4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 892

[Docket No. FDA-2026-N-6535]

Medical Devices; Radiology Devices; Classification of the Radiological Machine Learning-Based Quantitative Imaging Software with Predetermined Change Control Plan

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the radiological machine learning-based quantitative imaging software with predetermined change control plan into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for classification of the radiological machine learning-based quantitative imaging software with predetermined change control plan. We are taking this action because we have determined that classifying the device into class II will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on February 24, 2023.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the radiological machine learning-based quantitative imaging software with predetermined change control plan into class II (special

controls), which we have determined will provide a reasonable assurance of safety and effectiveness of the device. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified into, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) modified the De Novo classification process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a premarket notification (510(k)) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On September 28, 2022, FDA received Caption Health, Inc.'s request for De Novo classification of the Caption Interpretation Automated Ejection Fraction Software device. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see section 513(a)(1)(B) of the FD&C Act). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on February 24, 2023, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 892.2055.[1] We have named the generic type of device "radiological machine learning-based quantitative imaging software with predetermined change control plan," and it is identified as 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.

FDA has identified the risks to health associated with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Risks to Health and Mitigation Measures for Radiological Machine Learning-Based Quantitative Imaging Software With Predetermined Change Control Plan

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); and Certain labeling information identified in special control (4)

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

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); and Certain activities identified in special controls (1)
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); and Labeling information identified in special control (4)(vii)

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness of the device. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this final order.

Under the FD&C Act, submission of a premarket notification under section 510(k) is required to reasonably assure the safety and effectiveness of class II devices unless FDA determines that the device type should be exempt under section 510(m) of the FD&C Act. At this time FDA has not made this determination for radiological machine learning-based quantitative imaging software with predetermined change control plan. This device is therefore subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not normally have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 regarding quality management system regulation have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR part 801 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 892

Medical devices, Radiation protection, X-rays.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 892 is amended as follows:

PART 892--RADIOLOGY DEVICES

1. The authority citation for part 892 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l*, 371.

2. Add § 892.2055 to subpart B to read as follows:

§ 892.2055 Radiological machine learning-based quantitative imaging software with predetermined change control plan.

(a) *Identification*. 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.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(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, 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; and

(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.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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