September 21, 2021

Paige.AI, Inc.
Emre Gulturk
Senior Director of Quality Assurance and Regulatory Affairs
11 Times Square 37th Floor,
New York City, NY 10036

Re: DEN200080

Trade/Device Name:	Paige Prostate
Regulation Number:	21 CFR 864.3750
Regulation Name:	Software algorithm device to assist users in digital pathology
Regulatory Class:	Class II
Product Code:	QPN
Dated:	December 29, 2020
Received:	December 31, 2020

Dear Emre Gulturk:

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 Paige Prostate, a prescription device with the following indications for use:

> Paige Prostate is a software only device intended to assist pathologists in the detection of foci that are suspicious for cancer during the review of scanned whole slide images (WSI) from prostate needle biopsies prepared from hematoxylin & eosin (H&E) stained formalin-fixed paraffin embedded (FFPE) tissue. After initial diagnostic review of the WSI by the pathologist, if Paige Prostate detects tissue morphology suspicious for cancer, it provides coordinates (X,Y) on a single location on the image with the highest likelihood of having cancer for further review by the pathologist.
>
> Paige Prostate is intended to be used with slide images digitized with Philips Ultra Fast Scanner and visualized with Paige FullFocus WSI viewing software.
>
> Paige Prostate is an adjunctive computer-assisted methodology and its output should not be used as the primary diagnosis. Pathologists should only use Paige Prostate in conjunction with their complete standard of care evaluation of the slide image.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Paige Prostate, and substantially equivalent devices of this generic type, into Class II under the generic name software algorithm device to assist users in digital pathology.

FDA identifies this generic type of device as:

Software algorithm device to assist users in digital pathology. A software algorithm device to assist users in digital pathology is an in vitro diagnostic device intended to evaluate acquired scanned pathology whole slide images. The device uses software algorithms to provide information to the user about presence, location, and characteristics of areas of the image with clinical implications. Information from this device is intended to assist the user in determining a pathology diagnosis.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On December 31, 2020, FDA received your De Novo requesting classification of the Paige Prostate. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Paige Prostate 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 Paige Prostate 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:

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Mitigation Measures
False negative classification (loss of accuracy)	Certain design verification and validation, including certain device descriptions, certain analytical studies, and clinical studies. Certain labeling information, including certain device descriptions, certain performance information, and certain limitations.
False positive classification (loss of accuracy)	Certain design verification and validation, including certain device descriptions, certain analytical studies, and clinical studies. Certain labeling information, including certain device descriptions, certain

	performance information, and certain limitations.

In combination with the general controls of the FD&C Act, the software algorithm device to assist users in digital pathology is subject to the following special controls:

1. The intended use on the device's label and labeling required under 21 CFR 809.10 must include:
   i. Specimen type;
   ii. Information on the device input(s) (e.g., scanned whole slide images (WSI), etc.);
   iii. Information on the device output(s) (e.g., format of the information provided by the device to the user that can be used to evaluate the WSI, etc.);
   iv. Intended users;
   v. Necessary input/output devices (e.g., WSI scanners, viewing software, etc.);
   vi. A limiting statement that addresses use of the device as an adjunct; and
   vii. A limiting statement that users should use the device in conjunction with complete standard of care evaluation of the WSI.

2. The labeling required under 21 CFR 809.10(b) must include:

   i. A detailed description of the device, including the following:
      A. Detailed descriptions of the software device, including the detection/analysis algorithm, software design architecture, interaction with input/output devices, and necessary third-party software;
      B. Detailed descriptions of the intended user(s) and recommended training for safe use of the device; and
      C. Clear instructions about how to resolve device-related issues (e.g., cybersecurity or device malfunction issues).

   ii. 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, medical history, user experience, and scanning equipment, as applicable.

   iii. Limiting statements that indicate:

      A. A description of situations in which the device may fail or may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), including any limitations in the dataset used to train, test, and tune the algorithm during device development;
      B. The data acquired using the device should only be interpreted by the types of users indicated in the intended use statement; and
      C. Qualified users should employ appropriate procedures and safeguards (e.g., quality control measures, etc.) to assure the validity of the interpretation of images obtained using this device.

3. Design verification and validation must include:

    i. A detailed description of the device software, including its algorithm and its development, that includes a description of any datasets used to train, tune, or test the software algorithm. This detailed description of the device software must include:

        A. A detailed description of the technical performance assessment study protocols (e.g., regions of interest (ROI) localization study) and results used to assess the device output(s) (e.g., image overlays, image heatmaps, etc.);
        B. The training dataset must include cases representing different pre-analytical variables representative of the conditions likely to be encountered when used as intended (e.g., fixation type and time, histology slide processing techniques, challenging diagnostic cases, multiple sites, patient demographics, etc.);
        C. The number of WSI in an independent validation dataset must be appropriate to demonstrate device accuracy in detecting and localizing ROIs on scanned WSI, and must include subsets clinically relevant to the intended use of the device;
        D. Emergency recovery/backup functions, which must be included in the device design;
        E. System level architecture diagram with a matrix to depict the communication endpoints, communication protocols, and security protections for the device and its supportive systems, including any products or services that are included in the communication pathway; and
        F. A risk management plan, including a justification of how the cybersecurity vulnerabilities of third-party software and services are reduced by the device's risk management mitigations in order to address cybersecurity risks associated with key device functionality (such as loss of image, altered metadata, corrupted image data, degraded image quality, etc.). The risk management plan must also include how the device will be maintained on its intended platform (e.g. a general purpose computing platform, virtual machine, middleware, cloud-based computing services, medical device hardware, etc.), which includes how the software integrity will be maintained, how the software will be authenticated on the platform, how any reliance on the platform will be managed in order to facilitate implementation of cybersecurity controls (such as user authentication, communication encryption and authentication, etc.), and how the device will be protected when the underlying platform is not updated, such that the specific risks of the device are addressed (such as loss of image, altered metadata, corrupted image data, degraded image quality, etc.).

    ii. Data demonstrating acceptable, as determined by FDA, analytical device performance, by conducting analytical studies. For each analytical study, relevant details must be documented (e.g., the origin of the study slides and images, reader/annotator qualifications, method of annotation, location of the study site(s), challenging diagnoses, etc.). The analytical studies must include:

        A. Bench testing or technical testing to assess device output, such as localization of ROIs within a pre-specified threshold. Samples must be representative of the entire

spectrum of challenging cases likely to be encountered when the device is used as intended; and

B. Data from a precision study that demonstrates device performance when used with multiple input devices (e.g., WSI scanners) to assess total variability across operators, within-scanner, between-scanner and between-site, using clinical specimens with defined, clinically relevant, and challenging characteristics likely to be encountered when the device is used as intended. Samples must be representative of the entire spectrum of challenging cases likely to be encountered when the device is used as intended. Precision, including performance of the device and reproducibility, must be assessed by agreement between replicates.

iii. Data demonstrating acceptable, as determined by FDA, clinical validation must be demonstrated by conducting studies with clinical specimens. For each clinical study, relevant details must be documented (e.g., the origin of the study slides and images, reader/annotator qualifications, method of annotation, location of the study site(s) (on-site/remote), challenging diagnoses, etc.). The studies must include:

A. A study demonstrating the performance by the intended users with and without the software device (e.g., unassisted and device-assisted reading of scanned WSI of pathology slides). The study dataset must contain sufficient numbers of cases from relevant cohorts that are representative of the scope of patients likely to be encountered given the intended use of the device (e.g., subsets defined by clinically relevant confounders, challenging diagnoses, subsets with potential biopsy appearance modifiers, concomitant diseases, and subsets defined by image scanning characteristics, etc.) such that the performance estimates and confidence intervals for these individual subsets can be characterized. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., sensitivity, specificity, predictive value, diagnostic likelihood ratio, etc.).

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the software algorithm device to assist users in digital pathology 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 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act); 21 CFR 1000-1050.

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

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

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Arpita Roy at 240-402-4807.

Sincerely,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics
and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health