A Test of the Emergency (Use Authorization) System: Challenges in FDA Regulation of COVID-19 Diagnostics

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> "If we fail to learn from this global tragedy, we will have betrayed our nature as the animal-that-learns. We will have left this global disaster unredeemed, and we will be unprepared for the next."[1]

ABSTRACT

Addressing the COVID-19 pandemic has created many challenges for the Food and Drug Administration (FDA). One of the largest challenges in coping with COVID-19 has stemmed from the ongoing need for access to accurate diagnostic tests for the virus. FDA has well-established programs for reviewing in vitro diagnostic (IVD) tests. The agency also has had experience with accelerating the introduction of new IVDs in response to a public health emergency by granting Emergency Use Authorizations. However, no other new virus has overwhelmed FDA's resources and decision-making capacity the way the novel coronavirus has. This Article examines FDA's evolving approach to regulation of COVID-19 tests since the beginning of the pandemic, assesses the impact of FDA policies on IVD manufacturers and clinical laboratories and on the quality and availability of tests, and recommends areas for improvement. There is an urgent need for prompt FDA examination of its role in overseeing COVID-19 tests so the agency can evaluate what has gone well—and much has—and what can be improved. FDA should learn from COVID-19 how to regulate the new diagnostic tests needed for the next pandemic.

I. INTRODUCTION

From the start of the COVID-19 pandemic, access to accurate and reliable testing for SARS-CoV-2 was identified as a critical element of an effective public health response. On January 31, 2020, the Secretary of the Department of Health and Human Services (HHS) declared a Public Health Emergency.[2]

Although the Food and Drug Administration (FDA) was not mentioned in that announcement or the accompanying press release, it was clear from the outset that testing was urgently needed to diagnose individuals with active symptoms, to identify

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1 JONATHAN SACKS, MORALITY: RESTORING THE COMMON GOOD IN DIVIDED TIMES 323 (2020).

2 News Release, U.S. Dep't of Health & Hum. Servs., Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus (Jan. 31, 2020), http://web.archive.org/web/20210101172922/https://www.hhs.gov/about/news/2020/01/31/secretary-azar-declares-public-health-emergency-us-2019-novel-coronavirus.html [https://perma.cc/8VKF-JVVF].

(through contact tracing) and quarantine potentially exposed individuals, and to detect antibodies in individuals' blood as an indicator of current or previous infection.[3] As the pandemic extended into fall 2020, the need for testing became critical to schools and universities seeking to safely resume in-person instruction and to employers seeking a way for their employees to return to the workplace safely, as well as to public health officials trying to assess, manage, and control the pandemic. The advent of vaccines in early 2021 has not diminished the need for diagnostic testing, especially as new variants, such as omicron, emerge.[4] Vaccination also created a new, non-diagnostic, role for antibody tests, both to demonstrate proof of vaccination (i.e., "vaccine passports")[5] and to monitor antibody levels over time.[6] Although FDA initially warned against the use of antibody tests to evaluate immunity,[7] the agency (as this Article was going to press) reversed course and announced that serology tests for the quantitative measurement of antibody titers and for the quantitative detection of neutralizing antibodies would be prioritized for review.[8]

FDA has wielded enormous control over COVID-19 diagnostics from the earliest days of the outbreak and has faced enormous challenges throughout the pandemic in regulating these new diagnostics. To be sure, FDA already had significant infrastructure, in the form of well-established programs for reviewing in vitro

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[3] *See, e.g.*, Elizabeth Hillebrenner, *Remarks at FDA Virtual Town Hall Series* (Mar. 25, 2020), https://www.fda.gov/media/136518/download [https://perma.cc/93ZE-ET2A] (explaining that FDA's initial efforts were meant "to achieve more rapid testing capacity").

[4] Daniel P. Oran & Eric J. Topol, *Beyond 'Vaccinopia': Rapid Tests Should Play a Role in Biden's Covid-19 Plan*, STAT (Sept. 16, 2021), https://www.statnews.com/2021/09/16/beyond-vaccinopia-larger-role-rapid-tests-fighting-covid/?campaign_id=9&emc=edit_nn_20210921&instance_id=40916&nl=the-morning&regi_id=119565717&segment_id=69476&te=1&user_id=50f9477848de62f4b78d2ee3e1f12167 [https://perma.cc/EU9K-ZC8H]; Lori Aratani, *U.S. Airports Will Aid Effort to Monitor Omicron Variant*, WASH. POST (Dec. 1, 2021, 7:24 PM), https://www.washingtonpost.com/transportation/2021/12/01/us-airports-omicron-variant/ [https://perma.cc/3Y48-E72H]; Michael D. Shear, Sheryl Gay Stolberg, John Yoon, Aina J. Khan & Raphael Minder, *Covid News: U.S. to Tighten Testing for Travelers Amid Omicron Worries*, N.Y. TIMES (Updated Dec. 3, 2021, 5:08 AM), https://www.nytimes.com/live/2021/11/30/world/omicron-variant-covid [https://perma.cc/T4YX-M2PV].

[5] *See, e.g.*, John Torres, *'Vaccine passports': Will They be Available in the U.S. in Time for Summer?*, NBC NEWS (Mar. 14, 2021), https://www.nbcnews.com/health/health-news/vaccine-passports-will-they-be-available-u-s-time-summer-n1261022 [https://perma.cc/26N6-YD7U]; *see also* Cat Ferguson & Joshua Mitnick, *Israel's "Green Pass" Is an Early Vision of How We Leave Lockdown*, MIT TECH. REV. (Mar. 1, 2021), https://www.technologyreview.com/2021/03/01/1020154/israels-green-pass-is-an-early-vision-of-how-we-leave-lockdown/ [https://perma.cc/3SBG-SCFK]. The use of "vaccine passports" has been controversial, as illustrated by Florida legislation seeking to ban them. *See Governor Ron DeSantis Signs Landmark Legislation to Ban Vaccine Passports and Stem Government Overreach*, GOVERNOR RON DESANTIS (May 3, 2021), https://www.flgov.com/2021/05/03/governor-ron-desantis-signs-landmark-legislation-to-ban-vaccine-passports-and-stem-government-overreach/ [https://perma.cc/CM73-ECCY].

[6] *See, e.g.*, David S. Khoury, Deborah Cromer, Arnold Reynaldi, Timothy E. Schlub, Adam K. Wheatley, Jennifer A. Juno, Kanta Subbarao, Stephen J. Kent, James A. Triccas & Miles P. Davenport, *Neutralizing Antibody Levels are Highly Predictive of Immune Protection from Symptomatic SARS-CoV-2 Infection*, 27 NAT. MED. 1205, 1205 (May 17, 2021) (online ahead of print).

[7] *FDA Safety Communication Antibody Testing Is Not Currently Recommended to Assess Immunity After COVID-19 Vaccination*, U.S. FOOD & DRUG ADMIN. (May 19, 2021), https://www.fda.gov/medical-devices/safety-communications/antibody-testing-not-currently-recommended-assess-immunity-after-covid-19-vaccination-fda-safety [https://perma.cc/V8F9-HH2M].

[8] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR DEVELOPERS AND FDA STAFF, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED) 8 (Nov. 15, 2021), https://www.fda.gov/media/135659/download [https://perma.cc/P353-UK9A] [hereinafter NOVEMBER 15 GUIDANCE].

diagnostic (IVD) tests during routine times, as well as prior experience accelerating the introduction of new IVDs in response to the emergence of new, life-threatening pathogens (e.g., the Zika Virus, the Ebola Virus, and H1N1).[9] FDA had exercised its Emergency Use Authority for IVDs well before COVID-19 arrived.[10]

However, no previous virus or prior public health emergency so severely challenged, and at times overwhelmed, FDA's resources or its ability to manage its workload. FDA's regulatory approach to COVID-19 testing has brought many successes, including the granting of numerous Emergency Use Authorizations (EUAs).[11] FDA has also devoted significant resources to providing information to companies seeking to offer tests, including issuing multiple guidance documents and Frequently Asked Questions (FAQs), holding more than seventy Town Hall meetings[12] to discuss policy and answer questions from test developers, and responding to tens of thousands of queries. As of the date of this writing, FDA has, for example, issued more than 427 EUAs for IVDs, including 270 molecular diagnostic (e.g., PCR) tests, 90 serology tests, 40 antigen tests, and 27 laboratory developed tests (LDTs).[13]

At the same time, FDA's handling of COVID-19 testing has at times prompted controversy and criticism. Some of this criticism arises from FDA's specific policy choices that critics asserted were not in the best interest of public health, such as requiring clinical laboratories to obtain EUAs for their LDTs.[14] Another basis for criticism relates to FDA's *manner* of engaging with regulated industry. FDA has been criticized for inadequate transparency and the failure to listen to, or communicate clearly and consistently with, regulated industry and, in particular, with applicants seeking EUAs for their tests.[15] Based on our experiences, the gaps in FDA transparency, clarity, and consistency have sometimes had a negative impact on companies' ability to market their tests; some potentially useful assays were excluded from the market or were never reviewed by FDA.

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[9] *See, e.g.*, Chris A. Whitehouse, Sina Bavari & Mark D. Perkins, *United States FDA's Emergency Use Authorization of Ebola Virus Diagnostics: Current Impact and Lessons for the Future*, 15 EXP. REV. MOL. DIAGN. 1231, 1231 (2015); Elitza S. Theel & D. Jane Hata, *Diagnostic Testing for Zika Virus: A Postoutbreak Update*, 56 J. CLINICAL MICROBIOLOGY 1, 1 (2018).

[10] *Id.*

[11] *See* Nina El-Badry, *Emergency Use Authorization for IVD Products*, *in* DIAGNOSTICS AT A CROSSROADS: NAVIGATING IVD REGULATION IN A CHANGING ENVIRONMENT 245, 250–52 (Jeff Gibbs & Allyson Mullen eds., 2020) (providing an overview of the EUA process).

[12] FDA has held these meetings weekly since March 25, 2020. *See Virtual Town Hall Series – Coronavirus (COVID-19) Test Development and Validation*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-town-hall-series-coronavirus-covid-19-test-development-and-validation-06092021-06092021 (last updated Nov. 11, 2021) [https://perma.cc/8VYY-8ST4].

[13] *See In Vitro Diagnostics EUAs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas (last updated Nov. 15, 2021) [https://perma.cc/9VN6-BGRG] (providing tables of individual EUAs for molecular, serology, and antigen tests).

[14] *See* AMANDA K. SARATA, CONG. RSCH. SERV., HHS ANNOUNCEMENT ON FDA PREMARKET REVIEW OF LABORATORY-DEVELOPED TESTS (LDTS) (Dec. 3, 2020), https://crsreports.congress.gov/product/pdf/IN/IN11548#:~:text=On%20August%2019%2C%202020%2C%20the,FDA%20premarket%20review%20of%20LDTs [https://perma.cc/2USJ-5VBT] (detailing HHS's announcement that FDA "may not require premarket review," including EUAs, for LDTs).

[15] *See infra* notes 26, 28, 31, 33–36, 49, 135, 182.

The goal of this Symposium Article is to provide an account of FDA's handling of COVID-19 test oversight—one that incorporates our perspectives as practitioners who worked with scores of laboratories, diagnostics companies, and potential end users of their products and services (e.g., universities) as they attempted to navigate and understand the EUA process—and to provide recommendations for improvements. This vantage point has given us, we believe, valuable real-world insights into the challenges faced by the agency, regulated industry, and other stakeholders, and the consequences of certain regulatory decisions. While we have provided sources to document our assertions where possible, much of what we are reporting in this Article was gained during the course of representing clients, and therefore the details cannot be disclosed. Nevertheless, we hope that these insights will provide useful perspectives to policy makers and other interested parties. We further hope that FDA will thoroughly examine what went well—and there are many such areas—and what aspects could be strengthened. As part of this searching scrutiny, FDA should solicit feedback from industry and other stakeholders—potentially including review by an independent organization—in order to identify areas that can be improved.

Nobody knows what the next major outbreak will be or when it will occur. However, nobody should have been surprised that this one occurred.[16] And nobody should be surprised when another one does occur, or if it is more dangerous or more transmissible than COVID-19.[17] Ultimately, FDA needs to learn from its experience with COVID-19 to be better prepared to regulate the new diagnostic tests that will be needed for the next pandemic.

Two major caveats are in order with respect to this Symposium Article. The first is that the Article is not attempting to cover all of the different IVD-related issues that have arisen during this pandemic. That would be far too broad a goal. Rather, we focus on what we view as some significant events and provide certain illustrative case studies. We have categorized these case studies into two categories: those that reflect FDA policy choices and those that provide insight into the myriad challenges faced by manufacturers and others involved in producing SARS-CoV-2 tests in navigating the EUA process.

The second caveat is that this Article cannot be current. Events are happening rapidly, and there will certainly be important new developments between the completion of this Article and its publication, and yet more developments after publication. We do not know what surprising new developments will occur next. We do know, though, that just as the virus evolves, the issues relating to regulation of COVID assays will also continue to evolve.

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[16] For example, an article written in 1992 warned about the risks of zoonotic outbreaks originating in Southeast Asia, noting "such pandemics can still sweep around the globe in a single winter season and remain a very real threat." Christoph Scholtissek, *Cultivating a Killer Virus*, 1 NAT. HIST. 2, 2 (1992); *see also* FRANK M. SNOWDEN, EPIDEMICS AND SOCIETY: FROM THE BLACK DEATH TO THE PRESENT 457 (2019) (quoting Nobel Prize winner Joshua Lederberg as stating that "[w] can also be confident that new diseases will emerge, although it is impossible to predict their individual emergence in time and place").

[17] Miriam Berger, *Covid-19 'Not Necessarily the Big One,' WHO Warns*, WASH. POST (Dec. 29, 2020), https://www.washingtonpost.com/world/2020/12/29/coronavirus-2020-the-big-one-who-pandemics [https://perma.cc/JG5M-ZKPX].

II. POLICY CHOICES AND THEIR RAMIFICATIONS: THE LAW OF UNINTENDED CONSEQUENCES

It is a truism that policy choices made by government frequently have unintended consequences.[18] As an agency responsible for ensuring the safety and effectiveness of medical products, FDA routinely makes decisions that have far-reaching public health impact.[19] COVID-19 brought to FDA's doorstep a whole new set of decisions about a wide range of drugs and devices which implicated profound public policy questions. And because of the speed and size of the pandemic, the agency was often forced into a reactive mode.

There were some key differences between FDA's approach to COVID and its usual modus operandi. The first relates to the standards that FDA enforces under the Federal Food, Drug, and Cosmetic Act (FDCA). Under "normal" circumstances, FDA reviews a submission for a new medical device to determine whether the manufacturer has provided "reasonable assurance" of the product's safety and effectiveness.[20] However, in the context of reviewing EUA requests, Congress directed FDA to apply a lower standard, namely, that the medical countermeasure "may be effective" for its intended use and that the "known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product."[21] In making this benefit-risk determination, Congress directed FDA to "take[] into consideration the material threat posed by" the infectious or other agent the Secretary identifies in the declaration of emergency.[22] This assessment should consider the totality of the evidence.[23]

The second difference is that FDA policy decisions are typically made with input from stakeholders, through the process of notice and comment rulemaking,[24] issuance

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[18] *See, e.g.*, Kathryn Oliver, Theo Lorenc, Jane Tinkler & Chris Bonell, *Understanding the Unintended Consequences of Public Health Policies: The Views of Policymakers and Evaluators*, 19 BMC PUB. HEALTH 1057, 1057 (2019).

[19] *See, e.g.*, *FDA's Decision Regarding Plan B: Questions and Answers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-decision-regarding-plan-b-questions-and-answers (last updated Dec. 7, 2015) [https://perma.cc/T7U2-38WC]; Charlie Savage, *Justice Dept. Stops F.D.A. From Regulating Death-Penalty Drugs*, N.Y. TIMES (May 14, 2019), https://www.nytimes.com/2019/05/14/us/politics/justice-dept-fda-death-penalty-drugs.html [https://perma.cc/6GGY-HHB8].

[20] A medical device subject to a 510(k) must demonstrate "substantial equivalence" to a "predicate device." However, this does not obviate the need to establish the device's safety and effectiveness; rather, the demonstration of substantial equivalence serves as an abbreviated pathway for demonstrating that the device is safe and effective. Establishing safety and effectiveness are embedded into the 510(k) review process. *See* Jeffrey K. Shapiro, *Substantial Equivalence Premarket Review: The Right Approach for Most Medical Devices*, 69 FOOD & DRUG L.J. 365 (2014).

[21] FDCA, 21 U.S.C. § 564.

[22] *Id.* at § 564(c)(2)(B).

[23] News Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes Drug for Treatment of COVID-19 (June 24, 2021), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19 [https://perma.cc/NRM9-A2XL].

[24] *See FDA Rules and Regulations*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/regulatory-information/fda-rules-and-regulations (last updated June 1, 2020) [https://perma.cc/5KFP-T7CV].

of draft and final guidance documents,[25] the convening of advisory committees, and other public forums convened by the agency. For example, FDA's Good Guidance Practices, which generally require that FDA issue guidance documents in draft form and solicit comments, was issued in response to concerns that FDA was adopting new policies through guidance without any input from stakeholders.[26] In contrast, FDA made multiple decisions regarding COVID tests, such as which SARS-CoV-2 tests would require an EUA, what standards would apply, and which types of tests to prioritize, without prior notice or the opportunity for meaningful public engagement.

Clearly, the pandemic dictates a more rapid pace of decision-making that is not amenable to lengthy comment periods on proposed rules or guidances or extensive review of such comments prior to implementation. As FDA explained, "In light of the need to act quickly and efficiently to respond to the COVID-19 public health emergency, FDA anticipates that prior public participation will not be feasible or appropriate before FDA implements COVID-19-related guidance documents."[27] But, by making regulatory decisions based solely on the agency's own internal perspective, without seeking comments on an expedited basis or strongly encouraging and then incorporating immediate feedback after issuance, FDA deprived stakeholders of insight into FDA's thinking,[28] and FDA missed the opportunity to obtain alternative, outside viewpoints that could have informed the agency's decision-making.

The case studies below provide examples of FDA decisions that had significant impact on the quality and availability of, and the public's access to, SARS-CoV-2 tests. Each of these decisions had consequences—some of which were unintended—for the response to the COVID pandemic.

A. Laboratory Developed Tests: No Enforcement Discretion

There are a number of reasons that SARS-CoV-2 testing was slow to begin and failed to keep up with the needs of the healthcare system.[29] Among them were decisions FDA made in the first weeks of the pandemic. Given the novel nature of SARS-CoV-2, no IVD test kits or LDTs existed in the United States when HHS declared a public health emergency on February 4, 2020. That same day, FDA issued an EUA to the Centers for Disease Control and Prevention (CDC) for the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)-PCR

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[25] 21 C.F.R. § 10.115.

[26] *See Fact Sheet: FDA Good Guidance Practices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/transparency-initiative/fact-sheet-fda-good-guidance-practices (last updated Dec. 4, 2017) [https://perma.cc/B7XE-8XLQ].

[27] Process for Making Available Guidance Documents Related to Coronavirus Disease 2019, 85 Fed. Reg. 16,949, 16,949 (Mar. 25, 2020).

[28] FDA's COVID documents typically stated what was required but not the rationale for the requirement. *See, e.g.*, *In Vitro Diagnostics EUAs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas (last updated May 24, 2021) [https://perma.cc/E9FV-U2SP] (providing instructions for composing EUA submissions without rationales for the requirements). Thus, the documents focused on the "what," but not the "why."

[29] Sheri Fink & Mike Baker, *'It's Just Everywhere Already': How Delays in Testing Set Back the U.S. Coronavirus Response*, N.Y. TIMES (Mar. 16, 2021), https://www.nytimes.com/2020/03/10/us/coronavirus-testing-delays.html [https://perma.cc/5Z7E-SZLM].

Diagnostic Panel.[30] The plan was for the CDC to ship the testing materials to CDC-qualified public health laboratories around the country so that they could perform the CDC assay.[31] However, some laboratories quickly discovered that one of the negative controls provided by the CDC was faulty and produced an erroneous positive result so that laboratories could not internally validate test performance.[32] Although the CDC ultimately modified the protocol,[33] its initial misstep led to a delay in tests being available.[34]

Although the U.S. laboratory community offered to step in and develop SARS-CoV-2 assays, FDA initially rebuffed these overtures.[35] On February 24, 2020, the Association of Public Health Laboratories (APHL) submitted a request asking FDA to exercise "enforcement discretion" with respect to LDTs for SARS-CoV-2 by public health laboratories,[36] a request that the American Association of Clinical Chemistry supported.[37]

This exercise of enforcement discretion would have enabled public health laboratories around the country to develop their own assays, rather than being

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[30] Letter from RADM Denise M. Hinton, Chief Scientist, U.S. Food & Drug Admin. to Robert R. Redfield, Director, Centers for Disease Control & Prevention (Dec. 1, 2020), https://www.fda.gov/media/134919/download [https://perma.cc/R2W2-XHM6].

[31] *FDA Declines APHL Request to Make Own SARS-CoV-2 Test Kits*, 360DX (Feb. 27, 2020), https://www.360dx.com/regulatory-news-fda-approvals/fda-declines-aphl-request-make-own-sars-cov-2-test-kits#.X_YiedhKjIU [https://perma.cc/P3Y6-4Z2K].

[32] *Diagnostic Testing*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/lab/testing.html (last updated Aug. 5, 2020) [https://perma.cc/YA62-89ZY].

[33] *See Diagnostic Tests for COVID-19,* CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/lab/testing.html (last updated Aug. 5, 2020) [https://perma.cc/VD2S-3TKT]; Letter from UWE Scherf, Director, Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Office of Product Evaluation and Quality, Center for Devices and Radiological Health, U.S. Food & Drug Admin. to Wendi Kuhnert-Tallman, EOC Laboratory Task Force Lead, CDC Covid-19 Response, CDC (June 12, 2020), https://www.fda.gov/media/138931/download [https://perma.cc/LTX4-PUEU].

[34] Carlos Lozada, *Why America Failed to Control the Pandemic*, WASH. POST (June 4, 2021), https://www.washingtonpost.com/outlook/2021/06/04/plague-year/ [https://perma.cc/EC8S-7UU5] (quoting LAWRENCE WRIGHT, THE PLAGUE YEAR: AMERICAN IN THE TIME OF COVID (2021)) (This was "perhaps the lowest point the history of a very proud institution."); Shawn M. Schmitt, *Senator: CDC Wasted Time Early in Pandemic By Insisting On Being Sole COVID-19 Test Developer*, MEDTECH INSIGHT (Oct. 1, 2021), https://medtech.pharmaintelligence.informa.com/MT144529/Senator-CDC-Wasted-Time-Early-In-Pandemic-By-Insisting-On-Being-Sole-COVID-19-Test-Developer [https://perma.cc/S3H7-DRDN];William Wan, *America is Finally About to Get a Lot More Coronavirus Tests. The Question Now: How Best to Use Them?*, WASH. POST (Dec. 18, 2020), https://www.washingtonpost.com/health/2020/12/18/coronavirus-tests-plans/ [https://perma.cc/VCJ9-5C7F] (describing problems with testing the "original sin" in the U.S. response).

[35] *See* Madeleine Johnson, *Lab Directors Discuss Unprecedented Challenges and Scrambling for Solutions During COVID-19 Pandemic*, GENOMEWEB (Nov. 18, 2020), https://www.genomeweb.com/clinical-lab-management/lab-directors-discuss-unprecedented-challenges-and-scrambling-solutions#.X9fGGNhKg2w [https://perma.cc/S4V5-ACJU].

[36] Adam Bonislawski, *APHL Asks FDA to Make Own Tests as CDC Struggles to Provide SARS-CoV-2 Test Kits*, 360DX (Feb. 25, 2020), https://www.360dx.com/clinical-lab-management/aphl-asks-fda-make-own-tests-cdc-struggles-provide-sars-cov-2-test-kits#.X_Yjm9hKjIU [https://perma.cc/B6ND-JVQ8].

[37] Letter from Carmen L. Wiley, President of the Am. Ass'n for Clinical Chemistry, to Stephen M. Hahn, Commissioner, U.S. Food & Drug Admin. (Feb. 28, 2020), https://www.aacc.org/-/media/files/health-and-science-policy/legislative-issues/2020/fda,-d-,coronavirus,-d-,final.pdf [https://perma.cc/J3Z7-WLC].

dependent on the CDC's test. Nevertheless, FDA declined the APHL's request, stating that all LDTs for SARS-CoV-2 would be required to undergo the agency's EUA process.[38] Many commercial and academic laboratories with the expertise to develop COVID-19 tests were also deterred from initiating development of new assays because of uncertainty about whether FDA would exercise enforcement discretion and, subsequently, the daunting prospect of obtaining an EUA.[39]

FDA's decision to not exercise enforcement discretion had a similarly chilling effect on researchers working to understand the spread of COVID in communities that were hit hard by the pandemic early on. In May 2020, FDA halted a clinical study being conducted by the Seattle Coronavirus Assessment Network (SCAN), a testing initiative backed by Bill Gates and approved by the state health department, to conduct laboratory testing on home-collected specimens.[40] FDA raised concerns about the risks of home-based specimen collection and asserted that the study could not continue without an EUA (a request had been submitted to FDA several weeks prior to FDA's order to stop testing). According to reports, the program had already conducted about 8,500 COVID tests and had identified dozens of cases, including in asymptomatic individuals, that previously had been undiagnosed.[41]

FDA halted the SCAN study, and rejected APHL's request, despite the fact that the agency itself had not yet provided any public guidance to clinical laboratories (or the IVD industry more broadly) as to the process for obtaining an EUA for a SARS-CoV-2 diagnostic test[42]—essentially placing clinical laboratories in a "holding pattern" until FDA gave them direction.

On February 29, 2020, FDA issued its first guidance document addressing the EUA process for COVID-19 tests.[43] With respect to LDTs, the guidance stated that

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[38] *FDA Declines APHL Request to Make Own SARS-CoV-2 Test Kits*, 360DX (Feb. 27, 2020), https://www.360dx.com/regulatory-news-fda-approvals/fda-declines-aphl-request-make-own-sars-cov-2-test-kits#.YL0suPlKiUk [https://perma.cc/Q8GN-WXZC].

[39] Ronald Bailey, *How Government Red Tape Stymied Testing and Made the Coronavirus Epidemic Worse*, REASON (Mar. 11, 2020), https://reason.com/2020/03/11/how-government-red-tape-stymied-testing-and-made-the-coronavirus-epidemic-worse/?itm_source=parsely-api [https://perma.cc/TEJ3-TSDE].

[40] Erin Brodwin, *Experts Decry FDA's Halting of a High-Profile Covid-19 Study Over Approvals*, STAT (May 27, 2020), https://www.statnews.com/2020/05/27/coronavirus-testing-seattle-bill-gates-fda/ [https://perma.cc/YKV9-Z9BQ].

[41] Sandi Doughton, *Coronavirus Surveillance Program in King County Put on Hold Because of FDA Concerns*, SEATTLE TIMES (May 13, 2020), https://www.seattletimes.com/seattle-news/health/coronavirus-surveillance-program-in-king-county-put-on-hold-due-to-fda-concerns/ [https://perma.cc/WDZ7-XGJP].

[42] Although FDA had issued a general guidance outlining the EUA process in 2017, the guidance did not address specific requirements for IVD EUAs, and therefore did not provide developers of SARS-CoV-2 tests sufficient information regarding the data requirements to support an EUA. *See* U.S. FOOD & DRUG ADMIN. GUIDANCE FOR INDUSTRY, EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES (Jan. 2017), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities [https://perma.cc/JX7H-9ZRJ].

[43] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POLICY FOR DIAGNOSTICS TESTING IN LABORATORIES CERTIFIED TO PERFORM HIGH COMPLEXITY TESTING UNDER CLIA PRIOR TO EMERGENCY USE AUTHORIZATION FOR CORONAVIRUS DISEASE-2019 DURING THE PUBLIC HEALTH EMERGENCY (Feb. 29, 2020), https://www.fda.gov/media/135659/download [https://perma.cc/5APW-WCGJ]. This guidance document was superseded by a guidance document issued May 4, 2020, which in turn was superseded by a guidance issued May 11, 2020. *See also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH

commercial, academic, or government laboratories that had obtained certification for high-complexity tests under the Clinical Laboratory Improvement Amendments (CLIA)[44] could develop and begin using validated COVID-19 tests before FDA completed its review of the EUA.[45] The guidance directed laboratories to notify the agency via email when they began testing and to submit a completed EUA within two weeks of such notification.[46]

The guidance document was helpful in that it provided a pathway for the development of novel COVID-19 LDTs and allowed testing to be offered in parallel with FDA review. FDA granted the first EUA for an LDT developed by a commercial laboratory on March 16, 2020,[47] with many others following in succeeding weeks and months.

FDA subsequently expanded and modified the guidance document on March 16, 2020[48] by creating an alternate pathway for LDTs under which states could elect to take responsibility for ensuring the accuracy of SARS-CoV-2 assays developed by laboratories within their jurisdiction. Only nine states and territories chose to do so.[49] Why more states did not pursue this option is unclear; the relevant state health agencies perhaps determined they did not have the necessary expertise or resources, or that they were uncertain regarding the interplay between FDA's general EUA authority and the role that states would play under this guidance.

FDA's decision to require EUAs for LDTs was not mandated by law. FDA has long asserted jurisdiction to regulate LDTs under the medical device provisions of the

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EMERGENCY (REVISED) (May 11, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised [https://perma.cc/CS2P-GKOL].

[44] 42 C.F.R. § 263a; *see generally* Serra J. Schlanger, *CLIA and State Laboratory Licensure*, *in* DIAGNOSTICS AT A CROSSROADS: NAVIGATING IVD REGULATION IN A CHANGING ENVIRONMENT (Jeff Gibbs & Allyson Mullen eds., 2020).

[45] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED) 8–15 (May 11, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised [https://perma.cc/M22J-K2Q7].

[46] *Id.*

[47] Letter from Denise M. Hinton, Chief Scientist, U.S. Food & Drug Admin., to Brian Krueger, Assoc. Vice President, Research and Dev., Lab'y Corp. of Am., EUA for COVID-19 RT-PCR Test (Dec. 9, 2020), https://www.fda.gov/media/136148/download [https://perma.cc/R33M-XHZK].

[48] Press Release, Stephen M. Hahn, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Provides More Regulatory Relief During Outbreak, Continues to Help Expedite Availability of Diagnostics (Mar. 16, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-more-regulatory-relief-during-outbreak-continues-help [https://perma.cc/3RNW-4N33].

[49] These are: Puerto Rico Department of Health; State of Colorado; State of Connecticut; State of Maryland; State of Mississippi; State of Nevada; State of New Jersey; State of New York Department of Health Wadsworth Center; and Washington State Department of Health. *See FAQs on Testing for SARS-CoV-2, What States or Territories Have Chosen to Authorize Laboratories Within that State or Territory to Develop and Perform a Test for COVID-19 Under the Policy Outlined in Section IV.B of the Policy for Coronavirus Disease-2019 Tests?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2 (last updated Mar. 25, 2021) [https://perma.cc/XW5P-QWXE]. Given subsequent developments described below, there will not be additional states taking on this task.

FDCA, but this position has been controversial.[50] In practice, for decades the agency has exercised enforcement discretion (meaning has not regulated) most LDTs.[51]

Moreover, legal scholars have questioned whether Section 564 of the FDCA—which specifies the scope of FDA's EUA powers—even *permits* FDA to require EUAs for LDTs.[52] Their argument is that while Section 564 allows FDA to grant EUAs for medical "products," defined as drugs, devices, and biological products, the statutory language "grants no new powers for the FDA to regulate clinical laboratory *services*."[53] The only mention of clinical laboratories under Section 564 occurs in the context of FDA's authority to categorize the complexity of a "laboratory examination or procedure associated with such device."[54] By drawing a distinction between "laboratory examinations or procedures" that are not subject to Section 564 and "products," which are subject to Section 564, the statutory language makes FDA's assertion of jurisdiction to require EUAs for clinical laboratory tests suspect.

Even if FDA has authority to require EUAs for COVID-19 LDTs, the agency could have, through the exercise of enforcement discretion, chosen not to prevent labs from running samples for SARS-CoV-2 using their LDTs. Indeed, enforcement discretion has been FDA's approach generally with LDTs.[55] Nevertheless, FDA chose to take the more restrictive approach and regulate these particular LDTs. FDA's prohibition on offering LDTs for COVID-19 without FDA authorization meant there were no alternatives available for several crucial weeks at the beginning of the outbreak in the United States.[56] Laboratories were ready, willing, and able to develop and offer LDTs, but were blocked by FDA's policy.[57]

Because FDA did require EUAs for LDTs, a number of laboratories submitted EUAs for these assays. FDA has stated that in its analysis of 125 EUA applications from laboratories, 82 of them contained design or validation issues that the agency

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[50] *See* Gail H. Javitt, *FDA Regulation of LDTs*, *in* DIAGNOSTICS AT A CROSSROADS: NAVIGATING IVD REGULATION IN A CHANGING ENVIRONMENT (Jeff Gibbs & Allyson Mullen eds., 2020); *COVID-19 Tests Highlight Need for Strengthened FDA Oversight and Diagnostics Legislation*, THE PEW CHARITABLE TRUSTS (May 19, 2021), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/05/covid-19-tests-highlight-need-for-strengthened-fda-oversight-and-diagnostics-legislation [https://perma.cc/4M26-9D4D].

[51] Hyman, Phelps & McNamara, P.C., Citizen Petition, Docket No. FDA-2020-P-0152-0001 (Jan. 9, 2020); Am. Clinical Lab. Ass'n, Citizen Petition, Docket No. FDA-2013-P-0667-0001 (June 4, 2013); Washington Legal Foundation, Citizen Petition, Docket No. 2006P-0402 (Sept. 28, 2006); *See* Javitt, *supra* note 50.

[52] Barbara J. Evans & Ellen Wright Clayton, *Deadly Delay: The FDA's Role in America's COVID-Testing Debacle*, 130 YALE L.J.F. 78 (2020).

[53] *Id.* at 80.

[54] FDCA § 564(m)(1).

[55] *See, e.g.*, U.S. FOOD & DRUG ADMIN., DISCUSSION PAPER ON LABORATORY DEVELOPED TESTS (LDTS) 4, 12 (Jan. 13, 2017), https://www.fda.gov/media/102367/download [https://perma.cc/D39M-AWSK]; *see also* CONG. RSCH. SERV., FDA REGULATION OF LABORATORY DEVELOPED TESTS 1 (LDTs) (Dec. 16, 2019), https://crsreports.congress.gov/product/pdf/IF/IF11389 [https://perma.cc/BGW5-NDGD].

[56] *See supra* notes 29, 31, 34, 36, 37.

[57] Michael D. Shear, Abby Goodnough, Sheila Kaplan, Sheri Fink, Katie Thomas & Noah Welland, *The Lost Month: How a Failure to Test Blinded the U.S. to Covid-19*, N.Y. TIMES (Mar. 28, 2020), https://www.nytimes.com/2020/03/28/us/testing-coronavirus-pandemic.html [https://perma.cc/8LS5-EZBV].

believed needed to be resolved before an EUA could be authorized.[58] It is not clear, however, what impact these design or validation "issues" would have had on actual clinical performance. Design or validation "issues" can, for example, stem from incomplete documentation or lack of clarity in the submission, rather than reflect subpar accuracy.[59]

In short, FDA's decision to restrict the use of LDTs for SARS-CoV-2 significantly delayed the availability of accurate tests. The adverse consequences of FDA regulation of LDTs in the time of a pandemic was foreseeable. This is not a case of hindsight being 20/20—the need for LDTs during disease outbreaks had been anticipated in comments to FDA criticizing past FDA efforts to limit LDTs.[60] FDA's decision to require EUAs for SARS-CoV-2 LDTs also stood in contrast to the agency's exercise of enforcement discretion for LDTs for the detection of H1N1 during the 2009 pandemic,[61] which has been credited with enabling rapid and widespread availability for H1N1 testing.[62]

Remarkably, on August 19, 2020, HHS issued a statement announcing that FDA could not regulate *any* LDTs—including those for SARS-CoV-2—without first going through rulemaking.[63] The HHS notice specifically stated that this position meant that laboratories did not need EUAs to offer LDTs.[64] While this new policy applied to FDA regulation of any LDT, the HHS notice was reportedly prompted by FDA's requirements of prior review of LDTs for COVID.[65] Although HHS's terse

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[58] *COVID-19 Tests Highlight Need for Strengthened FDA Oversight and Diagnostics Legislation*, THE PEW CHARITABLE TRUSTS (May 19, 2021), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/05/covid-19-tests-highlight-need-for-strengthened-fda-oversight-and-diagnostics-legislation [https://perma.cc/49Z9-3R2C].

[59] In assisting companies with EUAs, we have encountered numerous situations where the FDA reviewer has asked for additional clarifying information regarding the product design or the validation studies. It is unclear whether FDA would consider these submissions to have had validation or design issues, even though the questions could be addressed or the requested information was not essential to evaluating the product's clinical performance.

[60] *See, e.g.*, Am. Clinical Lab. Ass'n, Citizen Petition, Docket No. FDA-2013-P-0667-0001, 15–16 (June 17, 2013) (noting that LDTs allow for real-time response to emergent infectious diseases that is critical to the welfare of patients and the public health and that requiring FDA marketing authorization under such circumstances could have "potentially catastrophic consequences").

[61] Madeleine Johnson, *In Coronavirus Assay Validation for Emergency Use, Labs Encounter Multiple Pain Points*, 360DX (Mar. 11, 2020), https://www.360dx.com/pcr/coronavirus-assay-validation-emergency-use-labs-encounter-multiple-pain-points#.X_YqEthKjIU [https://perma.cc/CA7C-AQU2].

[62] *See, e.g.*, Swati Kumar & Kelly J. Henrickson, *Update on Influenza Diagnostics: Lessons from the Novel H1N1 Influenza A Pandemic*, 25 CLINICAL MICROBIOLOGY REVS. 344, 351 (2012) (stating that a "significant share of the surge capacity for the specific diagnosis of [H1N1] was met by laboratory-developed assays," several of which "reported equal or better sensitivities than those of the available FDA-cleared assays."); Jan A. Nowak & Karen L. Kaul, *The Role of Community Molecular Diagnostics Laboratories in the H1N1 Pandemic*, 11 J. MOL. DIAGNOSTICS 369, 369–70 (2009).

[63] *See* Gail H. Javitt & Jeffrey N. Gibbs, *HHS Reverses Its Position and No Longer Requires EUAs for COVID-19 LDTs*, FDA LAW BLOG (Aug. 20, 2020), https://www.fdalawblog.net/2020/08/hhs-reverses-its-position-and-no-longer-requires-euas-for-covid-19-ldts/ [https://perma.cc/Y8LX-C2KK].

[64] *Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests*, U.S. DEP'T OF HEALTH & HUM. SERVS. (Aug. 19, 2020), https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html [https://perma.cc/RVQ5-ZFD8]; *see also* Javitt & Gibbs, *supra* note 63.

[65] Adam Bonislawski, *HHS Move Upends FDA Role in Laboratory-Developed Test Regulation*, 360DX (Aug. 21, 2020), https://www.360dx.com/regulatory-news-fda-approvals/hhs-move-upends-fda-role-laboratory-developed-test-regulation#.YOXIEOhKiUl [https://perma.cc/B9WA-JZR8]; Adam

announcement provided no legal justification for the agency's abrupt decision, a pre-decisional memorandum prepared by HHS General Counsel Robert Charrow concluded that FDA's approach to LDT regulation was "inconsistent with" the rulemaking requirements of the Administrative Procedure Act and also raised concerns about how FDA has interpreted the scope of the FDCA.[66]

Following HHS's August pronouncement, FDA announced on October 7, 2020 that the agency would no longer accept for review *any* EUA submissions for COVID-19 LDTs, even from clinical laboratories that wanted to obtain an EUA.[67] Laboratories with pending EUA submissions received letters from FDA informing them that their submissions would not be reviewed.[68] It is not clear why FDA waited more than three months from the release of the HHS notice to notify laboratories it would no longer review EUAs for LDTs, including EUAs that were then pending. During that period, laboratories spent time and resources to prepare and submit applications that the agency ultimately did not review. This waste of time and effort could have been avoided had FDA publicly stated in August that no more LDTs would be reviewed or stated that any new applications submitted after a certain date would not be considered.

The very public spat between HHS and FDA did not end there. FDA's refusal to grant EUAs even to those laboratories that voluntarily sought them meant that these laboratories would not be eligible for the liability protections afforded by the PREP Act, discussed further below. In response to concerns raised by universities, on November 16, 2020, HHS directed FDA to review EUA submissions for LDTs that were submitted by laboratories.[69] At the same time, HHS directed FDA to speed up its review of LDTs.[70] In a call with reporters, the then-Assistant Secretary of Health, Admiral Brett Giroir, stated that he "formally instructed the FDA that they must review

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Cancryn & Sarah Owermohle, *HHS Chief Overrode FDA Officials to Ease Testing Rules*, POLITICO (Sept. 15, 2020), https://www.politico.com/news/2020/09/15/hhs-alex-azar-overrode-fda-testing-rules-415400 [https://perma.cc/R9C8-SCTC].

66 Memorandum from Robert Charrow, Gen. Couns. to Stephen Hahn, Comm'r of Food and Drugs, Pre-Decisional Memorandum: Federal Authority to Regulate Laboratory Developed Tests (June 22, 2020). This memorandum, by attacking the foundations of FDA regulation of LDTs without rulemaking, may complicate any future efforts by the new administration to resume efforts to establish guidance documents governing LDTs.

67 *See FAQs on Testing for SARS-CoV-2*, *What are FDA's Priorities with Respect to Review of EUA Requests for COVID-19 Tests?* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2#general (last updated Oct. 7, 2020) [https://perma.cc/V2WM-FVSM]. Even though FDA's long-standing policy of exercising enforcement discretion meant that laboratories did not need to submit marketing applications for IVDs, some companies voluntarily did submit marketing applications and obtain FDA approval. *Myriad MyChoice CDx - P190014*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/recently-approved-devices/myriad-mychoice-cdx-p190014 (last updated Oct. 23, 2019) [https://perma.cc/BBe9-4QVS]; *FoundationOne CDx, P170019/S017*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/recently-approved-devices/foundationoner-cdx-p170019s017 (last updated Nov. 30, 2017) [https://perma.cc/D5DQ-PWEQ].

68 While these individual letters cannot be shared, the FDA policy underlying them was articulated in one of the agency's FAQs. *See FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., http://web.archive.org/web/20201008024622/https:/www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2 (last updated Oct. 7, 2020) [https://perma.cc/CCM4-XZ42] ("FDA is declining to review EUA requests for LDTs at this time.").

69 Greg Slabodkin, *In Shift, FDA Ordered to Provide 'Timely' EUA Reviews for COVID-19 Lab Developed Tests*, MEDTECH DIVE (Nov. 17, 2020), https://www.medtechdive.com/news/giroir-directs-fda-to-provide-timely-eua-reviews-for-covid-19-lab-develop/589159/ [https://perma.cc/T3BG-TLPT].

70 *Id.*

EUA applications for LDTs in a timely manner" and that if the agency "is unable to complete these reviews in a timely manner, I will request that the National Cancer Institute (NCI) assist the FDA in the timely review of these EUA applications."[71] It is unclear whether HHS carried through with this directive and whether the NCI assisted with the review of COVID-19 LDT EUAs. Currently, there does not appear to be any public information showing that the NCI is playing any role in reviewing these LDT assays.

The August 2020 decision by HHS allowed laboratories to bring LDTs more quickly to market if they chose to. But both liability concerns and customer demand for EUA-authorized tests meant that some labs still needed EUAs in practice. At the same time, FDA's desire to devote its resources more efficiently, to tests for which an EUA was necessary to distribute the test in the United States, is understandable. After HHS's announcement, LDT EUAs no longer fell into that category.

The open disagreement between HHS and FDA regarding LDT EUAs during the previous administration was unusual, and clinical laboratories were caught in the crossfire. Each action by HHS, and reaction by FDA, had ripple effects that created confusion and uncertainty on the part of EUA holders.[72] These broader policy decisions seem to have been made without adequate attention to some of the very practical questions that they created for laboratories and their customers.

For example, ordinarily a laboratory holding an EUA would need to submit an amendment for FDA's approval in order to make certain changes, such as adding a new collection device.[73] However, FDA's decision to no longer review EUAs created confusion about how amendments should be handled. We are aware of instances in which laboratories with authorized LDT EUAs wanted to modify their tests. They were not certain, however, whether they were free to change their tests, since the test specifications and conditions of use were specified in the previously granted EUA, whether FDA would even be willing to review EUA amendments for LDTs after the October 7 announcement, or whether, in the absence of such review, their updated, modified LDTs could still be represented as "authorized" by FDA and therefore continue to be eligible for PREP Act liability protection.

The lack of clarity did not affect only laboratories; it also led to questions about the interplay between IVD and LDT EUAs. FDA has generally required COVID test manufacturers to submit an EUA amendment for FDA authorization before making a change to their product (for example, adding a new specimen type for which the test

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71 Joyce Frieden, *HHS Pushes FDA to Speed Up EUAs for Some COVID-19 Tests*, MEDPAGE TODAY (Nov. 17, 2020), https://www.medpagetoday.com/infectiousdisease/covid19/89726 [https://perma.cc/LE95-C2PX].

72 Madeleine Johnson, *Lab Directors Discuss Unprecedented Challenges and Scrambling for Solutions During COVID-19 Pandemic*, GENOMEWEB (Nov. 19, 2020), https://www.genomeweb.com/clinical-lab-management/lab-directors-discuss-unprecedented-challenges-and-scrambling-solutions#.X9fGGNhKg2w [https://perma.cc/Q3AS-7EVF]; Adam Bonislawski, *HHS Move Upends FDA Role in Laboratory-Developed Test Regulation*, GENOMEWEB (Aug. 21, 2020), https://www.genomeweb.com/regulatory-news-fda-approvals/hhs-move-upends-fda-role-laboratory-developed-test-regulation#.X9fM1dhKg2w [https://perma.cc/76HF-R6U7].

73 *FAQs on Emergency Use Authorizations (EUAs) for Medical Devices During the COVID-19 Pandemic*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/faqs-emergency-use-authorizations-euas-medical-devices-during-covid-19-pandemic (last updated Apr. 23, 2021) [https://perma.cc/YD3F-93ET] (explaining that "the Conditions of Authorization . . . in [the applicant's] letter of authorization will provide information about what can be amended in your EUA with concurrence of FDA").

is validated).[74] Furthermore, many EUAs specify other products with which the product may be used. For example, a manufacturer's collection device may be validated for use with a different manufacturer's test kit, in which case this validation is reflected in each manufacturer's EUA.[75] Thus, an amendment to one manufacturer's EUA could also trigger the need for an amendment of the other manufacturer's EUA. This requirement for reciprocal authorization presented a conundrum for laboratories once FDA stopped regulating LDTs; laboratories were unsure whether making changes to their tests—which no longer required EUA amendments—would prevent their IVD manufacturer partners from continuing to use their test. It was not clear that FDA would even accept an EUA amendment for an LDT if a laboratory prepared one. In the absence of such FDA acceptance, it was unclear whether IVD manufacturers would be able to market their product with a modified LDT.

FDA provided no public explanation for how the parties should proceed in this scenario. Laboratories had to weigh the risks of not making beneficial updates to their products against the risk, to themselves and their commercial partners and customers, of modifying their LDT without clarity from FDA as to whether doing so complied with the agency's requirements. These very practical dilemmas were precipitated by the HHS announcement, and not by any action of FDA. Nevertheless, when further clarity was not forthcoming from FDA, the effect was to cast numerous laboratories into regulatory limbo.

In another remarkable turn of events, on November 15, 2021 (as this Article was about to go to press), the Biden Administration withdrew the previous HHS policy that had effectively blocked FDA regulation of LDTs for more than a year.[76] Secretary Xavier Becerra stated that, as a consequence, "HHS no longer has a policy on LDTs that is separate from FDA's longstanding approach in this area."[77] Concurrently, FDA issued updated guidance explaining how the agency intended to regulate LDT EUAs going forward, including the need for laboratories to submit EUAs for their COVID assays within sixty days or cease testing.[78] The updated guidance introduces a whole new set of criteria, and concomitant ambiguities, that IVD manufacturers and labs must quickly respond in order to stay on the market.[79] While FDA stated that the HHS

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[74] *See* FDA Virtual Town Hall Series, Transcript, 3 (June 24, 2020) (statements by Toby Lowe), https://www.fda.gov/media/139618/download [https://perma.cc/37ZZ-B2NJ]; *see also* U.S. FOOD & DRUG ADMIN., POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED), IMMEDIATELY IN EFFECT GUIDANCE FOR CLINICAL LABORATORIES, COMMERCIAL MANUFACTURERS, AND FOOD AND DRUG ADMINISTRATION STAFF, 10 (May 11, 2020), https://www.fda.gov/media/135659/download [https://perma.cc/LM8X-RAY5].

[75] *See, e.g.*, U.S. FOOD & DRUG ADMIN., EUA FOR CRSP SARS-COV-2 REAL-TIME REVERSE TRANSCRIPTASE (RT)-PCR DIAGNOSTIC ASSAY CLINICAL RESEARCH SEQUENCING PLATFORM (CRSP), LLC AT THE BROAD INSTITUTE OF MIT AND HARVARD (Dec. 18, 2020), https://www.fda.gov/media/139858/download [https://perma.cc/NLW4-W9MZ] (referencing Color Genomics collection device).

[76] News Release, U.S. Dep't of Health & Hum. Servs., Statement by HHS Secretary Xavier Becerra on Withdrawal of HHS Policy on Laboratory-Developed Tests (Nov. 15, 2021), https://www.hhs.gov/about/news/2021/11/15/statement-hhs-secretary-xavier-becerra-withdrawal-hhs-policy-laboratory-developed-tests.html [https://perma.cc/C523-6VE2].

[77] *Id.*

[78] NOVEMBER 15 GUIDANCE, *supra* note 8.

[79] *See* Allyson B. Mullen, Gail H. Javitt & Jeffrey N. Gibbs, *HHS Revokes Trump-Administration LDT Policy*, FDA LAW BLOG (Nov. 29, 2021), https://www.thefdalawblog.com/2021/11/hhs-revokes-trump-administration-ldt-policy/?utm_source=rss&utm_medium=rss&utm_campaign=hhs-revokes-trump-administration-ldt-policy [https://perma.cc/RK99-Q3JA].

policy change "will help ensure that COVID-19 tests are accurate and reliable,"[80] the impact of this policy reversal on test quality and availability remains to be seen.[81]

B. Serology Test Kits

In contrast to FDA's restrictive approach to LDTs, the agency initially adopted a permissive stance with respect to lateral flow serology[82] test kits for SARS-CoV-2 antibodies. These products are designed to test for the presence of antibodies formed in response to exposure to SARS-CoV-2, as compared to testing for the presence of the virus itself.[83] Serology tests are different from antigen tests, which test for the presence of proteins indicative of the SARS-CoV-2 virus, and from polymerase chain reaction (PCR) tests, which detect genetic material from the virus.[84]

FDA's February 29, 2020 guidance document stated that manufacturers of serology tests could begin marketing their tests without an EUA so long as they had appropriate analytical and clinical test validation data on file and submitted a "notification" to FDA of their intent to distribute.[85] Companies rushed to validate their tests according to FDA's recommendations and put distribution networks in place.

i. Point of Care Testing

FDA's approach to serology tests created several different issues. One problem that emerged early in the pandemic related to the lack of clarity as to the settings in which serology tests could and could not be used. This ambiguity created major confusion among manufacturers and potential customers, which included state and local governments and healthcare systems.

These serology tests are simple, single-use cassettes that require only a small quantity of blood and that provide a visible response within minutes.[86] This technology typically requires no special training to use. Many stakeholders, including manufacturers, healthcare facilities, and the authors, therefore believed that FDA's policy would allow the use of these tests at the point of care (POC), rather than only

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[80] News Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Updates Test Policies to Help to Ensure Accuracy and Reliability of Tests and Increase Access to At-Home Tests (Nov. 15, 2021), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-updates-test-policies-help-ensure-accuracy-and-reliability-tests-and [https://perma.cc/5QYH-XZ53].

[81] *See* NOVEMBER 15 GUIDANCE, *supra* note 8.

[82] *See Introduction to Lateral Flow Rapid Test Diagnostics,* NANOCOMPOSIX (Jan. 7, 2020), https://nanocomposix.com/pages/introduction-to-lateral-flow-rapid-test-diagnostics#target [https://perma.cc/VGA8-PEAU]. Home pregnancy tests may be the best-known example of lateral flow tests.

[83] *Serology/Antibody Tests: FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/serologyantibody-tests-faqs-testing-sars-cov-2 (last updated May 19, 2021) [https://perma.cc/H9HW-RSP6] (stating that "such testing cannot be used for diagnosis of infection").

[84] *Coronavirus Disease 2019 Testing Basics*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/coronavirus-disease-2019-testing-basics (last updated Apr. 7, 2021) [https://perma.cc/VA9X-YRB8].

[85] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR CLINICAL LABORATORIES, COMMERCIAL MANUFACTURERS, AND FDA STAFF, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED) 1 (2020).

[86] *See, e.g.*, Emergency Use Authorization Letter for Assure COVID-19 IgG/IgM Rapid Test Device from U.S. Food & Drug Admin. to Frank Lou, Dir., Azure Biotech, Inc. (Sept. 23, 2020), https://www.fda.gov/media/139789/download [https://perma.cc/3J6S-WTBV].

at laboratories. Permitting tests at the point of care expands access and allows patients to get results much more rapidly.

FDA's written policy reinforced this expectation by stating that serology test kits were intended for use by clinical laboratories and healthcare providers "at the point of care."[87] On its face, this policy appeared to allow the tests to be sold to and used in POC settings, such as doctors' offices and drive-through testing facilities. Providing rapid results of antibody testing to patients at the POC provides significant benefits to those patients and the healthcare system.

However, unless a test is classified by FDA as "CLIA waived," non-laboratorians cannot use the test pursuant to CLIA.[88] Limiting a test to use in a CLIA high complexity or moderate complexity laboratory significantly reduces the number of sites that can conduct the testing. These clinical laboratories must meet numerous CLIA requirements.[89] Although physician offices and pharmacies are not precluded by law from obtaining one of these licenses, the cost and regulatory complexity is rarely worthwhile for these facilities. In contrast, a CLIA-waived test can be used in many other primary healthcare settings, such as physician offices and pharmacies.

It was reasonable to infer from FDA's announced serology test policy that FDA considered these tests to be CLIA-waived, because most providers "at the point of care" could, in practice, use them only if they were CLIA-waived. FDA personnel appeared to confirm this inference at an early Town Hall meeting.[90] Additionally, this inference made sense given that POC settings are well suited for these types of tests and allowing their use would expand access to rapid testing for the presence of antibodies, which was a major policy goal.

Without CLIA-waived status, however, a test that is labeled "point of care" cannot actually be used in POC settings. After receiving multiple inquiries on the subject, and providing less-than-clear responses in Town Hall meetings,[91] the agency posted an "FAQ"[92] on its website in April stating that serology tests had not been categorized as waived, even though waived status is ordinarily a prerequisite for testing at the POC.[93]

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[87] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR CLINICAL LABORATORIES, COMMERCIAL MANUFACTURERS, AND FDA STAFF, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED) 12 (2020).

[88] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, RECOMMENDATIONS FOR CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 (CLIA) WAIVER APPLICATIONS FOR MANUFACTURERS OF IN VITRO DIAGNOSTIC DEVICES (2020).

[89] Schlanger, *supra* note 44 at 173.

[90] *See* Elizabeth Hillebrenner, Remarks at the U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 6 (Mar. 25, 2020), https://www.fda.gov/media/136518/download [https://perma.cc/X7EN-XCRX].

[91] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 4 (Apr. 1, 2020), https://www.fda.gov/media/136681/download [https://perma.cc/R4NQ-BQPL].

[92] The FAQ page of FDA's website was a mechanism FDA frequently used to provide clarification on FDA's policies for SARS-CoV-2 tests. It had the advantage of allowing FDA to quickly reach stakeholders. But FDA frequently used the FAQs to announce substantive policy changes (such as POC testing) or to explain nuanced but important issues (such as the difference between surveillance, screening, and diagnostic testing). Unless one knew to check the FAQs frequently, it was easy to miss major announcements. And the FAQs allowed only one-way communication, without a clear mechanism to obtain further clarification when the answers did not resolve the question.

[93] *Lab Update: FDA Clarifies CLIA-waived Status for Point-of-Care SARS-CoV-2 Tests under Emergency Use Authorizations*, CTRS. FOR DISEASE AND CONTROL AND PREVENTION (Apr. 9, 2020),

As a consequence of FDA's decision on CLIA waiver,[94] the use of serology tests under the "notification" policy was limited to laboratories certified as "high complexity" laboratories under CLIA.[95] Because doctors' offices, pharmacies, and other similar facilities are rarely high complexity laboratories, this limitation effectively precluded tests from being offered at most of these locations. In order for manufacturers to sell their tests to these facilities, they first would need to conduct additional studies to obtain CLIA-waived status. Conducting these studies would entail demonstrating adequate performance of their test when used by healthcare personnel at the POC.[96]

In explaining why FDA had taken this stance, the agency appeared to say that its hands were tied due to a decision by another component of HHS, the Centers for Medicare & Medicaid Services (CMS). According to a statement by FDA's Director of the Office of In Vitro Diagnostics, it

> was not [FDA's] intention to limit the use of rapid serology tests that are otherwise designed to be used in a point of care setting. However, because of the limits that we have in law, it is in the opinion of [CMS] that these can be performed in high-complexity labs.[97]

This assertion is surprising, in light of a May 21, 2020 CMS memorandum providing guidance to the directors of state laboratory survey agencies regarding the different types of SARS-CoV-2 tests and their associated regulatory requirements.[98] In particular, the memorandum addressed the CLIA requirements applicable to different types of tests and under different FDA regulatory pathways.[99] According to the memorandum, antigen tests to detect SARS-CoV-2 antigens present in the blood for which a notification had been submitted to FDA but that was not authorized under an EUA "must meet requirements for *High Complexity Testing (regardless of whether manufacturer intends for test to be point-of-care/waived)*."[100] In contrast, the memorandum was silent concerning the requirements for serology tests under the same circumstances, arguably implying that serology tests were not limited to use in a high

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https://www.cdc.gov/csels/dls/locs/2020/fda_clarifies_clia-waived_status.html [https://perma.cc/WL99-VX5A].

[94] *Id.*

[95] 42 U.S.C. § 263a (2020). High complexity laboratories are subject to the most extensive requirements. 42 C.F.R. §§ 493.1441-1495 (2021).

[96] *CLIA Waiver by Application*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clia-waiver-application (last updated Feb. 25, 2020) [https://perma.cc/H7LV-AZYP]; *COVID-19 Test Settings: FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-settings-faqs-testing-sars-cov-2 (last updated Dec. 10, 2020) [https://perma.cc/US7Y-3ALS].

[97] Madeleine Johnson, *Faced with Confusion*, *Questionable Claims, FDA Addresses Coronavirus Serology Testing*, 360DX (Apr. 9, 2020), https://www.360dx.com/immunoassays/faced-confusion-questionable-claims-fda-addresses-coronavirus-serology-testing#.X_YwKNhKjIU [https://perma.cc/W7N4-7AXN].

[98] CTRS. FOR MEDICARE & MEDICAID SERVS., 20-06-CLIA, CMS SARS-COV-2 LABORATORY TESTING COMPARISON (2020), https://www.cms.gov/files/document/admin-info-20-06-clia.pdf [https://perma.cc/ABS2-RZAD].

[99] *Id.*

[100] *Id.* (emphasis added).

complexity setting.[101] Moreover, contemporaneously with FDA's FAQ, the CMS announced that serology testing was eligible for reimbursement under Medicare and Medicaid when performed at *pharmacies*, which typically hold a CLIA certificate of waiver and are not certified for high complexity testing.[102] FDA's position that serology rapid tests needed to be conducted by high complexity laboratories, however, functionally prevented patients from getting the tests that CMS agreed to pay for at pharmacies.[103]

Furthermore, FDA adopted this restrictive interpretation at a time when the agency acknowledged that such tests "are growing in importance . . . to aid the determination of patient immunity and prior exposure."[104] While FDA could have enabled POC testing by, for example, exercising enforcement discretion and allowing the lateral flow serology tests to be used at these facilities, it failed to do so.[105] As a result of COVID, FDA chose to exercise discretion numerous times regarding device regulatory requirements.[106] Thus, FDA's decision to restrict POC tests to use by laboratories with high complexity CLIA licenses was not foreordained.

Whether FDA or CMS ultimately was responsible for the decision to limit POC testing, FDA's clarification of its position led some companies to quickly cease

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[101] *Id.*

[102] CTRS. FOR MEDICARE & MEDICAID SERVS., MLN MATTERS: SE20017, MEDICARE PHARMACIES AND OTHER SUPPLIERS MAY TEMPORARILY ENROLL AS INDEPENDENT CLINICAL DIAGNOSTIC LABORATORIES TO HELP ADDRESS COVID-19 TESTING (2020), https://www.cms.gov/files/document/se20017.pdf [https://perma.cc/S8U6-NH3N] ("This will provide additional laboratory resources to meet the urgent need to increase COVID-19 testing capability.").

[103] Jeffrey N. Gibbs, McKenzie E. Cato & Serra J. Schlanger, *New FDA Policy Significantly Limits Serological Testing*, FDA LAW BLOG (Apr. 13, 2020), https://www.thefdalawblog.com/2020/04/new-fda-policy-significantly-limits-serological-testing/ [https://perma.cc/3SKU-NW2C].

[104] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series - Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 2 (Apr. 8, 2020), https://www.fda.gov/media/136833/download [https://perma.cc/P28H-QWMM].

[105] In contrast to FDA's strict construction of CLIA, a law CMS is responsible for enforcing, CMS itself did exercise enforcement discretion in other areas. For example, CMS permitted pathologists to review cases in remote settings, thereby enabling pathologists to examine tissue via digital pathology from their homes. CTRS. FOR MEDICARE & MEDICAID SERVS., QSO-20-21-CLIA, CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA) LABORATORY GUIDANCE DURING COVID-19 PUBLIC HEALTH EMERGENCY (2020), https://www.cms.gov/files/document/qso-20-21-clia.pdf-0 [https://perma.cc/58JW-3G7X]. Another example of CMS discretion? *See, e.g.*, *SNF: Enforcement Discretion Relating to Certain Pharmacy Billing*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/medicare/covid-19/snf-enforcement-discretion-relating-certain-pharmacy-billing (last updated Apr. 20, 2020) [https://perma.cc/9U4S-PXGQ]. FDA exercised enforcement discretion to allow digital pathology equipment to be used remotely as well. U.S. FOOD & DRUG ADMIN., ENFORCEMENT POLICY FOR REMOTE DIGITAL PATHOLOGY DEVICES DURING THE CORONAVIRUS DISEASE 2019 (COVID19) PUBLIC HEALTH EMERGENCY GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, HEALTHCARE FACILITIES, PATHOLOGISTS, AND FOOD AND DRUG ADMINISTRATION STAFF (2020), https://www.fda.gov/media/137307/download [https://perma.cc/KXH8-DC2X].

[106] *See, e.g.*, U.S. FOOD & DRUG ADMIN., COAGULATION SYSTEMS FOR MEASUREMENT OF VISCOELASTIC PROPERTIES: ENFORCEMENT POLICY DURING THE CORONAVIRUS DISEASE 2019 (COVID-19) PUBLIC HEALTH EMERGENCY (REVISED) GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2021), https://www.fda.gov/media/145135/download [https://perma.cc/FQ8X-7MCD]; U.S. FOOD & DRUG ADMIN., ENFORCEMENT POLICY FOR NON-INVASIVE REMOTE MONITORING DEVICES USED TO SUPPORT PATIENT MONITORING DURING THE CORONAVIRUS DISEASE 2019 (COVID-19) PUBLIC HEALTH EMERGENCY (REVISED) GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2020), https://www.fda.gov/media/136290/download [https://perma.cc/C5ZS-3B3B].

distribution for POC use and revise labeling and marketing materials to note the tests' high-complexity status. Some companies that did not attend every Town Hall or were not aware of the FAQs on FDA's website continued distribution for POC use until they later learned of FDA's interpretation. Although both the Town Hall meetings and FAQs were valuable tools for disseminating information, FDA could have done more to publicize these viewpoints and to make clear that significant policy changes would be communicated through these channels. Historically, FDA has not communicated important modifications in policy through FAQs. In the future, FDA should consider means by which stakeholders could better be updated about material changes in policy set forth in FAQs.

FDA's decision meant that tests could not be run at many sites where they would have been most useful. The agency should reassess this position on POC testing in the event future national health emergencies occur for which POC testing would benefit the public health. Furthermore, FDA and HHS should better coordinate policy decisions. As illustrated by the discussion above regarding LDTs, conflicts in FDA and HHS policy create confusion and impose costs on regulated industry and the public. With serology tests, FDA's interpretation of CLIA—a statute enforced by the CMS—arguably undermined policy objectives established by CMS to broaden testing.

Compounding the lack of availability of POC serology tests was the fact that FDA was slow to provide a path forward for manufacturers seeking a POC indication. A company seeking CLIA-waived status must perform certain assessments, such as usability and flex studies, to show that the performance of its test is not sensitive to environmental conditions and challenges.[107] During the Center for Devices and Radiological Health's (CDRH) Town Hall meetings, companies requested information from FDA regarding the agency's expectations for these studies, and FDA stated that guidance would be forthcoming.[108] FDA did not add these data expectations to the serology test EUA template—a document setting forth the specific data requirements for authorization—until weeks later.[109] While this pace is much faster than typical, in the interim it left companies with no clear path forward as to how to meet an obvious need: POC serology tests.

Throughout the pandemic, FDA has used templates to communicate its expectations for different types of tests.[110] In the absence of a template, discerning FDA's expectations could be difficult. Upon individual request, some reviewers provided the usability and flex study expectations to companies before the template was issued. While this feedback did allow those companies to begin their tests, companies who did not know to ask for this "off the record" guidance—or who did ask for it but did

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[107] *CLIA Waiver by Application*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clia-waiver-application (last updated Feb. 25, 2020) [https://perma.cc/CL42-EYB5].

[108] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 13 (Apr. 22, 2020), https://www.fda.gov/media/137426/download [https://perma.cc/GA62-U7HH].

[109] *In Vitro Diagnostics EUAs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas [https://perma.cc/MN7D-9G5Y] (last updated May 24, 2021) (listing the current version of the various templates).

[110] *Id.*

not get it—were left at a disadvantage.[111] Another challenge for companies resulted from FDA's unannounced changes to templates, which could cause disruption to studies or submissions already in progress. As this Article was going to press, FDA substantially revised its templates for Molecular and Antigen Home Use Template and issued a Supplemental Template for Molecular and Antigen Diagnostic COVID-19 Tests for Screening with Serial Testing.[112] Companies whose tests do not meet the expectations set out in the latest templates are unlikely to receive an EUA.

FDA granted its first EUA for a POC serology test in September 2020; to date only thirteen have been issued.[113] The number of POC serology EUA submissions that FDA received but either rejected or never reviewed has not yet been publicly disclosed. In announcing this authorization, the then-Commissioner of FDA extolled the benefits of POC serology testing compared to the prior authorizations which were limited to CLIA-certified laboratories:

> serology test samples were generally only able to be evaluated in a central lab, which can be time consuming and use additional resources to transport samples and run the test. As more and more point-of-care serology tests are authorized, they will help conserve those resources and may help reduce processing time for other types of COVID-19 tests, as less time is spent on serology tests.[114]

This recognition of the public health value of POC testing makes FDA's earlier decision in May 2020 to restrict POC testing even more questionable.

ii. Quality of Antibody Test Kits

The controversy over POC testing was overshadowed by an even more public and more pressing concern, namely, the performance (sensitivity and specificity)[115] of, and

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[111] *See* Richard A. Lewis, *Shhh! It's a Secret! FDA is Not Providing Key Details in the EUA Templates*, FDA LAW BLOG (Apr. 12, 2021), https://www.thefdalawblog.com/2021/04/shhh-its-a-secret-fda-is-not-providing-key-details-in-the-eua-templates/ [https://perma.cc/BGM5-TCMZ].

[112] *See, e.g.*, U.S. FOOD & DRUG ADMIN., ANTIGEN TEMPLATE FOR TEST DEVELOPERS (Nov. 9, 2021), https://www.fda.gov/media/140615/download [https://perma.cc/DV9P-NY3J] (for molecular and antigen home use tests); U.S. FOOD & DRUG ADMIN., SUPPLEMENTAL ANTIGEN TEMPLATE FOR TEST DEVELOPERS (Oct. 25, 2021), https://www.fda.gov/media/146695/download [https://perma.cc/4UMB-VAZD] (for molecular and antigen tests for screening with serial testing).

[113] These are listed on an FDA webpage. *See In Vitro Diagnostics EUAs – Serology and Other Adaptive Immune Response Tests for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-serology-and-other-adaptive-immune-response-tests-sars-cov-2#individual-serological (last updated Sept. 24, 2021) [https://perma.cc/R2ZM-RHVK]; *see, e.g.*, Letter from Denise M. Hinton, Chief Scientist, U.S. Food & Drug Admin. to Christoffer Riska, Vice President Regul. Affs., Quality Assurance, Salofa Oy regarding EUA for Sienna-Clarity COVIBLOCK COVID-19 IgG/IgM Rapid Test Cassette (Jan. 5, 2021), https://www.fda.gov/media/140079/download [https://perma.cc/5Q7M-USPL] (on file with U.S. Food & Drug Admin.).

[114] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes First Point-of-Care Antibody Test for COVID-19 (Sept. 23, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-point-care-antibody-test-covid-19 [https://perma.cc/S7SR-7QQ9].

[115] U.S. FOOD & DRUG ADMIN., A CLOSER LOOK AT CORONAVIRUS DISEASE 2019 (COVID-19) DIAGNOSTIC TESTING (2021), https://www.fda.gov/media/143737/download [https://perma.cc/W4Z7-

claims being made for, some serology tests being distributed pursuant to the notification pathway.[116] Shortly after FDA issued its March 16 guidance, reports began to surface of serology tests that had low or inconsistent performance.[117] FDA was roundly criticized in the press and by members of Congress for allowing serology test kits onto the market that it had not reviewed.[118] An April 24, 2020 publication of a report based on an investigation[119] conducted by the House Committee on Oversight and Reform castigated FDA for allowing antibody test kits from more than 100 manufacturers on the market without any review and for failing to take enforcement action against manufacturers making allegedly fraudulent claims. The memorandum also faulted FDA for failing to release an EUA template describing the information required as part of a serology test kit submission and for providing insufficient guidance to healthcare providers and patients on serology tests.[120] The memorandum concluded that the "White House plans to reopen the economy are flawed by their dependence on coronavirus antibody tests, which face unanswered scientific questions of utility and accuracy."[121]

FDA leadership subsequently acknowledged the agency's responsibility for helping to create the "flawed"[122] situation that allowed poor quality serology tests to enter the

7HJD] (defining sensitivity as "the fraction of positive cases that the test correctly identifies as positive" and specificity as "the fraction of negative cases that the test correctly identifies as negative").

116 Madeleine Johnson, *Clinical Labs Face Myriad of Obstacles as They Validate COVID-19 Serology Tests*, 360DX (Apr. 27, 2020), https://www.360dx.com/infectious-disease/clinical-labs-face-myriad-obstacles-they-validate-covid-19-serology-tests#.X_Yxu9hKjIU [https://perma.cc/A9R4-HNAJ]; Madeleine Johnson, *As Concerns Deepen, FDA Tells Companies to Prove Antibody Tests Work*, 360DX (May 4, 2020), https://www.360dx.com/regulatory-news-fda-approvals/concerns-deepen-fda-tells-companies-prove-coronavirus-antibody-tests#.X_YyRNhKjIU [https://perma.cc/A9R4-HNAJ].

117 *Certain COVID-19 Serology/Antibody Tests Should Not Be Used – Letter to Clinical Laboratory Staff and Health Care Providers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/letters-health-care-providers/certain-covid-19-serologyantibody-tests-should-not-be-used-letter-clinical-laboratory-staff-and (last updated June 19, 2020) [https://perma.cc/MHP9-UTAV].

118 *See* Laurie McGinley, *Dozens of Coronavirus Antibody Tests on the Market Were Never Vetted by the FDA, Leading to Accuracy Concerns*, WASH. POST (Apr. 19, 2020), https://www.washingtonpost.com/health/2020/04/19/fda-antibody-tests-coronavirus-review/ [https://perma.cc/FHE5-9F4W]; Zachary Brennan & David Lim, *FDA Pushed Through Scores of Inaccurate Antibody Tests Without Agency Review*, POLITICO (Apr. 27, 2020), https://www.politico.com/news/2020/04/27/reliable-antibody-tests-coronavirus-207589 [https://perma.cc/E5QL-RHSS]; Thomas M. Burton, *FDA Sets Standards for Coronavirus Antibody Tests in Crackdown on Fraud*, WALL ST. J. (May 4, 2020), https://www.wsj.com/articles/fda-sets-standards-for-coronavirus-antibody-tests-in-crackdown-on-fraud-11588605373 [https://perma.cc/78ET-7MB3].

119 A subsequent briefing was held by the Subcommittee on Economic and Consumer Policy addressing "COVID-19 Antibody Testing: Uses, Abuses, Limitations, and the Federal Response." *COVID-19 Antibody Testing: Uses, Abuses, Limitations, and the Federal Response: Briefing by the H. Subcomm. Econ. & Consumer Policy*, HOUSE COMMITTEE ON OVERSIGHT & REFORM (June 9, 2020), https://oversight.house.gov/legislation/briefings/subcommittee-on-economic-and-consumer-policy-covid-19-antibody-testing-uses [https://perma.cc/WRV6-E43Q].

120 Memorandum from Subcomm. on Econ. & Consumer Policy Staff to Democratic Members of the Subcomm. on Econ. & Consumer Policy regarding Preliminary Findings of the Subcommittee's Coronavirus Antibody Testing Investigation (Apr. 24, 2020), https://oversight.house.gov/sites/democrats.oversight.house.gov/files/ECP%20Staff%20Report%20on%20Preliminary%20Findings%20of%20the%20Subcommittee%E2%80%99s%20Coronavirus%20Antibody%20Testing%20Investigation.pdf [https://perma.cc/TZ73-7RAX].

121 *Id.*

122 Jeffrey Shuren & Timothy Stenzel, *The FDA's Experience with COVID-19 Antibody Tests*, 384 NEW ENG. J. MED. 592, 592 (2021).

market. In a 2021 article in *The New England Journal of Medicine*, CDRH Director Jeffrey Shuren and Office of In Vitro Diagnostics and Radiological Health (OIR) Director Timothy Stenzel, stated that: "Knowing what we know now, we would not have permitted serology tests to be marketed without FDA review and authorization, even within the limits we initially imposed. Although other factors may have driven unauthorized products to flood the marketplace, our March 16 policy allowed it to happen."[123]

Faced with mounting criticism, on May 4, 2020, FDA abruptly ended its notification policy for serology tests and announced that all manufacturers would need to submit an EUA by May 18, 2020.[124] Those that submitted EUAs within the fourteen-day deadline would be able to continue marketing the products while their submission was under review, while those who failed to submit the required information would be placed on a public list of companies not permitted to distribute in the United States.[125] Along with the May 4, 2020 guidance, FDA distributed a "template" document that set forth the kinds of data required to be included in the submission and FDA's expectations for how well the product would perform.[126]

In announcing the policy change, CDRH's Director both defended the agency's initial "flexible" approach as having been necessary at the time and blamed industry for the need for the change in position.[127] Dr. Shuren cited "unscrupulous actors marketing fraudulent test kits" as well as manufacturers who have "falsely claimed that their tests can diagnose COVID-19 or that they are for at-home testing."[128] FDA also cited "a concerning number of commercial serology tests [that] are being promoted inappropriately, including for diagnostic use, or are performing poorly based on an independent evaluation by FDA."[129]

Thus, FDA seemed at the time to largely blame industry's promotional practices for the need to change policy. Yet, if the primary motivating concern was improper promotion of tests, then requiring the submission of EUAs with performance data was a remedy that did not match the perceived problem. A crackdown on improper promotion could have been initiated without requiring the submission of data within two weeks.

In any event, the consequences of FDA's initial relaxed approach were foreseeable. Although many companies could offer well-validated assays to help fill the testing

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[123] *Id.* at 593 (emphasis in original).

[124] *See* Anand Shah & Jeff Shuren, *Insight into FDA's Revised Policy on Antibody Tests: Prioritizing Access and Accuracy* (May 4, 2020), https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy; *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (Revised) (2020).

[125] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (Revised) (2020).

[126] *See In Vitro Diagnostics EUAs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas [https://perma.cc/7RAB-43NJ].

[127] Anand Shah, *Insight into FDA's Revised Policy on Antibody Tests: Prioritizing Access and Accuracy*, U.S. FOOD & DRUG ADMIN.: FDA VOICES (2020), https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy [https://perma.cc/X3AW-QVAS].

[128] *Id.*

[129] *Id.*

shortage, given the demand for tests throughout the United States, it was predictable that some companies would take advantage of lax regulation to provide incompletely validated tests—or even tests with poor performance—onto the market. In contrast with LDTs offered by U.S. laboratories regulated under CLIA, companies offering serology tests—many of which originated outside of the United States—could distribute tests without any U.S. government scrutiny of their quality. In any future crisis, FDA should be—and almost certainly will be—warier about opening the door broadly to allow tests by entities essentially unregulated within the United States.

C. Asymptomatic Testing

Throughout the spring and summer of 2020, the CDC issued guidance encouraging testing in asymptomatic populations to facilitate a return to work.[130] FDA, however, indicated that the bar for obtaining an EUA with a claim for asymptomatic testing would be high—and would require "a study powered well enough to demonstrate the capability of detecting an asymptomatic person."[131] According to OIR Director Tim Stenzel, who fielded numerous questions about asymptomatic testing during the weekly Town Hall meetings, deciding how to test asymptomatic individuals returning to work was "a very important question" but "exactly how this should be done is still an unknown scientifically."[132] Thus, although FDA stated its willingness to authorize a test for use in asymptomatic individuals, the data FDA would require to support test performance in an asymptomatic population—including the percentage of asymptomatic carriers that would test positive—were "not necessarily easy studies to carry out" and that "designing them to assess whether or not somebody is an asymptomatic carrier . . . would require some discussion with our FDA team."[133] FDA issued a template in June 2020 for test developers interested in seeking an asymptomatic claim.[134]

FDA acknowledged the apparent inconsistency between its decision not to allow asymptomatic claims and the CDC's decision to endorse this use. In an FAQ, FDA recognized that its sister agency had issued "guidance related to screening and that organizations may want to conduct screening of asymptomatic individuals as part of a strategy to assure the safety of their employees, patients, students, and others."[135] FDA recommended that such screening be conducted "using a highly sensitive test" and

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[130] CTRS. FOR DISEASE CONTROL & PREVENTION, *Overview of Testing for SARS-CoV-2 (COVID-19)* (2021), https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html [https://perma.cc/N3ED-3MKP].

[131] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series (Apr. 29, 2020), https://www.fda.gov/media/137764/download [https://perma.cc/XM4S-KFW6].

[132] *Id.*

[133] *Id.*

[134] *See* Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: Facilitating Diagnostic Test Availability for Asymptomatic Testing and Sample Pooling (June 16, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-facilitating-diagnostic-test-availability-asymptomatic-testing-and [https://perma.cc/68RC-CUPV].

[135] *Pooled Sample Testing and Screening Testing for COVID-19*, U.S. FOOD & DRUG ADMIN. (2020), https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/pooled-sample-testing-and-screening-testing-covid-19 [https://perma.cc/4PGR-GTLT].

noted that the agency had issued templates with "validation recommendations designed to establish high sensitivity for tests."[136]

FDA also finessed the apparent inconsistency with the CDC by distinguishing between the requirements for a manufacturer to make a claim about asymptomatic testing and the use of a SARS-CoV-2 in an asymptomatic population. While the former was within FDA's purview, FDA deferred judgment on the latter to the physician ordering the test:

> As our knowledge grows about asymptomatic patients, and what methods may be able to be used to detect whether somebody is an asymptomatic carrier or shatter, and what sample type is best, what swab type might be best, maybe there are multiple sites, maybe there are multiple swab types that would be useful. But for the time being and how evidence is presented in some way to the FDA, we are very open to claims around asymptomatic testing. But for now, our statement is on our website now that testing of asymptomatic individuals who are suspected of COVID-19 is at the discretion of the health care provider. And so that can be somebody, you know, it's up to the healthcare prescriber and so we have offered from at least in FDA perspective, maximal flexibility for use of that.[137]

FDA did finally authorize EUAs for screening of asymptomatic individuals with no known exposure—initially with a physician order required,[138] and then without.[139] However, after granting these authorizations, FDA then recommended to healthcare providers that they use tests with EUAs for symptomatic patients "off-label" to test asymptomatic patients, effectively telling healthcare providers that comparable results could be obtained from tests that did not have the asymptomatic indication.[140] This policy, while helping to meet public health needs, did undercut the value of the work done by those companies that had undertaken the extensive testing in asymptomatic populations needed to satisfy FDA's requirement. While these companies could actively promote their tests for asymptomatic use, companies with products labeled only for symptomatic populations could point to FDA's recommendation that these tests be used in asymptomatic settings. FDA's encouragement of off-label use (itself unusual) also discouraged subsequent applicants from seeking an asymptomatic indication in their EUA.

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136 *Id.*

137 Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series (May 6, 2020), https://www.fda.gov/media/137986/download [https://perma.cc/6AFE-H2T3].

138 U.S. FOOD & DRUG ADMIN., EUA FOR CENTOSURE-SARS-COV-2 RT-PCR ASSAY (Aug 13, 2020), https://www.fda.gov/media/142539/download [https://perma.cc/6U72-X7B9].

139 Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes First Diagnostic Test for Screening of People Without Known or Suspected COVID-19 Infection (July 24, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-diagnostic-test-screening-people-without-known-or [https://perma.cc/Z8AF-LMEY]; U.S. FOOD & DRUG ADMIN., EUA FOR ELLUME COVID-19 HOME TEST (Dec. 15, 2020), https://www.fda.gov/media/144457/download [https://perma.cc/88VB-RKT4].

140 Madeleine Johnson, *FDA Encourages Off-Label Use of Authorized COVID-19 Tests for Asymptomatic Results*, 360Dx (Dec. 17, 2020), https://www.360dx.com/regulatory-news-fda-approvals/fda-encourages-label-use-authorized-covid-19-tests-asymptomatic [https://perma.cc/LG88-RAKE].

In March 2021, FDA announced[141] that the agency would allow developers of COVID-19 tests to market their products for regular at-home use without first submitting data establishing their sensitivity in asymptomatic individuals.[142] The agency acknowledged what scientists and public health officials had been saying for months,[143] namely, that expanding access to testing to allow repeated testing, even if tests were less sensitive, could help bring the pandemic under control and facilitate return to school and work.[144] Agency officials stated that the policy change would "pave the way for further expanding the availability of tests authorized for screening asymptomatic individuals, help bolster existing and new testing programs and increase consumer access to testing."[145] Thus, FDA took close to a year to shift from requiring rigorous data for a company to obtain an EUA labeled for the testing of asymptomatic patients pursuant to a prescription to allowing asymptomatic consumer self-testing.

This fast-moving pandemic forced FDA to address many policy issues in an unusually rapid, and flexible, manner. Yet, it is not just 20/20 hindsight to say that FDA could have adopted a different approach towards the testing of asymptomatic individuals from the outset, or at least changed its policy much more rapidly and more explicitly.[146] The delayed, multi-step shift in policy caused confusion, limited testing of asymptomatic patients—some of whom would have been found to be positive—and created an uneven playing field for companies.

D. At-Home Specimen Collection

The advantages of allowing a potentially infected individual to collect a specimen at home, without the need to go to a physician's office or other public area, would seem to be obvious, particularly at the height of the pandemic. However, FDA initially appeared unreceptive to requests by manufacturers for at-home collection because of significant concerns about the ability of the public to collect a specimen independently. FDA did not issue a template for at-home specimen collection EUAs until late May 2020[147] and did not begin to identify at-home specimen collection as a high priority

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[141] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series (Mar. 17, 2021), https://www.fda.gov/media/146819/download [https://perma.cc/5EHP-YJVV].

[142] David Lim, *FDA Opens Door to Widespread At-Home Covid-19 Tests*, POLITICO (Mar. 16, 2021), https://www.politico.com/news/2021/03/16/fda-at-home-covid-tests-476355 [https://perma.cc/HCE9-L7ZL].

[143] *See, e.g.*, Patrice A. Harris, *We Must Expand COVID-19 Testing Capacity Before Restarting the Economy*, American Medical Association (2020), https://www.ama-assn.org/about/leadership/we-must-expand-covid-19-testing-capacity-restarting-economy [https://perma.cc/5YR6-GBAV].

[144] Michael J. Mina, Roy Parker & Daniel B. Larremore, *Rethinking Covid-19 Test Sensitivity – A Strategy for Containment*, 383 NEW ENG. J. MED. 120 (2020).

[145] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Takes Steps to Streamline Path for COVID-19 Screening Tools, Provides Information to Help Groups Establishing Testing Program (Mar. 16, 2021), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-steps-streamline-path-covid-19-screening-tools-provides [https://perma.cc/W4KG-AYLN].

[146] Toby Lowe, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series (May 19, 2021), https://www.fda.gov/media/149074/download [https://perma.cc/5JDX-3Q33].

[147] *FDA Adds At-Home Self-Collection Template to SARS-CoV-2 Emergency Use Authorization Guidance*, GENOMEWEB (May 30, 2020), https://www.genomeweb.com/regulatory-news-fda-approvals/fda-adds-home-self-collection-template-sars-cov-2-emergency-use#.X9fphdhKg2w [https://perma.cc/D3HB-DH55] [hereinafter *FDA Adds At-Home Self-Collection Template*].

until the end of 2020 (nearly a year after the pandemic began).[148] FDA did issue a handful of EUAs for at-home collection devices prior to issuing the template,[149] but some companies delayed submission of EUAs for at-home tests until the template was issued. Many companies that elected to defer submission were understandably concerned that FDA would release a template with new requirements after submission of an EUA and before authorization. Had that happened, FDA would have applied the requirements in that template to already-pending applications.

The at-home collection kit EUA template specified the additional information that applicants would need to include in their EUAs, which included studies to validate the collection kits using contrived (positive) samples and negative samples, a shipping study that includes subjecting the samples to varying temperatures, and a "usability study" in which kits are used by at least thirty people in an "actual use environment or simulated environment."[150] These thirty people need to be participants without prior training and who represent "varying educational levels and ages."[151] In explaining these additional requirements, CDRH Director Shuren stated that at-home collection

> raises unique concerns about safety and accuracy—for example, can the sample be collected safely and properly by a layperson, can the sample be shipped in a way that's stable to ensure an accurate result once it reaches the lab, among other factors—which is why these tests require FDA review, to ensure they work as they should and are safe for all involved.[152]

Home-based specimen collection kits do raise additional considerations. Yet, there is room for debate regarding whether all of the testing mandated in the template was necessary, particularly weighing the likelihood that these factors would introduce test error against the benefits of expanding access to tests, enabling more frequent testing of individuals, and keeping potentially positive patients at home. The company that obtained the first EUA for a home collection test described the benefits as follows: "With this authorization, we can help more people get tested, reduce the spread of the virus and improve the health of our communities."[153] Arguably, even if tests using

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[148] *COVID-19 Test Development and Review: FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://web.archive.org/web/20201217171446/https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-development-and-review-faqs-testing-sars-cov-2 [https://perma.cc/B5NY-TTRF] (updated Dec. 2, 2020).

[149] Erin Brodwin, *FDA Greenlights First Covid-19 Test with At-Home Sample Collection*, STAT NEWS (Apr. 21, 2020), https://www.statnews.com/2020/04/21/fda-clears-covid-19-test-home-sample-collection-labcorp/ [https://perma.cc/B43Y-VL9X].

[150] U.S. FOOD & DRUG ADMIN., HOME SPECIMEN COLLECTION MOLECULAR DIAGNOSTIC TEMPLATE 12 (May 29, 2020), https://web.archive.org/web/20200620023458/https://www.fda.gov/media/138412/download [https://perma.cc/JEC5-RGSN].

[151] *FDA Adds At-Home Self-Collection Template*, *supra* note 147.

[152] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Takes Steps to Streamline Development of Tests With At-Home Sample Collection (May 29, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-steps-streamline-development-tests-home-sample-collection [https://perma.cc/R7NL-4WDK].

[153] Press Release, Labcorp, Labcorp Receives FDA Authorization to Make At-home COVID-19 Collection Kits Available Through Retail (Dec. 9, 2020), https://www.labcorp.com/coronavirus-disease-covid-19/news/labcorp-receives-fda-authorization-make-home-covid-19-collection-kits-available-through-retail [https://perma.cc/7PN4-SFNU] [hereinafter Labcorp Press Release].

samples collected at home resulted in a slightly higher percentage of false positives or false negatives, the overall advantages to the healthcare system of at-home testing outweighed these risks.[154] But FDA did not give any public indication that the agency had considered these arguments or why the agency appeared to reject them.

FDA took even longer to permit lay users to initiate the request for a collection device, without first getting a physician order for testing. Ultimately, FDA did allow some collection kits to be sold "OTC"—meaning without the need for a physician order.[155]

Given that home collection does raise some different questions than collection by healthcare professionals, it was appropriate for FDA to ask for some additional information. In doing so, though, FDA did not publicly discuss the benefits of greatly expanding at-home collection against the risks that some consumers would not properly collect specimens and there could therefore be erroneous results. Rather, FDA focused on the potential downside. In evaluating devices, FDA routinely weighs both benefits and risks.[156] It is not clear why FDA, when discussing at-home collection, seemed to focus predominantly on the risk side of the equation.[157]

E. At-Home Testing

While it took FDA only a few months to provide guidance on collection of samples at home, it took the agency far longer to define a pathway for over the counter (OTC) serology testing—i.e., a device that an individual could purchase at a drugstore or online, without a physician order, perform at home, and view the results within minutes. FDA did not establish a pathway until March 2021.[158] This delay presumably was not due to a lack of recognition of the importance of such a test. In announcing this authorization, Stephen Hahn, the then-Commissioner, stated, "This new testing option is an important diagnostic advancement to address the pandemic and reduce the public burden of disease transmission . . . . Today's action underscores the FDA's ongoing commitment to expand access to COVID-19 testing."[159]

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[154] Mina et al., *supra* note 144; Harris, *supra* note 143; Labcorp Press Release, *supra* note 153 ("With the first over-the-counter at-home collection kit ever authorized by the FDA for COVID-19, we are empowering people to learn about their health and make confident decisions . . . . With this authorization, we can help more people get tested, reduce the spread of the virus and improve the health of our communities.").

[155] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes First Standalone At-Home Sample Collection Kit That Can Be Used With Certain Authorized Tests (May 16, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-standalone-home-sample-collection-kit-can-be-used [https://perma.cc/BBJ5-6R8G].

[156] *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, FACTORS TO CONSIDER WHEN MAKING BENEFIT-RISK DETERMINATIONS IN MEDICAL DEVICE PREMARKET APPROVAL AND DE NOVO CLASSIFICATIONS (2019), https://www.fda.gov/media/99769/download [https://perma.cc/FEV3-YR6L].

[157] Stenzel, *supra* note 108 at 3–4; Stenzel, *supra* note 91 at 17.

[158] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Takes Steps to Streamline Path for COVID-19 Screening Tools, Provides Information to Help Groups Establishing Testing Programs (Mar. 16, 2021), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-steps-streamline-path-covid-19-screening-tools-provides [https://perma.cc/AU89-WZRA].

[159] Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes First COVID-19 Test for Self-Testing at Home (Nov. 17, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-covid-19-test-self-testing-home [https://perma.cc/U24C-HA25].

Nevertheless, there are still only a limited number of home antigen tests available, and the agency has yet to issue a template for OTC serology tests. As of this writing, only eleven OTC antigen tests currently have EUAs.[160] The impact of this limited availability of convenient OTC tests may become more apparent, and more burdensome to the public, as society reopens and people seek to engage in activities, such as international travel, that require rapid testing.[161]

F. Sensitivity and Specificity Thresholds

One of the principles that has been consistently applied is FDA's expectation that the assays would demonstrate high levels of sensitivity. The specific cut-offs have varied by methodology and indication; for some PCR indications companies have been expected to meet a minimum sensitivity of 90% while for others it has been 95% required, and for antigen tests it has been between 80% and 90% depending on indication (e.g., professional v. home use). While the agency did not make public its rationale for selecting sensitivity thresholds for different types of tests, it has been clear that applicants who failed to meet those defined thresholds—even by small amounts—were unlikely to receive an EUA.[162]

However, the standard that Congress prescribed for reviewing EUA submissions was intended to be lower than that required for other types of submissions. FDA can grant an EUA if an applicant shows the product "may be effective;" FDA is directed to evaluate risks in light of both the actual and the potential benefits of the proposed product.[163] These benefits can relate to the site of use, as FDA explained in authorizing the first home antigen test: "This test, like other antigen tests, is less sensitive and less specific than typical molecular tests run in a lab. However, the fact that it can be used completely at home and return results quickly means that it can play an important role in response to the pandemic."[164] Yet notwithstanding the direction to be more flexible, FDA did not appear to incorporate this "may be effective" standard into many reviews, with reviewers often focusing on very narrow aspects of documentation of product performance.

Whether the standards that FDA set were the optimal public health strategy for population-based testing in the midst of a pandemic is a topic that epidemiologists, public health officials, government officials, and other stakeholders will debate at

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[160] *See In Vitro Diagnostics EUAs - Antigen Diagnostic Tests for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2 (last updated Sept. 10, 2021) [https://perma.cc/6CK8-69PH].

[161] David Leonhardt, *Where are the Tests?*, N.Y. TIMES (Sept. 21, 2021), https://www.nytimes.com/2021/09/21/briefing/rapid-testing-covid-us.html [https://perma.cc/N8M8-HK7H].

[162] There is no standard criterion for different types of IVDs. FDA has cleared 510(k)s with sensitivity of varying levels.

[163] U.S. FOOD & DRUG ADMIN., EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES GUIDANCE FOR INDUSTRY & OTHER STAKEHOLDERS (Jan. 2017), https://www.fda.gov/media/97321/download [https://perma.cc/Y9ZN-FXUU].

[164] *See* Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Authorizes Antigen Test as First Over-the-Counter Fully At-Home Diagnostic Test for COVID-19 (Dec. 15, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-antigen-test-first-over-counter-fully-home-diagnostic?utm_medium=email&utm_source=govdelivery [https://perma.cc/C2PC-BJXR].

length.[165] The agency's focus on test sensitivity has been criticized by some as being detrimental by reducing access to tests.[166] By their account, expanding the pool of tests, even with lower sensitivity, would allow frequent testing, which would be more effective at controlling the spread of disease.[167] While exploring the merits of this broader epidemiological debate is outside the scope of this Article, FDA's decision to limit EUAs to tests with high sensitivity during the first year of the pandemic reduced the availability of tests. Whether this tradeoff was justified should be carefully evaluated before the next infectious disease emerges, as should the question of what levels of sensitivity and specificity are appropriate, and how that choice is made and explained. Whereas FDA's focus is typically on the individual patient and seeking a high sensitivity for infectious agents, a pandemic may require different, more nuanced assessments, including other tools, such as population-based modeling. More broadly, the lessons of COVID-19 raise questions as to the role that other considerations, such as accessibility, higher rates of testing, maintaining social distancing, and convenience, should play in evaluating tests for other diseases, where the public health benefits of less sensitive but more frequent tests can potentially exceed the benefits of fewer but more sensitive tests.[168]

III. FDA ENGAGEMENT WITH STAKEHOLDERS

During the pandemic, there have been many changes in FDA policy, and appropriately so. The unprecedented outbreak required FDA to develop multiple policies from scratch and then modify them as new information was gleaned.[169] FDA should be lauded for the tremendous effort that agency personnel put into "following the science" as more was learned. The enormous influx of EUA submissions for diagnostics also stretched FDA's resources to the breaking point, as the agency simply

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[165] *See, e.g.*, Giorgia Guglielmi, *Rapid Coronavirus Tests: A Guide for the Perplexed*, NATURE (Feb. 9, 2021), https://www.nature.com/articles/d41586-021-00332-4 [https://perma.cc/F7Y3-VNRX].

[166] *See* Leonhardt, *supra* note 161.

[167] Mina et al., *supra* note 144; Harris, *supra* note 143; Rita Rubin, *The Challenges of Expanding Rapid Tests to Curb COVID-19*, 324 JAMA 1813 (Oct. 21, 2020), https://jamanetwork.com/journals/jama/fullarticle/2772299 [https://perma.cc/RKJ2-SZE3]; William Wan, *America Is Finally About to Get a Lot More Coronavirus Tests. The Question Now: How Best to Use Them?*, WASH. POST (Dec. 18, 2020), https://www.washingtonpost.com/health/2020/12/18/coronavirus-tests-plans/ [https://perma.cc/9ZVD-Q5PF]; Kelly Lienhard, *FDA Ramps Up Requirements for COVID-19 Tests Amid Deregulatory Push*, INSIDEHEALTHPOLICY (Oct. 1, 2021), https://insidehealthpolicy.com/daily-news/fda-ramps-requirements-covid-19-tests-amid-deregulatory-push [https://perma.cc/WUG9-Q4SE].

[168] In assigning priority for reviews, FDA did consider the applicant's manufacturing capacity, i.e., the volume of tests that an applicant could actually produce, as a factor. *See, e.g.*, U.S. FOOD & DRUG ADMIN., ANTIGEN TEMPLATE FOR TEST DEVELOPERS (Oct. 6, 2021), https://www.fda.gov/media/137907/download [https://perma.cc/S9S3-W88C]. It is not clear how this non-traditional factor was utilized in FDA reviews of EUA submissions. *See also* Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series 27–28 (May 12, 2021), https://www.fda.gov/media/148740/download [https://perma.cc/ZU3C-A48A] (stating FDA is "declining to review" tests that are not high throughput); U.S. Food & Drug Admin. Virtual Town Hall Series 17–18 (June 23, 2021), https://www.fda.gov/media/150378/download [https://perma.cc/LA78-C5NV]. More recently, FDA established an expectation that test manufacturers would be able to provide 500,000 tests per week. NOVEMBER 15 GUIDANCE, *supra* note 8, at 7.

[169] *See* Jeff Shuren, CDRH Update: CDRH Response to COVID-19, Presentation at FDLI Annual Meeting (May 19, 2021) (on file with the authors).

did not have enough trained reviewers of tests for infectious diseases to manage the workload, and reviewers were moved from other Divisions within CDRH to assist.[170]

At the same, many companies struggled with a lack of FDA guidance, both as to broader policies and as to their own application. Many companies found themselves unable to engage interactively with their reviewer—or *any* reviewer—for months on end. EUA applicants had applications rejected for failing to have provided data of a certain type, even though the agency had never stated that such data were needed. Other EUA applicants had their applications denied because they were never given the chance to respond to a reviewer's concern, or, because when they did respond, the reviewer cited new standards that had been established in the intervening months.[171]

Lack of timely feedback has also been an ongoing problem for EUA applicants. During the early months of the pandemic, reviewers responded rapidly and substantively to serology EUA submissions. The collaborative nature of the interactions, based on our clients' experiences and as further reflected in calls by companies during Town Hall meetings, declined after FDA revised its policy in May 2020.

The reduction in collaborative discourse was no doubt attributable to the overwhelming onslaught of submissions received by CDRH, without a concomitant increase in internal FDA staffing resources. FDA has received thousands of EUA requests since March 2020—for both IVDs and myriad other devices to address the pandemic.[172] Beyond reviewing those submissions, the agency has had to develop numerous policies, address product shortages, and respond to myriad inquiries.[173] It was physically impossible for FDA, with current staffing levels, to review these submissions in anywhere close to a timely manner.

But while the lack of substantive feedback was understandable, the lack of any interaction became problematic.[174] Emails sent requesting updates on EUA status were

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[170] *Id.*

[171] Inconsistent reviews—including reviews by government officials—can be due to a variety of factors, including "noise." As Nobel Prize winner Daniel Kahneman and his co-authors note in their new book, noise can lead to unjust outcomes, and it is incumbent upon organizations to implement measures to mitigate these factors. DANIEL KAHNEMAN, OLIVIER SIBONY & CASS R. SUNSTEIN, NOISE: A FLAW IN HUMAN JUDGMENT (2021). The authors further note that "Wherever there is judgment, there is noise, and more of than you think." *Id.* at 255. FDA's COVID-19 templates left ample room for judgment by reviewers.

[172] Not all EUAs were for IVDs. FDA received EUAs for dozens of other devices used to treat patients with COVID, such as respiratory assist devices as well as ventilators and ventilator accessories. *Respiratory Assist Devices EUAs*, U.S. FOOD & DRUG ADMIN. (June 30, 2021), https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/respiratory-assist-devices-euas [https://perma.cc/A3F9-VQ6E]; *Ventilators and Ventilator Accessories EUAs*, U.S. FOOD & DRUG ADMIN. (Apr. 28, 2021), https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/ventilators-and-ventilator-accessories-euas [https://perma.cc/NF2R-TZNA].

[173] *See* Jeff Shuren, *supra* note 169, at 8. As of May 14, 2021, FDA had received an estimated 6,604 EUAs for devices overall; it is unclear how many of these have been for IVDs specifically. As of the same date, only 372 tests have been granted EUAs.

[174] *See, e.g.*, U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 25 (May 13, 2020), https://www.fda.gov/media/138240/download [https://perma.cc/2KVU-RHQ5]; U.S. Food & Drug Admin. Virtual Town Hall Series - Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests, 11 (Sept. 9, 2020), https://www.fda.gov/media/142352/download [https://perma.cc/NE4C-8JBL]; U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 22 (Oct. 14, 2020), https://www.fda.gov/media/143085/download [https://perma.cc/ETF6-RBTW].

frequently met with silence or received a boilerplate response: "We appreciate your patience during this time. Unfortunately, we are not able to provide estimates of review timelines." After months of going without any communication with the reviewer, a company's query elicited this response: "Thank you for reaching out. We are currently reviewing your EUA request and do not have an update at this time." Companies were unable to get status reports, and unable to make commercial plans because of the lack of transparency.

The lag time between submission and review also left companies in regulatory limbo for months. In the intervening period, FDA sometimes imposed new standards (either tacitly or through updates to the template[175]), so that a submission that might have met FDA's expectations when submitted was no longer adequate when FDA finally reviewed it months later. FDA would apply these newer standards to applications that had long been pending, without notifying companies that the agency's expectations had changed or providing a clear mechanism to amend the EUA to address the changed standards.

Even recognizing the unprecedented challenge FDA faced, it is also the case that FDA's manner of engaging with stakeholders created confusion and frustration among EUA-seekers, inefficiencies in the review process, and economic harm to some companies that spent considerable resources to develop their products. This section presents some illustrative examples.

A. When Voluntary Isn't: The NCI "Voluntary" Review Program

In an attempt to speed review times while ensuring test quality, FDA unveiled a new pathway for serology test manufacturers to demonstrate the validity of their tests in late April 2020. FDA described the process as voluntary.[176] Manufacturers could submit their tests to the NCI for validation testing rather than conducting independent clinical validation testing and submitting an individual EUA.[177] NCI had established a standard panel of blood samples, and then evaluated the performance of the serology test on thirty different confirmed positive specimens and additional specimens known to be negative because they were obtained before the COVID-19 pandemic.[178] If the validation testing conducted by NCI showed that the test met minimum performance standards outlined by FDA, the test was to be authorized under an "umbrella" EUA established by FDA.[179] FDA explained that the process was intended to cut down on

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[175] *See, e.g.*, Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: Daily Roundup October 26, 2020 (Oct. 26, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-october-26-2020 [https://perma.cc/APT5-52FG] (stating that FDA updated the template for antigen test developers with "recommendations regarding studies to support claims for screening asymptomatic individuals and multiplexed antigen tests").

[176] *See* Norman E. Sharpless, *At NCI, A Robust and Rapid Response to the COVID-19 Pandemic*, NAT'L CANCER INST. (Apr. 17, 2020), https://www.cancer.gov/news-events/cancer-currents-blog/2020/covid-19-cancer-nci-response [https://perma.cc/NL7P-TB7Y].

[177] *Id.*

[178] *NCI Part of Federal Effort to Evaluate Antibody Tests for Novel Coronavirus*, NAT'L CANCER INST. (May 5, 2020), https://www.cancer.gov/news-events/cancer-currents-blog/2020/covid-19-nci-antibody-testing-review [https://perma.cc/W7MR-VQW7].

[179] U.S. FOOD & DRUG ADMIN., REVOKED MEMORANDUM FROM FOOD & DRUG ADMIN. ON UMBRELLA EUA FOR SEROLOGY TESTS (Apr. 28, 2020), https://www.fda.gov/media/137470/download [https://perma.cc/GXA9-YXWL].

FDA's review burden because FDA would not have to perform in-depth reviews of individual EUA submissions.[180] The NCI test data (whether favorable or unfavorable) would be made publicly available.[181]

While the concept of establishing a central, standardized U.S. testing site had merit, the execution of the program was rocky and the details unclear. Companies that volunteered to have their tests evaluated by the NCI appeared to be given priority in the form of continued communication with FDA regarding their submissions, while other companies that elected not to participate in this voluntary program often failed to receive feedback from FDA. FDA, though, did not clearly or publicly state that companies that submitted their tests to FDA would receive priority, or that failing NCI testing would result in a denial of a company's EUA (although it could be inferred from responses by FDA officials to specific questions posed in Town Hall meetings—if one was paying close attention).[182]

We are aware of a number of companies that chose not to pursue the "voluntary" NCI pathway (e.g., used a commercial testing laboratory instead). There were some limitations to the umbrella EUA through NCI: for example, it allowed for authorization for use in only moderate- or high-complexity CLIA laboratories. If companies wanted to pursue a POC authorization, an individual EUA was required. However, companies that submitted clinical validation studies with their individual EUA were sometimes told by reviewers that they would still need to submit test kits to the NCI for testing to "confirm" their clinical validation results to obtain an EUA. Others found their EUAs stalled while reviewers inquired repeatedly whether their tests had been submitted to the NCI, even though NCI review was at least nominally voluntary. FDA did not say NCI testing was mandatory and yet FDA reviewers told many companies to submit test kits to the NCI for testing. This confusion could have been avoided with a clear, unambiguous pronouncement by FDA to industry and reviewers as to whether or not NCI testing entirely voluntary.

The implementation of serology testing by the NCI also created other challenges for manufacturers. NCI data, which used a "validation panel" generated under controlled laboratory conditions with a relatively small set of samples,[183] did not always reflect performance in the field. The NCI used a curated panel of specimens that, because of small sample size and limited range of antibody levels, would not necessarily demonstrate what might be observed in the real-world setting when evaluating "all-comers" as part of a clinical study.[184] The NCI itself acknowledged "the panel may not be representative of all sample types that may be encountered in a

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[180] U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 9 (July 8, 2020), https://www.fda.gov/media/140218/download [https://perma.cc/A9SM-8RFQ].

[181] *See* Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Publicly Shares Antibody Test Performance Data from Kits as Part of Validation Study (June 4, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-publicly-shares-antibody-test-performance-data-kits-part-validation [https://perma.cc/HR84-DAGV].

[182] U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 21–22 (Aug. 26, 2020), https://www.fda.gov/media/141817/download [https://perma.cc/22VA-DJCW]; U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 13 (Oct. 28, 2020), https://www.fda.gov/media/143596/download [https://perma.cc/4W3E-94MC].

[183] Sharpless, *supra* note 176.

[184] *Id.*

large population."[185] The test report that NCI provided acknowledged these limitations, stating that the "[s]ensitivity [percent positive agreement] and specificity [negative percent agreement] estimates in this report may not be indicative of the real-world performance of the [Company] [Device Name]."[186] The report explained that the NCI results are "based on serum and plasma samples only and may not be indicative of performance with other sample types, such as whole blood, including finger stick blood."[187] Additionally, the report stated that the "number of samples in the panel is a minimally viable sample size that still provides reasonable estimates and confidence intervals for test performance, and the samples used may not be representative of the antibody profile observed in patient populations."[188]

Notwithstanding NCI's acknowledgement of these notable limitations, FDA in practice treated NCI results as determinative. FDA rejected EUAs based on NCI data that failed to meet FDA's threshold for sensitivity, even if the manufacturer provided large, robust data sets from other sources that met FDA's threshold. Even though the review of an EUA was supposed to consider the totality of the data,[189] and despite the noted limitations of NCI testing, unfavorable NCI test results were often outcome determinative.[190]

Three months after announcing the "umbrella" pathway, on July 21, 2020, FDA announced that the umbrella EUA was being revoked.[191] Although FDA asserted that nobody had actually used this pathway it had created, this was only partially true; we (the authors) are aware of tests that were in the pipeline awaiting authorization under the umbrella pathway at the time of this announcement.

FDA couched the decision as solely "administrative" in nature, but its implications—at least initially—seemed potentially far-reaching. Applicants who had pursued the NCI testing pathway were left uncertain over the fate of their submissions and concerned about whether they needed now to undertake independent clinical validation in lieu of the NCI data. It took several days for regulators to clarify that pending individual submissions would not be adversely affected by the change to the umbrella policy.[192] This confusion could have been avoided had FDA more clearly

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[185] *Id.*

[186] *See, e.g.*, U.S. FOOD & DRUG ADMIN., SEROLOGY TEST EVALUATION REPORT FOR "VIRUSEE® COVID-19 IGM/IGG LATERAL FLOW ASSAY" FROM GENOBIO PHARMACEUTICAL CO. LTD 5 (July 15, 2020) https://www.accessdata.fda.gov/cdrh_docs/presentations/maf/maf3323-a001.pdf [https://perma.cc/5APR-QJ6P].

[187] *Id.* at 5.

[188] *Id.*

[189] U.S. FOOD & DRUG ADMIN., EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES GUIDANCE FOR INDUSTRY AND OTHER STAKEHOLDERS 8 (Jan. 2017), https://www.fda.gov/media/97321/download [https://perma.cc/VJ69-KEQJ] (stating that an EUA should be "based on the totality of the scientific evidence available").

[190] *See* U.S. Food & Drug Admin., *supra* note 180 at 13.

[191] U.S. FOOD & DRUG ADMIN., SEROLOGY UMBRELLA AUTHORIZATION REVOCATION LETTER (July 21, 2020), https://www.fda.gov/media/140351/download [https://perma.cc/M559-MJTD]; U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 2–3, 26 (July 22, 2020), https://www.fda.gov/media/140462/download [https://perma.cc/A97D-FH3C].

[192] *See* Shah & Shuren, *supra* note 124; *see also* U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 2–3 (July 22, 2020), https://www.fda.gov/media/140462/download [https://perma.cc/A97D-FH3C].

communicated what the change meant. Indeed, a great deal of confusion and uncertainty could have been avoided had FDA more clearly articulated the goals and elements of the NCI process at the outset.

B. A Rollercoaster Ride for Serology Test EUAs

FDA's handling of serology test EUAs has been marked by shifts in policy, followed by a lack of clarity as to the status of applications.

When FDA announced on May 4, 2020 that EUAs would be required for serology tests, the agency gave two weeks' notice for the submission of applications, after which time a serology test would be placed on the "do not distribute" list, meaning applicants could no longer sell their products in the United States.[193] Those that did submit an EUA could continue to distribute their tests while the submission was pending.[194]

FDA quickly became overwhelmed by the influx of EUA serology submissions. When companies requested status updates on FDA's review of their EUA request, the agency would reference the large "backlog" of submissions. Multiple companies reported having their applications sitting in a queue for months, with no visible progress and no meaningful communications with FDA. Their frustration also came through in some of the calls to the weekly Virtual Town Hall meeting on COVID-19 diagnostics.[195]

These delays had adverse commercial consequences for manufacturers. FDA did not adequately communicate to the public that the agency was permitting the distribution of serology tests while their EUAs were pending, or that the length of time a submission was pending did not correlate with the quality of the underlying products. Many potential purchasers demanded to see a manufacturer's EUA and understandably were skeptical when told the product could be lawfully purchased without one.

Moreover, customers purchasing serology test kits without an EUA faced a distinct disadvantage. Under the PREP Act, products granted EUAs are eligible for broad liability protections, which cover not only the manufacturer but also distributors and users of the product.[196] Customers purchasing a non-EUA test kit were not eligible for

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[193] *See* Shah & Shuren, *supra* note 124; *see also* U.S. FOOD & DRUG ADMIN., POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUB. HEALTH EMERGENCY (REVISED) IMMEDIATELY IN EFFECT GUIDANCE FOR CLINICAL LABORATORIES, COMMERCIAL MANUFACTURERS., AND FOOD & DRUG ADMIN. STAFF (May 4, 2020), http://web.archive.org/web/20200504142918/https://www.fda.gov/media/135659/download [https://perma.cc/8FE4-849Q].

[194] *See* Shah & Shuren, *supra* note 124.

[195] Piero Holitecio, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 10 (July 1, 2020), https://www.fda.gov/media/139775/download [https://perma.cc/T59L-NZ5S]; Kodamuti Venkat, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 25 (Aug. 5, 2020), https://www.fda.gov/media/140975/download [https://perma.cc/DK2D-P27N] (asking about backlogs and waiting for NCI testing for two months); Sean Gamel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests 17–18 (Sept. 30, 2020), https://www.fda.gov/media/142810/download [https://perma.cc/ZVX7-6JZ9] (waiting three and a half months for EUA response and stating that there had been no feedback from the reviewer).

[196] *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., ADVISORY OPINION ON THE PUBLIC READINESS AND EMERGENCY PREPAREDNESS ACT AND THE MARCH 10, 2020 DECLARATION UNDER THE ACT (Apr. 17,

such protections.[197] Understandably, customers with product liability concerns were wary about buying from manufacturers who did not have EUAs, even if the product could be legally sold.

When companies with pending assays finally did receive feedback, they were sometimes given as little as forty-eight hours to respond to FDA's questions. Companies that could not meet the deadline risked being placed on FDA's "do not distribute" list. Whether additional time would be granted depended on the reviewer. Companies did question the fairness of having forty-eight hours to respond to questions regarding an application that had been pending for months.

Only a few months after FDA moved to require EUA submissions, anecdotal reports that the agency was going to "deprioritize" serology test EUAs began to circulate. The agency put serology reviews on hold long before FDA announced, in somewhat roundabout fashion, that it had done so. Many serology test applicants were left waiting for months, periodically sending in queries to FDA and hoping in vain that their EUAs would be authorized. Other companies continued to work on submissions, even after the agency's unannounced change in review priorities meant that these EUAs would never be reviewed. A great deal of wasted effort could have been avoided had FDA clearly and explicitly announced its policy of not reviewing serology EUAs, or that the reviews would not take place for a defined period.[198]

Not until October 2020, however, did FDA make public the agency's prioritization scheme for COVID-19 IVDs, again by using its FAQs. The prioritization scheme encompassed both serology tests and other methodologies (e.g., PCR, antigen) and included both laboratory-developed and commercially distributed tests. In an FAQ published on FDA's website on October 7, 2020,[199] FDA announced its EUA review priorities for COVID-19 tests as follows:

> We are currently in a different phase of the pandemic with respect to tests than we were previously, where many COVID-19 tests are now authorized to be run in labs. We prioritize review of EUA requests for tests taking into account a variety of factors, including those discussed in the Emergency Use Authorization of Medical Products and Related Authorities Guidance, such as the public health need for the product and the availability of the product. We have, for example, prioritized review of EUA requests for tests where authorization would increase testing accessibility (e.g., point of care (POC) tests, home collection tests, at-home tests) or would significantly increase testing capacity (e.g., tests that reduce reliance on test supplies, high-throughput, widely distributed tests). In light of this and the recent HHS announcement that FDA will not require premarket review of LDTs, to make the best use of our resources for the greatest public health benefit, FDA is declining to review

2020 as modified on May 19, 2020), https://www.hhs.gov/sites/default/files/prep-act-advisory-opinion-hhs-ogc.pdf [https://perma.cc/6F9P-7CL4].

[197] *Id.*

[198] Jeffrey K. Shapiro, *Beware EUA Deprioritization!*, FDA LAW BLOG (Feb. 25, 2021), https://www.fdalawblog.net/2021/02/beware-eua-deprioritization/ [https://perma.cc/3D9Y-YW99].

[199] *FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN. (Oct. 7, 2020), http://web.archive.org/web/20201008024622/https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2 [https://perma.cc/MSZ2-T2Q3].

> EUA requests for LDTs at this time. FDA continues to prioritize review of EUA requests for POC tests, home collection tests, at-home tests, tests that reduce reliance on test supplies, and high-throughput, widely distributed tests.[200]

The omission of serology tests from this statement was striking. Under the new prioritization scheme, many serology EUAs that were submitted will not be reviewed. As is the case for the LDTs for which review has been discontinued, this represents a waste of the resources that went into developing the validation data to support the EUA and the preparation of EUA submissions. It also means that the time FDA staff spent doing initial reviews of these applications was for naught. Longer-term, FDA's decisions to cease reviews of applications with little to no notice—no matter how understandable from the agency's internal perspective of resource allocation at the moment—may affect the willingness of companies to step up and submit applications when another national emergency occurs.

FDA seemed to believe that the impact on companies whose submissions had been deprioritized would be limited, as companies would still be able to distribute their tests.[201] This perspective, though, ignored the real-world impact of lack of an EUA: that such products would be less likely to be purchased due to the lack of both PREP Act protection and the imprimatur that an EUA conferred. Thus, whether by design or inadvertently, FDA created two distinct marketplaces: some serology tests were being offered pursuant to FDA's revised policy, which allowed distribution during the pendency of FDA's review, while others had an EUA.

FDA undoubtedly needs discretion to prioritize its resources when confronted with a pandemic, and Section 564 affords the agency a good deal of discretion in carrying out its EUA authority.[202] Nor should there be any question that priorities can—and should—change over time, as the circumstances change. But there should also be no real question that FDA ought to communicate explicitly what the priorities are, and what the agency will do with submissions that are deemed lower priority. Moreover, once the agency has changed its prioritization scheme, it should let stakeholders immediately know that the change has occurred and what it means. Clearly articulating what the priorities are—and then clearly and promptly informing stakeholders when they change—would lead to fewer wasted resources by FDA and industry, and greater transparency.[203]

The consequences of FDA's changes in requirements for serology EUAs, retroactive application of new standards to pending EUAs, failure to clearly

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[200] *Id.* (emphasis added).

[201] Timothy Stenzel, Remarks at U.S. Food & Drug Admin. Virtual Town Hall (Mar. 3, 2021), https://www.fda.gov/media/146615/download [https://perma.cc/Z4ZA-4FKV].

[202] FDCA § 564(i), 21 U.S.C. § 360bbb-3(i) ("Actions under the authority of this section . . . are committed to agency discretion.").

[203] On November 15, 2021, FDA announced that its review priorities going forward would include, among others, molecular and antigen tests intended for point of care or home use, laboratory-based molecular diagnostic tests that are highly sensitive, high throughput, and intended for pooling, home specimen collection, screening, or detection of multiple analytes, and lab-based or POC serology tests for quantitative measurement of antibody titers or quantitative detection of neutralizing antibodies. The guidance stated that FDA would prioritize EUA requests for such tests that were submitted by experienced test developers with high manufacturing capacity (500,000 tests per week within three months of the EUA). NOVEMBER 15 GUIDANCE, *supra* note 8, at 7, 19.

communicate when new standards had been implemented, delays in communication with applicants, and the lack of recourse for adverse decisions are illustrated by the following example.

We are aware of a small healthcare company that began to import serology tests in March 2020, relying on FDA's initial notification approach.[204] When FDA pivoted in May 2020 and required that EUAs be submitted within two weeks' time,[205] the company scrambled to put together an EUA—its first ever submission to the agency. The submission then languished for months without any reviewer feedback. When the company finally received feedback requesting additional information, it responded immediately, and then did not hear back from the reviewer for several more weeks.

In the meantime, FDA's expectation for serology test EUAs appeared to have changed, although this was not communicated to the company. While apparently the reviewers had concerns about certain aspects of the company's data, it took many attempts at contact and intervention of the CDRH Ombudsman[206] before the reviewers communicated those concerns to the company. When FDA did finally tell the company its concerns about the accuracy of the source data, the agency provided only a few days to provide confirmatory evidence. This evidence apparently did not satisfy the reviewers. However, without articulating why the information was unsatisfactory or providing the company the opportunity to address whatever the residual concerns were, FDA placed the company on the "do not distribute" list, thereby prohibiting their products from being sold.[207] The company thereafter submitted additional data that would likely have fully addressed FDA's concerns. However, by this point months had elapsed, and the reviewer responded that the submission had been "deprioritized," meaning that the additional data that the company had obtained would not be considered. The upshot is that this small company, which had many customers ready and waiting to purchase its test once the EUA was issued, spent considerable resources on its pursuit of an EUA, without receiving a final substantive decision. It is doubtful that their additional data will ever be reviewed or that they will ever receive an EUA.

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[204] U.S. FOOD & DRUG ADMIN., *supra* note 85.

[205] *See* Shah & Shuren, *supra* note 124; *see also* U.S. FOOD & DRUG ADMIN., POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY (REVISED): IMMEDIATELY IN EFFECT GUIDANCE FOR CLINICAL LABORATORIES, COMMERCIAL MANUFACTURERS, AND FOOD AND DRUG ADMINISTRATION STAFF (May 4, 2020), http://web.archive.org/web/20200504142918/https://www.fda.gov/media/135659/download [https://perma.cc/JU5A-Z8XJ] (this was subsequently replaced by a May 11 guidance document).

[206] The CDRH Ombudsman's roles include helping to address disputes—including procedural ones—between device companies and reviewers. *CDRH Ombudsman*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-ombudsman#:~:text=The%20CDRH%20Ombudsman%20investigates%20complaints,%2C%20regulatory%2C%20or%20procedural%20nature (last updated Mar. 29, 2018) [https://perma.cc/MW4Y-SMZQ]. This can entail helping companies who have had difficulty receiving feedback from CDRH regarding a submission.

[207] The notification pathway typically allows for interactive requests that receive timely attention and review from FDA because, in part, these tests are already on the market. This leads to short response timelines on most, if not all, requests for additional information from the agency. If an applicant does not respond by the prescribed deadline, FDA may deny the EUA and the test may be placed on the public "Do Not Distribute List." *Removal Lists of Tests That Should No Longer Be Used and/or Distributed for COVID-19: FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/removal-lists-tests-should-no-longer-be-used-andor-distributed-covid-19-faqs-testing-sars-cov-2 (last updated Sept. 24, 2021) [https://perma.cc/NM87-DXJ3].

While the details may be unique to this company, the themes are not: long periods without FDA feedback; the need to respond quickly when FDA posed questions; lack of notice about shifting priorities and expectations; and, ultimately, no EUA. As FDA has noted, it has granted numerous EUAs for IVDs in a relatively short time; there have been more than 427 EUAs as of this writing.[208] Yet focusing on the EUAs that were granted overlooks the numerous EUAs that were unsuccessful.[209] When the crisis abates, FDA should consider what lessons can be learned from these submissions that can lead to a more efficient submission and review process when the next public health emergency occurs. This review should go beyond placing the entire fault on companies for inadequate submissions. As the above case study shows, the explanation can be more nuanced than that.

C. Lack of Recourse

Compounding the challenges described above has been the lack of recourse to appeal adverse FDA decisions. Under normal circumstances, FDA has a well-defined pathway for appealing adverse decisions on device applications.[210] Companies are given clear, tight deadlines for submitting an appeal for defined "significant decisions,"[211] and CDRH must reach a decision within a specified timeframe.[212] The appeal process provides FDA with a mechanism for correcting errors that harm individual companies and a source of information for FDA regarding areas where changes in policy and practice may be warranted.

There is no parallel process for EUA denials. The EUA statutory provisions do not prescribe a formal appeals mechanism and in general grants FDA broad latitude in reviewing EUAs.[213] Nor is it clear whether FDA's general supervisory appeal provisions provided under 21 C.F.R. § 10.75 could be invoked in the case of an EUA denial.[214]

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[208] *See In Vitro Diagnostics EUAs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas (last updated Nov. 15, 2021) (providing tables of individual EUAs for molecular, serology, and antigen tests) [https://perma.cc/9VN6-BGRG].

[209] *See* Jeff Shuren, CDRH Update: CDRH Response to COVID-19, Presentation at FDLI Annual Meeting, 6 (May 19, 2021) (on file with author).

[210] U.S. FOOD & DRUG ADMIN., CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) APPEALS PROCESS: GUIDANCE FOR INDUSTRY, AND FOOD AND DRUG ADMINISTRATION STAFF (July 2, 2019) [hereinafter CDRH APPEALS], https://www.fda.gov/media/128444/download [https://perma.cc/35SW-JMQF].

[211] *See* FDCA § 517A, 21 U.S.C. § 360g-1 (outlining "significant decisions" as including but not limited to agency decision on substantial equivalence for 510(k)s and approvable decisions for Premarket Approval/Humanitarian Device Exemption).

[212] *Id.* at 9.

[213] *See* FDCA § 564, 21 U.S.C. § 360bbb-3; U.S. FOOD & DRUG ADMIN., EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES: GUIDANCE FOR INDUSTRY AND OTHER STAKEHOLDERS (Jan. 2017), https://www.fda.gov/media/97321/download [https://perma.cc/JA46-YZ3U].

[214] Whether the general supervisory appeal processes specified in 21 C.F.R. § 10.75 provide an avenue for appeal of an EUA denial is ambiguous. This provision states: "Each request by an interested person for review of a decision within the Center for Devices and Radiological Health shall also comply with 800.75 of this chapter." *Id.* § 10.75(e). Section 800.75 has the CDRH-specific appeal provisions. In the CDRH-specific provisions, only "517A decisions" can be appealed. *Id.* § 800.75. EUA denials are not listed as a type of 517A decision that can be appealed. *Id.* § 800.75(a)(2). While CDRH has detailed guidance for

According to one official at CDRH, EUA denials, which were signed by someone within the Office of the Commissioner, could not be reversed by someone at the CDRH level.[215] While another CDRH official informally stated that the general supervisory appeal mechanisms provided under 21 C.F.R. § 10.75 could be used to appeal an EUA denial,[216] this appeal pathway was not clearly spelled out or publicized by the agency, the result being that many applicants were unaware whether they had any recourse and, if so, what it was.

Furthermore, even if an appeal can be sought, there are no prescribed time limits for issuing a decision or criteria for reversing a decision. Thus, as a practical matter, EUA applicants have no meaningful recourse to appeal an EUA denial, even if the denial is not well-grounded. The lack of an internal appeal mechanism is particularly concerning given that the Administrative Procedure Act (APA) would appear to exempt from review[217] most agency decisions made pursuant to the EUA statute.[218]

Based on our own experiences in representing EUA applicants, we believe that there were instances in which denials were not well-founded, and supervisory review could have corrected an erroneous result. It would be hubris for the agency to take the position that no errors occurred, especially given the need to deploy CDRH staff not familiar with reviewing IVDs for infectious diseases. While recognizing the extraordinary strain COVID has placed on agency resources, it is our view that the public, EUA applicants, and FDA itself would be better served if there were a clearly defined mechanism—even if only a streamlined, abbreviated one—by which decisions could be reviewed by senior management.

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the mechanism for appealing the rejection of various types of applications, those processes are inapplicable to EUAs. *See* CDRH APPEALS, *supra* note 210.

[215] Email from Abiy B. Desta, Ombudsman, CDRH, FDA, to Jeffrey N. Gibbs, Director, HPM (Oct. 14, 2020).

[216] Email from Ellen Flannery, Deputy Center Directory for Policy, CDRH, FDA, to Jeffrey N. Gibbs, Director, HPM (Oct. 21, 2020) (stating that supervisory review of an EUA denial could be obtained pursuant to 21 CFR § 10.75).

[217] Administrative Procedure Act, Pub. L. No. 79-404, 60 Stat. 237 (1946). This is because, while the APA in general permits challenges to agency actions that are "arbitrary, capricious or [an] abuse of discretion," 5 U.S.C. § 706(2)(A), the statute bars review of "agency action [that] is committed to agency discretion by law." 5 U.S.C. § 701(a)(2). The EUA statute provides that "[a]ctions under the authority of this section by the Secretary, by the Secretary of Defense, or by the Secretary of Homeland Security are committed to agency discretion." 21 U.S.C. § 360bbb-3(i). *See also* Ass'n of Am. Physicians & Surgeons v. FDA, No. 20-1784, 2020 U.S. App. LEXIS 30622, at *8 (6th Cir. Sept. 24, 2020) ("[E]mergency-use authorizations are exempt from review under the APA."). On the other hand, courts have said that a statute's grant of broad discretion to an agency does not in all situations render the agency's decisions completely nonreviewable under the "committed to agency discretion by law' exception." See, e.g., Robbins v. Reagan, 780 F.2d 37, 45 (D.C. Cir. 1985) (per curiam); Drake v. FAA, 291 F.3d 59, 70–72 (D.C. Cir. 2002), leaving open the possibility that certain EUA-related decisions by FDA could be subject to judicial review under the APA.

[218] In contrast, agency decisions made under statutory provisions that are not committed to agency discretion by law could be reviewable under the APA. *See, e.g.*, Order at 100, Florida v. Becerra, No. 8:21-cv-839-SDM-AAS (M.D. Fla. filed June 18, 2021), ECF No. 91 (granting Florida's motion for a preliminary injunction and holding that CDC's "conditional sailing order" was arbitrary and capricious because it "imposes vague and shifting (but binding) legal requirements and because the order fails to offer any reasoned explanation about the inadequacy of local measures."). The U.S. Court of Appeals initially issued a stay pending appeal but ultimately denied appellant's request. Florida v. Sec'y, Dept. of Health & Hum. Servs., No. 21-12243 (11th Cir. filed July 23, 2021).

IV. CONCLUSION

As observed in a 2020 report issued by Johns Hopkins Center for Security Studies, diagnostic testing for infectious disease "is a mainstay of not only clinical medicine but also epidemiologic investigation."[219] This is because an infectious disease outbreak "of any size" must first be detected before it can be identified.[220] Reliance "exclusively on clinical criteria may result in inexact diagnoses, fail to capture asymptomatic or minimally symptomatic cases, and severely limit the practitioner's ability to learn anything about the etiologic agent (including its identity)."[221]

COVID-19 will almost certainly not be the last major outbreak of an infectious disease. It is imperative that FDA—and other public health agencies with which FDA collaborates—learn from the current pandemic in preparation for the next one. Eric Lander, Director of the White House Office of Science and Technology, stressed the need to learn from the COVID-19 pandemic. "As public health emergencies recede, societies often quickly forget their experiences – and fail to prepare for future challenges. For pandemics, such a course would be disastrous."[222]

At the height of the pandemic, FDA could not have been expected to conduct a thorough internal evaluation of the agency's response to this unprecedented challenge, but it is critical that a timely examination take place, while institutional memory is still fresh. This examination should do more than simply point to third-party shortcomings, such as the inadequacies of laboratories and manufacturers, poor promotional practices, the ignorance and misuse of tests by healthcare providers, and insufficient legislative authority from Congress.[223]

A February 2021 publication by FDA officials focusing specifically on FDA's regulation of serology tests during the pandemic provides some indication that FDA has begun this process of introspection by acknowledging ways in which the agency's initial approach to serology test regulation could have been improved.[224] However, the agency seems to blame third parties for the problems that were experienced. For example, the authors cite the "scientific and medical communities" for their inadequate understanding of how to "appropriately use test results in general to inform patient care" and criticize industry for violating FDA's policies and marketing poorly

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[219] Johns Hopkins Bloomberg School of Public Health, *At-Home Diagnostic Testing for Infectious Diseases: A Tool for Accelerating COVID-19 Diagnosis and Building Pandemic Preparedness for the Future* 6 (June 2020), https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2020/200625-At-Home-Diagnostic-Testing.pdf [https://perma.cc/5SL8-4EUE].

[220] *Id.* at 3.

[221] *Id.* at 6.

[222] Eric Lander, *What It Will Take to Stop the Next Pandemic*, WASH. POST, Aug. 5, 2021, at A25. Dr. Lander's goals for the next pandemic include "[d]iagnostics simple and cheap enough for daily home testing to limit spread and target medical care." *Id.*

[223] Jeffrey Shuren & Timothy Stenzel, *COVID-19 Molecular Diagnostic Testing—Lessons Learned*, 383 NEW ENG. J. MED. e97(1) (2020).

[224] Jeffrey Shuren & Timothy Stenzel, *supra* note 122. The article does not note that, particularly at the outset of the emergence of COVID-19 in the United States, many of the only available tests came from Asia because the outbreak began there.

performing tests, particularly from overseas.[225] While these are contributing factors, FDA must also look within to see what it can do better.[226,227]

Several recurring themes can be observed from this recounting of FDA's regulation of SARS-CoV-2 diagnostics. One of the challenges has been the lack of clear guidance and transparency regarding policy modifications. For example, as noted above, FDA modified its prioritization scheme for reviewing EUAs. This change, which has a profound effect on many companies, was communicated only after it had been implemented, and then only in an elliptical fashion.[228] While changes in FDA policy are essential during a fast-moving pandemic, it is also essential that those changes be clearly and unequivocally communicated to stakeholders. Moreover, policy reversals should be minimized. The policy shifts towards LDTs, POC serology tests, EUAs for serology assays, and asymptomatic testing have all caused uncertainty and hindered testing.

Another area FDA should address relates to mechanisms by which applicants can obtain review of agency decisions. While we fully appreciate that FDA had an enormous task thrust upon it, that very enormity meant that FDA reviewers—some of whom had no experience reviewing diagnostic submissions—sometimes made mistakes. The current system provides neither meaningful recourse for companies whose applications were erroneously denied nor an efficient way of presenting data to address reviewers' concerns. This system has resulted in the rejection of EUAs that likely would have benefited the public health. The lack of even an abbreviated appeals process also deprived FDA of valuable feedback that could have improved performance.

The LDT and serology test case studies described above also point to several issues that require resolution before the next public health emergency. First, with respect to LDTs specifically, we believe LDTs—which are already used in tens of thousands of different medically critical tests without prior FDA review—should not be subject to the EUA requirement under current law.[229] And if LDTs are going to be regulated, then there should be clear, consistent policies; the zig-zagging that has occurred here

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[225] *Id.* at 592–94; *Emergency Use Authorization of COVID-19 Tests: Independent Assessment of the FDA's Response*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/emergency-use-authorization-covid-19-tests-independent-assessment-fdas-response (last updated Oct. 13, 2021) [https://perma.cc/TTD6-GN6J].

[226] The agency should not wait to the end of this pandemic to make adjustments and improvements, given that FDA anticipates that the termination of the Public Health Emergency "is not something that we would expect to happen for quite a while." Toby Lowe, Remarks at U.S. Food & Drug Admin. Virtual Town Hall Series 4–5 (June 9, 2021), https://www.fda.gov/media/150145/download [https://perma.cc/27RR-ZFG2].

[227] FDA has learned lessons from COVID relating to "flexibility" and "engagement." *See* Jeff Shuren, CDRH Update: CDRH Response to COVID-19, Presentation at FDLI Annual Meeting (May 19, 2021) (on file with author). Those are profound lessons that will help FDA and industry in the future, but FDA should also look inward to see what it could do better in the event of another public health emergency.

[228] *COVID-19 Test Development and Review: FAQs on Testing for SARS-CoV-2*, U.S. FOOD & DRUG ADMIN. (Dec. 2, 2020), https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-development-and-review-faqs-testing-sars-cov-2 [https://perma.cc/4ANC-8ZDT].

[229] See, e.g., the recently introduced VALID Act (Verifying Accurate Leading-edge IVCT Development Act, H.R. 4128, 117th Cong. § 1 (2021)). *See* Blake E. Wilson, *IVDs And LDTs: Evolving Visions Of FDA Oversight Under The VALID Act*, MED DEVICE ONLINE (July 29, 2019), https://www.meddeviceonline.com/doc/ivds-and-ldts-evolving-visions-of-fda-oversight-under-the-valid-act-0001 [https://perma.cc/C4VS-4BVR].

creates confusion and inefficiencies. Second, policies for emergency situations should be put in place prospectively whenever possible because changing policies in the midst of a public health crisis can result in confusion, wasted resources, and inefficiencies; abrupt revisions of policy come with costs, both to FDA and industry. This does not mean FDA is locked into its initial policy. However, the agency should carefully consider whether a change is needed and, if so, clearly and quickly communicate it to all stakeholders. Companies rely on the continuation of an articulated policy. Revisions with significant implications to many stakeholders should not be conveyed primarily through updates to FAQs or remarks at Town Hall meetings, which can easily be overlooked. The agency can deploy other more effective tools to announce and highlight changes in policy.

Third, changes in policy that are applied retroactively (e.g., that apply to applications that have already been submitted) are particularly problematic, and therefore should be done sparingly, after weighing the impact of retroactively imposing the change on access to tests and test performance. For example, if FDA states that in a study of asymptomatic consumers, the participants should explicitly declare that they did not have COVID symptoms within fourteen days of the test, should the data from a completed clinical study be challenged—or even discarded—because the sponsor asked consumers, before FDA had articulated its views, if they had ever had COVID symptoms? Each application takes time and effort; many need to be supported by substantial test data. FDA does need the flexibility to adapt to changing circumstances and information. At the same time, the agency needs to be much more cognizant of the costs that sudden changes impose on stakeholders and to minimize the adverse impact when it determines that a change in policy must be made. When new policies must be applied retroactively, and therefore require changes to pending applications, applicants should be given an adequate opportunity to address the agency's new standards rather than having their applications rejected for failing to meet expectations that did not exist when the applications were submitted.[230]

At some point—and, we hope, soon—COVID-19 will be brought under control. It will then be critical that a thorough, non-partisan, scientifically based and objective review of FDA's handling of COVID-19 testing be conducted to evaluate what went right and what needs to be improved. FDA and all stakeholders need to learn from these experiences so that we are all more prepared for the next pandemic.

The author of the 2019 book *Epidemics and Society* presciently wrote, "Finally, and perhaps most compellingly, epidemic diseases merit attention because their history is far from over. Emerging disease such as SARS, Ebola, and Zika have provided a reminder of this ongoing susceptibility . . . ."[231] We can now add SARS-CoV-2 to this list. While we do not know what disease will come next, we do know that COVID-19 is not the last, and we know that diagnostic testing will play an essential role in addressing that outbreak. FDA will play a critical role in helping to manage that next

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[230] Under the Administrative Procedure Act, when an agency reverses a prior policy that "has engendered serious reliance interests," the law requires that these interests "be taken into account," FCC v. Fox Television Stations, Inc., 556 U.S. 502, 515 (2009), and that the agency make an effort to accommodate them, Dep't of Homeland Security v. Regents of Univ. of California, 140 S. Ct. 1891, 1913–15 (2020). Even though the APA does not apply, this concept of reliance is still one that affects companies that are relying upon FDA consistency and predictability.

[231] FRANK M. SNOWDEN, EPIDEMICS AND SOCIETY: FROM THE BLACK DEATH TO THE PRESENT 3 (2019).

pandemic. The lessons from COVID-19 need to be learned and implemented before that outbreak arrives.