October 6, 2023

Foundation Medicine, Inc.
Anika Schaedle
Manager, Regulatory Affairs
150 Second Street, 1st Floor
Cambridge, MA 02141

Re: P170019/S043
Trade/Device Name: FoundationOne®CDx (F1CDx)
Product Code: PQP
Filed: March 2, 2023
Amended: April 7, 2023, July 10, 2023, and July 26, 2023

Dear Anika Schaedle:

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 for the FoundationOne CDx (F1CDx) to include a companion diagnostic indication for *RET* fusions in patients with solid tumors who may benefit from treatment with RETEVMO® (selpercatinib). This device is indicated for the following:

> 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 when using the DNAx extraction method. The test is intended for detection of substitutions and indels in 324 genes, CNAs in 15 genes and select gene rearrangements, as well as genomic signatures including MSI and TMB using DNA isolated from FFPE tumor tissue specimens when using the CoExtraction method for DNA isolation. 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 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**

| Tumor Type | Biomarker(s) Detected | Therapy |
|---|---|---|
| Non-small cell lung cancer (NSCLC) | *EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations | EGFR Tyrosine Kinase Inhibitors (TKI) approved by FDA* |
| | *EGFR* exon 20 T790M alterations | Tagrisso® (osimertinib) |

| Tumor Type | Biomarker(s) Detected | Therapy |
|---|---|---|
| | *ALK* rearrangements | Alecensa® (alectinib), Alunbrig® (brigatinib), Xalkori® (crizotinib), or Zykadia® (ceritinib) |
| | *BRAF* V600E | Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) |
| | *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping | Tabrecta® (capmatinib) |
| | *ROS1* fusions | Rozlytrek® (entrectinib) |
| Melanoma | *BRAF* V600E | BRAF Inhibitors approved by FDA* |
| | *BRAF* V600E and V600K | Mekinist® (trametinib) or BRAF/MEK Inhibitor Combinations approved by FDA* |
| | *BRAF* V600 mutation-positive | Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib) |
| Breast cancer | *ERBB2* (HER2) amplification | Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab) |
| | *PIK3CA* C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations | Piqray® (alpelisib) |
| Colorectal cancer | *KRAS* wild-type (absence of mutations in codons 12 and 13) | Erbitux® (cetuximab) |
| | *KRAS* wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4) | Vectibix® (panitumumab) |
| Ovarian Cancer | *BRCA1/2* alterations | Lynparza® (olaparib) |
| Cholangiocarcinoma | *FGFR2* fusions and select rearrangements | Pemazyre® (pemigatinib) or Truseltiq™ (infigratinib) |
| Prostate cancer | Homologous Recombination Repair (HRR) gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*) alterations | Lynparza® (olaparib) |
| | *BRCA1, BRCA2* alterations | Akeega® (niraparib + abiraterone acetate) |
| Solid Tumors | MSI-High | Keytruda® (pembrolizumab) |

| Tumor Type | Biomarker(s) Detected | Therapy |
|---|---|---|
| | TMB ≥ 10 mutations per megabase | Keytruda® (pembrolizumab) |
| | *NTRK1/2/3* fusions | Rozlytrek® (entrectinib)<br>Vitrakvi® (larotrectinib) |
| | *RET* fusions | Retevmo® (selpercatinib) |

*For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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 is 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 12 months; DNA samples may be stored at 4°C for up to 6 weeks and -20°C for up to 3 years. 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.

FMI will provide the following software and cybersecurity information in a post-approval report within 6 months of approval of this PMA supplement:

1. FMI must submit a list of the cumulative changes and in sufficient detail acceptable to FDA, made between the currently deployed genomics platform, which includes analytical pipeline software version v3.25.0 (AP v3.25), and the AP versions used in the clinical validation studies in this supplement.

2. FMI must submit a detailed description of the validation activity conducted to support the version change, including the associated risk assessments for each change, and the rationale, acceptable to FDA, that the validation performed supports reasonable assurance that the modification has not affected the performance or raised new concerns regarding the safety and effectiveness of the device.

3. FMI must provide evidence, acceptable to FDA, that performance expectations with the currently deployed genomics platform, including AP v3.25.0, are representative of the performance in the clinical validation study in this supplement and analytical validation studies that are leveraged. Such evidence may include regression testing using the clinical and analytical datasets to perform *in silico* reanalysis of the results obtained in the validation studies and confirmation that there is little or no deviation in the quality metrics for each of the samples to support that the performance of the assay remains the same.

4. FMI must submit and complete documentation for cybersecurity, interoperability, risk assessment, risk management tests, traceability and validation, acceptable to FDA, including providing copies of associated documents (i.e., reference documents, letters, original reports, etc.), as required by section 524B of the Federal Food, Drug and Cosmetics Act, to ensure F1CDx and FMI's overall computational environment is cybersecure. The documentation should include a complete evaluation of all potential threats and vulnerabilities (e.g., software, instrumentation, software environment), validation of the use of third-party and Off-the-Shelf software, a complete anomaly assessment, security features installed on mobile devices, detailed protocols associated with the evaluation and review of software release candidates, and all relevant referenced documents.

Be advised that failure to comply with any post-approval requirement constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

You must obtain approval of your post-approval study (PAS) protocol(s) within 60 days from the date of this order. Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a

complete protocol of your post-approval study described below. Your PMA supplement should be clearly labeled as a "PMA Post-Approval Study Protocol" as noted below 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.

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 every six (6) months for the first year and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA. The Final PAS Report should be submitted no later than three (3) months after study completion (i.e., last subject's last follow-up date).

1. FMI must provide clinical outcome data as assessed by overall response rate from additional tissue agnostic patients enrolled into the LIBRETTO-001 clinical trial in the post-market setting to confirm the clinical effectiveness of F1CDx as a companion diagnostic (CDx) device for identification of patients with solid tumors with *RET* fusions who may benefit from treatment with RETEVMO.

The clinical study protocol to address the Condition of Approval listed above should be submitted within 30 days of the PMA approval date, and the study data and conclusions should be submitted within 3 years of the PMA approval date.

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number.

Be advised that failure to comply with any post-approval requirement constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

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 in accordance with 21 CFR 814.46(a)(3)-(4).

Be advised that protocol information, interim and final results will be published on the Post-Approval Studies Program Database 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 Premarket Approval Application Order" (https://www.fda.gov/media/71327/download).

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 post-marketing 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 post-marketing 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 post-marketing 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 Home Page 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 Brittany Aguila at Brittany.Aguila@fda.hhs.gov.

Sincerely,

Donna M. Roscoe -S

Donna Roscoe, Ph.D.
Acting Director
Division of Molecular Genetics
and Pathology
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Office of Product Evaluation and Quality
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