AZmed SAS
℅ Patricia Massako
QARA Manager
6 rue Leonard de Vinci
Laval, Pays de la Loire 53000
FRANCE

June 2, 2022

Re: K220164
Trade/Device Name: Rayvolve
Regulation Number: 21 CFR 892.2090
Regulation Name: Radiological computer assisted detection and diagnosis software
Regulatory Class: Class II
Product Code: QBS
Dated: April 12, 2022
Received: April 29, 2022

Dear Patricia Massako:

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,

Jessica Lamb, Ph.D.
Assistant Director
Imaging Software Team
DHT8B: Division of Radiological Imaging Devices and Electronic Products
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)*
K220164

Device Name
Rayvolve

Indications for Use *(Describe)*
Rayvolve is a computer-assisted detection and diagnosis (CAD) software device to assist radiologists and emergency physicians in detecting fractures during the review of radiographs of the musculoskeletal system. Rayvolve is indicated for adults only (≥ 22 years old). Rayvolve is indicated for radiographs of the following industry-standard radiographic views and study types.

Study Type (Anatomic Area of interest) / Radiographic Views supported:
Ankle / Frontal, Lateral,Oblique
Clavicle / Frontal
Elbow / Frontal, Lateral
Forearm / Frontal, Lateral
Hip / Frontal, Frog Leg Lateral
Humerus / Frontal, Lateral
Knee / Frontal, Lateral
Pelvis / Frontal
Shoulder / Frontal, Lateral, Axillary
Tibia/fibula / Frontal, Lateral
Wrist / Frontal, Lateral, Oblique
Hand / Frontal, Lateral
Foot / Frontal, Lateral

*For the purposes of this table, "Frontal" is considered inclusive of both posteroanterior (PA) and anteroposterior (AP) views.
+Definitions of anatomic area of interest and radiographic views are consistent with the American College of Radiology (ACR) standards and guidelines.

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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K220164

510(k) SUMMARY

Content

K220164

1 Submitter

AZmed
6 rue Léonard de Vinci
53000, Laval, France

Contact Person: Patricia Massako – Quality and regulatory Manager
Phone: +336 25 84 69 88

Prepared date: 22nd April 2022

2 Device identification

Name of the Device	Common or Usual Name	Regulatory section	Classification	Product Code	Panel
Rayvolve	**Rayvolve**	**21 CFR 892.2090**	**Class II**	**QBS**	**90 (Radiology)**

3 Predicate device

The legally marketed device for which AZmed is claiming equivalence is identified as follows:

Manufacturer	Product Name	510K Number
Imagen Technologies	FractureDetect (FX)	K193417

4 Device description

The medical device is called Rayvolve. It is a standalone software that uses deep learning techniques to detect and localize fractures on osteoarticular X-rays. Rayvolve is intended to be used as an aided-diagnosis device and does not operate autonomously. It is intended to work in combination with Picture Archiving and communication system (PACS) servers. When remotely connected to a medical center PACS server, Rayvolve directly interacts with the DICOM files to output the prediction (potential presence or absence of fracture). Rayvolve does not intend to replace medical doctors. The instructions for use are strictly and systematically transmitted to each user and used to train them on Rayvolve's use.

The dataset used to develop the Rayvolve deep learning algorithm is composed of labeled osteoarticular radiographs. The osteoarticular radiographs have been collected from multiple centers (different types of medical imaging centers: public hospitals, private clinics, generalist medical imaging centers, and musculoskeletal medical imaging centers) from different countries (France, Israel, Germany, Switzerland, Belgium, United-Kingdom, Argentina, Brazil, and Nigeria) to have the largest diversity and variety. This diversity allows the Rayvolve algorithm to have a high generalization ability.

5 Intended use/Indication for use

Rayvolve is a computer-assisted detection and diagnosis (CAD) software device to assist radiologists and emergency physicians in detecting fractures during the review of radiographs of the musculoskeletal system. Rayvolve is indicated for adults only (≥ 22 years old). Rayvolve is indicated for radiographs of the following industry-standard radiographic views and study types.:

Study type (Anatomic Area of interest)	Radiographic Views supported*
Ankle	Frontal, Lateral, Oblique
Clavicle	Frontal
Elbow	Frontal, Lateral
Forearm	Frontal, Lateral
Hip	Frontal, Frog Leg Lateral
Humerus	Frontal, Lateral

Knee	Frontal, Lateral
Pelvis	Frontal
Shoulder	Frontal, Lateral, Axillary
Tibia/fibula	Frontal, Lateral
Wrist	Frontal, Lateral, Oblique
Hand	Frontal, Lateral
Foot	Frontal, Lateral

Table 1 Rayvolve indication for use - Anatomical regions

*For this table, "Frontal" is considered inclusive of both posteroanterior (PA) and anteroposterior (AP) views.
+ Definitions of an anatomic area of interest and radiographic views are consistent with the American College of Radiology (ACR) standards and guidelines.

6 Substantial equivalence Discussion

The comparison chart below provides evidence to facilitate the substantial equivalence determination between Rayvolve to the predicate device (K193417) concerning the intended use, technological characteristics, and principle of operation.

	FractureDetect(FX)	**Rayvolve Subject device**	**Comparison**
Number	K193417	TBD	/
Applicant	Imagen Technologies	AZmed	/
Device Name	FractureDetect (FX)	Rayvolve	/
Classification Regulation	892.2090	892.2090	**Same**
Product Code	QBS	QBS	**Same**

Intended use /Indication for use	FractureDetect (FX) is a computer-assisted detection and diagnosis (CAD) software device to assist clinicians in detecting fractures during the review of radiographs of the musculoskeletal system. FX is indicated for adults only.	Rayvolve is a computer-assisted detection and diagnosis (CAD) software device to assist radiologists and emergency physicians in detecting fractures during the review of radiographs of the musculoskeletal system. Rayvolve is indicated for adults only (≥ 22 years old).	**Same**
Image Modality	X-ray	X-ray	**Same**
Study Type (Anatomic Areas of Interest)	Ankle Clavicle Elbow Femur Forearm Hip Humerus Knee Pelvis Shoulder Tibia / Fibula Wrist	Ankle Clavicle Elbow Forearm Hip Humerus Knee Pelvis Shoulder Tibia / Fibula Wrist Hand Foot	Rayvolve covers 2 more anatomical regions than FX; but the intended use is similar since both FX and Rayvolve are intended to identify fractures in radiographs, and all those anatomical regions are included in the definition of anatomic area of interest and radiographic views consistently with the American College of Radiology (ACR) standard and guidelines.
Clinical Finding	Fracture	Fracture	**Same**

Patient Population	Adults ≥ 22 years of age	Adults ≥ 22 years of age	**Same**
Intended User	Clinicians	Clinicians (MSK and non-MSK radiologist and emergency physicians)	**Same**
Machine Learning Methodology	Supervised Deep Learning	Supervised Deep Learning	**Same**
Platform	Secure local processing and delivery of DICOM images	Secure local processing and delivery of DICOM images	**Same**
Image Source	DICOM node (e.g., imaging device, intermediate DICOM node, PACS system, etc.)	DICOM node (e.g., imaging device, intermediate DICOM node, PACS system, etc.)	**Same as FX**
Image Viewing	PACS system, image annotations toggled on or off	PACS system, image annotations made on a copy of the original image	**Same, with a copy of the original image**
Privacy	HIPAA compliant	HIPAA compliant	**Same**

AZmed claims the substantial equivalence of Rayvolve with the predicate FX based on the **functional principle** of the software algorithms, the same technological characteristics, and the **intended purpose** of the software algorithm.

7 Performance data

7.1 Software verification and validation testing

The device's software development, verification, and validation have been carried out following FDA guidelines. The software was tested against the established software design specification for each test plan to assure the device's performance as intended. The device hazard analysis was completed and risk control was implemented to mitigate identified hazards. The testing results support that all the software specifications have met the acceptance criteria of each module and interaction of processes. Rayvolve device passes all the testing and supports the claims of substantial equivalence with the predicate.

Validation activities included a usability study of Rayvolve under normal conditions for use. The study demonstrated:

- Non-invasive usability because users' habits are unchanged
- Comprehension of the instructions for use provided with the device

7.2 Biocompatibility testing

There are no direct or indirect patient-contacting components of Rayvolve. Therefore, patient contact information is not needed for this device.

7.3 Electrical safety and electromagnetic compatibility (EMC)

Rayvolve is a software-only device, therefore; electrical safety and EMC testing are not applicable.

7.4 Bench Testing

AZmed conducted a standalone performance assessment on 2626 radiographs for all the study types (anatomic areas of interest) and views in the indication for Use.

7.4.1 Acceptance criteria / Endpoints

Regarding the performance standalone study:

- The primary endpoint of the standalone study is to characterize the detection accuracy of Rayvolve for detecting adult patient fractures.
- The secondary endpoint is to demonstrate Rayvolve's ability to perform across different subgroup variables. More precisely, the goal is to compute Rayvolve AUC, sensitivity, and specificity for all the potential and relevant observable subgroups such as gender, age, anatomic region, machine acquisition, machine view, as well as Rayvolve performances depending on weight-bearing and complex & uncommon cases.

Regarding the MRMC study:

- The primary objective of the clinical reader study is to determine whether the diagnostic accuracy of readers aided by Rayvolve **is superior** to reader accuracy when unaided by Rayvolve, as determined by the AUC of the ROC curve: H0: T-test for p (no statistical difference) > 0.05; H1: T-Test for p (statistical difference) < 0.05
- The secondary objective is to report the sensitivity and the specificity of the Rayvolve-aided and unaided reads.

7.4.2 Data & Patient information

For both standalone and MRMC studies, the subgroups have been determined based on the data set composed with the following inclusion criteria:

- De-identified radiographs
- Frontal, LAT, Oblique and Axillary views
- Adult patient, minimum of 22 years of age

Regarding the performance standalone study:

Here are the different subgroups/confounders evaluated:

- Gender
- Age
- Anatomic region
- Machine acquisition
- Machine view
- Weight-bearing radiographs
- Complex and uncommon radiographs

Here is other information about the patients:

- The 2626 radiographs (samples) of the performance study were taken from 851 patients
- The number of samples is the number of radiographs, thus the study contains 2626 samples.
- Gender split: 440 female patients, 411 male patients.
- Age split: 468 patients between 22 and 60 (mean: 38 y.o., std: 12 y.o.), 383 patients above 60 (mean: 81 y.o., std: 18 y.o.)
- Ethnicity: no information was available regarding ethnicity.

Regarding the MRMC study:
Here are the different subgroups/confounders evaluated:

- Gender
- Age
- Machine acquisition

Here is other information about the patients:

- The 186 cases (samples) were taken from 186 patients - Regarding the MRMC study, a case is equivalent to a patient. Thus, the study contains 186 samples.
- Gender split: 96 male patients, 90 female patients.
- Age split: 79 patients between 22 and 60, 107 patients above 60.
- Ethnicity: no information was available regarding ethnicity.

7.4.3 Collected images

To ensure the independence between data for both standalone and MRMC studies, and Rayvolve training data, no radiograph in the validation (bench or clinical testing) study is part of Rayvolve's training set. Rayvolve training set has been established before the collection of the standalone and MRMC studies data.

Data were acquired from 4 sites in US.

7.4.4 Results

AZmed conducted a standalone performance assessment on 2626 radiographs for all the study types (anatomic areas of interest) and views in the Indications for Use. The results of standalone testing demonstrated that Rayvolve detects fractures of the musculoskeletal system radiographs with high sensitivity (0.98763, 95% Wilson's Confidence Interval (CI): 0.97559; 0.99421), high specificity (0.88558; 95% Wilson's CI: 0.87119; 0.89882) and high Area Under The Curve (AUC) of the Receiver Operating Characteristic (ROC) (0.98607; 95% Bootstrap CI: 0.98104; 0.99058). Additionally, the results demonstrated that Rayvolve performs with high accuracy across study types (anatomic areas of interest, views, patient age and sex and machine) and across potential confounders such as different x-ray manufacturers.

The results of the standalone testing demonstrated that Rayvolve detects fractures of the musculoskeletal system radiographs with high AUC across the following subgroups:

	AUC (Bootstrapped CI)
All (2626)	0.98607 (0.98104; 0.99058)

Anatomic Area (*Nb of images)*	**AUC (Bootstrapped CI)**
Ankle *(232)*	0.99137 (0.98374; 0.99727)
Clavicle *(171)*	0.97806 (0.94626; 0.99761)
Elbow *(192)*	0.9964 (0.99059; 1.0)
Forearm *(157)*	0.9953 (0.98909; 0.99937)
Humerus *(181)*	0.9955 (0.98960; 0.99943)
Hip *(198)*	0.95821 (0.93239; 0.98014)
Knee *(239)*	0.97742 (0.95084; 0.99592)
Pelvis *(149)*	0.97676 (0.95241; 0.99638)
Shoulder *(150)*	0.97814 (0.94147; 0.99958)
Tibia/Fibula *(232)*	0.98285 (0.95925; 0.9978)
Wrist *(225)*	0.99567 (0.99126; 0.99897)
Hand *(252)*	0.99552 (0.99074; 0.99898)
Foot *(248)*	0.99162 (0.98238; 0.99823)

Gender (*Nb of images)*	**AUC (Bootstrapped CI)**
Male *(1306)*	0.98822 (0.98186; 0.99409)
Female *(1320)*	0.98395 (0.97589; 0.99101)

View (*Nb of images)*	**AUC (Bootstrapped CI)**

Frontal *(1279)*	0.97872 (0.96845; 0.98805)
Lateral *(1033)*	0.99218 (0.98903; 0.99477)
Oblique *(268)*	0.9958 (0.98979; 0.99977)
Axillary *(46)*	0.99675 (0.98734; 1.0)

Age (*Nb of images)*	**AUC (Bootstrapped CI)**
22-60 (*1403)*	0.99049 (0.98359; 0.99598)
> 60 *(1223)*	0.98102 (0.97487; 0.98941)

Machine (*Nb of images)*	**AUC (Bootstrapped CI)**
GEHC Discovery XR 656 (*1234)*	0.98482 (0.97920; 0.99264)
Philips DigitalDiagnost (*840)*	0.98635 (0.97657; 0.99345)
Carestream Health DRX-1 (*552)*	0.98842 (0.97754; 0.99689)

Abbreviations: AUC=Area under the Curve; CI=confidence interval.
Four additional studies (comprising a total of 3574 cases) were used to demonstrate the generalizability of Rayvolve across multiple imaging devices. It was demonstrated that Rayvolve had reached similar and stable performance across different medical imaging acquisition device providers (Siemens Healthineers, Philips Healthcare, Carestream, GE Healthcare, Fujifilm, MinXray, Hologic, Shimadzu, Agfa, Duet, Primax, Kodak, Samsung and Thales).

Additionally, the performance of Rayvolve was validated for potential confounders including weight-bearing and non-weight bearing bone fractures, complex and uncommon fractures different X-ray Machine providers.

Particular groups (*Nb of images)*	**AUC (Bootstrapped CI)**
Complex & uncommon (*547)*	0.96102 (0.95223; 0.99615)

Non complex & uncommon (*2079)*	0.99607 (0.98862; 0.99701)
weight-bearing (*1298)*	0.98059 (0.96162; 0.99458)
Non-weight-bearing (*1328)*	0.99143 (0.97916; 0.99912)

7.5 Animal testing

Not applicable. Animal studies are not necessary to establish the substantial equivalence of this device.

7.6 Clinical data

AZmed conducted a fully-crossed multiple readers, multiple case (MRMC) retrospective reader study to determine the impact of Rayvolve on reader performance in diagnosing fractures.

The primary objective of the study was to determine whether the diagnostic accuracy of readers aided by Rayvolve ("Rayvolve-aided") is superior to the diagnostic accuracy of readers unaided by Rayvolve ("Rayvolve-unaided") as determined by the AUC of the Receiver Operating Characteristic (ROC) Curve. The secondary objective is to report the sensitivity and the specificity of the Rayvolve-aided and unaided reads.

24 clinical readers each evaluated 186 cases in Rayvolve's indication for use under both Rayvolve-aided and Rayvolve-unaided conditions. Each case had been previously evaluated by a panel of three US board-certified MSK radiologists to provide ground truth binary labeling indicating the presence or absence of fracture and the localization information for fractures. The MRMC study consisted of two independent reading sessions separated by a washout period of at least one month to avoid memory bias.

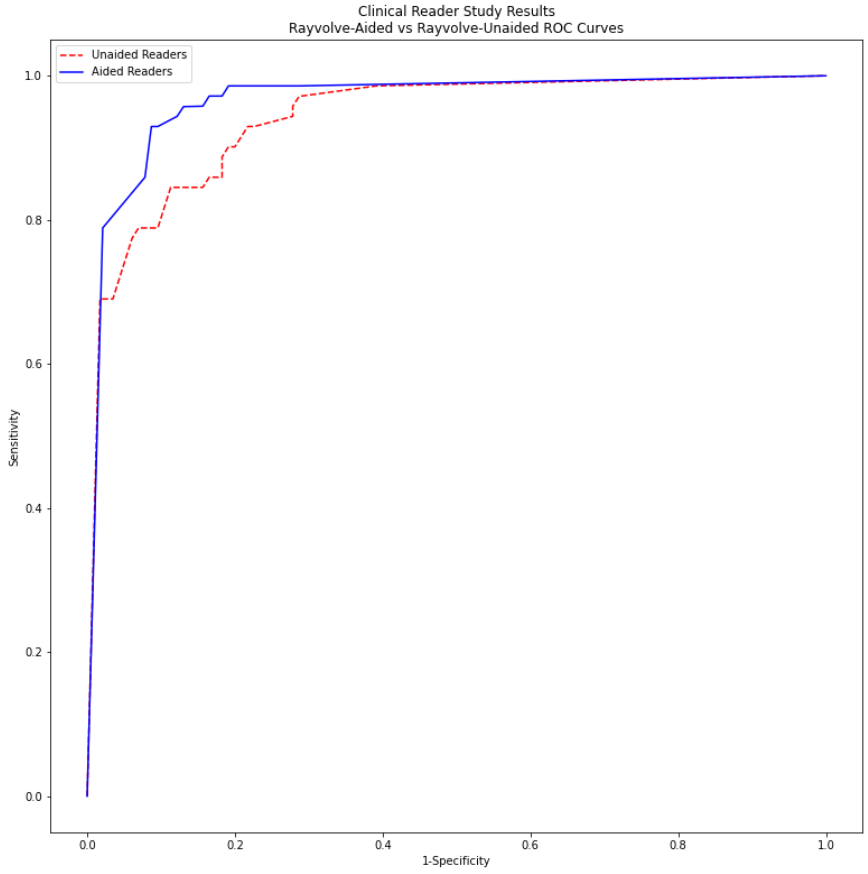
For each case, each reader was required to provide a binary determination of the presence or absence of a fracture and also to draw a bounding box around each fracture on the image to determine the localization of each fracture.

In addition to this binary decision of the readers regarding the presence or absence of fracture, each reader should also provide a report score with an ordinal value.

This report score has been collected for every case and for every reader with and without aid of Rayvolve device. The report score has been used for ROC data.

The results of the study found that the diagnostic accuracy of readers in the intended use population is superior when aided by Rayvolve than when unaided by Rayvolve, as measured at the task of fracture detection using the AUC of the ROC curve as calculated by the DBM modeling approach.

Clinical Reader Study Results
Rayvolve-Aided vs Rayvolve-Unaided ROC Curves



In particular, the study results demonstrated:

- Reader AUC was significantly improved from 0.84602 to 0.89327, a difference of 0.04725 (95% CI: 0.03376; 0.061542), across the 186 cases within Rayvolve's Indications for Use, spanning 13 study types (anatomic areas of interest) (p=0.0041).
- Reader sensitivity was significantly improved from 0.86561 (95% Wilson's CI: 0.84859, 0.88099) to 0.9554 (95% Wilson's CI: 0.94453, 0.96422)
- Reader specificity was improved from 0.82645 (95% Wilson's CI: 0.81187, 0.84012) to 0.83116 (95% Wilson's CI: 0.81673, 0.84467)

8 CONCLUSION

Both the proposed device (Rayvolve) and the predicate device (FX) are computer-assisted detection and diagnostic devices that accept as input radiographs in DICOM format and use machine learning techniques to identify and highlight fractures. The overall design of the software and the basic functionality that it provides to the end-user are the same. The differences in technological characteristics do not raise different questions of safety and effectiveness. The results of standalone and clinical studies demonstrate that Rayvolve performs according to the specifications and meets user needs and intended use and that Rayvolve can be found to be substantially equivalent to FX.