



Foundation Medicine, Inc.
Ryan Woodhouse
Director, Regulatory Affairs
150 Second Street
Cambridge, MA 02141

October 26, 2020

Re: P200006

Trade/Device Name: FoundationOne Liquid CDx (F1 Liquid CDx)

Product Code: PQP

Filed: March 5, 2020

Amended: July 20, 2020, July 24, 2020; July 28, 2020

Dear Ryan Woodhouse:

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) for the FoundationOne Liquid CDx (F1 Liquid CDx) for the following indication:

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 three (3) 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>EGFR</i> Exon 19 deletions and <i>EGFR</i> Exon 21 L858R alteration	IRESSA® (gefitinib) TAGRISSO® (osimertinib) TARCEVA® (erlotinib)
	<i>ALK</i> Rearrangements	ALECENSA® (alectinib)
Prostate cancer	<i>BRCA1</i> , <i>BRCA2</i> alterations	RUBRACA® (rucaparib)
Ovarian Cancer	<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)

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 should be reflexed to routine biopsy and their tumor mutation status confirmed using an FDA-approved tumor tissue test, if feasible.

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 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). 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 90 days; 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.

1. FMI must provide robust and detailed protocols, including acceptance criteria where appropriate, for the studies that are conditions of approval required by this order. These studies must be adequate to confirm the safety and effectiveness of the FoundationOne[®] Liquid CDx device and must include a detailed description of the numbers of sample to be tested, the type of samples to be tested, the tumor types for each sample, the complete testing protocol, and a robust statistical analysis plan. These protocols must be submitted to FDA no later than 60 days after approval.
2. All requested data must be generated, and a complete set of the requested data required by this order must be submitted within 1 year, unless otherwise specified.
3. FMI will provide robust and high confidence data from a well-designed and well-controlled study using cell free-DNA (cfDNA) input (at a target concentration of 30 ng) from intended use specimens for *ALK* fusions/rearrangements (NSCLC), *BRCA1/BRCA2* (ovarian cancer), *PIK3CA* mutations, and *ERBB2* copy number amplifications across other cancer types, to confirm an acceptable level of precision at or near the LoD concentration. FMI should provide data for each of the 4 different CDx *BRCA1* and *BRCA2* variant types [i.e., base substitutions (SNV), insertion/deletion (indel), rearrangement (RE), and homozygous deletions (HD)], *ALK* fusions/rearrangements, and a representative number of *PIK3CA* mutations. FMI should also include additional samples with *ERBB2* copy number amplifications across other cancer types to support a tumor profiling claim. The level of precision and reproducibility at the LoD must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens from the intended use population.
4. For the *BRCA1/BRCA2* companion diagnostic (CDx) claim (rucaparib) for the ovarian cancer indication, you must provide the following:
 - a. FMI will provide a robust and high confidence data set to confirm the analytical accuracy/concordance to a validated orthogonal NGS method that has been accepted by the FDA (as part of the protocol review) as suitable for this purpose. These studies must be performed to collect data for *BRCA1* and *BRCA2* indels, HD, and RE using the accepted comparator assay, using intended use ovarian cancer specimens. The level of analytical accuracy/concordance must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens from the intended use population.
 - b. FMI will provide a robust and high confidence data set from a well-designed and well-controlled contrived sample functional characterization study to demonstrate similar performance between ovarian cancer clinical cfDNA samples and contrived samples. The study should utilize clinical samples harboring *BRCA1* and *BRCA2* SNV, HD, and RE alterations and contrived samples with the same alterations and demonstrate equivalent hit rates across comparable dilutions close to and below LoD levels between the two sample types. The data from this study must be adequate to demonstrate

that clinically significant inaccurate results are minimized when used on specimens from the intended use population.

- c. FMI will provide robust and high confidence data from a guard-band study to test the limits of FoundationOne® Liquid CDx assay to confirm the specifications for cfDNA input. This study must be designed to assess cfDNA concentrations minimally including 2X below the minimum recommended cfDNA input level to confirm the cfDNA input guard-bands for *BRCA1* and *BRCA2* CDx variant types. The study must assess *BRCA1* and *BRCA2* indels, HD, and RE. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens from the intended use population.
5. FMI must provide robust and high confidence data from an appropriately designed limit of blank (LoB) study. The study should be performed using all steps in the FoundationOne® Liquid CDx assay's workflow for each replicate tested to confirm that the LoB of this assay is as claimed. The LoB data from this study must also be provided to FDA with and without germline alteration, and white blood cells must also be sequenced to confirm germline variants. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens from the intended use population.
6. FMI must provide data from a well-designed and well-controlled accuracy/concordance study using a comparator assay that has been accepted by the FDA (as part of the protocol review) as suitable for this purpose to confirm accuracy of the FoundationOne® Liquid CDx test results to a validated orthogonal method. The samples tested in this study must include SNVs and indels of genes (i.e., 78% of the total panel genes) that have not been tested in the existing premarket accuracy/concordance study as well as additional *ALK* fusions/rearrangements in lung cancer other cancers, and *ERBB2* copy number amplifications in additional cancers other than breast. The level of analytical accuracy/concordance must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens from the intended use population.
7. 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 SNVs and 10 pathogenic indels 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 CDx 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 CDx 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, you 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 in 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 collected in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes in 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.

8. Software:

- a. FMI must appropriately validate modifications to the curating and reporting of variant results, to align with the approved clinical CDx indications and the genes and variants authorized under the tumor profiling claim. FMI must provide software validation documentation, including example reports, adequate to demonstrate that these modifications do not adversely affect the safety and effectiveness of the device. The software modifications and validation data must be provided within 30 days of approval.
- b. FMI must appropriately validate modifications to the curating and reporting of variant results, including reporting levels for mutation profiling, and modifications to the report formatting that were made to the software following review. FMI must provide software validation documentation adequate to demonstrate that these modifications do not adversely affect the safety and effectiveness of the device.
- c. FMI must appropriately validate software infrastructure changes and migration to of the analysis pipeline and associated software to cloud services, including any impact of these software modifications on the cybersecurity of FoundationOne® Liquid CDx assay test system. FMI must provide software validation documentation adequate to demonstrate that these modifications do not adversely affect the safety and effectiveness of the device.

Be advised that failure to comply with any post-approval requirement, including the submission of the study protocols or validation data, 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 Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below.

You must obtain approval of your PAS protocol(s) within 60 days from the date of this order. 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.

1. FMI must provide robust and high confidence data in the form of real-world evidence from BRCA1/BRCA2 positive ovarian cancer patients consistent with the patient population enrolled into ARIEL2 clinical study to support the safety and effectiveness of the FoundationOne® Liquid CDx to identify patients who may benefit from treatment with rucaparib. This post-approval study should provide additional clinical outcome data in terms of confirmed objective response rate to confirm the clinical effectiveness of FoundationOne® Liquid CDx as a CDx device for identification of ovarian cancer patients with BRCA1/BRCA2 alterations who may benefit from treatment with rucaparib.

All requested data must be generated, and a complete set of the requested data required by this order must be submitted within 2 years, and the submission of the final study report should be within 3 months from study completion.

In addition, you must submit separate periodic reports on the progress of the clinical study intended to confirm the clinical effectiveness of FoundationOne® Liquid CDx as a CDx device for identification of ovarian cancer patients with BRCA1/BRCA2 alterations who may benefit from treatment with rucaparib as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter.

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, including clinical study intended to confirm the clinical effectiveness of FoundationOne® Liquid CDx as a CDx device for identification of ovarian cancer patients with BRCA1/BRCA2 alterations who may benefit from treatment with rucaparib, 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).

In addition to the conditions of approval above, you have agreed 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 October 26, 2020 in accordance with 21 CFR 820.1(e)(2).

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>).

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 Karen Bijwaard at 301-796-6162 or Karen.Bijwaard@fda.hhs.gov.

Sincerely,

Reena Philip -S

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