example where Company A entered the EUA market early with limited data requirements and Company B took an additional year to enter the EUA market. Due to the absence of a regulation for Zika, Company A had to submit a de novo submission which required extensive additional analytical and clinical sample testing. By waiting an additional year, Company B was able to leverage testing performed to support its EUA and demonstrate substantial equivalence to Company A as a predicate using a simpler 510(k) submission. Indeed, in the end, Company B received clearance not long after Company A.

Figure 2. Lessons Learned From the Zika Model

Company A	Company B
EUA: Minimal performance testing – authorized late 2016	**EUA**: More extensive performance testing – authorized late 2017
De Novo: Extensive additional testing, clinical performance against composite of laboratory assays – classification order mid-2019	**510(k)**: Supplemental performance testing, clinical performance to composite of PCR and Company A as a predicate – clearance mid-2019

2. **Design of analytical studies.** When preparing for an EUA to 510(k) transition, it is also important to consider both the design of analytical studies and the type of samples used for testing. For example, the FDA typically requests the use of natural specimens for analytical testing, but the EUA may be more flexible in allowing the use of natural or spiked specimens. With proper planning and access to critical biospecimens, analytical studies can be designed to achieve current state (EUA) while considering future state (marketing authorization), minimizing cost and time to market when transitioning.
3. **Communication with the FDA.** Early communication with the agency through the presubmission process can potentially accelerate guidance to support clearance for serology devices over the coming year. Moreover, staying on top of the EUA policies, templates, and methods for authorization as they evolve will be critical to success.

For manufacturers who are planning a future submission to the FDA for marketing authorization, it may be a good idea to test as many natural specimens as possible now—these can be leveraged to support de novo or 510(k) submission.

As of June 26, 2020, there are 23 tests on the FDA's list of EUA Authorized Serology Tests. There are a lot of players in the market, and planning for the transition from EUA to 510(k) cannot be done soon enough. It may be less important to get in line with your EUA if it means sacrificing study quality. Rather, well-designed and well-executed studies for EUA can potentially be leveraged for a 510(k) submission to FDA later, saving time and money in the long-term. Although exempted under EUA, developing your EUA device under design controls now can save time later when moving the product through its life cycle and into commercial manufacture and distribution. Thinking strategically around EUA vs 510(k) and mapping out how to leverage EUA studies for future submissions, as well as what additional studies may be required such as flex studies for waiver or user studies for home collection and testing, will be critical to success in this important but crowded market space.