November 16, 2023

4DMedical Limited
℅ Nichole Murray
Vice President, Regulatory Affairs & Quality Assurance
Level 7, 700 Swanston Street
Carlton, VIC 3053
AUSTRALIA

Re: K232392
Trade/Device Name: CT Lung Ventilation Analysis Software (CT:V)
Regulation Number: 21 CFR 892.1750
Regulation Name: Computed Tomography X-Ray System
Regulatory Class: Class II
Product Code: JAK
Dated: August 9, 2023
Received: October 17, 2023

Dear Ms. Murray:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the 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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Lu Jiang

Lu Jiang, Ph.D.
Assistant Director
DHT8B: Division of Radiologic Imaging
Devices and Electronic Products
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Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K232392

Device Name
CT Lung Ventilation Analysis Software (CT: V)

Indications for Use *(Describe)*

CT: V software is a non-invasive image processing technology that measures volume changes from paired inspiration-expiration CTs to quantify and visualize regional and global ventilation. These regional measures are derived entirely from the lung tissue displacement and lung volume change between the paired inspiration-expiration chest CTs.

CT: V is for use in adult patients. Quantification and visualizations are provided in the form of a report.

CT: V may be used when physicians need a better understanding of a patient's lung function and/or respiratory condition.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary: CT Lung Ventilation Analysis Software K232392

This 510(k) Summary of safety and effectiveness information is submitted as part of the Pre-Market Notification in accordance with the requirements of 21 CFR Part 807, Subpart E, Section 807.92

1. Submitter Information

Submitter:	4DMedical Limited Level 7 700 Swanston Street Carlton, VIC 3053 Australia
Primary contact person:	Nichole Murray Email: regulatory@4dmedical.com Ph: + 61 3 9545 5940
Secondary contact person:	Ruben Gaitan Ortiz Email: regulatory@4dmedical.com Ph: + 61 3 9545 5940
Date prepared:	November 09 2023

2. Subject Device

510(k) number:	K232392
Name of Device:	CT Lung Ventilation Analysis Software (CT: V)
Manufacturer:	4DMedical Limited
Regulation Number:	21 CFR 892.1750
Classification Name:	Computed Tomography X-ray System
Classification Class:	Class II
Product Code:	JAK

3. Legally Marketed Primary Predicate Device

510(k) number:	K151919
Name of Device:	Vitrea CT Lung Density Analysis Software
Manufacturer:	Vital Images, Inc.
Regulation Number:	21 CFR 892.1750
Classification Name:	Computed Tomography X-ray System
Classification Class:	Class II
Product Code:	JAK

4. Device Description

CT:V Software (i.e. the “Device”), also known as “CT:V”, is a software-based image processing technology that analyzes two non-contrast Computed Tomography (CT) images of the lungs to quantify the regional ventilation of pulmonary tissue to support clinicians in their assessment of patient lung conditions and diseases.

CT:V is provided on a ‘Software as a Service’ basis. The paired CT series, in DICOM format, are transferred electronically to 4DMedical. The images are input into the Software Device that operates in a cloud environment. The Device is fully automated and assesses the CT series and identifies and segments the lungs. CT:V measures ventilation captured in the

CTs by directly measuring the motion field of the lung tissue at thousands of points using a form of three-dimensional motion tracking. This motion tracking quantifies the expansion of lung tissue, and hence airflow (i.e. ventilation) is determined. These regional lung motion and ventilation measurements are used to provide quantitative outputs and color maps showing ventilation within a segmented region. An Analysis Report is generated for each completed workflow which is returned to the requesting physician. The ventilation data presented in the CT:V Report provides the user with additional functional information that may assist in characterizing the patient.

5. Indications for Use

CT:V software is a non-invasive image processing technology that measures volume changes from paired inspiration-expiration CTs to quantify and visualize regional and global ventilation. These regional measures are derived entirely from the lung tissue displacement and lung volume change between the paired inspiration-expiration chest CTs.

CT:V is for use in adult patients. Quantification and visualizations are provided in the form of a report.

CT:V may be used when physicians need a better understanding of a patient's lung function and/or respiratory condition.

6. Substantial Equivalence

Characteristic	Subject Device	Predicate Device	Comparison
Device Information			
Name of the Device	CT:V Software	Vitrea CT Lung Density Analysis Software	
Manufacturer of the Device	4DMedical Limited	Vital Images Inc	
Regulatory Comparison			
Regulation Number	21 CFR 892.1750	21 CFR 892.1750	Same
Risk Classification	Class II	Class II	Same
Product Code	JAK	JAK	Same
Regulation Name	Computed tomography x-ray system	Computed tomography x-ray system	Same

Clinical Characteristics			
Characteristic	**Subject Device**	**Predicate Device**	**Comparison**
Indication for Use	CT:V software is a non-invasive image processing technology that measures volume changes from paired inspiration-expiration CTs to quantify and visualize regional and global ventilation. These regional measures are derived entirely from the lung tissue displacement and lung volume change between the paired	The Vitrea Lung Density Analysis software provides CT values for the pulmonary tissue from CT thoracic datasets. Three-dimensional (3D) segmentation of the left lung and right lung, volumetric analysis, density evaluations and reporting tools are integrated in a specific workflow to offer the physician a quantitative support for diagnosis and	Similar

Clinical Characteristics			
Characteristic	**Subject Device**	**Predicate Device**	**Comparison**
	inspiration-expiration chest CTs. C:TV is for use in adult patients. Quantification and visualizations are provided in the form of a report. CT:V may be used when physicians need a better understanding of a patient's lung function and/or respiratory condition.	follow-up evaluation of lung tissue images.	
Intended User	Physicians, thoracic radiologists, and pulmonologists.	Thoracic radiologists and pulmonologists.	Similar
Patient Population	Adult patients with pulmonary diseases and abnormalities.	Patients with pulmonary diseases and abnormalities.	Same
Device Description	CT:V is a software-based image processing technology that analyses two non-contrast Computed Tomography (CT) images to quantify the regional ventilation of pulmonary tissue to support clinicians in their assessment of patient lung diseases.	Vitrea CT Lung Density Analysis assists in analyzing lung densities and volumes. It semi-automatically segments lung tissues with quantifiable controls and renderings to aid communication with the pulmonologist.	Similar

Technical Characteristics			
Characteristic	**Subject Device**	**Predicate Device**	**Comparison**
Device Input Modality	CT	CT	Same
Device Inputs	Non-contrast inspiration/expiration CT	Non-contrast inspiratory CT	Similar
Device Output- Lung Volume	Regional lung ventilation measurements, expressed as three volume measurements: inspiration volume, expiration volume and volume change (i.e., the difference between inspiration	Regional lung volume measurements.	Similar

Technical Characteristics Characteristic	Subject Device	Predicate Device	Comparison
	and expiration volumes).		
Device Output- Lung Visualization	Visualization of lung ventilation with color-defined specific ventilation ranges.	Visualization of lung density with color defined ranges.	Similar
Device Output- Lung Analysis	The heterogeneity of lung ventilation, presented as three values.	Lung density result quantification with volume measurements, lung density index and the PD15% measurement.	Similar
Device Output- Lung Voxels	Ventilation histogram of the classified lung voxel's relative frequencies including ventilation defect percentage.	Density histogram of the classified lung voxels' relative frequencies.	Similar
Device Output- Reporting	The device output data is provided in the form of a Report.	The device output data is provided in the form of a Report.	Same

7. Performance Testing

The CT:V Software was designed, developed, and tested in accordance with the ISO 62304 standard. Known hazards were identified and mitigated in accordance with the ISO 14971 standard. Unit level, performance, and integrated system testing were performed. The results of testing demonstrate that the device is effective and meets the manufacturer's intended performance criteria. Clinical and non-clinical studies were also conducted.

7.1 Verification

4DMedical has conducted performance testing in the form of verification across a wide range of pixel and slice spacings and Signal to Noise Ratios (SNRs). Testing of the quantitative measurements included a combination of synthetically generated phantom image data and clinically acquired data. The clinically acquired data included a range of models, manufacturers and institutions, a range of volume changes between the inspiration and expiration CTs, and a diverse range of patients. The primary sources of variability affecting the quantitative measurements are voxel size and signal-to-noise-ratio (SNR). The Device requires a minimum pixel spacing of 2.5mm x 2.5mm, and a slice spacing/slice thickness of 2.5mm. The verification testing demonstrated that the device was robust within acceptable performance limits across the entire range of these inputs.

The software verification was completed to assure that the software fully satisfies all expected system requirements and features. Test cases were executed against the system features and requirements.

7.2 Analytical Validation

The software analytical validation was completed to assure the software conforms to user needs and intended use. Workflow testing was conducted to provide evidence that the system requirements and features were implemented, reviewed and met.

7.3 Summary of Non-Clinical Tests

Benchtop Verification and Validation Testing was conducted on CT:V. This included generation of synthetic CT images that simulated breath-hold CT pair images of a human. A range of input parameters covering a spectrum of patient anatomies and breathing physiologies was used. These synthetic CT pairs, with known simulated lung physiologies and ventilation volumes (the 'ground truth') were then analysed using the CT:V Software. The ventilation measurements derived by CT:V were then compared to the 'ground truth' values.

7.4 Summary of Clinical Studies

The performance of CT:V was assessed across a diverse patient population in two clinical studies. These studies were conducted to demonstrate the safety and effectiveness of the Device and included patients presenting with symptoms including shortness of breath, frequent coughing, excessive phlegm (mucus) production and frequent chest tightness. The studies included patients across the spectrum of lung health and included healthy subjects and subjects with Asthma, Chronic Obstructive Pulmonary Disease and Lung Cancer.

The studies compared the regional ventilation measurements output by CT:V with gold-standard and best practice measures for respiratory diagnosis. The performance of the Device was assessed both quantitatively and qualitatively to determine consistency of the Device's outputs with the gold-standard measures including Pulmonary function testing (PFT) and Nuclear Medicine Imaging (SPECT and PET).

Clinical Study 1

The first clinical study was an observational comparison study conducted using data acquired in the USA with the objective of demonstrating agreement between CT:V and SPECT ventilation. This study consisted of quantitative, statistical analysis demonstrating the correlation between PFT and CT:V metrics, as well as qualitative analysis of five case studies which compared CT:V outputs with SPECT ventilation image data. The target population consisted healthy participants as well as participants with previously diagnosed lung diseases.

A total of 32 participants were included in the study. There were 19 male and 13 female study participants, and their ages ranged from 26 to 78 years of age. The body mass index of the subjects varied between 17.9 and 44.8 kg/m2. The participants' mean height was 67 inches, and their mean weight was 163 pounds. Fifteen (15) patients had received a previous diagnosis of COPD and the remainder were categorized as healthy. The participant cohort included patients presenting with symptoms including shortness of breath, frequent coughing, excessive phlegm production and frequent chest tightness. The study included participants from diverse racial demographic groups representative of the USA's population, with participants self-describing as: Asian or Pacific Islander 3% (n=1); Black or African

American 6% (n=2); Hispanic or Latino 22% (n=7); Multiracial or Biracial 3(n=1); and White or Caucasian 63% (n=20).

The study demonstrated the following:

- CT:V metrics correlated with PFT metrics. In particular, CT:V Inspiratory Volume, Expiratory Volume and Volume Change correlated with Total Lung Capacity (TLC), Functional Residual Capacity (FRC), and Vital Capacity (VC), respectively. Functional metrics ventilation heterogeneity (VH), ventilation heterogeneity small scale (VHSS), ventilation heterogeneity large scale (VHLS) and ventilation defect percentage (VDP) correlated with FEV1 (% predicted) and FEV1/FVC;
- CT:V provided information regarding regional ventilation that was complementary to global ventilation metrics provided by PFT; and
- CT:V visualizations were consistent overall with SPECT ventilation images, however provided additional clarity for assessment of regional distribution of ventilation.

The Computed Tomography Ventilation (CT:V) metrics and ventilation visualizations as tools for lung assessment were further assessed through the evaluation of five individuals, each characterized by different degrees of lung disease, inclusive of a healthy subject. The effectiveness of CT:V in providing visualization and quantifiable data pertaining to regional ventilation variability was demonstrated.

Clinical Study 1 showed the consistency of CT:V outputs with those of gold-standard measures. Specifically, the study supported the conclusion that there is substantial equivalence between CT:V and SPECT in the assessment of regional distribution of ventilation, with both modalities also shown to render functional and pathological details of the lungs. The study also demonstrated a statistically significant correlation between the CT:V and PFT outputs.

Clinical Study 2

The second study was performed using a publicly available dataset that was collected from a single institution, in Australia. The study comprised of seventeen (17) lung cancer patients undergoing radiotherapy, each of which had varying lung function. The participants were between 54 and 73 years of age.

This study quantitatively compared the CT:V outputs PET (positron emission tomography) using statistical analysis. Like CT:V and SPECT, PET outputs three-dimensional ventilation fields. The distribution of lung ventilation for individual lung lobes was reported as a proportion of the ventilation of the entire lung for both CT:V and PET.

The study demonstrated consistency between CT:V and Nuclear Medicine Imaging in the assessment of spatial ventilation distribution at both lobar and voxel levels. There were no systematic differences in the lobar ventilation between CT:V and PET. Furthermore, the absence of mean difference, systematic bias or heteroscedasticity demonstrated that the measurements from CT:V and PET detect similarly at the high or low range of lung ventilation. Similarly, voxel-wise analysis via Spearman correlations demonstrated strong association between CT:V and Nuclear Medicine Imaging spatial ventilation data.

Given the agreement between PET ventilation scanning and CT:V, it was concluded that the methods are substantially equivalent for the purpose of examining the regional distribution of ventilation.

Clinical Studies Conclusion
Overall, the clinical studies conducted for the device successfully demonstrated the feasibility of generating valid data that is reliable and consistent with Nuclear Medicine Ventilation imaging results.

Clinical Study 1 demonstrated the equivalence between CT:V and SPECT in the assessment of regional distribution of ventilation and that there was a statistically significant correlation between the CT:V and PFT outputs.

Based on the clinical performance documented in the clinical studies, CT:V Software was found to have a safety and effectiveness profile that is similar to the predicate device. Further, it demonstrated the capability of the device to provide this information without the use of contrast agents utilized by alternative methods.

Performance Testing Conclusion: The performance testing (verification, analytical validation, non-clinical tests and clinical studies) demonstrated that the CT:V Software was found to have a safety and effectiveness profile that is similar to the predicate device but without the need for contrast agents.

8. Consensus Standards

General software verification and validation tests were conducted to confirm proper function of the device's features. The CT:V Software complies with the following voluntary recognized consensus standards:

- ISO 14971:2019 Medical Devices – Applications of Risk Management to Medical Devices
- ISO 62304:2006/Amd1:2015 Medical device Software – Software lifecycle processes
- ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice
- ISO 15223-1:2016 Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements

9. Conclusion as to Substantial Equivalence

The subject device, CT:V Software, is substantially equivalent to the predicate device. Differences do not adversely impact the safety and effectiveness of the software when used within its intended use.