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August 10, 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: Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; FDA-2022-D-2275-0002

Dear Commissioner Califf:

Foundation Medicine appreciates the opportunity to comment on the final guidance *Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program* (hereafter referred to as the pilot program).[1] 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 (NGS) technology to identify molecular alterations across all cancers. Specifically, FoundationOne®CDx and FoundationOne®Liquid CDx are FDA-approved companion diagnostics (CDx) that match a patient to targeted therapies, immunotherapies, or clinical trials 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. Worse, some purport that the quality of the diagnostic test does not matter, just the safety and efficacy of the drug. 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 laboratory developed tests (LDTs). The quality and level of validation of tests used to select therapy can vary dramatically.[2] 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 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.

[1] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff. Document Issued on June 20, 2023.
[2] 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.

FDA faces a critical inflection point. Is the Agency's goal to encourage the development of well-validated, high-quality diagnostic tests that help propel the discovery of new cancer medicines? Or, is the goal to lower the bar and establish a minimum regulatory standard that a majority of test developers can meet, regardless of whether it is an appropriately rigorous standard? Last year, Foundation Medicine was proud to support diagnostic regulatory reform legislation known as the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2022 (S.4348). Foundation Medicine urges FDA to carefully consider the juxtaposition of the VALID Act with the pilot program: the former offered a unified regulatory framework designed to raise test quality standards for all patients, while the latter significantly erodes the FDA's regulatory standards for new cancer medicines and CDx.

Respectfully, Foundation Medicine urges FDA to withdraw its final guidance as the pilot program fails to protect patients from poorly validated tests. As discussed in greater detail below, Foundation Medicine offers the following observations regarding the pilot program:

- Tests are not required to be reviewed for the relevant biomarker;
- Test developers are permitted to make potentially false and misleading claims regarding a test's performance;
- Tests are not required to demonstrate clinical validity based on the false presumption that tests with the same underlying technology are the same and interchangeable;
- FDA does not require tests meeting minimum performance characteristics to meet basic quality standards; and
- FDA's guidance is final without stakeholder opportunity to prospectively address scientific or policy concerns before a drug sponsor is accepted into the pilot program.

I. Pilot Program Erodes the FDA "Gold Standard" by Enabling Tests to Claim FDA Compliance without Evaluating Test Performance for the Relevant Biomarker

Under the existing paradigm, FDA may require a drug manufacturer to codevelop a CDx to ensure the safe and effective use of a drug. CDx tests undergo extensive testing and a rigorous FDA review prior to being available for clinical use. To receive FDA approval, a CDx developer must demonstrate the test's analytical validity, clinical validity, and quality of manufacturing processes. The purpose is to assess whether a test accurately identifies biomarkers, uses a clinically-validated approach to predict treatment response, and adheres to the appropriate design and change controls and quality assurance protocols. This level of validation is appropriate and necessary given that a CDx test result may be the only information that a physician uses to determine whether a patient may respond to a particular therapy.

Currently, FDA has authorized more than 50 CDx tests for over 160 indications.[3] Multiple tests have been authorized for the same drug and indication, illustrating that despite what some may claim, there is no requirement that there only be one test for each drug. In fact, FDA has authorized a number of CDx claims for the same drug and indication through formal, statistically valid demonstrations of non-inferiority.[4] Existing CDx guidance makes clear that one or more

[3] See Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools Accessed August 10, 2023.

[4] See Summary of Safety and Effectiveness Template (SSED) for P210011. Table 3. Pages 9-10 of 107, describing five different tests from different manufacturers for KRAS variants and two different tests for NRAS variants, in addition to the test that is the subject of the SSED. https://www.accessdata.fda.gov/cdrh_docs/pdf21/P210011B.pdf Accessed August 10, 2023.

high-quality FDA authorized tests can be used to support drug safety and effectiveness, stating that "the therapeutic product labeling should specify use of an FDA approved or cleared IVD companion diagnostic device, rather than a particular manufacturer's IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product."[5] Neither the intent or the implementation of existing CDx guidance limits the number of CDx tests that could be authorized for a given oncology drug indication.

In contrast to FDA's current CDx policies, the pilot program allows certain oncology drugs to be approved with reliance on tests claiming to meet minimum analytical performance characteristics (MPCs) rather than an FDA-authorized CDx. The guidance states that for drugs enrolled in the pilot program, the drug manufacturer is required to collect validation information on FDA-provided templates for tests used to enroll patients into clinical trials. FDA's template for NGS tests allows representative validation, i.e. validation of types of genomic alterations over a variety of genomic contexts, but not necessarily of the biomarker in question.[6] If FDA approves an enrolled drug, then at the time of drug approval and after reviewing the templated data, FDA will recommend MPCs for tests used to identify patients for treatment with that drug. FDA anticipates that "the approved drug labeling will specify that the drug is indicated for patients identified as exhibiting a named biomarker by in vitro diagnostic tests that have FDA's recommended performance characteristics."[7]

FDA's justification for the pilot program is that "there is an urgent public health need to recommend minimum performance characteristics" to "address safety risks posed by the use of LDTs that are not properly validated and/or unable to identify the appropriate population for the corresponding drug products."[8] While Foundation Medicine shares FDA's concerns, FDA is establishing a dangerous precedent—one that is inconsistent with the U.S. Department of Health and Human Services' (HHS) stated diagnostic reform goals and potentially worse than the status quo. There is no requirement that a test claiming to meet MPCs must demonstrate that it can accurately detect the relevant biomarker. There is simply a voluntary, publicly-available benchmark for minimum analytical performance goals. The benchmark supplants the requirement to develop a CDx with verified clinical performance that would accurately identify the appropriate patient population for a drug. Further, permitting test developers to claim compliance with a regulatory standard without any assurance that the test meets such standard enables the promulgation of false and misleading claims to the public.

Transparency of analytical performance goals alone will not improve patient care. FDA already publishes on its website the Summaries of Safety and Effectiveness Data (SSEDs) for authorized CDx in the five technology categories eligible for the pilot program. SSEDs provide information regarding a test's technical data, including all performance data and labeling. If MPCs are set at a significantly lower level than the requirements outlined in the SSEDs for an FDA-authorized CDx, then the MPC approach is arbitrary and inconsistent with FDA's current regulation of CDx tests. Similarly, the guidance does not address how drug product labeling will differentiate between the use of a test meeting MPCs and a CDx for different indications, or provide justification for why one indication required a CDx approval while another indication did

[5] In Vitro Companion Diagnostic Devices; Guidance for Industry and Food and Drug Administration Staff. Document issued on August 6, 2014.
[6] See Next Generation Sequencing Template. Table 4. Page 9 of 12, describing a representative approach for analytical concordance between a CGA and comparator. Table 6. Page 11 of 12, describing a representative approach for precision. https://www.fda.gov/media/169619/download?attachment Accessed August 10, 2023.
[7] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff. Document Issued on June 20, 2023.
[8] Ibid.

not. Foundation Medicine assumes that an FDA-authorized CDx could make new claims based on meeting or exceeding MPCs without triggering a requirement for premarket review and approval.

II. Pilot Program Minimizes the Importance of Clinical Validation, Presenting Risks to Patients Particularly for Novel, Complex, or Rare Biomarkers

Oncology drug development is increasingly reliant on the validation of new biomarkers to stratify patients. Tests designed to detect these biomarkers may be difficult to validate, especially as drug manufacturers prioritize the development of targeted therapies for novel, complex, or rare biomarkers. The guidance states that FDA believes it is appropriate to "extrapolate" clinical validity from one test to another test using the same underlying technology, such as NGS, with similar analytical performance.[9] This belief is statistically unsupported. Extrapolation of clinical validity of the test(s) used in a clinical trial to other tests may pose risks to patients, even though appropriate mechanisms to demonstrate clinical validity exist and are routinely used during CDx development.[10,11]

Tests, especially tests of complex or new biomarkers, are not de facto interchangeable because they use the same underlying technology. A test's design, preanalytical and analytical methodology, instrumentation, structure and stability of the bioinformatics pipeline (in the case of NGS), as well as the method of clinical validation are critical to ensuring that a test functions appropriately. For example, a recently published analysis reported that when multiple local tests were used to enroll patients into a clinical trial based on the biomarker known as Tumor Mutational Burden (TMB), the biomarker did not appear to select a responsive population.[12] Foundation Medicine demonstrated that when patients are assessed with an appropriately designed, well-validated test with predetermined cut-offs, such as FoundationOne®CDx, TMB does select a responsive patient population.[13]

Another example of failed extrapolation of clinical validity is that of antibodies used to detect Programmed Death Ligand 1 (PD-L1) expression in tumors. Here the specific intended use of the antibody tests and the cut-offs developed are critical to yield correct results. The Blueprint PD-L1 Immunohistochemistry (IHC) Assay Comparison Project demonstrated that when using four different antibody clones directed against PD-L1, all of which were used to enroll clinical trials, clinical performance varied when the four antibodies were used on the same tumor.[14] Each antibody test had been analytically validated, and the clinical cut-off and clinical validity had been established for the specific drug indication for which they were approved. Although each of these antibodies have been approved as CDx to support different PD-L1-targeting drugs, they are not interchangeable. Extrapolation of clinical validity from one to another would result in a significant rate of incorrect results and likely negative clinical consequences for patients.

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[9] Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff. Document Issued on June 20, 2023.
[10] Li, M. 2015. Statistical Consideration and Challenges in Bridging Study of Personalized Medicine, J Biopharma Stats. 25:3,397-407.
[11] Li, M. 2016. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study. Stats Biopharma Res. 8:355-363.
[12] McGrail, D.J., et al. 2021. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann. Oncol. 32(5):661-672.
[13] Fabrizio, D., et al. 2021. Real-world prevalence across 159,872 patients with cancer supports the clinical utility of TMB-H to define metastatic solid tumors for treatment with pembrolizumab. Ann. Oncol. 32(9):1193-1194.
[14] Hirsch, F.R., et.al., 2017. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thor Oncol. 12:208-222.

Finally, as entities collect large databases of cancer genomic data, there is an increasing desire to use these data with sophisticated artificial intelligence (AI) and machine learning (ML) tools. Such capabilities may facilitate the discovery of new, complex signatures that are or will be biomarkers enabling the development of novel therapies. AI/ML-generated biomarkers will be dependent on the input data used for discovery. Each instance of such a discovery will likely use different inputs, depending on what is available and how cases and controls are selected. The resulting biomarkers will likely have unique features and it will not be possible to extrapolate clinical validity from one test to another. FDA risks adopting a regulatory framework that inadequately anticipates the future of innovation, the growing complexity associated with novel biomarker discovery, and the breadth of claims regarding the predictive nature of tests leveraging AI/ML capabilities.

III. Pilot Program Does Not Require Tests to Meet Basic Quality Controls

FDA is the principal agency responsible for protecting the public health by ensuring the safety and efficacy of medical devices. FDA has a long history of using adverse event monitoring to identify medical device problems and to take appropriate actions to protect patients, including working with manufacturers on voluntary recalls or issuance of safety communications. Adverse event reporting is particularly important for high-risk devices because problems with those devices are the most likely to put patients at risk of serious harm.

Under the pilot program, even if a test meets MPCs, the test developer is not subject to FDA's basic regulatory requirements, known as general controls, that apply to even the lowest risk tests. For example, test developers are not required to register their establishments with the FDA and list the tests they provide. Test developers are also not required to manufacture their tests under a quality system, report adverse events and malfunctions to FDA, or meet recent cybersecurity requirements passed by the United States Congress.[15] Further, there is no mechanism to ensure that a test meeting MPCs will not be modified in ways that would alter the test's performance, resulting in the test no longer satisfying the recommended criteria.

Foundation Medicine recognizes that a part of the problem is the ongoing debate regarding the regulation of LDTs. Foundation Medicine understands that FDA plans to issue proposed rulemaking implementing its enforcement authority. We hope that the proposed rule will require all tests to comply with the basic requirements described above. In the absence of a final rule, FDA should not proceed with the pilot program without the ability to fulfill its primary public health responsibility and impose basic requirements designed to protect patients. Foundation Medicine would be remiss if we failed to note that general controls do not resolve the fundamental problems with the pilot program, which is that a minimum analytical performance threshold is a poor substitute for an FDA-authorized CDx.

IV. FDA Issues Final Guidance Inconsistent with LDT Reform and without an Opportunity for Stakeholder Comments

Foundation Medicine is deeply disappointed that FDA issued final guidance without the opportunity for public comment. It was appropriate and feasible to solicit stakeholder feedback—just as the FDA did with current CDx policy and plans to do with future LDT rulemaking. A public comment period would have enabled FDA to prospectively identify and address scientific or policy concerns before a drug sponsor is accepted into the pilot program. FDA chose to

[15] Cybersecurity in Medical Devices: Refuse to Accept Policy for Cyber Devices and Related Systems Under Section 524B of the FD&C Act Guidance for Industry and Food and Drug Administration Staff . Document issued on March 30, 2023.

leverage an exception to providing a draft guidance under Good Guidance Practices under 21 CFR 10.115 for a select category of high-risk tests without citing a new safety concern. The guidance represents a significant departure from established FDA policy, affects a wide array of stakeholders, and creates an unacceptable precedent regarding patients and test developers' due process.

Additionally, the guidance is in direct conflict with Congressional technical assistance provided by HHS on the VALID Act. For example, HHS has stated that high-risk tests "have a greater potential to cause patient harm if an undetected inaccurate result occurs and therefore, individual premarket review is appropriate to assure that the test meets the applicable standard and adequately protects patients and the public health."[16] HHS also stated that "even if the technology is well-characterized and performance criteria are well-established, the IVCT would still be high risk if an undetected inaccurate result has the potential to cause serious harm or death to the patient."[17] Foundation Medicine agrees and notes that HHS' observations are consistent with the real-life examples provided in this letter.

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 cancer care. Foundation Medicine urges FDA to withdraw the pilot program and consider the serious, long-term implications of policies that will disincentivize high-quality, clinically validated tests, and adversely impact patients and public health. We appreciate FDA's consideration of these comments. If Foundation Medicine 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

[16] U.S. Department of Health and Human Services, "HHS Technical Assistance on the VALID Act of 2021," January 5, 2022.
[17] Ibid.