January 17, 2024

Imvaria, Inc
% Allison Komiyama
Principal Consultant
RQM+
2790 Mosside Blvd
Monroeville, PA 15146

Re: DEN220040
Trade/Device Name: Fibresolve
Regulation Number: 21 CFR 892.2085
Regulation Name: Radiology software for referral of findings related to fibrotic lung disease
Regulatory Class: Class II
Product Code: QWO
Dated: June 28, 2022
Received: June 29, 2022

Dear Allison Komiyama:

This letter corrects our previous classification order, dated January 12, 2024, to correct the correspondent.

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

> Fibresolve is a software-only device that receives and analyzes lung computed tomography (CT) imaging data in order to provide a diagnostic subtype classification in suspected cases of interstitial lung disease (ILD). The device supplements the standard-of-care workflow by providing a qualitative, diagnostic classification output of imaging findings based on machine learning pattern recognition, in order to provide adjunctive information as part of a referral pathway to an appropriate Multidisciplinary Discussion (MDD) or as part of an MDD. Specifically, the tool is used to serve as an adjunct in the diagnosis of idiopathic pulmonary fibrosis (IPF) prior to invasive testing. The results of Fibresolve are intended to be used only by clinicians qualified in the care of lung disease, specifically in caring for patients with ILD, in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment.
>
> The input to Fibresolve is a DICOM-compliant lung CT scan. Clinical case eligibility includes the following criteria:
> Age > 22 years old.
> Pulmonary symptoms suggestive of possible ILD including IPF.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Fibresolve, and substantially equivalent devices of this generic type, into Class II under the generic name Radiology software for referral of findings related to fibrotic lung disease.

FDA identifies this generic type of device as:

> **Radiology software for referral of findings related to fibrotic lung disease.** Radiology software for referral of findings related to fibrotic lung disease is a prescription image processing device that analyzes computed tomography images to suggest the presence of disease or of an imaging finding suggestive of disease. The output of this device is intended to be used as adjunctive information as part of a referral pathway in the overall diagnostic assessment process.

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 June 29, 2022, FDA received your De Novo requesting classification of the Fibresolve. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Fibresolve 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, the Fibresolve 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 |
|---|---|
| False positive findings leading to harmful incorrect and/or delayed management of a patient with an alternative underlying fibrotic lung disease. | Clinical performance testing<br>Postmarket surveillance<br>Labeling |
| False negative findings leading to harmful incorrect and/or delayed management of a patient with a fibrotic lung disease | Clinical performance testing<br>Postmarket surveillance<br>Labeling |
| Incorrect and/or delayed patient management due to the device being misused to analyze images from an unintended patient population or from images acquired with incompatible imaging hardware or image | Clinical performance testing<br>Postmarket surveillance<br>Labeling |

| | |
|---|---|
| acquisition parameters | |
| Incorrect and/or delayed patient management due to misinterpretation of device output or overreliance on device output for radiological image interpretation | Labeling |
| Device failure leading to the absence of results, delay of results, or incorrect results, leading to 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 referral of findings related to fibrotic lung disease is subject to the following special controls:

(1) Data obtained from premarket clinical performance validation testing and postmarket surveillance acquired under anticipated conditions of use must demonstrate that the device performs as intended when used to analyze data from the intended patient population, unless FDA determines based on the totality of the information provided for premarket review that data from postmarket surveillance is not required. The following must be met:
   (i) Validation report(s) must include a detailed description of the data, criteria, and methods used to define the reference standard that were used to evaluate device performance. The reference standard used in the clinical validation must be justified for the condition named in the device's indications for use.
   (ii) The performance of the device must be compared to an appropriate clinical control, e.g. the performance or agreement of clinicians performing the same task.
   (iii) The performance assessment must be based on pre-specified diagnostic accuracy measures (e.g., receiver operator characteristic plot, sensitivity, specificity, positive/negative predictive values, and diagnostic likelihood ratios).
   (iv) Test datasets must contain a sufficient number of cases from important cohorts (i.e., subsets defined by clinically relevant demographics, confounders, effect modifiers, concomitant diseases, challenging cases such as early disease, 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.

(2) Software verification, validation, and hazard analysis must be performed. Software documentation must include a detailed technical description of all image analysis algorithms, including the model inputs and outputs, each major component or block, and any model limitations.

(3) Labeling must include:
   (i) A detailed description of the clinical environment and context of use, including information on interpretation of outputs within the intended workflow;
   (ii) A detailed description of compatible imaging hardware and imaging protocols;
   (iii) A detailed summary of the performance testing for each device output, including: test methods, dataset characteristics, testing environment, results (with confidence intervals), and a summary of sub-analyses on case distributions stratified by relevant confounders;
   (iv) According to the timeframe specified in any postmarket surveillance protocol approved by FDA to satisfy the requirements in paragraph (1) of this section, a detailed summary of the postmarket surveillance data must be provided, including updates to the labeling to accurately reflect device performance based upon data collected during the postmarket surveillance experience; and
   (v) Limiting statements that indicate:

(A) A description of situations in which the device may fail or may not operate at its expected performance level (e.g., the impact of poor image quality on device performance or degraded performance in certain subpopulations), as applicable, including any limitations in the dataset used to train, tune, and test the algorithm during device development;
(B) A discussion of what the device detects in the context of diagnosing fibrotic lung disease; and
(C) A warning that users should use the device in conjunction with other clinical and diagnostic findings, including information obtained by alternative methods and clinical evaluation, as appropriate.

In order to satisfy special control (1) above, FDA has determined that you must collect and report postmarket surveillance data acquired under anticipated conditions of use to demonstrate that the device performs as intended when used to analyze data from the intended patient population. Specifically, you must conduct postmarket clinical validation performance testing of the Fibresolve device in cases from important cohorts including subsets defined by clinically relevant radiological usual interstitial pneumonitis (UIP) categories and in on-label CT slice thickness categories (≤ 3mm).

Recognizing that follow-up for cases with device-negative outputs would be difficult, FDA expects that the postmarket clinical validation performance testing will addresses the performance of Fibresolve using clinical diagnosis as the reference standard for cases identified as positive by the device. The study should include at least 150 cases, with prevalence-appropriate representation of cases that are determined to be true IPF. Using information on true positives and false positives, relevant metrics to understand the rate of false positives such as the positive predictive value (PPV) and rates of disease detection, true positives, and positive agreement should be calculated and reported. These results should be stratified by the important clinical and technical parameters included in labeling: radiological UIP category (Definite UIP, Probable UIP, Indeterminate for UIP, and Alternative Diagnosis) and in slice thicknesses (<1.5 mm, 1.5-3.0 mm noninclusive of 3.0 mm, and 3.0 mm).

Within 30 days of receipt of this order, you must submit a complete study protocol for your study as described above. FDA expects to work with you to approve your study protocol within 60 days of this order. Your submission should be clearly labeled as a "De Novo Postmarket Study Protocol" and submitted to the Agency as specified below. Please reference the De Novo number above to facilitate processing. If there are multiple protocols being finalized after granting of this De Novo request, please submit each protocol as a separate submission, identified by their unique study name(s).

From the date of postmarket study protocol approval, you must meet the following timelines:

- First subject enrolled within 15 months
- 20% of subjects enrolled within 30 months
- 50% of subjects enrolled within 45 months
- 100% of subjects enrolled within 60 months

In addition, you must submit separate periodic reports on the progress of the new enrollment postmarket study as follows:

- Postmarket surveillance progress reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the protocol approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting enrollment status reports every three (3) months in addition to your periodic postmarket surveillance progress reports, until enrollment has been completed or FDA notifies you otherwise.
- Submit the final postmarket surveillance report three (3) months from study completion (i.e., last subject's last follow-up date).

Additionally, to meet special control (3)(iv), you must update device labeling with the results produced by postmarket clinical validation performance testing within the timeframe specified in the approved postmarket surveillance protocol.

Each postmarket surveillance report should be submitted to the Agency as specified below, identified as a "De Novo Postmarket Surveillance Report" in accordance with how the study is identified above, and bearing the applicable De Novo reference number.

Be advised that failure to comply with any special control requirement, including the initiation, enrollment, completion, and reporting per the postmarket surveillance data requirements outlined above, may result in the adulteration and misbranding of your device.

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 radiology software for referral of findings related to fibrotic lung disease 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).

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above De Novo number to facilitate processing.

De Novo Postmarket Surveillance
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Alternatively, documents can be submitted electronically through the CDRH Portal. For more information on the CDRH Portal, please visit https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal.

If you have any questions concerning the contents of the letter, please contact Samuel Fielden at samuel.fielden@fda.hhs.gov.

Sincerely,

Robert Ochs

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