Imagen Technologies, Inc.
% Donna-Bea Tillman
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1555 King Street, Suite 300
Alexandria, Virginia 22314

May 24, 2018

Re: DEN180005
Trade/Device Name: OsteoDetect
Regulation Number: 21 CFR 892.2090
Regulation Name: Radiological Computer Assisted Detection and Diagnosis Software
Regulatory Class: Class II
Product Code: QBS
Dated: February 2, 2018
Received: February 5, 2018

Dear Donna-Bea Tillman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the OsteoDetect, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> OsteoDetect analyzes wrist radiographs using machine learning techniques to identify and highlight distal radius fractures during the review of posterior-anterior (PA) and lateral (LAT) radiographs of adult wrists.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the OsteoDetect, and substantially equivalent devices of this generic type, into Class II under the generic name Radiological Computer Assisted Detection and Diagnosis Software.

FDA identifies this generic type of device as:

> **Radiological Computer Assisted Detection and Diagnosis Software**. A radiological computer assisted detection and diagnostic software is an image processing device intended to aid in the detection, localization, and characterization of fracture, lesions, or other disease specific findings on acquired medical images (e.g. radiography, MR, CT). The device detects, identifies and characterizes findings based on features or information extracted from images, and provides information about the presence, location, and characteristics of the findings to the user. The analysis is intended to inform the primary diagnostic and patient management decisions that are made by the clinical user. The device is not intended as a replacement for a complete clinician's review or their clinical judgment that takes into account other relevant information from the image or patient history.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register classifying the device type.

On February 5, 2018, FDA received your De Novo requesting classification of the OsteoDetect. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the OsteoDetect into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request FDA has determined that, for the previously stated indications for use, the OsteoDetect can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Summary	
Summary of the Benefit(s)	The clinical MRMC study demonstrated a statistically significant improvement in reader performance in detecting distal radius fracture in adult patients (as measured by the primary endpoint of the ROC Area Under the Curve) when aided with OsteoDetect as compared to performance at the same task without OsteoDetect, according to clinical standard of care. AUCaided - AUCunaided = 0.889 - 0.840= 0.049 (two sided 95% confidence level [0.019,0.080]) OsteoDetect-aided read performance also showed statistically significant improvement as measured by sensitivity, specificity, PPV, and NPV as compared with the unaided read performance. Specifically, Imagen's study demonstrated a device-aided sensitivity of 80.3% (two sided 95% confidence interval for the mean: [78.5%,81.9%]) and device-aided specificity of 91.4% (two sided 95% confidence interval for the mean: [90.3%,92.4%]). By comparison, the study demonstrated non-aided sensitivity and specificity of 74.7% [72.8%,76.5%] and 88.9% [87.6%,90.0%], respectively.

	Earlier detection of a distal radial fracture will allow earlier intervention, potentially allowing closed reduction and casting instead of open reduction, minimizing the risk of delayed pain and post-traumatic arthritis.
Summary of the Risk(s)	There are minimal potential risks associated with use of the device, including: • The device could provide false positive results, which could contribute to the end user using this information to make a false positive diagnosis. Such a false positive diagnosis can result in unnecessary patient treatment or followup. • The device could provide false negative results, which could contribute to the end user using this information to make a false negative diagnosis. A false negative diagnosis could lead to delays in diagnosis and treatment of the fracture and increase the likelihood of negative outcomes such as incomplete fracture healing. • The device could be misused to analyze images from an unintended patient population or on images acquired with incompatible imaging hardware or incompatible image acquisition parameters, leading to inappropriate information regarding the presence/location of a fracture being provided to the end user. • The device could fail and lead to absence of results, delay of results, or incorrect results, which can lead to delayed or inaccurate patient diagnosis However, based on the performance data and the application of general controls and special controls established for this device type, use of this device is unlikely to increase the rate of false negative or false positive diagnoses of distal radius fracture as compared with the current clinical standard of practice. Further, possible misuse of the device does not present additional risks compared with the misuse of other types of radiological image processing devices.

Summary of Other Factors	Currently, injuries to the hand and wrist account for approximately 20% of visits to the emergency department, with a total of approximately 3.5 million hand and wrist injuries noted in 2009, for an incidence of 1130 injuries per 100,000 persons per year. (Hand (NY) 2012; 7:18-22) By detecting a potentially occult distal radial fracture earlier, pain, post-traumatic arthritis, and possible disability are alleviated, resulting in a potential significant improvement in US public health. This software tool brings the expertise of musculoskeletal radiologists and orthopaedic surgeons specializing in hand surgery to emergency medicine physicians and physician assistants, family practice physicians, and internal medicine physicians. Therefore, subspecialty expertise is potentially available to emergency rooms across the country with the use of this software device.
Conclusions Do the probable benefits outweigh the probable risks?	The benefited population would include adult patients with clinically suspected distal radius fracture. This software potentially brings subspecialty expertise of musculoskeletal radiologists and orthopaedic surgeons specializing in hand and wrist surgery to physicians and physician assistants working in emergency rooms across the country. The underlying statistics as discussed above justify that the performance of the device has been clinically validated in a fully crossed design. The 4 types of clinical providers (emergency medicine physicians, emergency medicine physician assistants, family medicine physicians, and internal medicine physicians) most likely to staff emergency rooms were separately evaluated, and all showed improvement in the detection of a distal radial fracture aided by the device. Given that the standard of care in 2018 is to cast and have a follow-up X-ray in 10-14 days or perform an MRI in cases where a distal radial fracture is clinically suspected in the face of a normal hand/wrist X-ray series, a software device that detects distal radial fracture earlier is a potential significant benefit to public health. Accordingly, the probable benefits of the device outweigh the probable risks, mainly a false positive diagnosis, given the combination of general controls and special controls established for this device type. The hand and wrist are the most commonly injured part of the body and 1 out of 6 of fractures presenting to emergency rooms are distal radial fractures. This software device has the potential to result in significant improvement in public health while introducing minimal additional clinical risks of extra follow-up, treatment, and imaging.

In combination with the general controls of the FD&C Act, the Radiological Computer Assisted Detection and Diagnosis Software is subject to the following special controls:

1. Design verification and validation must include:
    i. A detailed description of the image analysis algorithm, including but not limited to a description of the algorithm inputs and outputs, each major component or block, how the algorithm and output affects or relates to clinical practice or patient care, and any algorithm limitations.
    ii. A detailed description of pre-specified performance testing protocols and dataset(s) used to assess whether the device will provide improved assisted-read detection and diagnostic performance as intended in the indicated user population(s), and to characterize the standalone device performance for labeling. Performance testing includes standalone test(s), side-by-side comparison(s), and/or a reader study, as applicable.
    iii. Results from standalone performance testing used to characterize the independent performance of the device separate from aided user performance. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., receiver operator characteristic plot, sensitivity, specificity, positive and negative predictive values, and diagnostic likelihood ratio). Devices with localization output must include localization accuracy testing as a component of standalone testing. The test dataset must be representative of the typical patient population with enrichment made only to ensure that the test dataset contain a sufficient number of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, concomitant disease, and subsets defined by image acquisition characteristics) such that the performance estimates and confidence intervals of the device for these individual subsets can be characterized for the intended use population and imaging equipment.
    iv. Results from performance testing that demonstrate that the device provides improved assisted-read detection and/or diagnostic performance as intended in the indicated user population(s) when used in accordance with the instructions for use. The reader population must be comprised of the intended user population in terms of but not limited to clinical training, certification, and years of experience. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., receiver operator characteristic plot, sensitivity, specificity, positive and negative predictive values, and diagnostic likelihood ratio). Test datasets must meet the requirements described in 1(iii) above.
    v. Appropriate software documentation, including device hazard analysis, software requirements specification document, software design specification document, traceability analysis, system level test protocol, pass/fail criteria, testing results, and cybersecurity measures.

2. Labeling must include the following:
    i. A detailed description of the patient population for which the device is indicated for use.
    ii. A detailed description of the device instructions for use, including the intended reading protocol and how the user should interpret the device output.
    iii. A detailed description of the intended user, and any user training materials as programs that addresses appropriate reading protocols for the device to ensure that the end user is fully aware of how to interpret and apply the device output.
    iv. A detailed description of the device inputs and outputs.
    v. A detailed description of compatible imaging hardware and imaging protocols.
    vi. Warnings, precautions, and limitations must include situations in which the device may fail or

may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), as applicable.

vii. A detailed summary of the performance testing, including: test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders, such as anatomical characteristics, patient demographics and medical history, user experience, and imaging equipment.

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

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Radiological Computer Assisted Detection and Diagnosis Software they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD & C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD & C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). 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 (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Laurel Burk at 301-796-5933.

Sincerely,

for

Robert Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health