4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 892

[Docket No. FDA-2026-N-7954]

Medical Devices; Radiology Devices; Classification of the Fludeoxyglucose F18-Guided Radiation Therapy System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the fludeoxyglucose F18-guided radiation therapy system 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 fludeoxyglucose F18-guided radiation therapy system. 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 1, 2023.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the fludeoxyglucose F18-guided radiation therapy system 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 February 23, 2022, FDA received RefleXion Medical Inc's request for De Novo classification of the RefleXion Medical Radiotherapy System (RMRS). 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 the 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 1, 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 892.5060.[1] We have named the generic type of device "fludeoxyglucose F18-guided radiation therapy system," and it is identified as a device that combines the functionality of an emission computed tomography detection system and a linear accelerator. The device is intended for use with approved fludeoxyglucose F18. The emission computed tomography detection system acquires images of positron-emitting fludeoxyglucose F18 for the purpose of guiding the delivery of megavoltage X-rays for oncologic treatment with radiation therapy using an FDA-cleared, -authorized, or -approved linear accelerator.

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 Fludeoxyglucose F18-Guided Radiation Therapy Systems

Identified Risks to Health	Mitigation Measures
Device-specific modifications of fludeoxyglucose F18 use compared to the current approved drug label that affect safety and effectiveness of fludeoxyglucose F18	Clinical performance testing; Labeling; and Analysis of drug and device label differences
Postmarket modifications to fludeoxyglucose F18 labeling that affect safety and effectiveness when used with the device	Design verification and validation activities
Inaccurate therapeutic radiation dose delivery due to intra- or inter-	Non-clinical performance testing; Clinical performance testing; and

[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.

fractional changes of fludeoxyglucose F18 biodistribution	Labeling
Incompatibility of the linear accelerator and the positron emission tomography (PET) scanner leading to machine failures during treatment and treatment delay	Non-clinical performance testing; Electromagnetic compatibility testing; Electrical safety testing; and Software verification, validation, and hazard analysis
Inadequate reader and device interpretation of fludeoxyglucose F18 biodistribution for determining treatment eligibility	Labeling; Clinical performance testing; Non-clinical performance testing; Training; and Software verification, validation, and hazard analysis
PET evaluation failure leading to treatment delay and/or excess radiation exposure from fludeoxyglucose F18	Non-clinical performance testing; Clinical performance testing; Labeling; and Software verification, validation, and hazard analysis
Inaccurate therapeutic radiation dose delivery due to machine failure	Non-clinical performance testing; Labeling; and Software verification, validation, and hazard analysis
Uncertainty regarding external radiation dose delivered to healthy tissue	Non-clinical performance testing; and Software verification, validation, and hazard analysis

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of the 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 fludeoxyglucose F18-guided radiation therapy systems. 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; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 201 have been approved under OMB control number 0910-0572; the collections of information in 21 CFR parts 210 and 211 have been approved under OMB control number 0910-0139; 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, 360l, 371.

2. Add § 892.5060 to subpart F to read as follows:

§ 892.5060 Fludeoxyglucose F18-guided radiation therapy system.

(a) *Identification*. A fludeoxyglucose F18-guided radiation therapy system is a device that combines the functionality of an emission computed tomography detection system and a linear accelerator. The device is intended for use with approved fludeoxyglucose F18. The emission computed tomography detection system acquires images of positron-emitting fludeoxyglucose F18 for the purpose of guiding the delivery of megavoltage X-rays for oncologic treatment with radiation therapy using an FDA-cleared, -authorized, or -approved linear accelerator.

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

(1) An analysis must be provided of any effects on safety or effectiveness based on differences that exist in the use (i.e., concentration, rate of administration, route of administration; region, organ, or system of the body; or patient population) of fludeoxyglucose F18 with the device compared to the current approved drug labeling; and adequate justification, including support from clinical performance testing and labeling, must be provided that the differences do not adversely affect the safety and effectiveness of fludeoxyglucose F18 when used with the device.

(2) Design verification and validation activities must include monitoring of changes to the labeling and formulation of fludeoxyglucose F18, and addressing such changes so that they do not adversely affect the safety and effectiveness of the device and fludeoxyglucose F18 when used with the device.

(3) Clinical performance testing must demonstrate that the system performs as intended under anticipated conditions of use, including demonstrating: adequate reader performance for distinguishing patients with eligible versus ineligible radiopharmaceutical biodistribution on imaging; reproducibility across fractions; and sufficient signal strength to meet system sensitivity

requirements. Clinical performance testing under anticipated conditions of use must evaluate: dose ranging for identification of lowest safe and adequate dose; and all adverse events.

(4) Non-clinical performance testing under anticipated conditions of use must demonstrate:

(i) Compatibility of the linear accelerator and the tomography scanner;

(ii) Adequate positron emission tomography (PET) imaging performance for patient selection in comparison with a legally marketed diagnostic scanner's output;

(iii) Adequacy of the chosen imaging metrics for inter- and intra-fractional treatment delivery; and

(iv) Dosimetric concurrence between delivered dose distributions and treatment plan, including comparison of delivery isolating difference between guidance on and off conditions.

(5) Performance testing must demonstrate the electrical safety and electromagnetic compatibility of any electrical components.

(6) Software verification, validation, and hazard analysis must be performed for any software components of the device. Software documentation must include a detailed description of the dose delivery tracking algorithms, including the dose calculation methods, treatment boundaries, treatment delivery fluence calculation methods, system latency for moving targets, interface for post-treatment review, limitations of the algorithm, and accompanying verification and validation testing to ensure device and algorithm functionality as informed by the software requirements and hazard analysis.

(7) A training program must be included to ensure users can correctly interpret images to determine patient eligibility.

(8) The labeling must include the following:

(i) A detailed description of the patient population included in clinical testing specifying age, primary cancer type, cancer stage, and target volume locations and sizes;

(ii) A dedicated imaging agent section which includes a description of the use of fludeoxyglucose F18 with the device and a statement in the indications for use informing users where full prescribing information is available for fludeoxyglucose F18 in the current approved drug labeling and in the device labeling;

(iii) Detailed instructions for use of fludeoxyglucose F18 with the device to guide radiation therapy, including: uptake time needed, time window to deliver treatment, physician review of pre-delivery safety checks, image interpretation, tissue targeted for fludeoxyglucose F18 uptake, pre-treatment image criteria to determine patient eligibility, and other differences compared to the current approved fludeoxyglucose F18 drug labeling;

(iv) A detailed summary of the performance testing required under paragraphs (b)(3) and (b)(4) of this section, including test methods, dataset characteristics, and results;

(v) A detailed description of the user workflow; and

(vi) An instruction for users to plan for an alternative treatment if pre-treatment evaluation fails.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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