



June 16, 2020

Foundation Medicine, Inc.
Varun Pattani, Ph.D.
Associate Director, Regulatory Affairs
150 Second Street
Cambridge, MA 02141

Re: P170019/S016
Trade/Device Name: FoundationOne[®]CDx (F1CDx)
Product Code: PQP
Filed: April 1, 2020

Dear Dr. Varun Pattani:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement to expand the intended use of FoundationOne[®]CDx (F1CDx) to include high tumor mutational burden (TMB) at the cut-off of ≥ 10 mutations per megabase (mut/Mb) in patients with solid tumors who may benefit from treatment with KEYTRUDA[®] (pembrolizumab). This device is indicated as follows:

FoundationOne[®]CDx (F1CDx) is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif [®] (afatinib), Iressa [®] (gefitinib), Tagrisso [®] (osimertinib), or Tarceva [®] (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso [®] (osimertinib)
	<i>ALK</i> rearrangements	Alecensa [®] (alectinib), Xalkori [®] (crizotinib), or

Indication	Biomarker	Therapy
		Zykadia [®] (ceritinib)
	<i>BRAF</i> V600E	Tafinlar [®] (dabrafenib) in combination with Mekinist [®] (trametinib)
	<i>MET</i> single nucleotide variants (SNVs) and indels that lead to <i>MET</i> exon 14 skipping	Tabrecta [™] (capmatinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar [®] (dabrafenib) or Zelboraf [®] (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist [®] (trametinib) or Cotellic [®] (cobimetinib) in combination with Zelboraf [®] (vemurafenib)
Breast cancer	<i>ERBB2</i> (HER2) amplification	Herceptin [®] (trastuzumab), Kadcylla [®] (ado-trastuzumab-emtansine), or Perjeta [®] (pertuzumab)
	<i>PIK3CA</i> C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray [®] (alpelisib)
Colorectal cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix [®] (cetuximab)
	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3, and 4) and <i>NRAS</i> wild-type (absence of mutations in exons 2, 3, and 4)	Vectibix [®] (panitumumab)
Ovarian cancer	<i>BRCA1/2</i> alterations	Lynparza [®] (olaparib) or Rubraca [®] (rucaparib)
Cholangiocarcinoma	<i>FGFR2</i> fusions and select rearrangements	Pemazyre [™] (pemigatinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene (<i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>BARD1</i> , <i>BRIP1</i> , <i>CDK12</i> , <i>CHEK1</i> , <i>CHEK2</i> , <i>FANCL</i> , <i>PALB2</i> , <i>RAD51B</i> , <i>RAD51C</i> , <i>RAD51D</i> and <i>RAD54L</i>) alterations	Lynparza [®] (olaparib)
Solid tumors	TMB \geq 10 mutations per megabase	Keytruda [®] (pembrolizumab)

The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the Rubraca product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the device is to be distributed only with serial number-controlled instruments and only to Foundation Medicine, Inc. at 150 Second Street, Cambridge, MA 02141 and 7010 Kit Creek Road, Morrisville, NC 27560. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved as follows: library construction reagents, hybrid capture reagents, and sequencing reagents may be stored between 4°C and -20°C for up to 90 days; DNA samples may be stored at 4°C for up to 6 weeks and -20°C for up to 5 months. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following non-clinical information in a report, which may be followed by a PMA supplement where applicable.

1. You must provide data evaluating the effects of endogenous interfering substances including necrotic tissue and hemoglobin. The samples selected for this assessment will represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples. The data from

this study must be adequate to support that potential endogenous interfering substances in solid tumors do not adversely impact F1CDx TMB calling.

2. You must provide data from an evaluation to support robust TMB calling within the F1CDx stability claims for DNA and FFPE slide stability. You may leverage the existing F1CDx platform DNA and FFPE slide stability data (P170019); however, you must provide the study results with the data generated by the updated F1CDx bioinformatics pipeline v3.3.x. The samples included in the analyses to support DNA and FFPE slide stability with respect to TMB calling, respectively, must represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples. The data from this study must be adequate to support the F1CDx DNA and FFPE slide stability duration claims for TMB calling.
3. You must provide data from a guard banding study to support the performance of F1CDx TMB calling and the impact of process variation with regard to uncertainty in the measurement of DNA concentration at various stages of the process. You may leverage the existing F1CDx platform guard banding data (P170019); however, you must provide the study results with the data generated by the updated F1CDx bioinformatics pipeline v3.3.x. The samples included in the guard banding analysis must represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples.
4. You must provide the F1CDx intermediate precision results, including repeatability and reproducibility, for the TMB component alterations, i.e., percentage agreement of variant calls among the replicates under repeatability or reproducibility conditions. The data from this supplemental analysis must provide information regarding the F1CDx precision for the underlying component variants included in the TMB score.

Please send protocols for your proposals to address the Conditions of Approval listed above with study details and final sample numbers. All requested data must be generated, and a complete set of the requested data required by this order must be submitted within 1 year.

Be advised that failure to comply with any post-approval requirement, including the analyses requested above, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c).

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Separate PAS Progress Reports must be submitted for each study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. Each report, identified as a PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

5. You must provide a robust and high-quality data set and analysis to support reporting the quantitative TMB score. To support quantitative TMB reporting, you must include clinical validation data from a well-conducted clinical study for the quantitative TMB score measurement (i.e., clinically meaningful efficacy for every unit of change of each continuous output) by an appropriate statistical analysis where patients' response status is the response variable and TMB scores and cancer types are the predictor

variables. Sensitivity analysis should also be conducted on the missing quantitative TMB scores, and quantitative TMB scores should be compared among baseline demographic characteristics for statistical differences. The samples selected for these studies will represent a range of solid tumors and TMB scores across the intended use population. The data from the clinical study must be adequate to support that TMB score is a significant variable to predict patients' response status and clinically meaningful efficacy. The data from the analytical studies must be adequate to support robust quantitative TMB score reporting in the intended use population.

Please send protocols for your proposals to address the Condition of Approval listed above with study details and final sample numbers. All requested data must be generated, and a complete set of the requested data required by this order must be submitted within 1 year.

Be advised that failure to comply with any post-approval requirement, including the clinical and analytical studies to support reporting the quantitative TMB score requested above, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c).

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Be advised that protocol information, interim and final results will be published on the Post Approval Study Webpage https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (<https://www.fda.gov/media/71327/download>).

Within 30 days of your receipt of this letter, you must submit PMA supplements that include complete protocols of your post-approval studies described above. Your PMA supplements should be clearly labeled as a PMA Post-Approval Study Protocol" as noted above and submitted to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (UDI) rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). For more information on these requirements, please see the UDI website, <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system>.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" <https://www.fda.gov/media/81431/download>.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52 for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems> and on combination product postmarketing safety reporting is available at (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>).

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the postmarketing safety reporting requirements (21 CFR 4, Subpart B) for combination products, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls>.

CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals>. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under

section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with a copy of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Pamela Gallagher, Ph.D. at 301-796-3477 or Pamela.Gallagher@fda.hhs.gov.

Sincerely,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics
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