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October 27, 2023

Robert Califf, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Medical Devices; Laboratory Developed Tests. Proposed Rule; FDA-2023-N-2177

Dear Commissioner Califf:

Foundation Medicine appreciates the opportunity to comment on the proposed rule on Medical Devices; Laboratory Developed Tests, published on October 3, 2023 (hereafter referred to as the "proposed rule"). Foundation Medicine is a leading high-quality test innovator committed to transforming cancer care. Foundation Medicine offers comprehensive genomic profiling tests using next-generation sequencing technology to identify molecular alterations across all cancers. Specifically, our companion diagnostic tests, FoundationOne®CDx and FoundationOne®Liquid CDx, are approved by the U.S. Food and Drug Administration (FDA) and match a patient to a targeted therapy or immunotherapy, or indicate whether a patient is eligible for a clinical trial based on the genomic profile of that patient's tumor.

Precision oncology holds tremendous promise to redefine the way each person with cancer is treated. Fulfilling this promise hinges on the ability to accurately and reliably match patients to the most effective treatment options. Yet, too often, there is an assumption that because a test is available for clinical use, the test has been demonstrated to generate accurate and reliable results. Such assumptions are flawed and will perpetuate, if not exacerbate, the known quality gaps in tests used in clinical practice today.

Foundation Medicine commends FDA for raising concerns regarding the safety risks posed by poorly validated LDTs. The quality and level of validation of tests used to select therapy can vary dramatically.[1] Foundation Medicine has observed poorly validated testing that incorrectly identified patients as positive or negative for biomarkers, where patients may have lost the opportunity to try a potentially life-saving therapy or been exposed to a potentially toxic therapy with no benefit. Additionally, Foundation Medicine has experienced situations where our testing

[1] Pfeifer, J.D., et al., 2022. Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics, American Journal of Clinical Pathology, 157:628–638.

identified an incorrect diagnosis. One recent example is of a patient who was initially misdiagnosed with lung cancer, but through Foundation Medicine testing was found to have biomarkers consistent with metastatic skin cancer treatable with an FDA-approved targeted therapy.

As a company committed to offering the highest-quality genomic testing, Foundation Medicine supports a single, risk-based regulatory framework for all tests, regardless of where the test is manufactured. Foundation Medicine supports a modernized regulatory framework that enables future scientific research to drive medical discoveries, translates those discoveries to the clinical setting, and improves patients' access to personalized care. To achieve these goals, Foundation Medicine recommends that a regulatory paradigm exemplify the following principles:

- Establish a level playing field by treating all tests with a similar intended use equally;
- Protect patients by applying appropriately rigorous scientific standards to evaluate a new or modified test's analytical and clinical validity;
- Foster innovation through the consistent application of evaluation criteria that accommodate the rapid pace of scientific and technological change; and
- Adopt a patient-centered approach that appropriately balances risks and benefits while ensuring patients' and physicians' timely access to novel tests.

As FDA considers a unified framework for all diagnostic tests, Foundation Medicine respectfully offers the following comments:

- A single, risk-based regulatory framework is the best way to assess a test's risk and apply review requirements consistently according to a test's intended use;
- The regulatory framework should improve the review of diagnostics for rare diseases and lower risk modifications to tests;
- Leveraging other programs such as New York State Department of Health Clinical Laboratory Evaluation Program (NYS-DOH CLEP) would not apply the same standards or controls as those under FDA's existing medical device regulations, and would not achieve a single risk-based regulatory framework; and
- The proposed rule, Statements of Administration Policy on federal legislation to advance regulatory reform, and the recently announced oncology pilot program are philosophically inconsistent.[2]

I. FDA's Regulatory Paradigm Should Establish a Level Playing Field Based on a Test's Intended Use to Foster Innovation and High-Quality Care

Foundation Medicine supports a consistent framework for the assessment of a test's risk and the application of FDA review requirements, including validation standards, according to a test's intended use. A level playing field is critical to maintaining the integrity of FDA review, fostering innovation, and providing patients with high-quality care.

[2] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program. Document issued June 20, 2023. https://www.fda.gov/media/169616/download (Accessed 17 October 2023)

Risk-Based Framework

Foundation Medicine supports a risk-based framework for regulation of all tests. In a risk-based approach, FDA must review tests based on their intended use and subject tests with similar intended uses to the same regulatory requirements. The phase-out plan for enforcement discretion described in the proposed rule calls for premarket submissions at specified times for high-risk, moderate-risk, and low-risk tests.[3] Foundation Medicine supports FDA's proposal to address high-risk tests first; however, in any final rule, FDA should provide transparency around this terminology as it is not consistent with current statutory classification rules.

Grandfathering

In the proposed rule, FDA requests public feedback regarding whether to adopt a "grandfathering" policy, whereby currently available tests are exempt from premarket review. Foundation Medicine is concerned that a broad grandfathering policy would result in a large volume of tests that FDA will not have affirmatively approved and could appear to be FDA-approved. A broad grandfathering policy may also enable test developers to extensively modify their tests, evading the regulatory requirements. If FDA includes a grandfathering policy in its final rule, then Foundation Medicine believes it is critical that all grandfathered LDTs bear in all labeling, including the test report, a statement that reads as follows: "This test has not been reviewed by the Food and Drug Administration."[4] Foundation Medicine recommends that FDA consider guardrails, such as prohibiting modifications to grandfathered tests that would change a test's intended use. Furthermore, Foundation Medicine encourages FDA to establish a clear, easily accessible, and publicly available mechanism that would allow a user of a test or a recipient of a test result to ascertain the test's level of review.

Diagnostics for Rare Disease

In the proposed rule, FDA indicates that it has evidence demonstrating that enforcement discretion for tests for rare diseases would be inappropriate and instead noted that alternative pathways exist for sponsors, such as the Humanitarian Device Exemption (HDE) pathway. Foundation Medicine believes that the HDE pathway is a poor fit for diagnostic tests, as it applies only to tests that would be run on 8,000 or fewer patients and has significant limitations compared to 510(k), de novo, and Premarket Approval (PMA) pathways.[5] For tests that are used to select a rare subset from a larger population, or large panel tests that may include rare biomarkers, more than 8,000 tests may be necessary. However, key challenges still exist, such as the inability to access sufficient numbers of rare samples to demonstrate performance.

Rather than encouraging sponsors to use the HDE pathway, FDA should apply an evidence

[3] Proposed rule. VI. Description of Proposed Enforcement Policy, B. Stages. p. 68024.
[4] This requirement is consistent with the Verifying Accurate Leading-Edge IVCT Development (VALID) Act of 2023 (H.R.2369). Section 587G(a)(10).
[5] Limitations include post-approval requirements to gain IRB or appropriate local committee approval at a facility for clinical care, or use within a facility having IRB oversight, and periodic reporting including a statement that no other comparable device (other than another HUD under an HDE or a device under an approved IDE) is available to treat or diagnose the disease or condition.

development and risk/benefit framework appropriate for rare indications in diagnostics. For example, a diverse set of stakeholders, including Foundation Medicine, published a white paper that outlined how FDA could provide flexibilities within their current statutory and regulatory authorities to speed development and approval of certain companion diagnostics for rare biomarkers.[6] The paper proposes a number of premarket flexibilities, including defining minimum requirements for analytical validation together with waiving or shifting to the postmarket setting any studies of lesser importance, and exploring flexibilities in validation for rare cancers and biomarkers based on benefit-risk assessment. We note that the approach laid out in this white paper is distinct from that offered by the FDA's recently announced oncology pilot program in a critically meaningful way: although the white paper proposes ways to increase the validity of tests used to enroll patients in clinical trials, it does not advance the idea that this would be a sufficient surrogate for a companion diagnostic.

Prioritizing FDA Review of Higher Risk Modifications

In requiring premarket review for many LDTs, FDA should also reconsider its current framework for evaluating modifications to tests and focus review on the highest risk modifications. Under the current paradigm, even simple, low-risk modifications to PMA-approved tests are cumbersome and can require 180 days or more for FDA review, thus limiting the pace of innovation for such tests. In addition to encouraging greater use of the predetermined change protocol pathway (PCCP) by FDA, Foundation Medicine recommends the creation of a new pathway whereby low-risk modifications are reviewed on a 45-day timeline. FDA could leverage this pathway when a PCCP may not be possible or available for low-risk modifications, i.e., those that do not change the intended use, indications for use, or adversely affect the approved analytical or clinical performance of a test. Such a pathway would enable test developers to implement low-risk modifications more expeditiously, ensuring patients' access to cutting-edge technology and reducing FDA's review burden.

Use of Third-Party Programs as a Proxy for Review

In the proposed rule, FDA asked whether it was appropriate to leverage programs such as NYS-DOH CLEP or those within the Veterans Health Administration (VHA) in the review of LDTs and whether it may be appropriate to continue general enforcement discretion for LDTs reviewed by these programs. These programs, as they exist today, do not have the same scope and standards as FDA's existing medical device regulations. For example, NYS-DOH does not require robust clinical validation for many tests and does not apply FDA's general controls or equivalent (e.g., registration and listing, adverse event reporting). Foundation Medicine believes that any regulatory framework for diagnostic tests should hold tests of the same or similar intended use to the same review standard. Allowing external programs with differing standards to stand in for FDA regulation would not achieve the goal of a single risk-based regulatory framework.

[6] Friends of Cancer Research White Paper. 2022. Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications. Available at: https://friendsofcancerresearch.org/wp-content/uploads/Dx_For_Rare_Biomarkers_White_Paper.pdf

II. FDA's Oncology Pilot Program Jeopardizes Its Patient Safety Goals

As previously noted, Foundation Medicine supports a single, risk-based regulatory framework and commends FDA for recognizing the risks associated with poorly validated tests. In the preamble to the proposed rule, FDA highlights numerous concerns with LDTs used to drive patient treatment decisions and cites several studies calling into question the validity of many of these tests.[7,8,9] However, it is impossible to reconcile the underlying goals of the proposed rule with the Oncology Center of Excellence guidance entitled "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program."[10]

In the proposed rule, FDA states: "FDA has initiated a pilot program for certain oncology diagnostics as one step that may be helpful in reducing the risks associated with using certain LDTs to identify cancer biomarkers."[11] This pilot program, described in a final guidance issued without opportunity for public comment, undercuts FDA's rationale for the proposed rule.[12] Importantly, the pilot program would allow LDTs claiming to meet "minimum performance characteristics" (MPCs) to substitute for FDA authorized companion diagnostics for certain oncology drugs. These MPCs would be based on a minimum demonstration of analytical validity only, as FDA asserts that clinical validity can be "extrapolated" from one test to another.

Some may argue that FDA's proposed rulemaking to regulate all LDTs resolves any concerns with the oncology pilot program. It does not, however, because the pilot program suffers from a fundamental problem: a minimum analytical performance threshold is a poor substitute for an FDA-authorized, clinically validated companion diagnostic test. Tests that use the same technology are not interchangeable and extrapolation of clinical validity from one test to another is not scientifically justifiable nor does it improve the safety of tests. Companion diagnostics offer the only information available about a cancer patient's molecular tumor characteristics. As such, the test's performance is critical to assuring that the drug can meet its stated safety and effectiveness claims, while also accurately and reliably matching a patient to the right drug.

In fact, FDA acknowledges in the Preliminary Regulatory Impact Analysis accompanying the proposed rule that patients and providers cannot distinguish between LDTs and tests authorized by FDA.[13] The pilot program will amplify, rather than reduce, the risks to patients described in the proposed rule by encouraging the use of tests that are not clinically validated, resulting in

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[7] Pfeifer, J.D., et al., 2022. Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics, American Journal of Clinical Pathology, 157:628–638.
[8] Quy, et al. Inter-Assay Variability of Next-Generation Sequencing-Based Gene Panels. BMC Medical Genomics, 15: 86, 2022.
[9] Vega, et al. Aligning Tumor Mutational Burden (TMB) Quantification Across Diagnostic Platforms: Phase II of The Friends of Cancer Research TMB Harmonization Project. Annals of Oncology 32(12):1626-1636, 2021.
[10] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program. Document issued June 20, 2023. https://www.fda.gov/media/169616/download (Accessed 17 October 2023)
[11] See Footnote 7 of the proposed rule, p. 68010.
[12] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program. Document issued June 20, 2023. https://www.fda.gov/media/169616/download (Accessed 17 October 2023)
[13] "It is possible that, over time, patients and providers might learn the differences between competing tests and eventually stop purchasing ineffective tests regardless of regulation. However, in practice, without widespread awareness of the difference between IVDs offered as LDTs and IVDs aligned with FDA requirements, we expect that learning of this kind may be rare... As for patients, ability to internalize the relevant risks may be precluded by not knowing the difference between LDTs and FDA-approved IVDs or having meaningful informed choice in the purchase decision." Laboratory Developed Tests Proposed Rule. Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis. Docket No. FDA-2023-N-2177, p. 13.

further confusion. For these reasons, Foundation Medicine requests that FDA withdraw the guidance finalizing the oncology pilot program, irrespective of whether the proposed rule on LDTs is finalized.[14]

Foundation Medicine remains committed to championing comprehensive diagnostic regulatory reform. The legacy of reform should be patients' improved access to well-validated tests that transform the future of health care. We look forward to continuing to work with the FDA and Members of Congress to advance a regulatory framework that improves patients' access to well-validated tests. If we may be of further assistance or if FDA has questions regarding our comments, please do not hesitate to contact me at emansfield@foundationmedicine.com.

Sincerely,

Elizabeth Mansfield, Ph.D.
Vice President, Regulatory Policy
Foundation Medicine

[14] See Regulations.gov Docket FDA-2022-D-2275