July 28, 2026

Caristo Diagnostics Ltd.
% John Smith
Partner
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Washington, D.C., D.c. 20004

Re: DEN250042
Trade/Device Name: CaRi-Heart
Regulation Number: 21 CFR 870.2215
Regulation Name: Predictive indicator for long-term cardiovascular outcomes
Regulatory Class: Class II
Product Code: SIU
Dated: September 4, 2025
Received: September 4, 2025

Dear John Smith:

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 CaRi-Heart, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> CaRi-Heart is a software device used to produce analysis results to assist Healthcare Professionals in patient management. It helps operators assess vascular inflammation from coronary computed tomography angiography (CCTA) images and measure risk of cardiovascular mortality due to coronary inflammation and other clinical risk factors.
>
> CaRi-Heart and its analysis results are indicated for adults from 30 to 80 years old who have been referred for CCTA imaging.
>
> CaRi-Heart is to be used by trained operators. CaRi-Heart analysis results are to be used by Healthcare Professionals.
>
> CaRi-Heart analysis results should be reviewed with other clinical information which may include, but is not limited to: the patient's original CT images, clinical history, symptoms, clinical risk factors, results of other diagnostic tests, and the clinical judgement of appropriately qualified Healthcare Professionals.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the CaRi-Heart, and substantially equivalent devices of this generic type, into Class II under the generic name predictive indicator for long-term cardiovascular outcomes.

FDA identifies this generic type of device as:

> **Predictive indicator for long-term cardiovascular outcomes.** The predictive indicator for long-term cardiovascular outcomes uses software algorithms to analyze inputs such as medical imaging data and cardiovascular risk factors to calculate a risk score, category, or probability that predicts long-term cardiovascular outcomes. The device is intended for adjunctive use with other physical vital sign parameters and patient information for preventive care and is not intended to independently direct patient management. The device is not intended for use in acute care settings or to direct treatment of current disease.

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 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 request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. 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 announcing the classification.

On September 4, 2025, FDA received your De Novo requesting classification of the CaRi-Heart. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the CaRi-Heart 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, FDA has determined that, for the previously stated indications for use, the CaRi-Heart 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 the following table:

Risks to Health	Mitigation Measures
False positive or false negative result leading to incorrect treatment or diagnosis	Clinical performance testing Postmarket monitoring plan Labeling
Incorrect treatment or diagnosis due to model bias or failure to adequately generalize to the intended use population	Clinical performance testing Postmarket monitoring plan Labeling
Device used in unsupported patient population or with unsupported input/hardware	Human factors/usability assessment Labeling Software verification, validation, and hazard analysis
Overreliance on device output for follow-up	Human factors/usability assessment Labeling

In combination with the general controls of the FD&C Act, the predictive indicator for long-term cardiovascular outcomes is subject to the following special controls:

(1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following must be met:
   (i) Clinical validation must use a test dataset acquired from a representative patient population. Data must be representative of the range of data sources and data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment. The test dataset must be independent from data used in training/development and contain sufficient numbers of cases from important cohorts (e.g., demographic populations, subsets defined by clinically relevant confounders, comorbidities, and subsets defined by hardware and acquisition characteristics) such that the performance estimates and confidence intervals of the device for these individual subsets can be characterized for the intended use population and acquisition systems (e.g., acquisition hardware or preprocessing software). Study protocols must include a description of the adjudication process(es) for determining ground truth of training and test datasets;
   (ii) Output estimations must be compared directly to observed rates in the study population;
   (iii) Data must demonstrate consistency of the output over the full range of inputs;
   (iv) A justification for the performance goals must be provided that discusses the context of risks associated with follow-up testing or prevention;
   (v) Statistical measures that characterize the output's discrimination (*i.e.*, the extent to which a higher value corresponds to a higher risk for the predicted event) must be provided;
   (vi) If the output of the device is intended to represent a probability of occurrence:
      (A) Statistical measures that characterize the output's calibration (*i.e.*, the extent to which the probability associated with each output value is concordant with the actual observed risk in the intended use population) must be provided; and
      (B) Subjects and outcome events at each level across the output's intended range and consistent with its level of precision must be included in the dataset;
   (vii) The clinical data must include pre-specified methods for handling missing or censored data;
   (viii) Any cutoff thresholds must be pre-specified and justified;

(ix) The test dataset must include a minimum of 3 geographically diverse sites, separate from sites used in training of the model;
(x) Statistical performance of the device within clinical risk strata (*e.g.,* demographics, lifestyle risk factors, relevant comorbidities) must be reported;
(xi) Justification for the clinical utility of the device output must include:
(A) Comparison to that of other available predictive indicators that operate at the same clinical decision point (*e.g.,* from literature analysis, pairwise comparison), and;
(B) Discussion of how device output would be used in patient management to improve preventative care (*e.g.*, reference to clinical guidelines, outcomes study).

(2) The device manufacturer must develop and implement a postmarket performance management plan that ensures regular assessment of the generalizability and device performance in the intended patient population in real-world use. The plan must include:
(i) Data collection, analysis methods, and procedures for:
(A) Monitoring relevant performance characteristics and detecting changes in performance;
(B) Identifying sources of performance changes between validation and real-world environment over time; and
(C) Assessing the results from the performance testing on safety and effectiveness;
(ii) Procedures for communicating the device's current performance to the users.

(3) Software verification, validation, and hazard analysis must be performed. Software documentation must include:
(i) A full characterization of technical parameters of the software, including any algorithms or models used, all inputs and outputs for the software, and the supported patient population;
(ii) Description of the expected impact of all applicable sensor acquisition hardware characteristics on performance and any associated hardware specifications;
(iii) Specification of acceptable incoming sensor data quality control measures; and
(iv) Data documentation describing any training, tuning, or validation datasets used in algorithm development.

(4) Human factors/usability assessment must be provided to mitigate the risk of misinterpretation of the device output.

(5) Labeling must include the following:
(i) A summary of the performance testing methods, tested hardware, tested/supported patient population, results of the performance testing for tested performance measures/metrics, summary-level descriptions of patient demographics and associated subgroup analyses for training and test datasets, and the expected minimum performance of the device;
(ii) Device limitations or subpopulations for which the device may not perform as expected;
(iii) A statement that the device output should not replace a full clinical evaluation of the patient and that the output may not be sufficient as the sole basis for further testing;
(iv) Warnings identifying sensor acquisition factors that may impact prediction results;
(v) The type(s) of hardware sensor data used, including specification of compatible sensors for data acquisition.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

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 predictive indicator for long-term cardiovascular outcomes they intend to market prior to marketing the device.

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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the Quality Management System Regulation (QMSR) (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 FD&C Act; 21 CFR 1000-1050).

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System Rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

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.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn).

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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Jackson Hair at Jackson.Hair@fda.hhs.gov.

Sincerely,

HETAL B. ODOBASIC -S

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