

# Significant Regulatory, Compliance, and Enforcement Developments, 2021

STEPHANIE PHILBIN & LAUREN FARRUGGIA\*

The COVID-19 pandemic continued to dominate the U.S. Food and Drug Administration's (FDA or agency) priorities for 2021, with FDA making some substantial regulatory changes, including some spurred by the proliferation of new SARS-CoV-2 viral mutations. Meanwhile, FDA continued to devote significant regulatory attention to software as a medical device (SaMD), including those devices using artificial intelligence (AI) and machine learning (ML).

## COVID-19

Despite the availability of COVID-19 vaccines under Emergency Use Authorization (EUA) and FDA's marketing approval of the Pfizer-BioNTech vaccine in August 2021 and Moderna's vaccine in January 2022 following the agency's review of the biologics license application for each, COVID-19 continued to spread, in large part due to the emergence of SARS-CoV-2 viral mutations.<sup>1</sup> As new variants propagated throughout the year, FDA moved quickly to assess any impact on diagnostic test functionality and performance.

On January 8, 2021, FDA issued a safety communication alerting clinical laboratory staff and health care providers that the agency was actively monitoring the potential impact of viral mutations on authorized COVID-19 molecular tests.<sup>2</sup> This safety alert followed reports of false negative results where mutations occurred in the part of the virus's genome assessed by the affected tests. At the time, FDA identified three authorized molecular tests that could be impacted by SARS-CoV-2 genetic variants, but the agency clarified that any impact did "not appear to be significant."<sup>3</sup> Meanwhile, the agency continued to receive a high volume of new EUA submissions requiring additional resources to ensure adequate review, as Dr. Timothy Stenzel, Director, Office of In Vitro Diagnostics, Center for Devices and Radiological Health, noted

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\* Stephanie Philbin is a partner at Goodwin Procter LLP and a member of the firm's FDA practice. Lauren Farruggia is an associate at Goodwin Procter LLP and is also a member of the firm's FDA practice.

<sup>1</sup> Press Release, U.S. Food & Drug Admin., FDA Approves First COVID-19 Vaccine (Aug. 23, 2021), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine>; Press Release, U.S. Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Takes Key Action by Approving Second COVID-19 Vaccine (Jan. 31, 2022), <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine>.

<sup>2</sup> Press Release, U.S. Food & Drug Admin., FDA Issues Alert Regarding SARS-CoV-2 Viral Mutation to Health Care Providers and Clinical Laboratory Staff (Jan. 8, 2021), <https://www.fda.gov/news-events/press-announcements/fda-issues-alert-regarding-sars-cov-2-viral-mutation-health-care-providers-and-clinical-laboratory>.

<sup>3</sup> *Id.*

during FDA’s January 13, 2021 Virtual Town Hall Series on COVID-19 Test Development and Validation.<sup>4</sup>

Following this safety alert, in February 2021, FDA issued a guidance document, Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests, in further response to emerging variants and the potential impact on test development and performance post-authorization.<sup>5</sup> In this guidance, FDA indicated that during EUA review, it intends to consider the performance of a test across all known viral variants, as well as the developer’s plans for post-authorization monitoring for performance against future variants. The agency also revised a number of EUAs for molecular, antigen, and serological tests to establish conditions of authorization in response to the continued emergence of new variants. Notably, FDA recommended, but did not require, that test developers consider disclosing in an EUA request whether the test’s labeling should include limiting statements representing the time period and geographic location of which clinical specimens used in the test’s evaluation were collected, suggesting further that test developers disclaim that “the clinical performance has not been established in all circulating variants, and that performance may vary depending on the variants, and their prevalence, circulating at the time of patient testing.”<sup>6</sup>

In December 2021, FDA made available on its website a page devoted to assessing the impact of viral mutations on COVID-19 tests, including identifying a list of tests for which FDA has identified performance issues with respect to certain variants.<sup>7</sup>

The other major regulatory shift for test developers occurred on November 15, 2021, when FDA issued a revised Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (“Test Guidance”).<sup>8</sup> These revisions were shortly followed by a statement from the U.S. Department of Health and Human Services (HHS) announcing the withdrawal of a policy established in August 2020 that directed FDA not to require premarket review of laboratory developed tests (LDTs).<sup>9</sup>

In the revised Test Guidance, FDA significantly changed its enforcement policy to now require, with limited exceptions, EUAs or traditional marketing authorizations (e.g., a granted De Novo or 510(k) clearance) for COVID-19 LDTs and other diagnostic or serology tests. This ended FDA’s policy that previously allowed developers to offer their COVID-19 tests prior to or without an EUA after the product was validated and notification of such validation was provided to FDA. The agency

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<sup>4</sup> Transcript of FDA Virtual Town Hall Series—Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests at 6 (Jan. 13, 2021), <https://www.fda.gov/media/145290/download>.

<sup>5</sup> U.S. FOOD & DRUG ADMIN., POLICY FOR EVALUATING IMPACT OF VIRAL MUTATIONS ON COVID-19 TESTS—GUIDANCE FOR TEST DEVELOPERS AND FOOD AND DRUG ADMINISTRATION STAFF (Feb. 2021), <https://www.fda.gov/media/146171/download>.

<sup>6</sup> *Id.* at 8.

<sup>7</sup> *SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests*, U.S. FOOD & DRUG ADMIN. (Dec. 28, 2021), <https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests>.

<sup>8</sup> U.S. FOOD & DRUG ADMIN., POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY—GUIDANCE FOR DEVELOPERS AND FOOD AND DRUG ADMINISTRATION STAFF (Nov. 15, 2021), <https://www.fda.gov/media/135659/download>.

<sup>9</sup> Press 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>.

also identified its priorities for EUA review of certain types of tests, including at-home and point-of-care diagnostic tests that can be manufactured in high volumes and certain high-volume, high-throughput laboratory-based molecular diagnostic tests (and home collection kits for use with such tests). FDA clarified that COVID-19 LDTs offered prior to issuance of the revised Test Guidance now required submission of an EUA request within sixty days from the issuance of the revised Test Guidance, but generally such products could continue to be offered while FDA reviewed the EUA request. In addition, FDA opted not to recognize any additional states or territories for the regulation of COVID-19 testing as of the date of issuance of the revised Test Guidance. Thus, COVID-19 LDTs could continue to be offered without notification of test validation or submission of an EUA request to FDA where the test is designed, developed, and used within a single, high-complexity Clinical Laboratory Improvement Amendments certified laboratory that has been authorized by a state or territory, previously recognized by FDA, that has chosen to authorize laboratories within that state or territory to develop COVID-19 tests and perform specimen testing.

What will 2022 bring for the regulation of COVID-19 tests? The agency continues to assess the impact of the omicron and omicron BA.2 variants (and any new variants should they emerge) on test performance. Moreover, as public health needs change or more COVID-19 tests are authorized, FDA may reassess its priorities for review of such tests.

In addition, the agency will continue to step up its enforcement actions against those bad actors distributing counterfeit COVID-19 tests. FDA remains focused on pursuing violations for COVID-19-related devices. As was the case in 2020, FDA targeted manufacturers with enforcement action throughout 2021. As of May 1, 2022, FDA published on its website sixty-three Warning Letters issued to medical device manufacturers during 2021, including: 1) seventeen for COVID-19 test developers; 2) sixteen for mask manufacturers; 3) thirteen for thermographic device manufacturers; and 4) thirty-four for devices that were considered “Adulterated and Misbranded Products Related to Coronavirus Disease 2019 (COVID-19).”<sup>10</sup> Stakeholders can continue to expect enforcement activity in this space for the duration of the COVID-19 public health emergency, particularly as FDA’s regulatory treatment of COVID-19 tests continues to evolve in response to the stage of the pandemic and the emergence of new viral mutations.

Interestingly, there are some signs of returning to normal within CDRH. On June 7, 2022, the agency announced the withdrawal of its June 2020 guidance establishing that, for device marketing submissions and applications on hold, FDA did not intend to consider a submission or application to be withdrawn for an additional 180 days beyond the relevant response date.<sup>11</sup> This means that, as of July 7, 2022, FDA will generally consider a marketing submission or application to be withdrawn if the submitter or applicant does not provide a complete response to a major deficiency letter or an additional information letter consistent with preexisting guidance.

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<sup>10</sup> *Warning Letters*, U.S. FOOD & DRUG ADMIN. (current as of Apr. 28, 2022), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>.

<sup>11</sup> 87 Fed. Reg. 34,691 (June 7, 2022).

## SAMD, AI, AND ML

Although FDA’s COVID-19 response remained one focus of the agency’s time and effort, in 2021 FDA also devoted considerable attention to Software as a Medical Device (SaMD), including artificial intelligence and machine learning functionalities.

In January 2021, FDA released the agency’s first Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan (“Action Plan”).<sup>12</sup> This Action Plan was a follow-up to FDA’s April 2019 proposed AI/ML-based SaMD regulatory framework and discussion paper (“Discussion Paper”).<sup>13</sup> The Action Plan emphasized the deep potential for such technology to change patient outcomes and streamline health care delivery, but also recognized the need for continued stakeholder engagement to adequately establish the agency’s regulatory framework for AI/ML-based SaMD oversight.

The Action Plan identified several key action items for the agency as it continues to build out a regulatory framework for AI/ML-based SaMD. FDA attempted to progress through these action items throughout 2021, as detailed below:

- Announcement of Intention to Issue a Draft Guidance on Predetermined Change Control Plan: FDA signaled its commitment to refining a regulatory framework that would allow for some post-market SaMD modifications based largely on the establishment and utilization of SaMD Pre-Specifications and an Algorithm Change Protocol set forth in a proposed “Predetermined Change Control Plan.” Although FDA in its Action Plan told stakeholders to expect availability of a draft guidance later in 2021 addressing a Predetermined Change Control Plan, the agency has yet to publish it.
- Encourage Harmonization of Good Machine Learning Practice (GMLP) Development: FDA first used the term “GMLP” in its Discussion Paper and clarified that the GMLP framework is meant to be “akin to good software engineering practices or quality system practices.”<sup>14</sup> The agency stressed its active participation in worldwide GMLP development efforts, including its membership in the Xavier AI World Consortium Collaborative Community and the Pathology Innovation Collaborative Community. Following the Action Plan’s publication, in October 2021, FDA, Health Canada, and the U.K. Medicines and Healthcare products Regulatory Agency (MHRA)

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<sup>12</sup> U.S. FOOD & DRUG ADMIN., ARTIFICIAL INTELLIGENCE/MACHINE LEARNING (AI/ML)-BASED SOFTWARE AS A MEDICAL DEVICE (SAMD) ACTION PLAN (Jan. 2021), <https://www.fda.gov/media/145022/download>.

<sup>13</sup> U.S. FOOD & DRUG ADMIN., PROPOSED REGULATORY FRAMEWORK FOR MODIFICATIONS TO ARTIFICIAL INTELLIGENCE/MACHINE LEARNING (AI/ML)-BASED SOFTWARE AS A MEDICAL DEVICE (SAMD)—DISCUSSION PAPER AND REQUEST FOR FEEDBACK (Apr. 2019), <https://www.fda.gov/media/122535/download>.

<sup>14</sup> *Id.* at 9.

issued a set of ten guiding principles meant to aid the development of GMLP.<sup>15</sup>

- Public Workshop on Algorithm Transparency and Support of Algorithm Evaluation and Improvement: As previewed in the Action Plan, on October 14, 2021, FDA held a public workshop to seek feedback from stakeholders on how device labeling supports transparency to users and ways in which such transparency might enhance the safety and effectiveness of these devices. FDA also sought to gather input on the types of information that would be helpful for a manufacturer to include in the labeling and public facing information of AI/ML-enabled medical devices.<sup>16</sup> Separately, FDA emphasized in the Action Plan the need to carefully consider bias and generalizability in AI/ML-based medical devices and highlighted its support of numerous regulatory science research efforts to develop methods to evaluate and remediate these issues.
- Support of Stakeholders Piloting Real-World Performance (RWP) Process: FDA recognized the importance of real-world data collection and monitoring as a critical element of its proposed regulatory framework for oversight of modifications to AI/ML-based SaMD. FDA announced its intention to advance RWP monitoring pilots with stakeholders on a voluntary basis and seeks to build from these learnings to develop a framework for establishing and validating RWP parameters and metrics.

Building on these efforts, in September 2021, FDA's Digital Health Center of Excellence published a list of AI/ML-enabled medical devices on its website.<sup>17</sup> The identified devices include those cleared via 510(k) premarket notifications, authorized pursuant to De Novo requests, and approved via premarket approval applications. Although FDA cautioned that while not exhaustive or comprehensive, the list is intended to increase transparency and access to information on these devices that span across medical disciplines. FDA intends to update the list (which, as of May 1, 2022, included 343 devices) on a periodic basis. The list will surely grow as AI/ML-enabled medical devices continue to gain popularity and as AI/ML technology advances.

The agency has already taken steps in 2022 to further define its regulatory approach to AI/ML-enabled medical devices. FDA announced a virtual meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to be held on July 28, 2022.<sup>18</sup> The meeting will address approaches for evaluating the performance of algorithm-based skin lesion analyzer technology and its application in

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<sup>15</sup> U.S. FOOD & DRUG ADMIN., HEALTH CANADA & MEDS. & HEALTHCARE PRODS. REGUL. AGENCY, GOOD MACHINE LEARNING PRACTICE FOR MEDICAL DEVICE DEVELOPMENT: GUIDING PRINCIPLES (Oct. 2021), <https://www.fda.gov/media/153486/download>.

<sup>16</sup> *Virtual Public Workshop—Transparency of Artificial Intelligence/Machine Learning-enabled Medical Devices*, U.S. FOOD & DRUG ADMIN. (Oct. 14, 2021), <https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-public-workshop-transparency-artificial-intelligencemachine-learning-enabled-medical-devices>.

<sup>17</sup> *Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, U.S. FOOD & DRUG ADMIN. (Sept. 22, 2021), <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices>.

<sup>18</sup> 87 Fed. Reg. 32,172, 32,173 (May 27, 2022).

detecting skin cancers in various patient care settings. Interested stakeholders have until July 11, 2022 to comment on the public docket. The Advisory Committee meeting may provide FDA with additional perspective as the agency continues to assess AI/ML-enabled devices.