February 1, 2023

RefleXion Medical Inc
% Kathy O'Shaughnessy
VP, Regulatory/Quality Assurance
25841 Industrial Boulevard, Suite 275
HAYWARD CA 94545

Re: DEN220014
Trade/Device Name: RefleXion Medical Radiotherapy System (RMRS)
Regulation Number: 21 CFR 892.5060
Regulation Name: Fludeoxyglucose F18-guided radiation therapy system
Regulatory Class: Class II
Product Code: QVA
Dated: February 22, 2022
Received: February 23, 2022

Dear Kathy O'Shaughnessy:

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 RefleXion Medical Radiotherapy System (RMRS), a prescription device under 21 CFR Part 801.109 with the following indications for use:

> The RefleXion Medical Radiotherapy System is indicated for treatment planning and precise delivery of image-guided radiation therapy, stereotactic radiotherapy, or stereotactic radiosurgery for tumors or other targeted tissues anywhere in the body when radiation treatment is indicated, while minimizing the delivery of radiation to vital healthy tissue. The megavoltage X-ray radiation is delivered in a rotational, modulated, image-guided format in accordance with the physician approved plan.
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> The RefleXion Medical Radiotherapy System is also indicated for FDG-guided treatment which includes modeling, planning and precise delivery of FDG-guided radiation therapy, a type of Biology-guided Radiotherapy (BgRT), in five or fewer fractions for adults. It is indicated for tumor volumes in lung and bone subject to potential motion and positional uncertainty that have each been assessed with on-board PET/CT prior to delivery for adequate localization, sufficient FDG metabolic activity, local contrast and consistent biodistribution to meet the RMRS requirements, while minimizing the delivery of radiation to vital healthy tissue. BgRT involves the detection of signals from F18 during active beam delivery as a guide to deliver megavoltage X-ray radiotherapy in a rotational, modulated format in accordance with a physician approved treatment plan.
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> For complete fludeoxyglucose F18 prescribing information, refer both to the current medical imaging agent labeling and to this device labeling under “FDG Medical Imaging Agent Information”.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the RefleXion Medical Radiotherapy System (RMRS), and substantially equivalent devices of this generic type, into Class II under the generic name fludeoxyglucose F18-guided radiation therapy system.

FDA identifies this generic type of device as:

> **Fludeoxyglucose F18-guided radiation therapy system**. 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.

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 February 23, 2022, FDA received your De Novo requesting classification of the RefleXion Medical Radiotherapy System (RMRS). The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the RefleXion Medical Radiotherapy System (RMRS) 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 RefleXion Medical Radiotherapy System (RMRS) 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**
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 Analysis of drug and device label differences

Risks to Health	Mitigation Measures
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-fractional changes of fludeoxyglucose F18 biodistribution	Non-clinical performance testing Clinical performance testing Labeling
Incompatibility of the linear accelerator and the PET scanner leading to machine failures during treatment and treatment delay	Non-clinical performance testing Electromagnetic compatibility (EMC) testing Electrical safety testing 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 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 Software verification, validation, and hazard analysis
Inaccurate therapeutic radiation dose delivery due to machine failure	Non-clinical performance testing Labeling Software verification, validation, and hazard analysis
Uncertainty regarding external radiation dose delivered to healthy tissue	Non-clinical performance testing Software verification, validation, and hazard analysis

In combination with the general controls of the FD&C Act, the fludeoxyglucose F18-guided radiation therapy system is subject to the following special controls:

(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 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 (EMC) 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: 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 (3) and (4), 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.

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 fludeoxyglucose F18-guided radiation therapy system 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 Lora Weidner at 240-402-6424.

Sincerely,

Robert Sauer for

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