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# Early Development and Regulation of Diagnostic Testing for COVID-19: Frequently Asked Questions

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## Early Development and Regulation of Diagnostic Testing for COVID-19: Frequently Asked Questions

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China. Illnesses have since been linked to a disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. Despite containment efforts in China, the United States, and elsewhere, by late February there were indications that the COVID-19 outbreak had entered a new phase, with community spread occurring or suspected in several countries other than China, including in the United States. Since this time, the virus has spread widely, resulting in millions of cases and more than 500,000 deaths in the United States.

Diagnostic testing is a critical part of the public health response to and clinical management of COVID-19, the disease caused by the SARS-CoV-2 virus. The earliest efforts in the United States to develop and disseminate a test for COVID-19 faced challenges. Manufacturing and quality issues with the nation's first test—developed by the Centers for Disease Control and Prevention (CDC)—delayed access to testing throughout the country. In this context, on February 29, 2020, in an effort to facilitate the expansion of testing capacity as the first cases of community spread were confirmed in the United States, the Food and Drug Administration (FDA) announced a new COVID-19 diagnostics policy. The new policy, issued via agency guidance and effective immediately, allowed certain laboratories that had developed and validated their own COVID-19 diagnostic to begin to use the test prior to receiving an Emergency Use Authorization (EUA) from the agency.

FDA's February 29 guidance (subsequently updated March 16, May 4, and May 11 of 2020) supported the expansion of diagnostic testing from the public health setting into the clinical health care and commercial settings. An expansion of diagnostic testing was part of an early effort to help the country meet increasing and substantial demand for testing. Increasing demand was generated primarily by community spread of the disease and expanded clinical testing guidelines issued by the CDC at the time.

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On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China. Illnesses have since been linked to a disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. Despite containment efforts in China, the United States, and elsewhere, by late February there were indications that the COVID-19 outbreak may have entered a new phase, with community spread occurring or suspected in several countries other than China, including in the United States. Since this time, the virus has spread widely, resulting in millions of cases and more than 500,000 deaths in the United States.

Diagnostic testing is a critical part of the public health response to and clinical management of COVID-19. The earliest efforts in the United States to develop and disseminate a test for COVID-19 faced challenges. Manufacturing and quality issues with the nation's test—developed by the Centers for Disease Control and Prevention (CDC)—resulted in essentially all testing going through CDC's laboratory facility in Atlanta through early March 2020, despite distribution of test kits to state and local public health laboratories beginning in early February 2020. CDC's initial test kit had to be remanufactured and redistributed, which, along with other factors, delayed access to testing throughout the country early in the pandemic.<sup>1</sup> Early reports indicated that the CDC's Atlanta laboratory was under investigation by the Department of Health and Human Services (HHS) for possible quality issues related to its manufacture of the test kits, which may have led to the contamination of one reagent and thus to the quality issues with the test.<sup>2</sup> In June 2020, HHS Office of the General Counsel released findings of an internal investigation into CDC's production of its test kit, finding generally that the test was likely contaminated, and that time pressure may have “compromised sufficient QC/QA [quality control/quality assurance] to identify certain anomalies in data and realize the possibility of contamination before shipment.”<sup>3</sup> In addition, the matter is currently under investigation by HHS Office of the Inspector General, with an audit underway to “review CDC's process of producing and distributing the COVID-19 test kits.”<sup>4</sup> This report is reportedly expected sometime in FY2021.

In this context, on February 29, 2020, in an effort to facilitate the expansion of testing capacity as the first cases of community spread were confirmed in the United States, the Food and Drug Administration (FDA) announced a new COVID-19 diagnostic testing policy. This policy, issued via agency guidance and effective immediately, allowed certain laboratories—principally clinical and commercial laboratories—that had developed and validated their own COVID-19 diagnostics to begin to use the tests prior to the test receiving an Emergency Use Authorization (EUA) from the agency.<sup>5</sup> According to reporting at the time, this meant “the nation will become able virtually

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<sup>1</sup> University of Minnesota Center for Infectious Disease and Policy, “Glitch delays COVID-19 tests for states as first evacuees cleared,” February 12, 2021, <https://www.cidrap.umn.edu/news-perspective/2020/02/glitch-delays-covid-19-tests-states-first-evacuees-cleared>.

<sup>2</sup> “U.S. agency investigating production of faulty coronavirus test kits,” March 1, 2020, <https://www.reuters.com/article/us-china-health-test-kits/u-s-agency-investigating-production-of-faulty-coronavirus-test-kits-idUSKBN20P09Y>.

<sup>3</sup> *Washington Post*, “Summary of the Findings of the Immediate Office of the General Counsel's Investigation Regarding CDC's Production of COVID-19 Test Kits,” <https://www.washingtonpost.com/context/summary-of-the-findings-of-the-immediate-office-of-the-general-counsel-s-investigation-regarding-cdc-s-production-of-covid-19-test-kits/a750fbf7-9a4f-4062-8fcc-c6cf42600578/>.

<sup>4</sup> HHS OIG, “Audit of HHS's Production and Distribution of COVID-19 Lab Test Kits,” <https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000462.asp>.

<sup>5</sup> See generally FDA, “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,” May 11, 2020, <https://www.fda.gov/media/135659/download>; and FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” <https://www.fda.gov/news-events/>

overnight to test thousands of patients rather than the few hundred tested so far for the virus, known as Covid-19.”<sup>6</sup> This guidance, updated March 16, May 4, and May 11 of 2020, has been a pivotal part of FDA’s response to diagnostic testing during the pandemic.

In part because COVID-19 is caused by a novel pathogen, diagnostic testing was initially led and carried out through the country’s public health infrastructure. This infrastructure includes the CDC and the country’s network of state and local public health laboratories. In contrast, in normal situations with established pathogens, diagnostic testing is carried out by a number of entities, including private reference and commercial laboratories (e.g., Quest, LabCorp), hospital-based and other clinical laboratories, and laboratories in academic medical centers, among others. During the pandemic, community-based testing sites, drive-through testing sites, and retail pharmacies all have played a role in providing COVID-19 testing, both in terms of sample collection as well as providing point-of-care testing.

FDA’s COVID-19 diagnostics guidance supported the expansion of diagnostic testing from the public health setting into the clinical health care and commercial settings, leveraging significant standing resources across the country, including facilities, trained personnel, expertise, materials, and equipment. It was FDA’s intention that this expansion of diagnostic testing would help the country meet demand for testing generated both by community spread of COVID-19 as well as expanded clinical testing guidelines issued by CDC at the time.<sup>7</sup> In addition, because many cases of COVID-19 are mild or asymptomatic, widespread access to testing—which informs development of important metrics such as the case fatality rate—was critical to understanding the scope and extent of the disease in the United States, and to efficiently directing resources to mitigate its impact in the broader community, including in schools and workplaces.

Diagnostic tests—formally called in vitro diagnostic (IVD) devices—may be commercially developed and distributed as “kits” or developed, validated, and carried out by a clinical laboratory. This second type of test, when carried out in a single laboratory, is referred to by FDA as a laboratory-developed test (LDT), and is typically the more commonly used type of test in rapidly evolving situations because of its flexibility and differing federal regulatory requirements, among other reasons. CDC’s test was manufactured as a test kit and initially was authorized to be distributed only to specific CDC-qualified labs. FDA’s diagnostics guidance eventually applied to both manufacturers of “kits” as well as to clinical laboratories carrying out tests they developed and validated. The initial February 29 version of the guidance focused on tests carried out by high-complexity clinical laboratories only, including LDTs, as these tests were in many cases already developed and validated, and were able to be offered almost immediately, without needing to be manufactured and commercially distributed as kits. Two of the country’s largest clinical laboratories, Quest Diagnostics and LabCorp, almost immediately began carrying out their own COVID-19 molecular diagnostic testing in early March pursuant to the FDA guidance.<sup>8</sup>

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press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics.

<sup>6</sup> *Wall Street Journal*, February 29, 2020, “FDA to Allow Labs to Begin Use of High-Complexity Tests for Coronavirus,” [https://www.wsj.com/articles/fda-to-allow-labs-to-begin-use-of-high-complexity-tests-for-coronavirus-11582992472?mod=article\\_inline](https://www.wsj.com/articles/fda-to-allow-labs-to-begin-use-of-high-complexity-tests-for-coronavirus-11582992472?mod=article_inline).

<sup>7</sup> FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>.

<sup>8</sup> See for example, Quest, “COVID-19: Doing our Part,” <https://www.questdiagnostics.com/home/Covid-19/#:~:text=March%209%202020,was%20labeled%20a%20worldwide%20pandemic>.

# Diagnostic Tests

## Which Federal Agencies Have a Role in Diagnostic Test Regulation?

Federal agencies involved in the regulation of IVDs include FDA and the Centers for Medicare & Medicaid Services (CMS). FDA derives its authority to regulate the sale and distribution of medical devices, such as IVDs, from the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA). CMS's authority to regulate IVDs is through the Clinical Laboratory Improvement Amendments of 1988 (CLIA, P.L. 100-578), codified in the PHSA.<sup>9</sup> FDA regulates the safety and effectiveness of diagnostic tests, as well as the quality of the design and manufacture of the diagnostic test.<sup>10</sup> CMS regulates the quality of clinical laboratories and the clinical testing process.<sup>11</sup> All clinical laboratories in the United States, regardless of whether they are part of the country's public health infrastructure or part of the health care delivery system, are regulated by the CLIA program, administered by CMS. The CLIA program generally certifies clinical laboratories as able to carry out high or moderate complexity tests, or waived tests (usually referred to as point-of-care tests).

## What Are IVD Tests?

In vitro diagnostic devices are defined in FDA regulation as a specific subset of medical devices that include “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions ... in order to cure, mitigate, treat, or prevent disease ... [s]uch products are intended for use in the collection, preparation, and examination of specimens taken from the human body.”<sup>12</sup> As indicated by this definition, an IVD may also include *components* of tests, which can include both non-diagnostic ingredients, called general purpose reagents (GPRs), and the active ingredient(s) in a diagnostic test, referred to as the analyte specific reagent (ASR).

In general, as noted above, an IVD device may be a *commercial test kit* (a self-contained commercial product developed, produced, and distributed by a manufacturer to multiple laboratories) or a *laboratory developed test* (a product developed by and used in a clinical laboratory). LDTs may use components (e.g., general purpose reagents like a buffer) that are either manufactured in-house by the laboratory or acquired by the laboratory commercially, and were previously referred to as “home-brew tests.”

The FDA defines an LDT as a class of IVD that is designed, manufactured, and used within a *single* clinical laboratory.<sup>13</sup> LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new strains of known infectious diseases) or are the subject of advancing scientific research (e.g., genomic testing for cancer). The majority of genetic tests—a type of IVD that analyzes various aspects of an individual's genetic material (e.g., DNA, RNA)—are LDTs.

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<sup>9</sup> PHSA §353 [21 U.S.C. §263a].

<sup>10</sup> FDA, “Overview of IVD Regulation,” <https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation>.

<sup>11</sup> CMS, “Clinical Laboratory Improvement Amendments (CLIA),” <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA>.

<sup>12</sup> 21 C.F.R. §809.3(a)

<sup>13</sup> FDA, “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs),” October 3, 2014, <https://www.fda.gov/media/89841/download>.

Many COVID-19 diagnostics are LDTs, most commonly molecular tests such as polymerase chain reaction (PCR) tests.

## How Are IVD Tests Regulated?

As with other medical devices, the application of FDA regulatory requirements to IVDs depends on the IVD's risk classification according to its intended use. Classification is based, in turn, on the risk the device poses to the patient.<sup>14</sup> For IVDs, which are informational tests, the risk to the patient is that of an incorrect test result, either a false positive or a false negative result, either of which may cause serious harm to the individual. In the case of infectious diseases—for example, COVID-19—the risk of a false negative test extends beyond the individual patient into the community at large. In addition, false positive results may result in wasted clinical resources and exposure of healthy individuals to infected individuals. The FDA classifies medical devices based on their risk to the consumer: Class I (low risk), Class II (moderate risk), and Class III (high risk). Regulatory controls are dependent on the class of a given medical device.<sup>15</sup> If the manufacturer was seeking to market a test outside of an emergency situation, a COVID-19 diagnostic would likely fall into Class II, requiring clearance (through 510(k) notification) prior to marketing, or possibly Class III, requiring a premarket approval (PMA) prior to marketing. In the case of a novel low- or moderate-risk product, it could receive marketing authorization through FDA's De Novo pathway.<sup>16</sup>

## How Are LDTs Regulated?

The regulation of LDTs has been the subject of ongoing debate over at least the past 20 years, driven in large part by an increase in the number and complexity of genetic tests over this time.<sup>17</sup> In general, the FDA has maintained that it has clear regulatory authority over LDTs, as it does with all IVDs that meet the definition of medical device in the FDCA.<sup>18</sup> However, the FDA traditionally exercised enforcement discretion over LDTs—choosing not to enforce applicable statutory and regulatory requirements with respect to such tests—meaning that most of these tests have neither undergone premarket review nor received FDA clearance or approval for marketing.<sup>19</sup> To date, FDA instead focused its enforcement efforts on test kits, which are broadly commercially marketed. In recent years, despite the absence of specific agency guidance on the regulation of LDTs, FDA has nevertheless begun to assert authority over certain LDTs that it considers to be higher-risk.<sup>20</sup>

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<sup>14</sup> FDA, “Overview of IVD Regulation,” <https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation>.

<sup>15</sup> See CRS In Focus IF11083, *Medical Product Regulation: Drugs, Biologics, and Devices*.

<sup>16</sup> See FDA, “FDA Permits Marketing of First SARS-CoV-2 Diagnostic Test Using Traditional Premarket Review Process,” <https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-sars-cov-2-diagnostic-test-using-traditional-premarket-review-process>.

<sup>17</sup> See CRS In Focus IF11389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*.

<sup>18</sup> The term *device* is defined in FDCA §201(h) [21 U.S.C. §321(h)].

<sup>19</sup> FDA, “Laboratory Developed Tests,” <https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests>.

<sup>20</sup> FDA Law Blog, Hyman, Phelps, and McNamara, “Regulation of Laboratory Developed Tests by FDA: Time for the Agency to Cease and Desist Until Congress Enacts Legislation,” <https://www.fdalawblog.net/2019/10/regulation-of-laboratory-developed-tests-by-fda-time-for-the-agency-to-cease-and-desist-until-congress-enacts-legislation/>.

## What Is CLIA and How Is It Involved in LDT Regulation?

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) provided CMS with authority to regulate clinical laboratories.<sup>21</sup> CLIA establishes quality standards for clinical laboratory testing and a certification program for clinical laboratories that perform testing using IVD devices. All laboratories in the United States that perform diagnostic testing for health-related reasons (i.e., with results returned to the patient or a health care practitioner) are regulated by CMS under the authority of CLIA. For CLIA to apply, testing must be carried out on a human specimen. CLIA certification is based on the level of complexity of testing that the laboratory performs, specifically (1) low (therefore, waived) complexity, (2) moderate complexity, and (3) high complexity. FDA is responsible for categorizing tests according to their level of complexity.<sup>22</sup> CLIA requirements are used to evaluate a test's *analytical validity*, defined as the ability of a test to detect or measure the analyte it is intended to detect or measure.<sup>23</sup> Laboratories that perform moderate- and high-complexity testing must meet specific standards and requirements as a condition of certification, including proficiency testing (PT), patient test management, quality control, personnel qualifications, and quality assurance. All LDTs default to high-complexity under CLIA, and therefore may only be carried out by clinical laboratories certified to do high-complexity testing.<sup>24</sup> In addition, under the FDA's COVID-19 diagnostics guidance, during the pendency of agency EUA review, all tests are to be performed only in high complexity clinical laboratories; upon EUA authorization, a test may be carried out in settings specified in the Letter of Authorization, including high or moderate complexity laboratories or waived settings (for use at the point-of-care).<sup>25</sup>

## How Are IVDs Regulated by the FDA During an Emergency Such as the COVID-19 Pandemic?

In certain public health or other emergency situations, the HHS Secretary may declare that existing circumstances justify the use of unapproved medical products for certain uses, or approved medical products for unapproved uses.<sup>26</sup> This declaration facilitates access to not-yet-approved medical products in an expedited manner during certain emergency situations. In the case of the COVID-19, then-HHS Secretary Azar determined that there is a public health emergency and declared that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the novel coronavirus.<sup>27</sup> On the basis of this declaration, FDA issued an EUA authorizing the emergency use of the CDC-developed diagnostic test for COVID-19.<sup>28</sup> The FDA issued the second diagnostics EUA under this authority, and the first pursuant to its COVID-19 diagnostics guidance, to the New York State Department of Public

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<sup>21</sup> PHS § 353 [42 U.S.C. § 263a].

<sup>22</sup> FDA, "CLIA Categorizations," <https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clia-categorizations>.

<sup>23</sup> 42 C.F.R. § 493.1253(b)(2).

<sup>24</sup> 42 C.F.R. § 493.17; and CDC, "Test Complexities," <https://www.cdc.gov/clia/test-complexities.html>.

<sup>25</sup> FDA, "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," May 11, 2020, p. 14, <https://www.fda.gov/media/135659/download>.

<sup>26</sup> FDCA § 564 [21 U.S.C. § 360bbb-3].

<sup>27</sup> FDA, "Coronavirus Disease 2019 (COVID-19) Emergency Use Authorizations for Medical Devices," <https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices>.

<sup>28</sup> Letter of authorization from FDA to CDC, dated December 1, 2020, <https://www.fda.gov/media/134919/download>.

Health for a real-time PCR test, and has since issued hundreds of EUAs for COVID-19 diagnostics, including for molecular, antigen and serology tests.<sup>29</sup>

## How Does the Emergency Use Authority Apply to LDTs If They Are Generally Exempt from Premarket Requirements?

During an emergency, all laboratory-developed tests testing for the relevant pathogen (in this case, SARS-CoV-2) were traditionally required to be approved, cleared, or authorized under an EUA to be legally marketed. Although FDA generally waives most regulatory requirements (e.g., premarket review) for LDTs in normal situations, LDTs have nevertheless traditionally only been able to be used clinically with authorization (e.g., EUA) during an emergency declaration pursuant to FFDCASection 564.<sup>30</sup> That is, statutory requirements under FFDCASection 564 have applied to LDTs as they do to other medical products, and they have applied to both commercial test kits—which are normally subject to FDA regulatory requirements—and to LDTs.<sup>31</sup> However, notably, on August 19, 2020, HHS announced that, effective immediately, it was rescinding all guidance, compliance manuals, website statements, or other informal issuances concerning FDA premarket review of LDTs.<sup>32</sup> The announcement applies to all LDTs—including COVID-19 LDTs—and states that FDA may not require premarket review for these tests absent a notice-and-comment rulemaking process. Per the announcement, premarket review includes PMA, premarket notification (510(k) notification), and EUA. HHS noted that laboratories may voluntarily submit an EUA request, PMA, or 510(k) for LDTs.<sup>33</sup>

The EUA process is usually used to expedite access to medical products that would otherwise need premarket approval or clearance in emergency situations. However, because premarket approval requirements for LDTs are generally waived through enforcement discretion by the agency, the EUA represented additional regulatory requirements for the use of an LDT in emergency situations. In the case of a communicable disease, the test result has implications beyond the individual being tested, and so a false negative result could have consequences for the community. Therefore, FDA had stated that these tests need EUA in an emergency prior to clinical use as do other medical products. In contrast, for commercial test kits, the EUA represents an abbreviated mechanism that allows the unapproved product to be used without undergoing the full premarket review typically required.

Despite a request from the Association of Public Health Laboratories (APHL) to FDA in February 2020, the agency at that time declined to exercise enforcement discretion with respect to COVID-19 LDTs and the requirement that they receive EUA prior to clinical use. APHL maintained that clinical laboratories are regulated by CLIA, and that this regulatory oversight is sufficient.<sup>34</sup>

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<sup>29</sup> FDA Letter of Authorization to New York State Department of Public Health, initially dated February 29 2020, <https://www.fda.gov/media/135661/download>; and FDA, “In Vitro Diagnostics EUAs,” <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>.

<sup>30</sup> FFDCASection 564 [21 U.S.C. §360bbb–3].

<sup>31</sup> FDA, “Emergency Use Authorization of Medical Products and Related Authorities,” p. 28, <https://www.fda.gov/media/97321/download>.

<sup>32</sup> HHS, “Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests,” <https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html>.

<sup>33</sup> For more information, see CRS Insight IN11548, *HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests (LDTs)*.

<sup>34</sup> 360dx, “APHL Asks FDA to Make Own Tests as CDC Struggles to Provide SARS-CoV-2 Test Kits,” February 25, 2020, [https://www.360dx.com/clinical-lab-management/aphl-asks-fda-make-own-tests-cdc-struggles-provide-sars-cov-](https://www.360dx.com/clinical-lab-management/aphl-asks-fda-make-own-tests-cdc-struggles-provide-sars-cov-2-test-kits)

However, partially in response to these concerns, FDA issued its COVID-19 diagnostics guidance allowing certain clinical laboratories that have developed and validated COVID-19 tests, including LDTs, to begin to use the test clinically *prior* to it receiving an EUA from the agency but *after* validation of the test and notification of the agency (see “What Steps Did FDA Take to Expand Testing Capacity in Response to the Issues with CDC’s Test?”).<sup>35</sup>

## The CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel

### How Does the CDC’s COVID-19 Diagnostic Test Work?

The diagnostic test developed by the CDC, called the 2019-Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel, is a complex molecular diagnostic test that relies on generally standard molecular biology laboratory techniques. Specifically, the test uses a technique called Polymerase Chain Reaction (PCR), a standard *in vitro* technique for amplification and identification of target DNA. Because the SARS-CoV-2 virus is an RNA<sup>36</sup> virus, the RNA must be first reverse transcribed to generate copy DNA, or cDNA, which is then amplified (multiple copies are generated) using PCR. PCR relies on primers—very short single stranded pieces of DNA that are complementary to and bind with specific regions of the viral genome and thus define the specific genomic region to be amplified. The test then relies on a probe, or a single-stranded piece of DNA that is chemically or radioactively labelled, that can bind to and thus detect the amplified target portion of the viral genetic material.

CDC’s original test used three sets of primers and probes: two to target specific regions of a designated gene within the SARS-CoV-2 viral genome, and a third that was specific to all SARS-like coronaviruses (see “What Quality Problems Did the CDC’s Test Experience on Rollout to the State and Local Public Health Laboratories?”). The test also includes a number of authorized control samples, including a positive control for SARS-CoV-2 and a “no template control” to test for system contamination. Together, these controls help ensure that the test is functioning properly, and it was the performance of these controls that provided the first indication that the CDC test was contaminated.<sup>37</sup>

### What Type of IVD Is the CDC’s Test and Who May Carry It Out?

The CDC’s test is a kit and was initially authorized to be distributed to state and local public health laboratories to augment public health testing capacity. The test received an EUA from the

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2-test-kits?trendmd-shared=0&utm\_medium=TrendMD&utm\_campaign=0&utm\_source=TrendMD#.XmKIwqhKiUm.

<sup>35</sup> See generally FDA, “Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised),” originally dated February 29, 2020, <https://www.fda.gov/media/135659/download>.

<sup>36</sup> RNA stands for ribonucleic acid. RNA is genetic material with a slightly different chemical composition from DNA, or deoxyribonucleic acid.

<sup>37</sup> *Washington Post*, “Summary of the Findings of the Immediate Office of the General Counsel’s Investigation Regarding CDC’s Production of COVID-19 Test Kits,” <https://www.washingtonpost.com/context/summary-of-the-findings-of-the-immediate-office-of-the-general-counsel-s-investigation-regarding-cdc-s-production-of-covid-19-test-kits/a750fbf7-9a4f-4062-8fcc-c6cf42600578/>.

FDA on February 4, 2020, under which “authorized laboratories” could carry out the test despite the fact that it is not FDA-approved or FDA-cleared, and that it does not meet all related regulatory requirements for marketing.<sup>38</sup> The EUA noted that “[t]esting is limited to qualified laboratories designated by CDC and, in the United States, certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA; 42 U.S.C. §263a), to perform high complexity tests.”<sup>39</sup> CDC-qualified laboratories with a CLIA certification for high-complexity testing able to receive the test kits included U.S. state and local public health laboratories, Department of Defense (DOD) laboratories, and select international laboratories.<sup>40</sup> Public health laboratories verify the test themselves prior to use, and were required initially to send presumptive positive cases back to the CDC in Atlanta for confirmatory testing by the agency. Subsequent amendments to the EUA for the CDC test expanded authorized laboratories to include all high-complexity clinical laboratories.<sup>41</sup>

## **What Quality Problems Did the CDC’s Test Experience on Rollout to the State and Local Public Health Laboratories?**

As noted above, the CDC’s test kit used three sets of probes and primers—or reagents—to detect and identify viral DNA beyond that specific to COVID-19. One of these reagents, the one meant to detect any SARS-like coronavirus including SARS-CoV-2, was returning inconclusive results. To address this, the CDC validated a new protocol for its test that allowed it to be run excluding the faulty reagent, running the test with only the other two diagnostic components. CDC had the authority to modify the test through enforcement discretion granted by FDA.<sup>42</sup> The agency determined that the exclusion of this reagent does not affect the accuracy of the test. Certain laboratories continued to experience problems running the test, even when using the modified protocol, with at least one laboratory reporting that the first reagent was also returning inconclusive results.<sup>43</sup> This problem limited the state and local public health laboratories’ ability to carry out the CDC’s test.

In response to these issues, the New York State Department of Public Health requested and was granted the FDA’s second EUA for its own laboratory-developed test, the New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel.<sup>44</sup> Testing was initially limited under the EUA to two laboratories in New York—the Wadsworth Center, New York State Department of Public Health, and the New York City Department of Health and Mental Hygiene, Public Health Laboratories. New York was one of the states that had continued difficulty implementing CDC’s original test kit, even with the modified protocol.

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<sup>38</sup> EUA Letter from FDA to CDC, originally dated February 4, 2020, <https://www.fda.gov/media/134919/download>.

<sup>39</sup> Ibid.

<sup>40</sup> CDC, “Shipping of CDC 2019 Novel Coronavirus Diagnostic Test Kits Begins,” <https://www.cdc.gov/media/releases/2020/p0206-coronavirus-diagnostic-test-kits.html>.

<sup>41</sup> Ibid.

<sup>42</sup> CDC, “Revision to Test Instructions: CDC 2019 Novel Coronavirus (nCoV) Real-Time RT-PCR Diagnostic Panel (EUA200001),” February 26, 2020, [https://www.aphl.org/Materials/Signed\\_CDC\\_Letter\\_to\\_PHLs-N3\\_Removal\\_Instructions\\_26Feb2020.pdf](https://www.aphl.org/Materials/Signed_CDC_Letter_to_PHLs-N3_Removal_Instructions_26Feb2020.pdf).

<sup>43</sup> NPR, “CDC Report: Officials Knew Coronavirus Test Was Flawed But Released It Anyway,” November 6, 2020, <https://www.npr.org/2020/11/06/929078678/cdc-report-officials-knew-coronavirus-test-was-flawed-but-released-it-anyway>.

<sup>44</sup> FDA Letter to NYSDOH, originally dated February 29, 2020, <https://www.fda.gov/media/135661/download>.

CDC manufactured new test kits after reportedly resolving the manufacturing issue that affected the original test kit. This time, however, CDC manufactured test kits with only the two reagents that were unaffected by the quality issue and those kits were made available to qualified CDC labs through the International Reagent Resource (IRR).<sup>45,46</sup>

Some believe that the CDC's choice to develop and mitigate quality problems with its own COVID-19 diagnostic when an accepted diagnostic was available through the World Health Organization (WHO), which was efficiently distributing a German-developed test globally early in the outbreak, was a decision that cost the United States time in its response to the virus's introduction and spread in the country.<sup>47</sup> Some speculated about the use of the third reagent and whether it had been strictly necessary if the test was still accurate at diagnosing COVID-19 without that reagent, and if it had instead overcomplicated the test.<sup>48</sup> In general, there have been questions raised about the CDC's handling of the development and distribution of its test, and its response to the quality problems that occurred, and the impact this may have had on the country's ability to detect community spread of the disease before it occurred more widely.<sup>49</sup> As previously noted, HHS conducted its own internal review of the CDC's manufacture of its test, and the HHS OIG is currently investigating this issue, as well.

## What Steps Did FDA Take to Expand Testing Capacity in Response to the Issues with CDC's Test?

FDA's COVID-19 diagnostic guidance was published at least partially in response to problems with the rollout of the CDC-developed diagnostic test. As noted, the policy was meant to immediately leverage clinical laboratory tests, including LDTs, developed in high-complexity commercial, reference, and clinical laboratories nationwide to expand testing capacity. Specifically, the new agency guidance allowed CLIA-certified high-complexity laboratories that had developed and validated their own COVID-19 diagnostics to use the tests while the laboratory is preparing, and FDA is reviewing, their EUA submission.<sup>50,51</sup>

The initial FDA guidance stated that laboratories had 15 days after validating their test and notifying the agency to submit an EUA application to FDA, and the guidance recommended confirming the test's first five negative and positive results against an EUA-authorized

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<sup>45</sup> GenomeWeb, Johnson, Madeleine, "CDC Revises SARS-CoV-2 Assay Protocol; Surveillance Testing on Track to Start Next Week," February 28, 2020, <https://www.genomeweb.com/pcr/cdc-revises-sars-cov-2-assay-protocol-surveillance-testing-track-start-next-week#.Xl63kqhKiUk>.

<sup>46</sup> "The International Reagent Resource (IRR) was established by the Centers for Disease Control and Prevention (CDC) to provide registered users with reagents, tools and information for studying and detection of Influenza Virus," see <https://www.internationalreagentresource.org/About/IRR.aspx>.

<sup>47</sup> Sheridan, Cormac, "Coronavirus and the Race to Distribute Reliable Diagnostics," *Nature*, February 19, 2020, <https://www.nature.com/articles/d41587-020-00002-2>.

<sup>48</sup> ProPublica, "Key Missteps at the CDC Have Set Back its Ability to Detect the Potential Spread of Coronavirus," February 28, 2020, <https://www.propublica.org/article/cdc-coronavirus-covid-19-test>.

<sup>49</sup> Politico, "How testing failures allowed the coronavirus to sweep the United States," March 6, 2020, <https://www.politico.com/news/2020/03/06/coronavirus-testing-failure-123166>.

<sup>50</sup> GenomeWeb, "FDA Provides SARS-CoV-2 Test Validation Guidance for High-Complexity Labs Seeking EUA," March 3, 2020, <https://www.genomeweb.com/pcr/fda-provides-sars-cov-2-test-validation-guidance-high-complexity-labs-seeking-eua#.Xl7JFqhKiUk>.

<sup>51</sup> FDA, originally titled "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," originally dated February 29, 2020, <https://www.fda.gov/media/135659/download>.

diagnostic. According to FDA, it “does not intend to object to the use of these tests for clinical testing while the laboratories are pursuing an EUA with the FDA. Importantly, this policy only applies to laboratories that are certified to perform high-complexity testing consistent with requirements under Clinical Laboratory Improvement Amendments.”<sup>52</sup> The guidance also included detailed information about FDA’s expected methods for test validation. As noted, FDA has since updated this guidance document three times to include recommendations related to manufacturers of commercial test kits, manufacturers of and clinical laboratories carrying out serology tests, and the authorization of clinical laboratory testing at the state level.<sup>53</sup>

### **CRS Products Related to COVID-19 Testing**

CRS In Focus IFI 1774, *COVID-19 Testing Supply Chain*

CRS In Focus IFI 1789, *COVID-19 Variants: Vaccines, Diagnostics, and Therapeutics*

CRS Report R46481, *COVID-19 Testing: Frequently Asked Questions*

CRS Insight INI 1548, *HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests (LDTs)*

CRS In Focus IFI 1516, *COVID-19 Testing: Key Issues*

CRS Report R46427, *Development and Regulation of Medical Countermeasures for COVID-19 (Vaccines, Diagnostics, and Treatments): Frequently Asked Questions*

CRS In Focus IFI 1389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*

CRS Report R43438, *Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests*

CRS In Focus IFI 1083, *Medical Product Regulation: Drugs, Biologics, and Devices*

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<sup>52</sup> FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” press release with link to guidance, February 29, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>. See also CRS In Focus IFI 1389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*.

<sup>53</sup> FDA, “Policy for Coronavirus Disease-2019 Tests During the Public Health 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>.

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