April 9, 2024

16 Bit Inc
% Dr. Catriona Syme
Head of Research & Quality
20 Bay Street, 11th Floor
TORONTO, ONTARIO M5J2N8
CANADA

Re: DEN230023
Trade/Device Name: Rho
Regulation Number: 21 CFR 892.1171
Regulation Name: Radiology software for opportunistic evaluation of low bone mineral density
Regulatory Class: Class II
Product Code: SAO
Dated: April 3, 2023
Received: April 3, 2023

Dear Dr. Catriona Syme:

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

> Rho is a software application intended for use opportunistically with standard frontal radiographs of the lumbar spine, thoracic spine, chest, pelvis, knee, or hand/wrist performed in patients aged 50 years and older. Rho provides a notification in the form of a report to aid radiologists and/or physician interpreters in identifying patients with possible low bone mineral density (BMD) at L1-L4 or the femoral neck to prompt a clinical assessment of bone health. Rho should not be used to rule out low BMD. Radiologists and referring clinicians should follow recommended practices for screening and assessment, regardless of the absence of Rho report.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies Rho, and substantially equivalent devices of this generic type, into Class II under the generic name radiology software for opportunistic evaluation of low bone mineral density.

FDA identifies this generic type of device as:

> **Radiology software for opportunistic evaluation of low bone mineral density**. This device is software which opportunistically assesses radiological images to estimate bone mineral density (BMD) intended to assist in a healthcare professional's decision to evaluate patients for possible low BMD within a bone health screening program. The software employs an algorithm that estimates BMD using eligible radiological image data obtained for other clinical purposes.

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 April 3, 2023, FDA received your De Novo requesting classification of Rho. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify Rho 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, FDA has determined that, for the previously stated indications for use, Rho 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**
Incorrect patient management due to misinterpretation of device output or overreliance on device output for radiological image interpretation	Clinical performance testing Labeling Postmarket monitoring plan
False positive findings leading to unnecessary radiation exposure to the patient and clinical work-up	Clinical performance testing Postmarket monitoring plan Labeling
False negative findings leading to missing or delayed patient assessment	Labeling
Device failure leading to the absence or delay of results, leading to missing, inaccurate, or delayed patient assessment	Software verification, validation, and hazard analysis

In combination with the general controls of the FD&C Act, the radiology software for opportunistic evaluation of low bone mineral density is subject to the following special controls:

(1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must fulfill the following:
   (i) The dataset used for training and development of the advanced algorithm must be distinct from the dataset used for testing to support generalizability of the algorithm.
   (ii) Results from clinical performance testing must characterize the performance of the device compared to a clinically justified ground truth (reference method or clinical comparator).

(iii) The test dataset must be representative of the intended patient population(s) to support a supplement to a screening program. Test datasets must have adequate representation of cases with clinically relevant confounders. The performance estimates and confidence intervals of the device for each individual confounding factor must be characterized in the performance testing.
(iv) Clinical performance must characterize the dependence of software output on the hardware specifications of the acquisition system.
(v) Clinical performance must characterize the device's reproducibility from repeated measurements on the same patients.
(vi) The testing report must include a detailed description of pre-specified performance testing protocols (including the study objectives, primary and secondary endpoints, statistical hypotheses, performance goals, sample size calculation, statistical analyses) and dataset(s) used.

(2) Software verification, validation, and hazard analysis must be performed.

(3) Labeling must include:
(i) A description of the intended patient population, the intended user, clinical environment, and context of use, including information on interpretation of outputs within the intended clinical workflow;
(ii) A summary of the performance testing for each device output, including test methods, dataset characteristics, testing environment, results (with confidence intervals), and a summary of clinical performance for all demographic subgroups from testing dataset(s);
(iii) A description of measurement reproducibility;
(iv) A description of situations in which the device may fail and clinical subpopulations or acquisition system characteristics in which device was not evaluated, if any;
(v) A statement that the device output should not be used to replace a screening program.

(4) The device manufacturer must develop and implement a post-market performance management plan that ensures regular assessment of the generalizability and device performance in the intended patient population in real-world use. The plan must include:
(i) Data collection, analysis methods, and procedures for:
(A) Monitoring relevant performance characteristics and detecting changes in performance;
(B) Identifying sources of performance changes between validation and real-world environment over time; and
(C) Assessing the results from the performance monitoring on safety and effectiveness.
(ii) Procedures for communicating the device's current performance to users.

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.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

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 radiology software for opportunistic evaluation of low bone mineral density 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 Smita Kakar at 301-796-3447.

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