August 28, 2023

Versant Medical Physics and Radiation Safety
Darrell R. Fisher, Ph.D.
Nuclear Medicine Physicist, Regulatory Division
119 N. Church Street
Kalamazoo, Michigan 49007

Re: K230221
Trade/Device Name: QDOSE® Multi-purpose Voxel Dosimetry (Personalized Dosimetry in Molecular Radiotherapy)
Regulation Number: 21 CFR 892.1100
Regulation Name: Scintillation (gamma) camera
Regulatory Class: Class I
Product Code: IYX
Dated: July 12, 2023
Received: July 25, 2023

Dear Darrell Fisher:

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 (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 located 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.

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 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 Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 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,

Daniel M. Krainak, Ph.D.
Assistant Director
DHT8C: Division of Radiological Imaging
and Radiation Therapy Devices
OHT8: Office of Radiological Health
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)*

K230221

Device Name

QDOSE® Multi-purpose Voxel Dosimetry (Personalized Dosimetry in Molecular Radiotherapy)

Indications for Use *(Describe)*

QDOSE® Multi-purpose Voxel Dosimetry is indicated for use to provide estimates of radiation absorbed dose to organs and tissues of the body from medically administered radiopharmaceuticals, and to calculate total-body effective dose. Radiation absorbed dose calculations are based on clinical measurements of radioactivity biodistributions and biokinetics. QDOSE® is intended for applications in clinical nuclear medicine, molecular radiotherapy, radiation safety evaluations, risk assessment, record-keeping, and regulatory compliance. QDOSE® is indicated for use by professionals (medical physicists, radiologists and oncologists including nuclear medicine physicians), radiologic imaging technologists, health physicists and radiation safety officers and administrators, students in training, and others having interest in ability to calculate internal radiation doses from medically administered radiopharmaceuticals.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) Summary

QDOSE® is a software tool for medical internal radiation dosimetry, the assessment and calculation of absorbed dose per unit administered activity due to radionuclides or radiopharmaceuticals in the body. Radiopharmaceuticals are employed for medical diagnostic exams or (cancer) therapy applications. Acquired nuclear medicine images from the patient, such as planar scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET), may be processed using QDOSE® to visualize and quantify the distribution of a radionuclide or radiopharmaceutical in the organs or tissues of a patient. The QDOSE® software processes these nuclear medicine imaging data, together with anatomical images from X-ray computed tomography (CT) or magnetic resonance imaging (MRI), to determine the total number of radioactive decays and emissions in organs and tissues of the body, and hence the radiation energy imparted. The software device includes all processing and calculation steps required for an internal dosimetry evaluation.

(a) The Submitter (Applicant)

Name: Versant Medical Physics and Radiation Safety
119 N. Church Street, Suite 201
Kalamazoo, MI 49007
Applicant Contact: Darrell R. Fisher
Telephone: (509) 539-3223
E-mail: darrell.fisher@versantphysics.com

Correspondent: Versant Medical Physics and Radiation Safety
Correspondent Contact: Darrell R. Fisher
Telephone: (509) 539-3223
E-mail: darrell.fisher@versantphysics.com

(b) Name of the Medical Device

QDOSE® Multi-purpose Voxel Dosimetry
(Personalized Dosimetry in Molecular Radiotherapy)

Regulation Number: 21 CFR §892.1100
Regulation Name: Scintillation (Gamma) Camera
Regulatory Class: Class 1
Classification Product Code: IYX

(c) The Predicate Device [21 CFR 807.92(a)(3)]

The following predicate device is identified as legally marketed in the United States as medical device software to which the applicant (Versant Medical Physics and Radiation Safety, Kalamazoo, Michigan) claims substantial equivalence through the 510(k) premarket notification process [21 CFR 807.92(a)(3)]:

K163687 OLINDA/EXM v. 2.0 Hermes Medical Solutions AB
Regulation Number 21 CFR 892.1100
Regulation Name: Scintillation (Gamma) Camera
Regulatory Class: Class I
Product Code: IYX

The predicate device OLINDA/EXM (2.0) is a software package for calculating radiation doses from clinically administered radiopharmaceuticals. Dosimetry is based on the use of calculated S values, determined for patient-like phantoms using a Monte Carlo method. The S values are equal to the average absorbed dose to a target organ generated by a unit of activity in a source organ. OLINDA/EXM dose calculations are performed by multiplying a source organ time-activity curve integral by the S value. Source-organ time-activity curves are determined from quantitative nuclear medicine imaging data, which when integrated yield an estimate of the number of radionuclide decays area-under-curve or time-integrated activity coefficient.

(d) Comparison of the Device Indications for Use

Both QDOSE® and OLINDA/EXM implement the MIRD dosimetry schema recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine, and therefore generate closely similar dosimetry results.

Device Name	**K230221 QDOSE® Multi-purpose Voxel Dosimetry**	**K163687 OLINDA/EXM v.2.0 (predicate)**
Indications for Use	QDOSE® Multi-purpose Voxel Dosimetry is indicated for use to provide estimates of radiation absorbed dose to organs and tissues of the body from medically administered radiopharmaceuticals, and to calculate total-body effective dose. Radiation absorbed dose calculations are based on clinical measurements of radioactivity biodistributions and biokinetics. QDOSE® is intended for	The intended use of OLINDA/EXM is to provide estimates (deterministic) of absorbed radiation dose at the whole organ level as a result of administering any radionuclide and to calculate effective whole-body dose. This is dependent on input data regarding bio distribution being supplied to the application.

	applications in clinical nuclear medicine, molecular radiotherapy, radiation safety evaluations, risk assessment, record-keeping, and regulatory compliance. QDOSE® is intended for use by professionals (medical physicists, radiologists and oncologists including nuclear medicine physicians), radiologic imaging technologists, health physicists and radiation safety officers and administrators, students in training, and others having interest in ability to calculate internal radiation doses from medically administered radiopharmaceuticals.	

Comparative analysis: Both the applicant software device and the predicate device perform similar calculations, resulting in estimates of organ or tissue absorbed dose and total-body effective dose. Both the applicant device and the predicate device are used for calculating radiation doses from administered radiopharmaceuticals. Both the applicant device and the predicate device are intended for use by similar classes of persons who typically perform internal dose calculations. Both the applicant device and the predicate device perform dose calculations based on the Medical Internal Radiation Dose (MIRD) schema using similar anthropomorphic models, similar radionuclide data bases, and for similar listings of body organs and tissues. Both the applicant device and the predicate device produce similar and comparable estimates of calculated radiation absorbed dose (Della Gala G., Bardiès M, Tipping J, and Strigari L, Overview of commercial treatment planning systems for target radionuclide therapy, Physica Medica 92:52-61; 2021). Intended applications in clinical nuclear medicine are similar. Therefore, differences between the applicant software device and the named predicate device are not critical to the use of the device, and the differences do not affect the safety and effectiveness of the device when used as labeled.

(e) Summary Comparison of Device Technological Characteristics

The following side-by-side comparison of the applicant software device and the predicate software device shows substantial similarities in technical basis and specifications.

Substantial Equivalency Comparison

	K230221 QDOSE® Multi-purpose Voxel Dosimetry	K163687 OLINDA/EXM v.2.0 (predicate)
Purpose	Calculate the radiation absorbed doses to various organs and tissues from medically administered radiopharmaceuticals	Calculate the radiation absorbed doses to various organs and tissues from medically administered radiopharmaceuticals
Source of data input	Clinical nuclear medicine diagnostic imaging	Clinical nuclear medicine diagnostic imaging
Graphical user interface	Direct import and processing of region-of interest image and activity data	Direct import and processing of region-of interest image and activity data
Computational formalism	Medical Internal Radiation Dose (MIRD) mathematical schema with complete ICRP computational framework	Medical Internal Radiation Dose (MIRD) mathematical schema
Time-dependent measurement data processing	Time-activity data analysis for curve-fitting, functional form definition, best-fit parameter analysis, and integration through complete disappearance	Time-activity data analysis for curve-fitting, functional form definition, best-fit parameter analysis, and integration through complete disappearance
Form of dose-calculation input data	Organ and tissue residence times (time-integrated activity coefficients) for specified source organs	Organ and tissue residence times (time-integrated activity coefficients) for specified source organs
Anatomical models	ICRP representative human phantom models for infants, children and adolescents (pediatric), and the adult male and female; ICRP Publications 110 (2009), 133 (2016), and 143 (2020).	RADAR Inc. representative human phantom models for infants, children and adolescents (pediatric), adult male and female, and pregnant female
Source and target organ models	83 different source regions irradiating 47 target tissues compatible with ICRP Publication 89 (2002) for listed adult anatomical phantoms	28 different source regions irradiating 28 target tissues compatible with ICRP Publication 89 (2002) for listed adult anatomical phantoms
S value database	Derived from the Radiation Dose Assessment Resource (RADAR) phantom series	Uses S values from the ICRP publication 110 adult reference phantoms for dose computation; derived from the ICRP publication 133 specific absorbed fractions
Radionuclide library and nuclear emissions database	Expansive list of available and optional radionuclides (up to 1252) to choose from based on ICRP Publication 107 (2008) and MIRD/Oak Ridge National Laboratory (2008) radionuclide database with comprehensive nuclear emission energies, decay products, and yields per decay for each listed radioisotope	Expansive list of available and optional radionuclides (up to 850) to choose from (Brookhaven National Laboratory nuclear database) with comprehensive nuclear emission energies, decay products, and yields per decay for each listed radioisotope
Radionuclide emission types and properties	Photons (gamma and x-ray), beta particles (electrons and positrons), alpha particles	Photons (gamma and x-ray), beta particles (electrons and positrons), alpha particles

Method for calculating specific absorbed fractions	Monte Carlo simulations for photons, and direct calculations for electrons and alpha particles	Monte Carlo simulations for photons, and direct calculations for electrons and alpha particles
Results of calculations	Organ absorbed dose per unit administered activity, and total body effective dose	Organ absorbed dose per unit administered activity, and total body effective dose
Tumor model simulations	Size-dependent spheres model with definable tissue density	Size-dependent spheres model
Archiving	Export of dose-calculation results to file database	Export of dose-calculation results to file database

(f) Reference Devices Used to Help Support a Substantial Equivalence Determination

User testing has involved the applicant's software device, the predicate device, and the following reference devices:

K191216 Hermes Voxel Dosimetry™ (Hermes Medical Solutions AB, Stockholm, Sweden),

K182966 PLANET® Onco Dose with PLANET® Dose (DOSIsoft SA, Paris, France)

K182624 SurePlan™-MRT Dosimetry (MIM Software Inc., Cleveland, Ohio)
The reference software devices typically process, reconstruct, and extract quantitative count data from medical images (planar diagnostics, positron emission tomography, single-photon emission computed tomography, computed axial x-ray tomography, and magnetic resonance imaging, etc.), perform image registration and segmentation, translate detected counts to radionuclide activity present in organs and tissue of the body using calibration standards, integrate total counts over serially obtained regions of interest, and calculate radiation absorbed doses to the major organs and tissues of the body.

(g) Description of the Device that is the Subject of this Premarket Notification Submission

QDOSE® is a software package for calculating internal radiation doses from clinically administered radiopharmaceuticals. Patient time-activity data may be imported to QDOSE® in DICOM files from nuclear medicine clinical imaging. Dosimetry performed within QDOSE® is based on the use of calculated S values, determined for patient-like phantoms using a Monte Carlo method. The S values provide the average absorbed dose to a target organ generated by a unit of activity in a source organ. Source-organ time-activity curves from quantitative nuclear medicine imaging data are integrated to yield an estimate of the number of radionuclide decays representing the area under a time-activity function, similarly to the mathematical process used by OLINDA/EXM. QDOSE® dose calculations are performed by multiplying a source organ time-activity curve integral by the S value generated from Monte Carlo calculations. The product of

the dose calculations is an output of radiation absorbed doses to specified target organs per unit administered activity.

Why is this device important for radiopharmaceutical dosimetry? The effects of radiation on living tissues are primarily dependent on the well-established measure "absorbed dose". Diagnostic and therapeutic administrations of radiopharmaceuticals should be both planned and verified; consequently "great efforts are needed to assess absorbed dose in cells, tissues, and organs as a prerequisite for treatment planning and for verification of absorbed doses" to human subjects (Lassmann M and Eberlein U, The relevance of dosimetry in precision medicine, J Nucl Med 59:1494-1499; 2018). The QDOSE® solution for personalized dosimetry provides an important capability for evaluating radiation absorbed doses from medically administered radiopharmaceuticals. The following subsections provide further descriptive information.

(1) QDOSE® product overview: QDOSE® calculates radiation absorbed doses to organs and tissues of the human body after medical administration of radiopharmaceutical products (as described on FDA form 3881). QDOSE® has applications in clinical nuclear medicine, molecular radiotherapy, radiation safety evaluations, risk assessment, record-keeping, and regulatory compliance. QDOSE® integrates all dosimetry steps from image data import and processing to analysis and reporting. QDOSE® features a comprehensive range of workflows, running in parallel, including planar (2D), hybrid (2.5D) and volumetric (3D) dosimetry, as well as a dedicated selective internal radiation therapy (yttrium-90-SIRT) dosimetry module.

(2) Input Data: Nuclear medicine images such as planar scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET) may be acquired to visualize the biodistribution of a radiopharmaceutical in a medical patient. The QDOSE® software is used to process these nuclear medicine image data as well as anatomical images like x-ray computed tomography (CT) and magnetic resonance imaging (MRI). The software includes all processing and calculation steps required for an internal dosimetry evaluation.

QDOSE® can import image data in DICOM format from multiple medical scanners (planar scintigraphy, SPECT, PET, CT, MRI). The images can be displayed and further processed by co-registering image data sets and performing segmentations on the image data for an organ or a lesion. The segmented regions or volumes of interest (ROI, VOI) are used to calculate the activity from nuclear medicine image data sets (planar scintigraphy, SPECT, PET) within the ROI/VOI using well-characterized radionuclide standards. In case multiple nuclear medicine data sets for different time points are available, the activity within a segmented region for the different time points can be displayed as time-activity curve. An exponential curve can be fitted to the time-activity curve. The area under the curve can then be calculated (which represents the cumulated activity).

(3) Internal Calculational Algorithm: The dosimetry of an administered radiopharmaceutical to the segmented organ or other organs can be calculated using QDOSE®. QDOSE® software incorporates a calculational engine module (IDAC-Dose2.1) that performs

dose calculations based on the measured cumulated activity for a segmented region. A phantom-based approach is used to calculate the doses for different organs and tissues based on the cumulated activity from one or more segmented organs. For tumors with an assigned volume, the dose based on the cumulated activity for that tissue may be estimated using a spherical model. For 3D image data sets, the dose statistics and the voxel-wise distribution of dose values within the segmented organ based on the cumulated activity from the segmented organ can also be calculated using a voxel-based approach.

(4) QDOSE® Process Workflows: The QDOSE® software product includes algorithms for automatic co-registration of different planar scintigraphy images and automatic 3D co-registration between CT or MR image data sets and between CT and SPECT/PET image data sets. QDOSE® software includes algorithms for automatic and semi-automatic segmentation of certain organs (such as liver, kidneys, and spleen) on CT images.

Process workflows in QDOSE® include two-dimensional and three-dimensional image co-registration, region-of-interest and volume-of-interest drawing and segmentation, curve fitting and function integration for time-activity curve determinations, and calculation of radiation absorbed dose to selected organs and tissues of the body. QDOSE® implements the medical internal radiation dosimetry (MIRD) schema recommended by the MIRD Committee of the Society of Nuclear Medicine and Medical Imaging. The software package incorporates the IDAC-Dose (version 2.1) calculation software (Andersson M, Johansson L, Eckerman K, et al., IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms, Europ J Nucl Med Medical Imag Res 7, 88; 2017; https://doi.org/10.1186/s13550-017-0339-3), which is used by the International Commission on Radiological Protection to generate radiation dose estimates given in ICRP Publication 110 (Adult Reference Computational Phantoms; 2010), and in ICRP Publication 133 (The ICRP computational framework for internal dose assessment for reference adults: specific absorbed fractions; 2016). QDOSE® software can be installed on most regular Windows® computer systems, and can import DICOM images from most computerized imaging modalities.

> *QDOSE® with IDAC-Dose 2.1 fully implements the MIRD schema, stylized models, and computational processes adopted for scientific recommendations by the International Commission on Radiological Protection (ICRP).*

QDOSE® builds on the JADA workflow interface developed by Professor Anna Celler, University of British Columbia, Canada, and uses the algorithm for automatic liver segmentation (AIT-Liverator) developed by the AIT Austrian Institute of Technology GmbH. Manufacturer (ABX-CRO) is licensed by the University of British Columbia and The Austrian Institute of Technology, and owns all rights to use and incorporate the segmentation algorithms, workflows, and interfaces in the QDOSE® dosimetry suite.

(h) Statement of Intended Use of the Device that is the Subject of this Premarket Notification Submission

(1) Indications for Use: QDOSE® Multi-purpose Voxel Dosimetry is indicated for use to provide estimates of radiation absorbed dose to organs and tissues of the body from medically administered radiopharmaceuticals, and to calculate total-body effective dose. Radiation absorbed dose calculations are based on clinical measurements of radioactivity biodistributions and biokinetics. QDOSE® is intended for applications in clinical nuclear medicine, molecular radiotherapy, radiation safety evaluations, risk assessment, record-keeping, and regulatory compliance. QDOSE® is indicated for use by professionals (medical physicists, radiologists and oncologists including nuclear medicine physicians), radiologic imaging technologists, health physicists and radiation safety officers and administrators, students in training, and others having interest in ability to calculate internal radiation doses from medically administered radiopharmaceuticals.

(2) Patient population for which the device is intended: Subjects typically include medical patients administered radioactive drugs for diagnostic or therapeutic applications, and research subjects entered into approved clinical trials involving radioactive drugs and radioimmunotherapy agents common to molecular nuclear medicine.

(3) Technological similarities between QDOSE® and the predicate device: QDOSE® and the predicate device enable personalized dosimetry in clinical practice by calculating radiation absorbed doses per unit administered radionuclide activity (mGy/MBq or cGy/mCi). Differences in computer programming code, algorithm development, implementation of image registration techniques, choice and use of stylized and personalized models, derivation of specific absorbed fractions, and integration of serial data plots normally differ slightly from one dosimetry software product to another; however constants such as the basic physics equations underpinning absorbed dose calculations and nuclear data applied remain constant and standardized between platforms--resulting in similar dosimetry results. Therefore, minor differences in embedded methodology are normal and not critical to the intended experimental, diagnostic, or therapeutic use of the device. With the QDOSE® software (as with the predicate device), it is common and not unusual for users to obtain slightly different numerical results in terms of absolute absorbed dose values; the main sources of difference are ostensibly level of user training and experience, calibration, reproducibility, and region of interest delineation, which are all factors involving professional judgement (Lassmann and Eberlein, op.cit.; 2018). QDOSE® and the named predicate device provide users with the capability for patient-specific internal dosimetry based on fundamental science principles and internationally accepted methods and phantom models. Hence, differences between software coding do not significantly affect the safety or effectiveness of the device when used as labeled and according to user guidance.

(i) Substantial Equivalence Assessments of Performance Data

This submission demonstrates conformation with predicate software systems, as has been evaluated in performance testing and internal dosimetry intercomparison studies. The FDA has approved predicate devices for medical internal radiation dosimetry. The following information summarizes ways in which the performance of the applicant's QDOSE® software compares to performance of the three, legally marketed predicate devices, named above.

(1) Purpose and use: The purpose and use of each commercial software package for radiopharmaceutical internal dosimetry, based on quantitative data from nuclear medicine imaging, is to allow flexible dosimetry calculations for a broad range of radionuclides and radioactive drug products for patient dosimetry in nuclear medicine diagnostics and therapy. The software for each may be used with a spectrum of different imaging systems (cameras), manufacturers, detection sensitivities, image qualities and quality assurance, institutions, and technologists/operators. QDOSE® is broadly applicable to a range of medical procedures involving or including systemic internal radiation therapy (radiolabeled antibodies and other proteins), diagnostic radiopharmaceutical examinations, and selective internal radiation therapy of radionuclides administered directly into a target organ or tissue. For example, QDOSE® can be used to perform post-treatment dosimetry of systemic internal radiation therapy. In these applications, nuclear medicine image data (planar scintigraphy images and/or SPECT or PET) are obtained at multiple time points after administration of a radiopharmaceutical to a patient. Image data sets can be co-registered, and regions-of-interest (ROIs) or volumes of interest (VOIs) can be drawn, and segmentations can be performed. For each segmentation over multiple time points, different curve fit models can be used to calculate the cumulated activity. Based on the cumulated activities for the segmentations, the absorbed doses may be calculated. These software systems also calculate the radiation protection quantity *effective dose*.

(2) Methods of calculation: QDOSE® and the predicate software packages may incorporate uniquely different methods, assumptions, and algorithms for dosimetry of specific organs and tissues. For example, methods may differ slightly for calculating dose to walls of organs with non-tissue volumes (stomach, urinary bladder, small and large intestines, gall bladder, heart, and so forth) with activity presumed to reside in wall tissue, contents, or both. In addition, different approaches may be taken for calculating dose to organs and tissues with non-contiguous boundaries, such as trabecular and cortical bone, bone surfaces, and red and yellow (fatty) marrow. Special assumptions may be made concerning the geometry and morphology of organs such as lens of eye, medulla and cortex of kidneys, lung subdivisions, and other sub-organ regions.

(3) Software improvements, revisions, and upgrades: Software for internal dosimetry evolves continuously with upgrades and improvements, corrections and added features. Each dosimetry software product strives toward reliability and dependability, utility, ease of use, flexibility, feature capability, and applicability to clinical needs. QDOSE® and the predicate software packages provide upgrade and improvement mechanisms to ensure that the software

remains current, and that problems, bugs, and other issues are dealt with in a timely manner, and that revisions are immediately available to the user community.

Developers typically benchmark new dosimetry software against earlier versions of their own software, against competing dosimetry software, and against methods, models, and calculational approaches described in the open scientific literature. As a result of specific differences in calculation method, it is not common for dosimetry software packages to provide identical numerical dosimetry results when compared one to another. For example, each of the three FDA-approved predicate software devices produces different numerical results for the same input parameters and assumptions; differences in calculated absorbed dose are usually relatively small or insignificant.

(j) Nonclinical Tests Submitted, Referenced, or Relied on in the Premarket Notification Submission for a Determination of Substantial Equivalence

Functionality evaluation and dosimetry intercomparison tests have been conducted (a) by the applicant, and (b) by others to determine the degree to which calculated radiation doses compare among the applicant's QDOSE® software and the three predicate devices named above in Section (3).

(1) Nonclinical testing by the applicant: QDOSE® comparative performance tests were conducted. The purpose of these tests was to assess the performance of QDOSE® version 1.1 and version 1.2 (including bug fix releases) in estimating dose values using phantom data. Tests were performed to show the correct calculation of the cumulated activity values for phantom datasets with defined image intensity values and time-activity curves. Further tests were performed by the applicant to show that the dose calculation results compare favorably to other, state-of-the-art internal dosimetry software packages.

The internal dose calculational engine in QDOSE® is IDAC-Dose version 2.1 (Andersson M, Johansson L, Eckerman K, and Mattsson S, IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms, Europ J Nucl Med Medical Imag Res 7:88; 2017). Applicant testing was performed to compare QDOSE® features, capabilities, and calculational results against those of Hermes Voxel Organ Dosimetry with OLINDA/EXM® (version 1.1). To evaluate the performance of QDOSE®, the calculated dose values from IDAC-Dose 1 and IDAC-Dose 2.1 were compared with the dose values obtained from OLINDA/EXM 1.1 and OLINDA/EXM 2.0 using similar assumptions[1].

[11] Each software (medical device) is based on and developed from different approaches, assumptions, models, and calculational methods. However, absolute ground truth in medical internal radiation dosimetry is not known; for example, it is not determinable whether one software package or dosimetry module provides an exactly correct estimate, the best estimate, or even the better estimate of organ or tissue absorbed dose compared to any other software. Newer software usually incorporates newer, fresher, or up-to-date best available information, methods, models, and calculational algorithms. More modern algorithms gain strength with advancements in medical imaging and image interpretation. In general, it is desirable for an applicant's software to compare favorably with those of predicate devices; indeed, the more current approaches usually provide the better dose estimates.

The steps involved in performance testing and data analysis for calculating time-integrated activity coefficients (critical input values for both IDAC-Dose 2.1 and OLINDA/EXM 2.0) include:

- Import of nuclear medicine scans (image data)
- Automatic 2D co-registration of all image timepoints to the first timepoint
- Definition of the region-of-interest (ROI)
- Segmentation of all pixels within the ROI
- Automatic 3D co-registration of all 3D image timepoints
- Definition of volume of interest (VOI)
- Segmentation of all voxels within the VOI
- Monoexponential curve fitting by least-squares regression analysis, and
- Integration of the monoexponential time-activity function to yield the activity coefficients (which represent the critical input values to the dosimetry modules in QDOSE® and Hermes Voxel Dosimetry with OLINDA/EXM).

(a.1) *Test results for calculating time-integrated cumulated activities for source organs*:

Time-integrated cumulated activity values were calculated for planar workflow, the hybrid workflow, and the volumetric workflow, and were compared against theoretical values from calculations. Phantom datasets were analyzed by co-registration of images, segmentation, curve fitting, and activity integration. The derived cumulated activities for the different workflows were calculated and compared to the expected theoretical values.

For the planar image workflow, the average deviation or difference of the measured effective half-lives for activities in the selected source organs, comparing QDOSE® and Hermes Voxel Dosimetry, was about 0.2%, and the average difference of the calculated cumulated activities was about 1.3%. For the hybrid workflow, the deviation of the cumulated activities was about 0.3%, and for the volumetric workflow was 0.04%. Overall, these outcomes indicated similar test results.

(a.2) *Test results for calculating organ absorbed dose, comparing IDAC-Dose 2.1 to OLINDA/EXM 2.0*:

Anthropomorphic phantoms used in QDOSE® (IDAC-Dose 2.1) and Hermes Voxel Dosimetry with OLINDA/EXM are slightly different, and therefore calculated absorbed doses per unit administered activity will be different but comparable. IDAC-Dose 2.1 uses the realistic voxelized phantom model, whereas OLINDA/EXM uses the traditional (older generation) stylized model.

For the radionuclides tested, the mean relative difference for all beta/gamma-emitting radionuclides (pooled data) was 7% for the adult male phantom and 8.8 % for adult female phantom. For alpha emitting nuclides, the mean relative differences were 10.7% for the adult male phantom and 11.6% for adult female phantom.

For a given radionuclide, the relative differences by individual organ between QDOSE® (IDAC-Dose 2.1) and Hermes Voxel Dosimetry with OLINDA/EXM varied by about 1% for kidneys, liver, spleen, and thyroid, to about 25% for red marrow. These differences reflect the assumed differences in anatomical geometry, mass, shape, position, and tissue composition between the two software packages that affect calculation of specific absorbed energy fractions.

As with OLINDA/EXM, the dosimetry module in QDOSE® (IDAC-Dose 2.1) also calculates absorbed doses for radionuclides in the software library to unit-density spheres of various diameters. The comparison of absorbed dose values using the spherical model for each module also showed agreement with less than 5% difference. Absorbed doses calculated by the Voxel S method in QDOSE® showed a mean difference relative to OLINDA/EXM of about 6%.

(2) Nonclinical tests conducted by others: Nonclinical intercomparison test have been performed by others, including the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and Medical Imaging. In these nonclinical intercomparisons, absorbed dose estimates obtained using the dose calculational module in QDOSE® (IDAC-DOSE 2.1) *compared favorably with OLINDA 1 and 2, ICRP Publication 128, and MIRDcalc 1.*

The observed variability in reported doses was generally small, and in the case of organ walls with contents (with higher output dose variability), all results were still within ±20%. and within the standard error usually assumed for medical internal radiation dose estimates.

(k) Clinical Tests Submitted, Referenced, or Relied on in the Premarket Notification Submission for a Determination of Substantial Equivalence

Determination of substantial equivalence for internal dosimetry software devices is usually based on software purpose and objectives, scientific and technical approaches employed, and output results calculated. Our analysis according to these criteria showed that QDOSE® is substantially equivalent to the predicate device.

The manufacturer's Clinical Evaluation Report for QDOSE® dated February 1, 2022, is provided in this submission as APPENDIX B. This clinical evaluation assessed the performance and safety of QDOSE® for medical internal radiation dosimetry.

(1) Intended purpose and use: In common practice, the medical device QDOSE® software facilitates the calculations of radiation absorbed dose to organs and tissues of the body, for example, based on intracorporal administration of radiopharmaceuticals in nuclear medicine and radiolabeled microspheres in oncology. QDOSE® is not specifically designed to be used for therapy planning. At a whole organ level, dose estimation is performed using deterministic phantom-based models; in single organs, a spherical model or the Voxel S model is applied. The input for QDOSE® comprises information based on patient quantitative imaging data that show time-dependent uptake and biodistribution of administered radionuclides, or

time-activity curves or cumulated activities for radiopharmaceuticals in organs. QDOSE® allows the user to display multimodal medical image data limited to x-ray computed tomography (CT) data sets in axial slices, magnetic resonance imaging (MRI) data sets in axial slices, positron emission tomography (PET), single-photon- emission computed tomography (SPECT), and planar nuclear medicine images. QDOSE® enables the user to perform measurements based on the data sets. Tools are available in QDOSE® allowing co-registration of image data sets, defining regions or volumes of interest (ROI/VOI) in data sets, performing fits of measurement data to mathematical functions by least-squares regression analysis, constructing time-activity curves for the best-fit functions, and calculating cumulated activities for major source organs that are imageable above background. Cumulated activity values are then used to calculate absorbed doses per unit administered radionuclide activity, based on deterministic models on whole organ level, subregions, or single organs.

(l) Software Validation Quality Assurance (Quality Management System)

The manufacturer of the QDOSE® medical device software (ABX-CRO, Dresden, Germany) has implemented a software validation and quality assurance process, as required by the FDA Quality System regulation (21 CFR 820). These activities are documented by the manufacturer, to confirm by examination and evidence that the software specifications conform to user needs and designed uses ("General Principles of Software Validation," (January 2002); found at the URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-principles-software-validation). The QDOSE® Software Quality Management Plan meets or exceeds the FDA's approach to validating a software system. Planning, verification, testing, traceability, configuration management, and many other aspects of good software engineering have been incorporated to support a conclusion that the software is validated. The software validation and verification activities continue throughout the entire software lifecycle.

(m) Safety and Performance

The differences QDOSE® and the predicate software devices named above do not raise new questions regarding safety and effectiveness of the device. The device, as designed, is as safe and effective as are its predicate devices.

(n) Planning for Selective Internal Radiation Therapy

For microspheres, pre-treatment planning is conducted using FDA-approved methods in the labeling of yttrium-90 SIR-Spheres and TheraSpheres, respectively. Post-treatment dose verification is performed using ^{90}Y PET. FDA stipulates that dose verification using surrogate 99mTc-MAA cannot be used for prospective dosimetry or patient retreatment.

(o) Conclusions

Based on comparisons of the Indications for Use, design, purpose, and functionality presented herein, the software package QDOSE® is substantially equivalent to the predicate device.

The medical device QDOSE® with dosimetry module IDAC-Dose 2.1 is a multi-purpose voxel dosimetry software package that allows the clinical user to perform quantitative nuclear medicine imaging studies using a variety of modalities. As with the predicate device, QDOSE® users may co-register multiple nuclear medicine image formats, plot time-versus-activity data and best-fit mathematical functions, and integrate the areas under curves for the major imageable source organs and the whole body to calculate time-integrated activity coefficients (formerly called *residence times*) as inputs to the dosimetry modules. The dosimetry modules may then calculate organ and tissue radiation absorbed doses (including cross-organ contributions) per unit activity administered to the patient. QDOSE® is a significantly useful tool for assessing radiation doses to patients for a broad range of radionuclides, radiopharmaceuticals, and radioimmunotherapy agents.

(o) 510(k) Summary Checklist [21 CFR 807.92]

(1)	Submitter's name, address, contact info, date prepared	√
(2)	Name of device, classification	√
(3)	Legally marketed predicate device	√
(4)	Description of device	√
(5)	Statement of intended use	√
(6)	Summary of technological characteristics	√
(7)	Nonclinical tests submitted or referenced	√
(8)	Clinical tests submitted or referenced	√
(9)	Conclusions drawn to demonstrate device is as safe, effective, performs as well or better than the predicate	√
(10)	Quality management system	√