**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
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November 26, 2014

HeartFlow, Inc.
Mr. Dustin Michaels
Vice President Clinical, Quality & Regulatory
1400 Seaport Boulevard, Building B
Redwood City, CA 94063

Re: DEN130045
HeartFlow $FFR_{CT}$ v.1.4
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 870.1415
Regulation Name: Coronary Physiologic Simulation Software Device
Regulatory Classification: Class II
Product Code: PJA
Dated: November 1, 2013
Received: November 6, 2013

Dear Mr. Michaels:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your *de novo* request for classification of the HeartFlow $FFR_{CT}$ v.1.4, a prescription device under 21 CFR Part 801.109 that is indicated for the following:

> HeartFlow $FFR_{CT}$ is a post-processing software for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography (CT) DICOM data for clinically stable symptomatic patients with coronary artery disease. It provides $FFR_{CT}$, a mathematically derived quantity, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT images. $FFR_{CT}$ analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. The results of HeartFlow $FFR_{CT}$ are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment. It is for prescription use only.

FDA concludes that this device should be classified into class II. This order, therefore, classifies the HeartFlow $FFR_{CT}$ v.1.4, and substantially equivalent devices of this generic type, into class II under the generic name, Coronary Physiologic Simulation Software Device.

FDA identifies this generic type of device as:

> **Coronary Physiologic Simulation Software Device** – A coronary vascular physiologic simulation software device is a prescription device that provides simulated functional assessment of blood flow in the coronary vascular system using data extracted from medical device imaging to solve algorithms and yield simulated metrics of physiologic information (e.g., blood flow, coronary flow reserve, fractional flow reserve, myocardial perfusion). A coronary vascular physiologic simulation software device is intended to generate results for use and review by a qualified clinician.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for *de novo* classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

On November 6, 2013, FDA received your *de novo* requesting classification of the HeartFlow $FFR_{CT}$ v.1.4 into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the HeartFlow $FFR_{CT}$ v.1.4 into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

After review of the information submitted in the *de novo* request and subsequent responses to deficiencies, FDA has determined that the HeartFlow $FFR_{CT}$ v.1.4 indicated for the following:

> HeartFlow $FFR_{CT}$ is a post-processing software for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography (CT) DICOM data for clinically stable symptomatic patients with coronary artery disease. It provides $FFR_{CT}$, a mathematically derived quantity, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT images. $FFR_{CT}$ analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. The results of HeartFlow $FFR_{CT}$ are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment. It is for prescription use only.

can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device

type. The identified risks and mitigation measures associated with the device type are summarized in Table 1.

**Table 1 – Identified Risks to Health and Mitigation Measures**

| Identified Risk | Mitigation Measures |
|---|---|
| False negative results improperly indicating diseased vessel as low probability for significant disease leads to delay of further evaluation/treatment | Software Verification, Validation, and Hazard Analysis<br>Non-clinical Performance Testing<br>Clinical Testing<br>Consistency (Repeatability/Reproducibility) Evaluation<br>Labeling |
| False positive results improperly indicating diseased vessel as high probability for significant disease leads to incorrect patient management | |
| Delayed delivery of results leading to delay of further evaluation/treatment | |
| Failure to properly interpret device results leads to incorrect patient management | Human Factors Testing<br>Labeling |

In combination with the general controls of the FD&C Act, the Coronary Physiologic Simulation Software Device is subject to the following special controls:

1. Adequate software verification and validation based on comprehensive hazard analysis with identification of appropriate mitigations must be performed including:
   a. Full characterization of technical parameters of the software, including any proprietary algorithm(s) used to model the vascular anatomy.
      i. Adequate description of the expected impact of all applicable image acquisition hardware features and characteristics on performance and any associated minimum specifications.
   b. Adequate consideration of privacy and security issues in the system design.
      i. Adequate mitigation of impact of failure of any subsystem components (signal detection and analysis, data storage, system communications and cybersecurity) with respect to incorrect patient reports and operator failures.

2. Adequate non-clinical performance testing must be provided to demonstrate the validity of computational modeling methods for flow measurement.

3. Clinical data supporting the proposed intended use must be provided, including the following:
   a. Output measure(s) must be compared to a clinically acceptable method and must adequately represent the simulated measure(s) the device provides in an accurate and reproducible manner.
   b. Clinical utility of the device measurement accuracy must be demonstrated by comparison to that of other available diagnostic tests (from literature analysis).

c. Statistical performance of the device within clinical risk strata (e.g., age, relevant comorbidities, disease stability) must be reported.
d. The dataset must be adequately representative of the intended use population for the device (e.g., patients, range of vessel sizes, imaging device models). Any selection criteria or limitations of the samples must be fully described and justified.
e. Statistical methods must consider the pre-defined endpoints.
    i. Estimates of probabilities of incorrect results must be provided for each endpoint.
    ii. Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification.
    iii. Report must provide appropriate confidence intervals for each performance metric.
f. Sensitivity and specificity must be characterized across the range of available measurements.
g. Agreement of the simulated measure(s) with clinically acceptable measure(s) must be assessed across the full range of measurements.
h. Comparison of the measurement performance must be provided across the range of intended image acquisition hardware.
i. If the device uses a cut-off threshold or operates across a spectrum of disease, it must be established prior to validation and it must be justified as to how it was determined and clinically validated.

4. Adequate validation must be performed and controls implemented to characterize and ensure consistency (repeatability and reproducibility) of measurement outputs.
    a. Acceptable incoming image quality control measures and the resulting image rejection rate for the clinical data must be specified.
    b. Data must be provided within the clinical validation study or using equivalent datasets demonstrating the consistency (i.e., repeatability/reproducibility) of the output that is representative of the range of data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment.
        i. Testing must be performed using multiple operators meeting planned qualification criteria and using the procedure that will be implemented in the production use of the device.
        ii. The factors (e.g., medical imaging data set, operator) must be identified regarding which were held constant and which were varied during the evaluation, and a description must be provided for the computations and statistical analyses used to evaluate the data.

5. Human factors evaluation and validation must be provided to demonstrate adequate performance of the user interface to allow for users to accurately measure intended parameters, particularly where parameter settings that have impact on measurements require significant user intervention.

6. Device labeling must be provided that adequately describes the following:
    a. The device's intended use, including the type of imaging data used, what the device measures and outputs to the user, whether the measure is qualitative and/or quantitative, the clinical indications for which it is to be used, and the specific population for which the device use is intended.
    b. Appropriate warnings specifying the intended patient population, identifying anatomy and image acquisition factors that may impact measurement results, and providing cautionary guidance for interpretation of the provided measurements.
    c. Key assumptions made in the calculation and determination of simulated measurements.
    d. The measurement performance of the device for all presented parameters, with appropriate confidence intervals, and the supporting evidence for this performance. Per-vessel clinical performance, including where applicable localized performance according to vessel and segment, must be included as well as a characterization of the measurement error across the expected range of measurement for key parameters based on the clinical data.
    e. A detailed description of the patients studied in the clinical validation (e.g., age, gender, race/ethnicity, clinical stability, current treatment regimen) as well as procedural details of the clinical study (e.g., scanner representation, calcium scores, use of beta-blockers/nitrates).
    f. Where significant human interface is necessary for accurate analysis, adequately detailed description of the analysis procedure using the device and any data features that could affect accuracy of results.

In addition, this is a prescription device and must comply with 21 CFR 801.109. Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Coronary Physiologic Simulation Software Device they intend to market prior to marketing the device and receive clearance to market from FDA.

Please be advised that FDA's decision to grant this *de novo* request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD & C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD & C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305),

Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the *de novo* request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Shawn Forrest at 301-796-5554.

Sincerely yours,

Jonette R. Foy -S

Jonette Foy, Ph.D.
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for Engineering and Science Review
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