July 26, 2024

Guardant Health, Inc.
Mirna Lopez, Ph.D., RAC
Senior Regulatory Affairs Director
505 Penobscot Drive
Redwood City, California 94063

Re: P230009
Trade/Device Name: Shield
Product Code: PHP
Filed: March 10, 2023
Amended: October 18, 2023; December 11, 2023; January 19, 2024

Dear Mirna Lopez:

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 Shield Test. This device is indicated for:

> The Shield test is a qualitative, in vitro diagnostic test intended to detect colorectal cancer derived alterations in cell-free DNA from blood collected in the Guardant Shield Blood Collection Kit.
>
> Shield is intended for colorectal cancer screening in individuals at average risk of the disease, age 45 years or older. Patients with a positive result should be followed by colonoscopy. Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.
>
> The test is performed at Guardant Health, Inc.

Based upon the information submitted, 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 available 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 all other applicable requirements, including those governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 12 months of shelf life for the Shield assay reagents at the recommended stored conditions. Whole blood specimens may be stored in Cell-Free DNA BCTs for up to seven (7) days after blood collection and prior to plasma isolation; plasma may be stored at -80°C (- 60°C to -90°C) for seven (7) months before cfDNA extraction; and cfDNA may be stored at -20°C ± 5°C for one (1) year. 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 must 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, under 21 CFR 814.82(a)(9), 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 prominently display in Shield's labeling the following precaution:

"Precaution: Based on data from clinical studies, Shield has limited detection (55%-65%) of Stage I colorectal cancer and does not detect 87% of precancerous lesions. One out of 10 patients with a negative Shield result may have a precancer that would have been detected by a screening colonoscopy. Shield demonstrated high detection of Stages II, III, and IV colorectal cancer."

Given the importance for the device's safe and effective use, under 21 CFR 814.82(a)(3), the prominent display of the precaution in the labeling and in the advertising of this device is a condition to the approval of the device.

Be advised that failure to comply with any post-approval requirement, including failure to include the prominent display of the precaution in the labeling and in the advertising of this device, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 21 CFR 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 PMA supplements that include complete protocols of your post-approval studies described below. Your PMA supplements 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 PAS listed below.

1. The **Shield Post-Approval Study (PAS)** is a prospective, longitudinal study supplemented with Real World Evidence (RWE) to evaluate the longitudinal performance of Shield in an average risk population. The PAS must meet the study requirements meeting the criteria below:

    - The study objective is to collect longitudinal data on subjects prescribed Shield over the course of 3 years.
    - Subjects will be enrolled at T0 and required to complete the Shield test at baseline (T0) and at year 3 (T3). Year 3 is defined as 33 months to 42 months post baseline. Subjects with a positive Shield test result at T0 will undergo diagnostic colonoscopy per the standard of care and then will be discontinued from the study. Subjects with negative Shield test results at T0 will remain in the study. Subjects will be offered repeat Shield testing at T3 and be expected to undergo a colonoscopy at T3. Subjects will be followed at T1 and T2 to evaluate for changes in medical history.
    - This study will enroll a sufficient number of subjects at average risk of developing colorectal cancer, age of 45 and 84, to ensure at least 1000 evaluable subjects with valid Shield test results and colonoscopy results at T3 and CRC cases can be observed at T3.
    - The study length will be 5 years including 3 years of longitudinal subject follow-up.
        - The first subject will be enrolled within 6 months of the study protocol approval date.
        - 20% of subjects enrolled within 12 months of the study protocol approval date.
        - 50% of subjects enrolled within 18 months of the study protocol approval date.
        - 100% of subjects enrolled within 24 months of the study protocol approval date.
    - The post-approval study will include the following co-primary performance measures:
        - Sensitivity for CRC, sensitivity for AA and specificity for non-advanced neoplasia at T3.
        - Positive predictive value (PPV) and negative predictive value (NPV) for CRC, AA and advanced neoplasia at T3.
    - The post-approval study will include the following exploratory performance measures:
        - The cumulative risk of false positive result (cFPR) and cumulative risk of a true positive result (cTPR).
        - The probability that a negative Shield result at baseline remains negative through 3 years.
        - The probability that a negative Shield result at baseline (T0) results in no CRC/AA through 3 years.
        - The distribution of colorectal epithelial lesions (by Category) among positive Shield subjects at T0 and at T3.
        - Adherence to repeat Shield at T3.
        - Cumulative compliance to colonoscopy following a positive Shield result.
        - Cross-over to alternative screening methodologies (e.g., FOBT, colonoscopy, other) at T1 & T2.
        - The rate of no Shield result (e.g., invalid result).
        - Supplemental real world evidence study to evaluate PPV at T0 and T3

FDA tracks and evaluates the conduct of a PAS through review of study reports submitted to the Agency. Guardant health Inc. must fulfill reporting requirements including Enrollment Status Reports, PAS Progress Reports which must be submitted every six months until subject enrollment has been completed, and

annually thereafter, as well as a Final Report. Guardant health Inc. must follow the reporting schedule, as required by the PMA approval order, until submitting the Final PAS Report.

From the date of study protocol approval, you must meet the following timelines:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up 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, including study objective, sample size, study endpoints and performance metrics outlined above, 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, available at 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. Under 21 CFR 814.39, 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 Part 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 available at 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. Additional information about changes that may require a PMA supplement are provided in 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.

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production and process controls (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 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 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 Part 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 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 Yu Han at Yu.Han@fda.hhs.gov.

Sincerely,

DONNA M. ROSCOE -S

Donna Roscoe, Ph.D.
Acting Director
Division of Molecular Genetics and Pathology
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