December 23, 2022

Nanovi A/S
% Meghan Cupp
Regulatory Affairs Director
NDA Partners
40 Commerce Lane, Suite D
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Re: DEN220017
Trade/Device Name: BioXmark
Regulation Number: 21 CFR 892.5727
Regulation Name: Phase-changing fiducial marker for radiation therapy
Regulatory Class: Class II
Product Code: QUV
Dated: March 3, 2022
Received: March 4, 2022

Dear Meghan Cupp:

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

> BioXmark is indicated for use to radiographically mark lung, bladder and lymph nodes in adult patients for whom it has been determined that radiographical marking of tissue for radiation treatment is indicated for their cancer treatment.
>
> BioXmark is implanted via image guided injection into tissue relevant for radiotherapy planning at a healthcare facility. BioXmark can be implanted in the tumor, lymph nodes or tissue adjacent to the tumor subject to irradiation or healthy tissue which should not be irradiated.
>
> BioXmark is intended to mark tissue for at least 3 months after implantation.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the BioXmark, and substantially equivalent devices of this generic type, into Class II under the generic name Phase-changing fiducial marker for radiation therapy.

FDA identifies this generic type of device as:

Phase-changing fiducial marker for radiation therapy. A phase-changing fiducial marker for radiation therapy is a single-use, sterile liquid material that changes phase *in situ* when injected in tissue for the purposes of aiding radiation therapy treatment. The device is intended to be visualized using one or more radiologic imaging modalities.

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.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on 08/13/2015 automatically classifying the BioXmark in class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, nor which was subsequently reclassified into class I or class II.

On March 4, 2022, FDA received your De Novo requesting classification of the BioXmark. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the BioXmark 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 responses to interactive deficiencies, FDA has determined that, for the previously stated indications for use, the BioXmark 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**
Adverse tissue reaction	Biocompatibility evaluation Animal performance testing
Interference with image-guided radiation therapy or radiotherapy response assessment	Clinical performance testing Non-clinical performance testing Labeling
Treatment delays due to device malfunction, marker migration, or inability to locate marker on imaging	Clinical performance testing Non-clinical performance testing Labeling
Infection	Sterilization validation Shelf life testing Labeling

Inaccurate radiation dose delivery due to incorrect marker positioning, marker migration, or implantation	Clinical performance testing Non-clinical performance testing Usability testing Labeling
Complications due to implantation of marker or marker migration	Clinical performance testing Animal performance testing Labeling

In combination with the general controls of the FD&C Act, the Phase-changing fiducial marker for radiation therapy is subject to the following special controls:

(1) Clinical performance data under anticipated conditions of use must evaluate:
   (i) Risk of marker migration in tissue during the course of radiation therapy through post-treatment follow-up;
   (ii) The ability to visualize the marker to allow for adequate localization during the course of radiation therapy through post-treatment follow-up;
   (iii) Risk of device interference with tumor response assessment post-treatment; and
   (iv) All adverse events.
(2) Animal performance data under anticipated conditions of use must evaluate device toxicity and the risk of marker migration.
(3) Non-clinical performance data under anticipated conditions of use must evaluate:
   (i) Maintenance of physical form throughout the course of therapy and post-treatment follow-up;
   (ii) Device visibility on one or more radiologic imaging modalities; and
   (iii) Device interference with radiation dose delivery.
(4) Performance testing must demonstrate the patient-contacting components of the device are biocompatible.
(5) Performance testing must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.
(6) Performance testing must demonstrate device sterility and non-pyrogenicity.
(7) Usability testing must demonstrate that the device can be positioned as indicated based solely on reading the directions for use.
(8) The labeling must include:
   (i) A detailed description of the device including materials and composition, chemical and physical properties, a description of the mechanism of the change of phase, and timeframe for achieving final state;
   (ii) Summary of all reported device-related adverse events from clinical testing;
   (iii) Information describing the injection procedure, including any use of image guidance, and the range of compatible injection needle gauges; and
   (iv) A shelf life.

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 Phase-changing fiducial marker for radiation therapy 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 Erin McFiren at 301-796-0534.

Sincerely,

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