

December 22, 2022

Foundation Medicine, Inc.
 Linlin Meng, Regulatory Affairs Specialist II
 150 Second Street
 Cambridge, MA 02141

Re: P190032/S004

Trade/Device Name: FoundationOne® Liquid CDx (F1LCDx)

Product Code: PQP

Filed: April 13, 2022

Amended: September 2, 2022

Dear Linlin Meng:

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 Liquid CDx (F1LCDx) to include companion diagnostic indications for *NTRK1*, *NTRK2*, *NTRK3* fusion in patients with solid tumors and for *ROS1* fusions in patients with non-small cell lung cancer who may benefit from treatment with ROZLYTREK® (entrectinib). The device is indicated for the following:

FoundationOne Liquid CDx is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements in eight (8) genes, and copy number alterations in three (3) genes. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit. The test is intended to be used 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.

Table 1: Companion diagnostic indications

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	<i>ALK</i> Rearrangements	ALECENSA® (alectinib)
	<i>EGFR</i> Exon 19 deletions and <i>EGFR</i> Exon 21 L858R alteration	<i>EGFR</i> tyrosine kinase inhibitors approved by FDA*
	<i>MET</i> single nucleotide variants (SNVs) and indels that lead to <i>MET</i> exon 14 skipping	TABRECTA® (capmatinib)
	<i>ROS1</i> fusions**	ROZLYTREK® (entrectinib)
Prostate cancer	<i>BRCA1</i> , <i>BRCA2</i> , and <i>ATM</i> alterations	LYNPARZA® (olaparib)
	<i>BRCA1</i> , <i>BRCA2</i> alterations	RUBRACA® (rucaparib)

Breast Cancer	<i>PIK3CA</i> mutations C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	PIQRAY® (alpelisib)
Solid Tumors	<i>NTRK1/2/3</i> fusions**	ROZLYTREK® (entrectinib)

*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#Group_Labeling

Additionally, FoundationOne Liquid CDx 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.

A negative result from a plasma specimen does not mean that the patient's tumor is negative for genomic findings. Patients who are negative for the mutations listed in Table 1 (see **Note for *NTRK1/2/3* and *ROS1* fusions) should be reflexed to routine biopsy and their tumor mutation status confirmed using an FDA- approved tumor tissue test, if feasible.

**Note: when considering eligibility for ROZLYTREK® based on the detection of *NTRK1/2/3* and *ROS1* fusions, testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing.

Genomic findings other than those listed in Table 1 of the intended use statement are not prescriptive or conclusive for labeled use of any specific therapeutic product.

FoundationOne Liquid CDx is a single-site assay performed at Foundation Medicine, Inc. in Cambridge, MA.

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. 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 for the library construction reagents, hybrid capture reagents and sequencing reagents that may be stored between 4°C and -20°C for up to 12

months; whole blood samples may be stored at the recommended temperature for up to 15 days and cfDNA 70°C for up to 33 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. The final study protocols for the above studies, study data, study conclusions, and labeling revisions should be submitted within 1 year of the PMA approval date.

1. FMI must provide robust and high confidence data to demonstrate the analytical accuracy, limit of detection, and precision for the most current version of FoundationOne Liquid CDx for the detection of *NTRK2* fusions. These results must be adequate to confirm the safety and effectiveness of the FoundationOne Liquid CDx device.
2. FMI must provide robust and high confidence data to demonstrate the analytical accuracy with 10 *ROS1* fusion positive samples for the most current version of FoundationOne Liquid CDx for the detection of *ROS1* fusions to an externally validated comparator assay that has been accepted by FDA as suitable for this purpose. *ROS1* fusion positive samples can be procured from the intended use population. These results must be adequate to confirm the safety and effectiveness of the FoundationOne Liquid CDx device.
3. Blood Collection Tubes
 - a. FMI must demonstrate clinically insignificant variability when different lots of the FoundationOne Liquid CDx Blood Collection tube are used with the FoundationOne Liquid CDx assay. FMI must provide data from a robust and high confidence precision study. This study must confirm the FoundationOne Liquid CDx assay's precision when the FoundationOne Liquid CDx cfDNA Blood Collection tubes are used and must use replicate samples from each of multiple different patients. Each patient who donates specimens for this study must have plasma collected in a total of four tubes, each from two tube lots; three lots are required to be represented in the study. This is important to assess variability between tube lots and across patient specimens. Each replicate must be run at or near the minimum standardized cfDNA input (i.e., at a target concentration of 30 ng). The samples must be collected from patients with at least 10 different tumor types and the study must include at

least 10 pathogenic substitutions, 10 pathogenic indels, and rearrangements that are identified by the FoundationOne Liquid CDx assay. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens collected in the FoundationOne Liquid cfDNA Blood Collection tubes in the intended use population.

- b. FMI must provide robust and high confidence data from a well- designed and well-controlled study which is intended to confirm the shelf-life claims for the FoundationOne Liquid cfDNA Blood Collection tubes when used in conjunction with the FoundationOne Liquid CDx assay. FMI must provide evidence that when samples from the same patient collected in newly manufactured tubes, as well as in tubes that are at the end of their shelf life, are used in the FoundationOne Liquid CDx assay, the FoundationOne Liquid CDx assay performance meets the clinical and analytical performance claim in the FoundationOne Liquid CDx assay authorized labeling.
- c. FMI must provide robust and high confidence data that the impact of preanalytical variables associated with the use of the FoundationOne Liquid CDx cfDNA Blood Collection tubes, such as hemolysis, has been validated for the FoundationOne Liquid CDx test system and that any impact of these factors on the FoundationOne Liquid CDx assay has been appropriately mitigated. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens collected in the FoundationOne Liquid CDx cfDNA Blood Collection tubes in the intended use population.
- d. To support use of results submitted in FMI's clinical study generated from samples collected within 24 hours from cancer patients, FMI must provide robust and high confidence data from an appropriately designed study to confirm the claimed stability of cfDNA in the FoundationOne Liquid CDx cfDNA Blood Collection tubes. This study must compare FoundationOne Liquid CDx results generated from freshly drawn blood specimens to FoundationOne Liquid CDx assay results generated from matched specimens (i.e., collected at the same time from the same patient) stored in the FoundationOne Liquid CDx cfDNA Blood Collection tube for a minimum of 24 hours. This study must be performed with replicate samples, when feasible, at each time point, and the samples tested must adequately represent all variant types across several tumor types at each tested time point. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens the intended use population.
- e. FMI must provide robust and high confidence data from a stability study which demonstrates acceptable stability of whole blood collected from the CDx intended use patients and stored in the FoundationOne Liquid CDx cfDNA Blood Collection tubes. The study must confirm the claimed cfDNA storage stability and must confirm the suppression of white blood cells lysis across multiple lots. This study must also use the amount of cfDNA isolated and electropherogram data as a comparator method, in addition to sequencing results and quality metrics. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens collected in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes in the intended use population.
- f. FMI must demonstrate clinically insignificant variability on the performance of the FoundationOne Liquid CDx assay when specimens collected in FoundationOne Liquid CDx

cfDNA Blood Collection tubes are handled at different centrifugation conditions. The study must assess conditions that are below and above recommended relative centrifugal force and centrifugation time to account for potential performance issues that could occur due to centrifuge malfunction or operator errors. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when expected handling conditions are used on specimens collected in the FoundationOne Liquid CDx cfDNA Blood Collection tubes in the intended use population.

Be advised that failure to comply with any post-approval requirement, including the analytical studies to support identification of patients with solid tumors with *NTRK1/2/3* fusions or NSCLC patients with *ROS1* fusions who may benefit from treatment with ROZLYTREK® (entrectinib) requested above constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

In addition to the conditions of approval above, you are required to implement alternate controls to address violations of the current good manufacturing practice requirements of the Quality System regulations found at Title 21, Code of Federal Regulations, Part 820 pursuant to the variance granted by FDA on August 26, 2020 in accordance with 21 CFR 820.1(e)(2).

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 Catherine Fischer, Ph.D., MPH, at 412-657-6918 or Catherine.Fischer@fda.hhs.gov.

Sincerely,

Donna M. Roscoe -S

Donna Roscoe, Ph.D.
Acting Director
Division of Molecular Genetics
and Pathology
OHT7: Office of In Vitro Diagnostics
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