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U.S. Food and Drug Administration
Center for Devices and Radiological Health
Office of Policy Staff
10903 New Hampshire Ave., Bldg. 66, Rm. 5445
Silver Spring, MD 20993-0002

FDA/CDRH/DCC

JUN 28 2024

RECEIVED

RE: Section 513(f)(3) petition for reclassification of next-generation sequencing oncology panels used for somatic or germline variant detection that include one or more companion diagnostic indications from class III to class II

To whom it may concern:

On January 31, 2024, the U.S. Food and Drug Administration (FDA) announced its intent to reclassify most in vitro diagnostic products (IVDs), including companion diagnostic IVDs, that are currently class III into class II. FDA has stated that it will complete the reclassification process by no later than November 6, 2027 in its final rule clarifying the regulation of laboratory developed tests as medical devices.

In response to FDA's announcement, Foundation Medicine, Inc. (Foundation Medicine) submits this petition in accordance with section 513(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to request reclassification of all next-generation sequencing oncology panel devices used for somatic or germline variant detection that include one or more companion diagnostic indications (categorized under product code PQP) from class III to class II. As detailed in the attached reclassification petition, Foundation Medicine believes there is sufficient information available to establish special controls that, if appropriately rigorous and combined with general controls, can provide a reasonable assurance of the safety and effectiveness of these devices.

Precision oncology can only be as good as the quality of tests. Genomic profiling tests are increasingly the only source of information used to guide therapy selection. New cancer medicines rely on testing for rare or complex biomarkers, which can be difficult for some clinical laboratories to validate. Sophisticated artificial intelligence and machine learning tools may facilitate the discovery of new biomarkers, but these tools could lead to misleading claims regarding the predictive nature of tests if not properly validated and subjected to rigorous controls. Absent a full premarket application (PMA), appropriately rigorous special controls are the only way to ensure that patients and physicians have access to high-quality tests and the

opportunity to benefit from the most effective therapy for their specific type of cancer.

Therefore, in accordance with 21 C.F.R. § 860.123, Foundation Medicine submits this petition in an original and two copies. If you have any questions regarding this petition, please contact me by email at emansfield@foundationmedicine.com.

Thank you for your consideration of this petition.

Sincerely,

A handwritten signature in black ink that reads "B. Mansfield". The "B." is smaller and positioned above the larger, more stylized "Mansfield".

Elizabeth Mansfield, Ph.D.
Vice President, Regulatory Policy
Foundation Medicine
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I. SPECIFICATION OF THE TYPE OF DEVICE

Currently, devices approved under product code PQP (“PQP devices”) are class III next-generation sequencing (NGS) oncology panels used for the qualitative detection of germline or somatic variants in one or more cancer-related genes and that include at least one CDx indication. These devices include gene panels with varying numbers of genes and product-specific genes and may report somatic-only or both somatic and germline mutations across a range of mutation types and complex biomarkers. These devices may query tumor-derived DNA and RNA isolated from tumor tissue or blood for one or more cancer types. Most of these devices include bioinformatic software using algorithmic methods to identify clinically significant variants and signatures (*e.g.*, complex biomarkers). Notably, all current PQP devices include CDx indications for one or more oncology therapeutic products and most PQP devices include tumor profiling for somatic and/or germline mutations in a variety of genes. Finally, these devices may be developed and offered by and for use in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or distributed as test kits to CLIA-certified high complexity laboratories.

As shown in [Table 1](#), nine devices have been approved via the premarket approval pathway that are categorized under the PQP product code (as of June 26, 2024).¹

Table 1. Premarket Approvals for PQP Devices (as of June 26, 2024).

Device	Applicant	PMA Number	Decision Date
FoundationFocus CDxBRCA	Foundation Medicine, Inc.	P160018	12/19/2016
Oncomine Dx Target Test	Life Technologies Corporation	P160045	06/22/2017
Praxis Extended RAS Panel	Illumina, Inc.	P160038	06/29/2017
FoundationOne CDx	Foundation Medicine, Inc.	P170019	11/30/2017
Guardant360 CDx	Guardant Health, Inc.	P200010	08/07/2020
FoundationOne Liquid CDx	Foundation Medicine Inc.	P190032 P200006 P200011	08/26/2020 10/26/2020 11/06/2020
ONCO/Reveal Dx Lung & Colon Cancer Assay	Pillar Biosciences	P200011	07/30/2021

¹ FoundationOne Liquid CDx was the subject of three original premarket approval applications (PMAs), but represents a single device. All three PMAs were approved with the same intended use.

<u>RESOLUTION ctDx FIRST</u>	Exact Sciences Corporation	P210040	12/12/2022
<u>xT CDx</u>	Tempus Labs, Inc.	P210011	04/28/2023

II. ACTION REQUESTED

Foundation Medicine requests that all devices approved under product code PQP be reclassified from class III (high risk) to class II (high risk with special controls). FDA recognizes that class II may be appropriate for high risk, as well as moderate risk, devices.² Further, Foundation Medicine requests that future devices that are NGS oncology panels used for the qualitative detection of germline or somatic variants in one or more cancer-related genes and include companion diagnostic indications be placed under the same regulation and classified as class II (high risk with special controls) in order to ensure that tests with a similar intended use are subject to the same regulatory requirements.

Only FDA should be tasked with review of these premarket submissions and granting of CDx indications due to complex review issues. FDA alone has necessary visibility and resources for CDx review that should occur hand-in-hand with review of the corresponding therapeutic product (*e.g.*, inter-center consultation and review, statistical review for CDx including simulations and *in silico* modeling, potential need for evaluation of real-world evidence). Additionally, due to the risks of CDx devices and the types of reviews required, FDA should not exercise enforcement discretion for NGS oncology panels used for the qualitative detection of germline or somatic variants in one or more cancer-related genes that also include companion diagnostic indications. Absent FDA review, there is no assurance of the safety and effectiveness of these devices, posing significant risks to the use of the associated therapeutic products.

This petition is submitted pursuant to section 513(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 C.F.R. §§ 860.123 and 860.134. In accordance with section 513(f)(1) of the FD&C Act, postamendments devices (devices not in commercial distribution before the Medical Device Amendments of 1976) are “classified automatically” into class III.³ Under section 513(f)(3) of the FD&C Act, device manufacturers may file a petition to reclassify a device classified under section 513(f)(1) from class III to class I or class II. PQP devices are postamendments devices that remain in class III and are eligible for reclassification under this provision.

² FDA, Regulatory Controls. <https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls> Accessed June 26, 2024.

³ Medical Device Classification Procedures: Incorporating Food and Drug Administration Safety and Innovation Act Procedures, 83 Fed. Reg. 64443, 64446. December 17, 2018. See also, section 513(f)(1) of the FD&C Act (21 U.S.C. § 360c(f)(1)).

III. RECLASSIFICATION RATIONALE

a. Basis of Disagreement with Present Classification Status

For the past 25 years, FDA's CDx policy has helped drive significant advancements in precision medicine. CDx are defined as devices that provide information that is "essential for the safe and effective use of a corresponding drug or biological product."⁴ Adoption of the policy articulated in the FDA guidance "In Vitro Companion Diagnostic Devices" has enabled the successful development of many targeted therapies and associated CDx. Since 1998, 66 therapies have been approved with CDx and 25 different test developers, including both laboratories and kit developers, have received CDx authorizations for over 170 CDx indications, including single therapies and combinations of therapies.⁵ Approval of these therapies and the associated CDx has realized meaningful benefits for patients in matching them to targeted therapies and clinical trials, reflected in an increase in overall survival of patients diagnosed with cancer.^{6,7} For example, in non-small cell lung cancer, evidence points to an observed shift in the five-year survival rate after diagnosis coincident with the availability of genomically targeted therapies.⁸ Patients can now expect less-toxic, more effective cancer therapies for many types of cancer.

In 2017, FDA approved FoundationOne®CDx, the first pan-cancer multigene NGS panel having multiple CDx claims as well as broad tumor profiling claims.⁹ FDA recognized that this approval "extend[ed] beyond the previous 'one test for one drug' model."¹⁰ This approval enabled a single test to be used to determine whether a patient is a candidate for one or more approved therapies or for clinical trials. In parallel, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination in 2018 that provides coverage and payment for NGS panels with FDA-authorized CDx claims to Medicare beneficiaries with advanced cancer.¹¹ This

⁴ FDA Guidance. In Vitro Companion Diagnostic Devices. Guidance for Industry and Food and Drug Administration Staff. August 2014. Available at: <https://www.fda.gov/media/81309/download>

⁵ 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 June 26, 2024.

⁶ Haslem D.S., et al., A retrospective analysis of precision medicine outcomes in patients with advanced cancer reveals improved progression-free survival without increased health care costs. J Oncol Pract. February 2017. doi: 10.1200/JOP.2016.011486

⁷ John A., et. al., Value of precision medicine in advanced non-small cell lung cancer: real-world outcomes associated with the use of companion diagnostics. The Oncologist. July 6, 2020. doi:10.1634/theoncologist.2019-0864

⁸ Hofmarcher T., et al., A global analysis of the value of precision medicine in oncology – The case of non-small cell lung cancer. Front. Med. February 2023. doi: 10.3389/fmed.2023.1119506

⁹ Tumor profiling can aid healthcare providers in understanding more about a patient's cancer and potentially enable a patient to enroll in therapeutic product clinical trials, but is not a substitute for CDx.

¹⁰ FDA, News Release: FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers. November 7, 2017. <https://wayback.archive-it.org/7993/20190423071311/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587273.htm>

¹¹ CMS, National Coverage Determination 90.2. Next-generation Sequencing. <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=372>

coverage policy, and those like it implemented by commercial payers in the intervening years, recognize the rigor of FDA review of CDx as a benchmark of clinical utility for these types of tests.

In the years since, FDA has approved additional PQP devices from multiple developers and has gained significant experience assessing NGS panels with CDx indications. For example, Foundation Medicine has continued to innovate, adding new tumor profiling biomarkers, complex biomarkers (*e.g.*, Tumor Mutational Burden or TMB), and therapeutic group indications all as approved CDx to our tissue-based FoundationOne CDx.¹² FDA has also added a variety of test configurations in the PQP product code such as blood-based testing with the approval of FoundationOne®Liquid CDx and other blood-based assays in 2020. Reflecting further innovation in this area, FDA approved 34 PMA or PMA supplements for PQP devices in 2023 alone.¹³

FDA has classified PQP devices as high risk because “inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences” and “erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy.”¹⁴ Accordingly, FDA has required extensive validation and premarket review prior to making tests available for clinical use. A CDx developer must demonstrate a test’s analytical validity, clinical validity, and quality of manufacturing processes and must supply final labeling for approval. The purpose of these demonstrations is to confirm that such a test accurately identifies biomarkers, uses a clinically-validated approach to predict treatment response, and adheres to the appropriate design and change controls as well as 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. Furthermore, well-validated CDx devices are essential to assurances of a corresponding approved therapy’s safety and effectiveness.

In January 2024, FDA announced its intent to initiate reclassification of most IVDs, including CDx devices, that are currently class III to class II, in line with its greater experience regulating many types of class III IVDs.¹⁵ FDA has noted that the high risk of these devices could be “mitigated through special controls.”¹⁶ Foundation Medicine agrees that these devices are high

¹² See FDA Guidance, Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products. April 2020. Available at: <https://www.fda.gov/media/120340/download>.

¹³ Accessed via search of PQP in FDA’s PMA database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm>

¹⁴ FDA Guidance. In Vitro Companion Diagnostic Devices. August 2014. Available at: <https://www.fda.gov/media/81309/download>

¹⁵ FDA, CDRH Announces Intent to Initiate the Reclassification Process for Most High Risk IVDs. January 31, 2024. <https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds>.

¹⁶ CDC, FDA Update: CLIAc. April 10, 2024. https://www.cdc.gov/cliac/docs/april-2024/4_FDA_Update.pdf.

risk, and that PQP devices should only be reclassified as class II (high risk with special controls) if the special controls are appropriately rigorous as proposed in this petition. Because rigorous special controls, such as those proposed in section IV, when combined with general controls, provide a reasonable assurance of safety and effectiveness for PQP devices, these devices may be classified as class II.¹⁷

Importantly, reclassification is not a process intended to *lower* the validation requirements or other requirements for a device type. Rather, reclassification from class III to class II is intended to reflect, in a standardized manner through special controls, those factors and assurances that together can provide the same level of assurance of safety and effectiveness as had been provided by a class III PMA. As FDA states on its website, “[t]he main purpose of reclassification is to apply the appropriate level of regulatory controls for a device type based on the most current information regarding its safety and effectiveness.”¹⁸ Therefore, significant deviations from the data, information, and performance requirements represented in approved PMAs for PQP devices should not be considered unless there is evidence that the different level of data, information, or performance would provide the same assurances. Additionally, appropriately rigorous special controls are consistent with the Medical Device Amendments of the FD&C Act, which charge FDA with protecting patients through risk-based regulation of IVDs to assure product quality and achieve a reasonable assurance of safety and effectiveness.

The petitioner is unaware of evidence justifying lowered validation requirements for PQP devices. In fact, a recent study demonstrates the value of FDA’s existing validation requirements, as the approved CDx tests accurately reported all variants for clinical and in silico samples while other IVDs offered as laboratory developed tests (LDTs) did not accurately report all variants or identify the same patient population as the approved CDx.¹⁹ Moreover, a review of the regulatory history of PQP devices demonstrates that rigorous analytical and clinical validation and compliant labeling are essential to the safety and effectiveness of this device type. Thus, these factors are critical to the development of special controls for any reclassification in order to continue to provide a reasonable assurance of safety and effectiveness for this device type. Absent appropriately rigorous special controls, healthcare providers and patients cannot be assured of test performance and patients may not be accurately and reliably matched to the correct therapy.

¹⁷ 21 C.F.R. § 860.123(a)(4); 21 U.S.C. § 360c.

¹⁸ <https://www.fda.gov/medical-devices/classify-your-medical-device/reclassification>. Accessed June 26, 2024.

¹⁹ Pfeifer, J.D., et al., Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics, American Journal of Clinical Pathology. April 2022.

<https://doi.org/10.1093/ajcp/aqab164>

b. Justification for How the Proposed Classification Will Provide a Reasonable Assurance of Safety and Effectiveness

PQP devices, which all have one or more CDx indications, are inherently high risk because an undetected incorrect CDx result has the potential to cause serious harm or death to the patient through non-optimal or inappropriate therapeutic management, and the result from such a test is generally the only information that identifies a cancer patient as a candidate for specific life-prolonging or curative therapies. As such, the proposed classification in this petition for PQP devices is class II (high risk with special controls) because there is sufficient information to establish effective special controls, not because such devices now have lower risks than originally expected. Class II may be appropriate when special controls can be articulated that impose similar conditions and standards as those demonstrated in the context of a PMA approval.

As FDA has established in the Effectiveness and Safety Conclusions and Benefit-Risk Determinations sections found within Summaries of Safety and Effectiveness Data (SSEDs) for PQP devices, the risks of such tests are generally two-fold: (1) patients who receive false positive results from a CDx test may be exposed to a drug or drug combination that does not provide a clinical benefit, may lead to adverse reactions, or may delay access to more effective treatments; and (2) patients who receive a false negative result may be prevented from accessing a potentially beneficial therapeutic. FDA also cites the potential for incorrect test result interpretation by the user, delayed results, and failure to generate a result as risks that require mitigation.²⁰ The significant risks associated with incorrect results are mitigated by the clinical and analytical studies provided and consistent FDA labeling conventions for clinical indications and biomarker information to help ensure that providers can correctly interpret test results. Further, since the PQP product code's first use in 2016, only seven medical device reporting (MDR) events have been reported to FDA and only nine recalls have been issued, none of which

²⁰ For example, the Safety Conclusions for P170019 (FoundationOne CDx) state “Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in cancer treatment. Patients with false positive results may undergo treatment with one of the therapies listed in Table 1 of the intended use statement without clinical benefit, and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with indicated therapy.” P170019 SSED at https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf.

SSEDs for the other eight devices approved under PQP have similar statements. Available at:

https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018B.pdf;
https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160045B.pdf;
https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160038B.pdf;
https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200010B.pdf;
https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032B.pdf;
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https://www.accessdata.fda.gov/cdrh_docs/pdf21/P210040B.pdf;
https://www.accessdata.fda.gov/cdrh_docs/pdf21/P210011B.pdf

were Class I recalls.²¹ The experience with MDRs and recalls together with the benefit-risk determinations demonstrates that the existing requirements and expectations for PQP devices are well-tailored to provide a reasonable assurance of safety and effectiveness, given the inherent risk of these devices.

Foundation Medicine's review of the regulatory history of PQP devices, based on information in publicly available SSEDs, has established that a relatively uniform approach to regulatory requirements has been implemented and can be established through special controls. In short, review of a common list of necessary preanalytical, analytical, and clinical validation performance parameters and sample requirements, together with review of labeling, software development and performance, and design and change control procedures, have been consistently necessary to support safety and effectiveness as well as positive benefit-risk profiles for PQP devices.

Foundation Medicine has also assessed the need for specific special controls related to bioinformatics processing pipelines. SSEDs for approved PQP devices show that for bioinformatic processing pipelines, FDA has relied on device descriptions and demonstrations of performance as part of the test systems in which they reside, rather than specific assessment of the underlying design of the algorithm. Further, because bioinformatic approaches and algorithms in PQP devices are highly variable, specific to individual device design, and proprietary, meaningful special controls with bioinformatics-specific requirements cannot feasibly be developed beyond standard FDA software requirements.²² Therefore, Foundation Medicine does not propose special controls related to bioinformatics, as clinical validation for PQP devices will be sufficient to assure adequacy of bioinformatics and that the results generated by the test system are acceptable.

In order to maintain a reasonable assurance of safety and effectiveness for PQP devices, Foundation Medicine requests appropriately rigorous special controls that must include the following requirements consistent with the PMA requirements for existing PQP devices and previous special controls advanced by FDA:

- Clear descriptions of the device and its functions, including descriptions of design and change controls and manufacturing processes.^{23,24}

²¹ Search of Manufacturer and User Facility Device Experience (MAUDE) Database and Medical Device Recalls Database for product code PQP. Searched on June 26, 2024.

²² FDA Guidance. Content of Premarket Submissions for Device Software Functions. Guidance for Industry and Food and Drug Administration Staff. June 14, 2023. Available at <https://www.fda.gov/media/153781/download>

²³ 21 CFR § 866.5960. Special controls for HLA typing Companion Diagnostic Tests require design verification and validation including a description of a plan on how to ensure the performance of a device does not change when certain modifications are made.

²⁴ FDA has previously issued special controls that include, among other things, a description of genomic coverage, detailed documentation of the methodology and protocols for each step of the test, a description of required

- Sufficient preanalytical and analytical validation data to assure that complex NGS systems can accurately and reliably measure numerous variants and CDx biomarkers of interest across a large genomic area within various sequence contexts.²⁵
- Independent clinical validation for each CDx indication.²⁶ There are several approaches that could be leveraged:
 - Direct use of device results in the therapeutic clinical trial;
 - Bridging studies using clinical trial samples;
 - Concordance studies using clinical samples representing the intended use population comparing the authorized CDx test performance to the new test performance;
 - Non-inferiority studies using clinical samples from the intended use population;
 - Observational studies demonstrating comparable clinical effectiveness in the intended use population; or
 - Real world evidence demonstrating clinical effectiveness in the intended use population.
- Provision of 21 CFR § 809.10 compliant labeling with a requirement to make such labeling publicly available upon authorization.²⁷

These requirements are all within parameters of conditions applicable to other Class II devices. Moreover, they are reflective of conditions and standards in SSEDs for past PQP approvals that are more than six years old. Importantly, descriptions of design and change control procedures in

instrumentation and equipment and any ancillary reagents, instrumentation or equipment, and a detailed documentation of device software. Furthermore, these special controls also require that labeling required under 809.10 include a summary of device description and summary information on how the test works. See, e.g., DEN210011. Available at: www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210011.pdf

²⁵ Special Controls regularly contain detailed requirements related to analytical validation. See, e.g., DEN210011 which required “detailed documentation of additional analytical validation studies, including endogenous and exogenous interfering substances, specimen and reagent stability, cross-reactivity, carryover and cross contamination, guard-banding, and index misassignment, as applicable. If specimens are pooled, index cross-contamination must be evaluated and demonstrate that pooling does not negatively impact test performance.” Available at: www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210011.pdf and DEN210035 which required “detailed documentation of studies demonstrating acceptable, as determined by FDA, analytical device performance using samples that are representative of the entire spectrum of challenging cases likely to be encountered when the device is used as intended. For each analytical study, relevant details must be documented (e.g., the origin of the study slides and images, reader/annotator qualifications, method of annotation, location of the study site(s), challenging diagnoses, etc.).” Available at: www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210035.pdf

²⁶ FDA has previously established special controls with specific requirements related to clinical validation. See, e.g., 21 CFR § 866.5960. (Special controls for HLA typing companion diagnostic tests require data that may include “summary reports from clinical trials, comparison studies using clinical samples, or an alternative approach determined to be appropriate by FDA.” “If the HLA test used in the clinical trials is different from the HLA CDx test in the premarket notification submission, the submission must include results of a bridging study, or an alternative approach determined to be appropriate by FDA”) and 21 § CFR 866.3170. (Special Controls for nucleic acid-based hepatitis C virus ribonucleic acid tests require that “... the design verification and validation must include detailed documentation of performance from a multisite clinical study”).

²⁷ FDA has previously established special controls that required certain labeling to be publicly and prominently available. See, e.g., DEN200070. Available at: www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200070.pdf

premarket submissions are critical to allow FDA and the public to have confidence that manufacturers of these high-risk tests have adequately managed their product design and changes to the design. Provision of these descriptions in the premarket submission provides essential information when no premarket approval inspection is performed, and FDA inspections for class II devices may not be scheduled for several years after authorization.

Several factors indicate that FDA should require developers of PQP devices to post labeling information publicly. First, the majority of sponsors provide PQP devices as central laboratory tests that are not distributed. For these types of tests, labeling meeting the requirements of 21 CFR § 809.10 and special controls is not otherwise available because no package insert or other electronic labeling would be available to aid new applicants and the broader clinical community in understanding test performance for purposes of establishing substantial equivalence. Second, given the variety of tests that may be offered with biomarkers that could be CDx, but are not approved as such, transparent labeling provides an additional compliance control to address FDA's concerns about promotional claims that are "false and misleading" and "mislead[...] the public about the safety or effectiveness of their IVDs."²⁸ To that end, Foundation Medicine believes the special controls proposed in section IV of this petition will provide, in the aggregate, necessary assurances of safety and effectiveness for all future NGS oncology panels used for the qualitative detection of germline or somatic variants in one or more cancer-related genes and that include at least one CDx indication.

c. Data and Information Known by Petitioner That are Unfavorable to the Proposed Classification

The petitioner is not aware of any information unfavorable to this proposal for reclassification of PQP devices to class II. As previously referenced, current evidence supports the safety and effectiveness parameters within this petition. A test's design, preanalytical and analytical methodology, instrumentation, structure and stability of the bioinformatics pipeline, as well as the methods of clinical validation are critical to ensuring that a test functions as intended. For these reasons, use of extrapolation of clinical validity across tests of the same type lacks support and is not an appropriate means of demonstrating safety and effectiveness.^{29,30} First, standardization of a qualitative test such as an NGS-based CDx implies that the correct threshold for positive/negative calls is known and clinically accurate. This is not the case for most therapeutics with a corresponding CDx. What is known is what test results were available in the

²⁸ Medical Devices; Laboratory Developed Tests, 89 Fed. Reg. 37,286, 37,292. May 6, 2024.

²⁹ FDA Guidance. Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff. June 20, 2023. Available at: <https://www.fda.gov/media/169616/download>

³⁰ In its final rule for laboratory developed tests (RIN 0910-AI85), FDA states that it "seeks to engage with the community on additional efforts to create standardization, such as through reference materials, so that clinical validity can be extrapolated to other tests of the same type in more cases." 89 Fed. Reg. at 37,431.

therapeutic product clinical trial(s) that allowed for a positive, but not necessarily optimal, trial outcome. The variables that affect response are generally not well-studied or well-understood. Standardization of CDx performance would limit opportunities to know whether there are performance characteristics that would enable therapeutic effectiveness across a more optimized (broader or more refined) spectrum of patients.

Second, NGS oncology panels have different designs for specific reasons. Typically, these panels cover a large portion of the “cancer genome” with tens to hundreds of genes and intragenic regions sequenced. Each test developer uses its own process to select the regions of the genome to sequence and the exact areas within genes to target in order to meet the identified clinical purpose. This can result in significantly different designs for tests with the same underlying technology, which may be quite different in scope, content, and validated performance (*e.g.*, specific genomic regions targeted, the depth of coverage observed within the targeted regions, and the accuracy with which sequenced reads are mapped to the correct location within the genome). Additionally, each test developer chooses its own post-sequencing bioinformatic processing design, such that post-sequence processing can be as highly variable as the genomic regions sequenced. Differences in alignment tools, reference genomes, purpose-built proprietary informatics tools, and filters used to refine data, to name a few, can result in differences in outputs that may be significant.

In Foundation Medicine’s experience with concordance testing using a variety of analytically validated tests as comparators, it is common for discordances to arise due to differing bait-set designs, reporting cutoffs, or designations of clinical significance. Alignment and filtering in the bioinformatic pipelines may also result in discordances, whereby one design aligns or filters in one way while another design uses a different approach.³¹ There is no single correct design for NGS panels, thus it is inappropriate and precarious to assume that tests using the same underlying technology and querying similar genomes, or portions thereof, must be equivalent in their clinical performance, even if analytically validated. Such an assumption would likely result in a significant rate of incorrect results with negative clinical consequences for patients.^{32,33}

³¹ For example, in several Foundation Medicine premarket submissions for a new CDx indication, comparison to a validated orthogonal method yielded a high proportion of discordances due to differences in calling threshold and differing bait set designs.

³² For example, McGrail, D.J., et al., High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann. Oncol. May 2021. doi: 10.1016/j.annonc.2021.02.006 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. However, Fabrizio, D., et al., 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. May 2021. doi: 10.1016/j.annonc.2021.05.805 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.

³³ Hirsch, F.R., et.al., PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thor Oncol. February 2017. 12:208-222. doi: 10.1016/j.jtho.2016.11.2228

CDx indications on NGS-based oncology panels must be clinically validated to ensure that they appropriately identify a patient's biomarkers for use in selection of corresponding therapeutic products. However, clinical samples representing intended use populations may be challenging to source for analytical and clinical validation studies in certain cancers. This petition proposes special controls that may help alleviate these challenges in Section IV(2)(iv)(5)-(10) and IV(2)(iv)(12). Specifically, the petition proposes streamlined analytical validation approaches for certain requirements, including for rare biomarkers, and describes scenarios in which synthetic, contrived and reference samples can be utilized. These approaches will allow clinical samples to be leveraged for clinical validation, where they are necessary because they represent the complexity of tumors with respect to variant allele frequency, presence of clonality, and other variables that are patient-specific.³⁴ Furthermore, the special controls in Section IV(2)(v) propose additional methodologies for demonstrating clinical validity, including for rare biomarkers.^{35,36} The proposed special controls would provide flexibility to test developers, but most importantly provide a reasonable assurance of safety and effectiveness to the cancer patients who rely upon these devices. The proposed special controls, developed from current PMA requirements for PQP devices, have allowed seven different sponsors to validate and receive approvals for nine devices.

IV. SPECIAL CONTROLS

Foundation Medicine proposes the following special controls for PQP devices and all future NGS oncology panels used for the qualitative detection of germline or somatic variants in one or more cancer-related genes and that include at least one CDx indication. These proposed special controls, in total, reflect the consensus of PMA requirements for PQP devices, including submissions from more than six years ago and publicly available SSEDs from more recent approvals. Collectively, the proposed special controls have an established record of reliability for

³⁴ Clinical tumor samples may exhibit varying degrees of clonality, stromal infiltration, and tissue-based potential interfering substances, factors that are not well-represented in non-clinical samples. While reference materials and contrived samples can be helpful in providing supportive data, they should not be relied upon as the primary source for demonstrating clinical validity due to the risk that they may not query all of the variables present in clinical samples, and thus result in overestimation of clinical performance of the test.

³⁵ For an example of methodology, see: Li M. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study, Statistics in Biopharmaceutical Research. September 2016. <http://dx.doi.org/10.1080/19466315.2016.1202859>

³⁶ While prospective observational studies and real-world data and evidence have not yet been used in PQP device approvals, they can be scientifically sound approaches to clinical validation. FDA has proposed that real-world data and evidence “[...]may be of sufficient quality to help inform or augment FDA’s understanding of the benefit-risk profile of devices at various points in their life cycle” and that such evidence may be potentially be used “as evidence to identify, demonstrate, or support the clinical validity of a biomarker”. FDA Guidance. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Guidance for Industry and Food and Drug Administration Staff. August 31, 2017. Available at: <https://www.fda.gov/media/99447/download>

supporting a reasonable assurance of safety and effectiveness.

- (1) Identification. A next-generation sequencing oncology panel test with companion diagnostic indications is identified as an in vitro diagnostic device intended for prescription use to detect and provide information from a multi-gene panel on germline and somatic mutations in nucleic acid sequences from tissue, plasma, or blood, for simultaneous tumor profiling and companion diagnostic use from patients with solid malignant neoplasms.
- (2) Premarket notification submissions must include the following information:
 - (i) Device description and principles of operation
 - 1) The intended use should specify the following:
 - (a) The nucleic acid type(s) that the test measures and a detailed description and a list of all genes, genomic regions including introns and specific transcripts queried with a list of signatures and specific mutation types (substitutions (SNVs), insertion and deletion alterations (indels), rearrangements, fusions, copy number alterations (CNAs), genomic signatures or complex biomarkers, and any other relevant biomarker type) that are intended to be detected and reported by the test.
 - (b) The proposed indications for use, which must specify the following:
 - i. The population for which the test is indicated (*e.g.*, patients already diagnosed with cancer).
 - ii. The intended specimen type(s) and matrix (*e.g.*, nucleic acids extracted from formalin-fixed, paraffin-embedded tissue, circulating cell-free DNA isolated from plasma).
 - iii. For each companion diagnostic indication, a detailed companion diagnostic biomarker definition as used in the therapeutic product clinical trial for the corresponding therapeutic product(s) (or therapeutic product group for group companion diagnostic claims), the name of the therapeutic product or therapeutic product group, and the scope of tissues and cancer types to which the companion diagnostic indication is proposed to apply.
 - iv. For each companion diagnostic indication, a detailed companion diagnostic biomarker definition as reported by the test.
 - (c) A description of the nature of the test, including the following:
 - i. The genomic coverage approach of the test (*e.g.*, targeted, whole exome, whole genome, transcriptome).
 - ii. A description of all genomic regions targeted by the test, including the distribution of sequencing coverage observed for each region, and the variant types reported in each region.

- iii. Whether the test is intended to report germline or somatic findings or both.
 - iv. For blood-based assays, if there are genes or genomic regions with enhanced coverage for increased sensitivity, a list of the genes/regions and the degree of enhancement of coverage.
 - v. Whether the test is quantitative, qualitative, semi-qualitative in nature. If more than one category applies, indicate how each will be applied in the test.
 - vi. A description of the technology/test method used to detect mutations/biomarkers, including the name and model of sequencing instrument system.
 - vii. The name and address of the testing facility or facilities, as applicable.
- 2) Provide a device description and describe principles of operation including the following:
- (a) A detailed description of all mutations and biomarkers that are intended to be detected by the test and the clinical evidence/rationale for inclusion of the genes in the panel and subsequent reporting to patients, including a listing of the following:
 - i. Companion diagnostic claims; and
 - ii. Criteria that establish what types and levels of evidence are used to define an alteration or biomarker as oncogenic.
 - (b) A description of the test in terms of genomic coverage, as follows:
 - i. Tabulated summary of all mutations and biomarkers reported, grouped according to gene and target region within each gene, along with the specific transcripts queried for each mutation or biomarker as applicable.
 - ii. A description of any within-gene targeted regions that cannot be reported and the data behind such conclusion.
 - iii. Expected distribution of coverage and minimum depth of coverage over the targets covered by the test.
 - (c) A detailed description of all test components, reagents, instrumentation/platform, and software required to produce a test result.
 - (d) Specifications for specimen requirements including any specimen collection devices and preservatives, specimen volume, minimum tumor content, specimen handling, nucleic acid extraction, and criteria for nucleic acid quality and quantity metrics that are prerequisite to performing the assay.
 - (e) A detailed description of the methodology and protocols for each step of the test, including description of the library preparation approach, any quality metrics including quality determinants and methods for ctDNA samples, thresholds, and filters, and any curation or other assessment at each step of the

- test that are implemented for final result reporting and a description of the metrics for run-failures, specimen-failures, and invalid results, as applicable.
- (f) For blood-based assays, a description of how germline and/or clonal hematopoiesis (CH) variants are excluded from analysis, and if so, how this is achieved. If such variants are not excluded from analysis, explain how CH and/or germline variants are managed so as not to provide incorrect results.
 - (g) A list of links accessed by the device for internal or external information (*e.g.*, decision rules or databases) supporting clinical significance of test results for the panel or its elements.
 - (h) A description of internal and external controls that are used together with control procedures. The description must identify those control elements that are incorporated into the testing procedure (*e.g.*, sample identity, contamination, in-process controls).
 - (i) A description of the sequencing quality metrics required to produce routine test results.
 - (j) For companion diagnostic indications, a description of quality metrics required to achieve necessary clinical performance in the context of the therapeutic product clinical trial.
 - (k) Prespecified variant classification rules used to determine the presence or absence of specific variants.
 - (l) Variant classification rules that define how variants will be reported as clinically significant, of unknown significance, or not reported (*e.g.*, benign).
- (ii) **Labeling**
- 1) Provide final labeling including any specimen collection kit labels. For tests developed by a laboratory, labeling must include technical specifications. Final labeling must be detailed and comprehensive and must be made publicly available at the time the cleared device is offered for clinical use.
 - 2) The 21 CFR § 809.10 compliant labeling and any product information and test output generated, must include an intended use statement specifying the following:
 - (a) The population for which the test is indicated (*e.g.*, patients already diagnosed with cancer).
 - (b) The intended specimen type(s) and matrix (*e.g.*, formalin-fixed, paraffin-embedded tumor tissue, circulating cell-free DNA isolated from plasma).
 - (c) The mutation types (*e.g.*, single nucleotide variant, insertion, deletion, copy number variation or gene rearrangement) for which validation data has been provided.
 - (d) Whether the test will report germline, somatic, or both types of variants.
 - (e) A description of any test outputs provided in addition to biomarker calling.

- (f) Companion diagnostic indications, including description of biomarker, applicable tumor type(s), and corresponding therapeutic product(s) or product class.
 - (g) The name of the testing facility or facilities, as applicable.
- 3) Specific Performance Characteristics – A detailed and comprehensive description of the device including the specific instrumentation required and summary of the results of the performance studies performed in accordance with relevant paragraphs of this section.
- 4) A detailed and comprehensive description of applicable test limitations, including as applicable:
- (a) A negative result does not rule out the presence of a mutation or biomarker below the limits of detection of the assay.
 - (b) Genomic findings other than those listed as companion diagnostic biomarkers in the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
 - (c) Any biomarker-specific limitations of the assay, including genomic regions not targeted by the test or for which low coverage is observed.
 - (d) Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
 - (e) For blood-based assays, potential for alterations to be reported that are not tumor-derived (*e.g.*, clonal hematopoiesis).
 - (f) The analytical accuracy for the assay has not been demonstrated across all genomic regions targeted by the test.
 - (g) The test is not intended to provide information on cancer predisposition
 - (h) Performance has not been validated for nucleic acid input below the specified minimum input.
- 5) Warnings and precautions as applicable, including:
- (a) If the test cannot distinguish between somatic and germline mutations, when reflex testing may be appropriate or necessary.
 - (b) The test is not intended as a replacement for germline testing for heritable mutations.
 - (c) Any discrepancy between externally reported mutation/biomarker frequency and assay-specific detected mutation/biomarker frequency.
 - (d) For blood-based assays, consequences of collection device underfill.

- (e) For tissue-based tests, a statement that biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The treating physician should determine whether the patient is a candidate for biopsy.
- (iii) Preanalytical methods and parameters
 - 1) Provide detailed study designs with sample types (*e.g.*, tissue, mutation/biomarker), numbers of samples used, study endpoints, study acceptance criteria, summary data, and statistical data analysis methods and conclusions.
 - 2) Provide data that adequately support the intended specimen type (*e.g.*, blood, plasma, formalin-fixed paraffin-embedded tumor tissue), specimen handling protocol if applicable, and nucleic acid extraction and purification methods for specific tumor types or for a multi-cancer claim.
 - 3) Provide data demonstrating establishment and validity of minimum sample input requirements, including:
 - (a) Minimum sample tumor content.
 - (b) For blood-based assays, minimum sample volume for blood or plasma.
 - (c) Nucleic acid input range.
- (iv) Analytical validation
 - 1) Include detailed study designs with sample types (*e.g.*, tissue, mutation/biomarker), numbers of samples used, study endpoints, study acceptance criteria, summary data, and statistical data analysis methods and conclusions.
 - 2) Provide information demonstrating analytical validity of the device according to the following analytical performance characteristics, evaluated specifically for each companion diagnostic biomarker and as indicated for other mutations and biomarkers.
 - (a) Data adequately supporting the limit of detection (95% confidence interval, or level at which 95% hit rate is observed) for each companion diagnostic biomarker or, if justified, variant type (*e.g.*, SNVs, indels, rearrangements, CNAs).
 - (b) For companion diagnostic indications for which limit of detection was previously established using representative alterations or for which contrived samples were used, data using clinical samples for limit of detection confirmation at 1-3x limit of detection.
 - (c) Precision data using clinical samples for positive and negative samples to adequately evaluate precision, at a minimum for, intra-run (replicates), inter-run, instrument system-to-instrument system, operator-to-operator, reagent lot-to-reagent lot including barcode lots where applicable.
 - i. Samples must cover a representation of all alteration types reported and include samples near the limit of detection of the device.
 - ii. Precision studies for companion diagnostic biomarkers must use a range of samples representative of the intended use population.

- iii. Precision must be assessed by agreement within replicates on the assay final result for each mutation/biomarker and must be supported by sequencing quality metrics.
 - iv. If the test is intended to be performed at multiple sites, provide site-to-site precision performance data.
 - v. Precision should be evaluated on end-to-end workflow, from sample to results.
 - (d) Data adequately supporting limit of blank (specificity).
- 3) Concordance data comparing the performance of the new test to that of an analytically validated test of the same type, as acceptable to FDA, using both mutation-positive and wild-type (for the mutation) clinical specimens representing the intended specimen type, mutations/biomarkers specified, and range of tumor types.
- (a) When clinical accuracy (*i.e.*, association of test results with clinical outcomes) can be established for CDx indications, analytical accuracy or concordance data from a comparison study (*i.e.*, comparison to an orthogonal method or standard samples) is not required.
 - (b) In the absence of clinical accuracy (*i.e.*, association of test results with clinical outcomes), for companion diagnostic claims, clinical specimens must include the intended specimen type, tumor type(s) and all aspects of the biomarker definition for the specific companion diagnostic claims, unless appropriate justification and supporting data are provided.
- 4) For tumor-profiling-only mutations whose clinical significance is based on evidence established in the intended specimen type (*e.g.*, tumor tissues) but for a different analyte type (*e.g.*, protein, RNA) and/or a measurement (*e.g.*, incorporating a score or copy number) and/or with an alternative technology (*e.g.*, IHC, RT-qPCR, FISH), evidence of accuracy must include clinically adequate concordance between results for the mutation and the medically established biomarker test (*e.g.*, evidence generated from an appropriately sized method comparison study using clinical specimens from the target population).
- (a) If evaluating concordance with another nucleic acid sequencing method, provide the name and analytical performance characteristics of the comparator or orthogonal method. An orthogonal method must have similar sensitivity as the candidate device for the biomarkers that are the subject of the evaluation.
 - (b) For tumor-profiling-only claims, clinical specimens must adequately represent the intended specimen and tumor types and must adequately represent the list of cancer mutations to be detected by the device.
- 5) For companion diagnostic biomarkers where all variants within the biomarker definition cannot be predicted (*e.g.*, rearrangement and fusion breakpoints), analytical performance may be evaluated using representative variants within the

same variant type and comparable genomic context defined by the companion diagnostic biomarker definition, with appropriate justification and supporting data.

- 6) Although synthetic, contrived, and reference samples may be used in some analytical performance studies with appropriate justification, analytical performance studies should include predominantly clinical samples from the intended use population. If available, incorporation by reference of prior analytical data for the same biomarker performed by the sponsor for the same device can demonstrate adequate analytical validity.
- 7) Where new variants are in the same genomic location as already-authorized variants and genomic coverage is sufficient, validation of the new variant is not required.
- 8) Where a biomarker is a companion diagnostic for multiple cancer types, analytical validation may be carried out in a subset of the cancer types, with appropriate justification.
- 9) If applicable, provide justification and supporting data for use of representative validation, including but not limited to: description of consistency of variant detection methods across the targeted regions, and sequencing coverage analyses categorizing targeted genomic regions.
- 10) For broad panel tests, the following should be performed at initial validation and in subsequent modifications if the initial validation does not apply to the updated intended use or change in scientific principle:
 - (a) Interfering substances. Provide data evaluating the effect on test results of potential interfering endogenous (sample-related) or exogenous (process-related) substances at various physiological or expected possible concentrations, across applicable variant types and signatures, including companion diagnostic biomarkers and tumor types.
 - (b) Inclusivity/Cross-reactivity. Provide data supporting the specificity of assay primers or baits and the adequacy of coverage of the test across targeted or queried genomic regions, including all supported variant types, to support test performance, including:
 - i. Coverage depth.
 - ii. Platform-wide and companion diagnostic region-specific genomic coverage.
 - iii. Mapping quality against reference genome(s) or transcriptome(s).
 - iv. Assessment of challenging genomic sequence areas.
 - (c) Guard-banding/robustness studies. Provide data for variant categories and tissue types, including all CDx tissue types, reported by the test demonstrating impact of process variation with regard to uncertainty in:

- i. Nucleic acid input concentration at various stages of processing (*e.g.*, library construction, capture, and sequencing).
 - ii. Temperature, as appropriate.
 - iii. Incubation times, as appropriate.
 - iv. When the assay is developed and offered by the same entity and process controls and instrumentation are controlled by the developer, temperature and incubation time guardbanding may be omitted with adequate justification.
- (d) Carry-over/contamination. Provide data for all variant types reported by the test adequately supporting the absence of sample and reagent carry-over or contamination between samples across a range of nucleic acid input amounts and variant categories during test processing, considering potential for both inter-run and intra-run contamination.
- (e) Sample and reagent stability. For critical reagents, provide stability protocols including acceptance criteria and stability data to adequately support sample and reagent stability in expected shipping, storage and operational environments.
- (f) Provide sample stability assessed across a range of tumor types and variants for primary specimens (*e.g.*, FFPE slides, blood/plasma tubes) as well as intermediate specimen products such as plasma, extracted nucleic acids and prepared libraries and any other intermediates created during nucleic acid processing.
- (g) Provide reagent stability data for closed container and shelf life in terms of result concordance between time of final manufacture (T_0) and selected time points across variant categories, assessed across three reagent lots of critical reagents. For test systems in which multiple-aliquot reagents are stored in an open state for use in different test runs, provide open reagent stability data to support claimed duration of use once opened.
- (h) Collection device concordance. For blood-based assays, provide data demonstrating collection device concordance where more than one collection device is included in the test system, and/or when clinical samples from clinical studies supporting companion diagnostic indications were collected in devices different from the collection device(s) included in the test system.
- 11) In addition to analytical validation requirements in sections (v)(2), for complex biomarkers the following considerations apply:
- (a) Limit of detection should be performed for complex genomic signatures, when appropriate. Clinically derived biomarker thresholds can inform when or whether limit of detection is appropriate. For some complex signatures, it may be appropriate to determine the limit of detection of underlying

biomarker components (*e.g.*, limit of detection of component variants counted to determine a score).

(b) For Categorical Biomarkers:

- i. Analytical validation should include an enrichment of samples near threshold. Samples used for validation should represent all reported biomarker categories (*e.g.*, high, low, and equivocal) and a range of reported values (as applicable).
- ii. Analytical validation should include an evaluation of true negatives.

(c) For Continuous Biomarkers:

- i. Analytical validation should include an evaluation of a sufficient representation of samples as identified by the intent-to-treat population across the reportable range (as applicable).
- ii. For some complex signatures, it may be appropriate to perform orthogonal concordance using underlying biomarker components (*e.g.*, component variants counted to determine a score).
- iii. If applicable, for continuous biomarkers whose values are proportional to clinical response, linearity should be evaluated.
- iv. When appropriate, reference range should be established.

12) Exceptions to analytical validation requirements in sections (2)(iv)(2)

(a) For cancer types or biomarker-defined subsets of cancer types with annual incidence of 1% estimated total annual incidence or lower in the US population, due to rarity of samples representative of the intended use population:

- i. For analytical validation sponsors may provide data from some combination of the following, as acceptable to FDA, instead of requiring use of clinical samples from the intended use population: appropriately contrived samples, clinical samples from similar tumor types/sample types, and representative variant validation.
- ii. With sufficient justification and supporting data, analytical performance for companion diagnostic biomarkers may be evaluated using representative variants within the same variant type and comparable genomic context defined by the companion diagnostic biomarker definition.

(v) Clinical performance

- 1) Provide detailed clinical performance study designs with sample types (*e.g.*, tissue, mutation/biomarker), numbers of samples used, study endpoints, study acceptance criteria, summary data, and statistical data analysis methods and conclusions, evaluated specifically for each companion diagnostic biomarker using one or more of the following approaches:

- (a) Direct clinical validation using clinical trial screen positive and screen negative samples, where the device was used as the sole clinical trial enrollment assay (CTA) for a therapeutic product clinical trial(s) that established efficacy in the indicated cancer and population for the corresponding therapeutic product.
 - (b) Bridging studies of performance between the device and enrollment CTA(s) using sufficient clinical samples from a therapeutic product clinical trial(s) that established efficacy in the indicated cancer and population for the corresponding therapeutic product.
 - (c) Non-inferiority studies using clinical samples representative of the therapeutic product intended use population demonstrating non-inferior performance to an FDA-authorized companion diagnostic test for which clinical samples from the therapeutic product clinical trial were used. Contrived or control samples may be used to supplement clinical specimens.
 - (d) Concordance studies using clinical samples representative of the therapeutic product intended use population demonstrating high concordance to an FDA-authorized companion diagnostic test. Contrived or control samples may be used to supplement clinical specimens.
 - (e) An observational study comparing clinical efficacy of a new test to an FDA-authorized test for a CDx indication, where both tests are performed for enrolled patients, clinical management is driven by the FDA-authorized test, and objective outcomes are available.
 - (f) Real-world evidence from a qualified database that meets current guidelines demonstrating clinical effectiveness of the test for the identification of patients for the corresponding therapeutic product in the intended use population.
- 2) Exceptions to clinical performance requirements in (2)(v)(1)
- (a) For cancer types or biomarker-defined subsets of cancer types with annual incidence of 1% estimated total annual incidence or lower in the US population, prevalence of the biomarker will be taken into consideration when determining the appropriate sample size for the evaluation of clinical validity of the companion diagnostic test.
- (vi) Design control and design change control
- 1) Provide a description of procedures used to control design and development of the test, including:
 - (a) Design and development planning.
 - (b) Design input and design output.
 - (c) Design review.
 - (d) Design verification and validation, including risk analysis and management strategies.
 - (e) Plans, protocols, and reports.

- (f) Design transfer.
 - (g) Design changes.
- (vii) Manufacturing
- 1) Provide workflow process diagrams and descriptions for all procedures and decision-making tools used in reaching a test result, including manual, automated, and bioinformatic processes.
 - 2) For devices manufactured and performed at the same site, provide a list of reagents, equipment, and software used to manufacture a test.
- (viii) Instructions for use/use protocols
- 1) In the case of laboratory developed tests where instructions for use are not included in labeling, provide detailed instructions or protocols on how the test is performed, from starting material to test output including specific instruments, reagents, and software functions required for the process.

V. FINANCIAL CERTIFICATION OR DISCLOSURE

Pursuant to 21 C.F.R. part 54, a financial certification or disclosure is not required for this reclassification petition.

VI. ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. §§ 25.34 and 25.40, an environmental impact statement is not required for this reclassification petition.

VII. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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