



December 19, 2018

CathWorks Ltd.
% Sheila Hemeon-Heyer
President
Heyer Regulatory Solutions LLC
125 Cherry Lane
Amherst, Massachusetts 01002

Re: K182149
Trade/Device Name: FFR_{angio}TM System
Regulation Number: 21 CFR 870.1415
Regulation Name: Coronary Vascular Physiologic Simulation Software
Regulatory Class: Class II
Product Code: QEK
Dated: December 17, 2018
Received: December 18, 2018

Dear Sheila Hemeon-Heyer:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the 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) for

devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<http://www.fda.gov/DICE>) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Shawn W.
Forrest -A

Digitally signed by Shawn W. Forrest -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130040334
1, cn=Shawn W. Forrest -A
Date: 2018.12.19 14:48:08 -05'00'

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known)
K182149

Device Name

FFRangio™

Indications for Use (Describe)

CathWorks FFRangio™ is a software device for the clinical quantitative and qualitative analysis of previously acquired angiography DICOM data for patients with coronary artery disease. It provides FFRangio™, a mathematically derived quantity, computed from simulated blood flow information obtained from a 3D computer model, generated from coronary angiography images. FFRangio™ analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis are provided as a supportive aid for qualified clinicians in the evaluation and assessment of coronary arteries physiology. The results of CathWorks FFRangio™ 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 evaluation.

Type of Use (Select one or both, as applicable)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted per the requirements of 21 CFR 807.92.

- A. Submitter:** Heyer Regulatory Solutions LLC
P.O. Box 2151
Amherst, MA 01004-2151
Contact: Sheila Hemeon-Heyer
Sheila@heyer-regulatory.com
- B. Manufacturer Contact:** CathWorks, Ltd.
Ilanit Frank Hakim
3 Rappaport St.
Kfar Saba 4465141, ISRAEL
Tel: +972 9 7467387
ilanit@cath.works
- C. Date Prepared:** December 19, 2018
- D. Device Name and Classification Information:**
- | | |
|----------------------|--|
| Trade Name: | FFR _{angio} TM System |
| Classification Name: | Coronary Vascular Physiologic Simulation Software Device |
| Common Name: | Digital FFR System |
| Regulation: | 21 CFR 870.1415 |
| Product Code: | QEK |
| Review Panel: | Cardiovascular |
| Class: | II |
- E. Predicate Device(s):** K161772 for FFR_{CT}, manufactured by HeartFlow, Inc.
- F. Summary Device Description:**

The FFR_{angio}TM system is a computer system installed on a mobile cart that is to be located inside the catheterization room or in an adjacent technical/viewing area. The cart holds the computer processing unit, user interface control station (LCD screen and keyboard/mouse), medical isolation transformer, and network isolator. Operation requires only connections to mains and a DICOM communication port. The system supports optional visual media output to the Cath Lab main displays, so the system GUI may be observed on both the system's LCD display and on the Cath Lab's main display (boom monitor).

FFR_{angio}TM uses standard angiographic images (angiograms) that are retrieved from the X-ray Imaging System (C-arm) in DICOM format. The user selects the images and, following the system prompts, marks key features on the images including the target lesion, ostium location, main vessel, target vessel, and its side branches. The system then matches the corresponding vessels among the projections and generates a 3D computer model of the vessels. The 3D model is used for blood flow analysis and determination of the FFR_{angio}.

G. Indications for Use Statement:

CathWorks FFR_{angio}TM is a software device for the clinical quantitative and qualitative analysis of previously acquired angiography DICOM data for patients with coronary artery disease. It provides FFR_{angio}TM, a mathematically derived quantity, computed from simulated blood flow information obtained from a 3D computer model, generated from coronary angiography images. FFR_{angio}TM analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis are provided as a supportive aid for qualified clinicians in the evaluation and assessment of coronary arteries physiology. The results of CathWorks FFR_{angio}TM 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 evaluation.

H. Comparison with Predicate Device

The CathWorks FFR_{angio}TM and the HeartFlow FFR_{CT} are both coronary physiologic simulation software devices that use data extracted from coronary imaging to provide a noninvasive assessment of fractional flow reserve (FFR). The primary difference between the two devices for the purposes of 510(k) substantial equivalence is that the FFR_{angio}TM uses data extracted from angiographic images, while the FFR_{CT} uses data extracted from CT scans. The table below provides a technological comparison between the two devices. Discussion of the differences is provided following the table.

	CathWorks FFR_{angio}TM	Predicate Device HeartFlow FFR_{CT}2.0
Indications for Use	CathWorks FFR _{angio} TM is a software device for the clinical quantitative and qualitative analysis of previously acquired angiography DICOM data for patients with coronary artery disease. It provides FFR _{angio} TM , a mathematically derived quantity, computed from simulated blood flow information obtained from a 3D computer model, generated from	HeartFlow FFR _{CT} is a coronary physiologic simulation software for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography 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

	CathWorks FFR_{angio}™	Predicate Device HeartFlow FFR_{CT}2.0
	coronary angiography images. FFR _{angio} ™ analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis are provided as a supportive aid for qualified clinicians in the evaluation and assessment of coronary arteries physiology. The results of CathWorks FFR _{angio} ™ 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 evaluation.	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.
System overview	Computer system with software that constructs and displays a 3D computer model of the coronary arteries to simulate blood flow	Computer system with software that constructs and displays a 3D computer model of the coronary arteries to simulate blood flow
Image source	Standard DICOM angiographic images taken in Cath Lab	Previously obtained CT images
Software controlled	Yes	Yes
On-line processing	Yes	No
Sensitivity*	93.5% (lower 95% CI, 87.8%)	84.2% (lower 95% CI, 75.8%)
Specificity*	91.2% (lower 95% CI, 86.0%)	84.9% (lower 95% CI, 80.4%)

*Sensitivity and specificity are the per vessel estimates as reported for the proposed and predicate device pivotal clinical studies.

Discussion of Differences

The key difference between the FFR_{angio}™ and FFR_{CT} devices is that FFR_{angio}™ analysis is based on standard angiograms taken in the cath lab, while FFR_{CT} uses previously obtained CT scans. This enables FFR_{angio}™ to be used on-line in the cath lab to provide the FFR measure during the procedure. Clinical data collected in the FFR_{angio}™ pivotal clinical study demonstrated high sensitivity and specificity. Subgroup analyses demonstrated that the FFR_{angio}™ system is effective for both symptomatic and non-symptomatic patients with coronary artery disease.

I. Performance Data to Support Substantial Equivalence

The following pre-clinical testing was presented to demonstrate the appropriate functionality of the software, the basis of the computational methods, and verification of hardware functionality. Some testing (e.g., biocompatibility, shelf life, etc.) was not applicable for this software only device. Animal testing was not conducted as animal models do not permit evaluation of the technology in relevant anatomic or physiologic models reflecting diseased human coronary vessels.

Software: Software documentation consistent with FDA's guidance "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," May 11, 2005, for moderate level of concern software including a comprehensive risk analysis, software verification and validation, off-the-shelf software integrity, and cybersecurity considerations.

Electrical Safety Testing: The FFR_{angio}TM computer system and cart were evaluated and found to be in compliance with the applicable requirements of IEC 60601-1:2005 (3rd Edition) +C1:2006 +C2:2007 +A1:2012, "Medical electrical equipment - Part 1: General requirements for basic safety and essential performance." All emissions and immunity tests were passed.

Electromagnetic Compatibility Testing: The FFR_{angio}TM computer system was tested and found to be in compliance with the applicable requirements of IEC 60601-1-2:2014 (4th edition), "Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests."

Hardware Verification Testing: The FFR_{angio}TM computer system and cart underwent type testing per an internal CathWorks protocol. All hardware requirements of the system were evaluated/tested and found to meet the pre-defined acceptance criteria.

Transportation Testing: The FFR_{angio}TM computer system and cart are shipped in a padded, wooden box. Transportation testing was conducted in accordance with ASTM D4169-16, "Standard Practice for Performance Testing of Shipping Containers and Systems." All tests were passed.

Human Factors Evaluation: Usability testing of the FFR_{angio}TM system and its operator manual was conducted in accordance with ANSI/AAMI/IEC 62366-1:2015, "Application of usability engineering to medical devices" and the FDA guidance document "Applying Human Factors and Usability Engineering to Medical Devices," February 3, 2016. Participants in the usability testing were 19 healthcare personnel including physicians, nurses, technicians, and imaging fellows. All critical tasks identified for the use of the FFR_{angio}TM system were completed in the usability testing without any use errors. All of the questions in the knowledge-based assessment were answered correctly with the exception of one question that was answered partially correctly by one participant.

Overall, the usability of the system was graded as a 4.5 out of 5 by the test participants. The conclusion of the testing was that the FFR_{angio}TM system can be used safely and effectively by the intended user population. No residual use-related risks were identified.

Clinical Studies:

Two clinical studies were conducted using the FFR_{angio}TM system. The first was a two-phase validation study using an earlier version of the operator interface but the same image processing and computation algorithms as the final device. The clinical validation study compared the FFR_{angio}TM to invasive FFR obtained from patients already scheduled for coronary assessment in the cath lab. The patient's angiographic images were shipped to an off-line location, where they were processed using the FFR_{angio}TM system by two independent operators who were blinded to the invasive FFR and blinded to each other. Analysis of the results from 203 coronary lesions with data collected at four centers (one in the US, one in the EU, and two in Israel) demonstrated sensitivity, specificity, and diagnostic accuracy for FFR_{angio} to be 88%, 95% and 93%, respectively. The average intraclass correlation coefficient for the two measurements of FFR_{angio}TM conducted by the two operators was 0.962 with a 95% confidence interval from 0.95 to 0.971 ($P < 0.001$).

The second study, the FAST-FFR Trial, was the pivotal clinical study to support the substantial equivalence of the FFR_{angio}TM system. FAST-FFR was a prospective, multicenter, international trial with the primary goal of determining the accuracy of FFR_{angio}TM as compared to invasive wire FFR. Coronary angiography was performed in a routine fashion in patients with suspected coronary artery disease. When clinically indicated, invasive FFR was measured in vessels with coronary lesions of varying severity using a coronary pressure wire and hyperemic stimulus. On-site hospital users who were blinded to the invasive FFR used the FFR_{angio}TM system following acquisition of the diagnostic angiograms to generate the patient's FFR_{angio}TM. The FFR_{angio}TM was not used for diagnostic or clinical decisions. Co-primary endpoints were the sensitivity and specificity of the dichotomously scored FFR_{angio}TM for predicting pressure wire-derived FFR using a cutoff value of 0.80. Secondary endpoints included the accuracy of FFR_{angio}TM and its correlation with invasive FFR.

The FAST-FFR study was conducted at 10 sites in 5 countries in the United States, Europe and Israel, from September 2017 to June 2018, with 382 subjects enrolled of which 30 were roll-in subjects and 352 were study subjects. 124 Subjects in total were enrolled at sites in the United States (32.5%).

Subjects had an overall mean age of $64.9 \pm (9.9)$ years and 74.6% were men. 92.5% were white and the remaining from other races. A total of 31.4% had diabetes mellitus, 69.1% had hypertension, and 76.2% had hyperlipidemia. 45.3% of subjects presented with stable angina, 31.4% with unstable angina, and 14.1% with silent ischemia. Overall 15.4% of the patient population had CCS classification 0 and were asymptomatic.

In total, 301 adult subjects and 319 coronary lesions with both a qualifiable invasive FFR and FFR_{angio}[™] measurements were available for efficacy analysis. Of these, 54% were LAD lesions, 24% RCA, 19% LCX and 3% Ramus. 14% of lesions involved a bifurcation and 24% were calcified. Diagnostic angiograms were acquired from all four C-arm types (Phillips (27%), GE (20%), Siemens (43%) and Toshiba (10%)), and coronary pressure and flow wires used included Abbott-St. Jude (48%), Opsens (6%) or Volcano-Phillips (46%). All invasive FFR data were reviewed post-hoc by an independent FFR physiology core laboratory and all FFR_{angio}[™] data were reviewed post-hoc by a core laboratory at CathWorks.

The co-primary endpoints were sensitivity and specificity of the dichotomously scored FFR_{angio}[™] measured index per vessel as compared with invasively-derived FFR; Index ≤ 0.80 was scored “positive” while Index > 0.8 was negative. The pre-specified performance goals identified by the Sponsor and agreed upon by FDA for sensitivity and specificity were 70% and 75%, respectively. The primary endpoint for study success required that the lower bounds of the 95% confidence intervals for both sensitivity and specificity be above these performance goals.

The per vessel sensitivity of FFR_{angio}[™] was 93.5% with a lower one-sided 95% CI of 87.8%. The per-vessel specificity of FFR_{angio}[™] was 91.2% with a lower one-sided 95% CI of 86.0%. Both of the lower one-sided confidence limits for sensitivity and specificity were significantly above the pre-specified target goals of 70% and 75%, respectively, and were considered acceptable. The results are shown in the table below.

	Statistic	95% CI limits	Performance goal / criteria
Sensitivity	93.5%	87.8% - 96.6%	70%
Specificity	91.2%	86.0% - 94.6%	75%
Correlation Coefficient (R)	0.80		0.65
Intercept	0.04	0.03 - 0.05	-0.20 - 0.20
Slope	0.93	0.92 - 0.95	0.80 - 1.20

As the FFR_{angio}[™] analysis was not used in any clinical decision making and did not add any risk to the study subjects, and the trial did not include clinical follow-up, only procedure-related adverse events were captured. Only two adverse events were reported, neither of which was related to the device.

The FAST-FFR study confirmed that FFR_{angio}[™] produces accurate results, with very high sensitivity and specificity for the measurement of FFR.

J. Compliance with Special Controls for 21 CFR 870.1415

Special Controls (abbreviated from regulation)	How Fulfilled
1) Adequate software verification and validation based on comprehensive hazard analysis, with identification of appropriate mitigations, must be performed.,	The FFRangio system software was designed, developed and tested in accordance with ISO 62304:2006 Medical device software -- Software life cycle processes and included comprehensive hazard analysis, identification of appropriate risk mitigations, and software testing at all stages of development to verify and validate the software algorithms, system operation, privacy/security issues, and the impact of failures (e.g., inadequate image quality, image data corruption, improper operation steps).
2. Adequate non-clinical performance testing must be provided to demonstrate the validity of computational modeling methods for flow measurement.	A series of in vitro and animal studies were conducted by CathWorks to validate the computational modelling methods for the FFRangio system.
3. Clinical data supporting the proposed intended use must be provided.	A multi-center clinical study was conducted to validate the sensitivity and specificity of the FFRangio in the intended use population. See the detailed summary of this study presented in Section I above.
(4) Adequate validation must be performed and controls implemented to characterize and ensure consistency (repeatability and reproducibility) of measurement output.	The clinical pivotal study was conducted at 10 sites with multiple device users at each site. A covariate analysis showed no site interaction on the FFRangio results. A reproducibility and repeatability analysis was performed in a separate clinical validation study.
(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.	A human factors study was conducted in accordance with FDA's Guidance Applying Human Factors and Usability Engineering to Medical Devices, 2016. The study evaluated the critical tasks associated with use of the device. The study results demonstrated that the intended use population was able to safety and accurately use the FFRangio system. No additional risk mitigations were identified from this study.
(6) Device labeling must be provided that adequately describes the following: (i) The device's intended use, (ii) Appropriate warnings	The device instructions for use include all of the elements required by this special control, including: <ul style="list-style-type: none"> • Intended use statement the device mechanism of action and intended patient

Special Controls (abbreviated from regulation)	How Fulfilled
(iii) Key assumptions (iv) The measurement performance of the device for all presented parameters (v) A detailed description of the clinical study subjects and results (vi) A detailed description of the analysis procedure using the device and any data features that could affect accuracy of results.	population <ul style="list-style-type: none"> • Appropriate warnings and precautions for safe use of the device, including factors that could adversely affect the device output and cautions to use the device output in context with other clinical factors for patient care • Limitations describing patient populations and lesion types for which the safety and effectiveness of FFR_{angio} has not been evaluated • Instructions for use providing guidelines for the compatible image acquisition systems and the required criteria for the images to process the FFR_{angio}. • Detailed steps for the system operation and analysis procedures • A detailed summary of the FAST-FFR clinical study protocol

K. Conclusion

The information and testing presented in this 510(k) demonstrate that the CathWorks FFR_{angio}TM is substantially equivalent to the HeartFlow FFR_{CT}. Performance data provided in this 510(k) demonstrate that the FFR_{angio}TM system is safe and effective for the non-invasive assessment of FFR from standard angiographic images obtained in the coronary cath lab.