Caption Health, Inc.
% Kelliann H. Payne
Partner
Hogan Lovells US LLP
1735 Market Street Floor 23
Philadelphia PA 19103

February 24, 2023

Re: DEN220063
Trade/Device Name: Caption Interpretation Automated Ejection Fraction Software
Regulation Number: 21 CFR 892.2055
Regulation Name: Radiological machine learning-based quantitative imaging software with predetermined change control plan
Regulatory Class: Class II
Product Code: QVD
Dated: September 28, 2022
Received: September 28, 2022

Dear Kelliann Payne:

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 Caption Interpretation Automated Ejection Fraction Software, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> The Caption Interpretation Automated Ejection Fraction software is used to process previously acquired transthoracic cardiac ultrasound images, to store images, and to manipulate and make measurements on images using an ultrasound device, personal computer, or a compatible DICOM-compliant PACS system in order to provide automated estimation of left ventricular ejection fraction. This measurement can be used to assist the clinician in a cardiac evaluation.
> The Caption Interpretation Automated Ejection Fraction Software is indicated for use in adult patients.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Caption Interpretation Automated Ejection Fraction Software, and substantially equivalent devices of this generic type, into Class II under the generic name radiological machine learning-based quantitative imaging software with predetermined change control plan.

FDA identifies this generic type of device as:

> **Radiological machine learning-based quantitative imaging software with predetermined change control plan**. A radiological machine learning based quantitative imaging software with

predetermined change control plan is a software-only device which employs machine learning algorithms on radiological images to provide quantitative imaging outputs. The device includes functions to support outputs such as view selection, segmentation and landmarking. The design specifications include planned modifications that may be made to the device consistent with an established predetermined change control plan.

Section 513(f)(2) of the Federal 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 28, 2022, FDA received your De Novo requesting classification of the Caption Interpretation Automated Ejection Fraction Software. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Caption Interpretation Automated Ejection Fraction Software 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 provided interactively in response to interactive deficiencies, FDA has determined that, for the previously stated indications for use, the Caption Interpretation Automated Ejection Fraction Software 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:

Identified Risks to Health	**Mitigation Measures**
Inaccurate device output leading to patient receiving incomplete or suboptimal treatment/diagnosis	Design verification and validation activities identified in special control (1); Certain labeling information identified in special control (4)
Implementation of modifications agreed in the authorized predetermined change control plan (PCCP) leads to algorithm producing inaccurate output, including: • Performance related to existing specifications at the time of clearance • Performance related to planned additional device capabilities and associated specifications	Special controls (2)-(3) and 4(vii); Certain activities identified in special controls (1)

Identified Risks to Health	Mitigation Measures
Misunderstanding of changes to the device input criteria, output performance, or other aspects of the design as changes are implemented under the PCCP, leading to misuse and incorrect treatment/diagnosis	Special control (2)-(3); Labeling information identified in special control (4)(vii)

In combination with the general controls of the FD&C Act, the radiological machine learning-based quantitative imaging software with predetermined change control plan is subject to the following special controls:

(1) Design verification and validation must include:

(i) A detailed description of the image postprocessing algorithms, including a detailed description of the algorithm inputs and outputs, each major component or block, and algorithm limitations.

(ii) Detailed description of training data including detailed annotation methods and important cohorts (e.g., subsets defined by patient demographics, clinically relevant confounders, and subsets defined by image acquisition characteristics).

(iii) Performance testing protocols and results that demonstrate that the underlying algorithms function as intended. The performance assessment must be based on objective performance measures (e.g., error metrics, Bland-Altman plots, dice similarity coefficient (DSC), Hausdorff distance, sensitivity, specificity, predictive value). The test dataset must be independent from data used in training/development and contain sufficient numbers of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, concomitant diseases, and subsets defined by image 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 imaging equipment.

(iv) Software verification, validation, and hazard analysis.

(2) As part of the design verification and validation activities, you must document the planned device modifications of the quantitative imaging software, and the associated methodology for the development, verification, and validation of modifications made consistent with the performance requirements in the plan.

(3) As part of the risk management activities, you must identify and assess the risks of the planned modification(s) and identify corresponding risk mitigations.

(4) Labeling must include:

(i) A detailed description of the patient population for which the device was validated;

(ii) A description of the intended user and expertise needed for safe use of the device;

(iii) A detailed description of the device inputs and outputs;

(iv) A detailed description of compatible imaging hardware and imaging protocols;

(v) A detailed summary of the current performance of the device and a summary of the performance testing conducted to support safe and effective use of the device including test methods, dataset characteristics (including demographics), testing environment, results (with confidence intervals), and a summary of sub-analyses on case distributions stratified by relevant confounders;

(vi) A description of situations in which the device may fail or may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), as applicable;

(vii) Labeling related to the predetermined change control plan (PCCP), including:

(A) A statement that the device has a PCCP;

(B) A description of modification(s) implemented for quantitative imaging and supporting algorithms, including a summary of current performance, associated inputs, validation requirements, and related evidence; and

(C) A version history, a description of how device modification(s) will be implemented, and a description of how users will be informed of device modification(s) made in accordance with the PCCP.

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.

FDA's classification decision also included the review of your predetermined change control plan (PCCP), titled "Caption Interpretation Core Algorithms Predetermined Change Control Plan" (Document Number 736-00741 Revision 8, provided in 001_Caption_De Novo AutoEF PCCP_01302023.pdf), which includes detailed descriptions of planned device modifications, and the associated methodology to develop validate and implement those modifications in a manner that ensures the continued safety and effectiveness of the Caption Interpretation Automated Ejection Fraction Software. Under 21 CFR 807.81(a)(3), a new premarket submission is required if there is a major change or modification in the intended use of a device, or if there is a change or modification in a device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process. Changes made that are inconsistent with the modifications described in your PCCP that was reviewed in this submission could be significant modifications that could significantly affect the safety and/or effectiveness of this device (e.g., such changes could compromise the clinical functionality or performance specifications that are directly associated with the intended use of the device), in which case a new premarket submission would be required (see 21 CFR 807.81(a)(3)). Additional information about changes to software that may require a new premarket submission is provided in FDA's guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device", and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device".

Failure to submit a new premarket submission for the changes described above would constitute adulteration and misbranding under sections 501(f)(1)(B) and 502(o) of the Act, respectively. Your device is also subject to, among other requirements, the quality systems (QS) regulation (21 CFR 820), which includes, but is not

limited to, 21 CFR 820.30, Design controls; 820.90 Nonconforming product; and 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 (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 radiological machine learning-based quantitative imaging software with predetermined change control plan 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 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 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.

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 Amir Khan at (301) 796-5565.

Sincerely,

for Robert Ochs, Ph.D.
Director
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health