January 31, 2024

Hologic Inc.
Bryce Dzialo
Regulatory Affairs Specialist
250 Campus Drive
Marlborough, Massachusetts 01752

Re: DEN210035
Trade/Device Name: Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm
Regulation Number: 21 CFR 864.3900
Regulation Name: Digital cervical cytology slide imaging system with artificial intelligence algorithm
Regulatory Class: Class II
Product Code: QYV
Dated: August 26, 2021
Received: August 27, 2021

Dear Bryce Dzialo:

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 Genius Digital Diagnostics System with the Genius Cervical AI algorithm, a prescription device with the following indications for use:

> The Genius Digital Diagnostics System with the Genius Cervical AI algorithm includes the Genius Digital Imager, Genius Image Management Server (IMS), the Genius Review Station, and the Genius Cervical AI algorithm. The Genius Digital Diagnostics System with the Genius Cervical AI algorithm is intended for the creation and viewing of digital images of scanned ThinPrep Pap Test glass slides. Objects of interest selected by the Genius Cervical AI algorithm from the scanned digital image are presented in a gallery format next to the image of the whole cell spot on the Genius Review Station for review and interpretation. The Genius Digital Diagnostics System with the Genius Cervical AI algorithm is intended to aid in cervical cancer screening for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions) and carcinoma, as well as all other cytological categories as defined by The Bethesda System for Reporting Cervical Cytology[1].
>
> After digital review with the Genius Cervical AI algorithm, if there is uncertainty in the diagnosis, then direct examination of the glass slide by light microscopy should be performed. Digital images from the Genius Digital Diagnostics System with the Genius Cervical AI algorithm should be interpreted by qualified cytologists and pathologists in conjunction with the patient's screening history, other risk factors, and professional guidelines which guide patient management.

[1] *Nayar R, Wilbur DC. (eds), The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 3rd ed. Cham, Switzerland: Springer: 2015*

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, and substantially equivalent devices of this generic type, into Class II under the generic name digital cervical cytology slide imaging system with artificial intelligence (AI) algorithm.

FDA identifies this generic type of device as:

> **Digital cervical cytology slide imaging system with artificial intelligence algorithm**. The digital cervical cytology slide imaging system with artificial intelligence (AI) algorithm is a prescription in vitro diagnostic device consisting of an automated digital slide creation, viewing, and management system intended to aid in the review of digital images of slides prepared from Pap test specimens and conventional Pap smears by selecting and presenting areas of interest to facilitate interpretation by the reader. The AI software algorithm uses machine learning techniques to provide information to the user about the presence, location, or characteristics of areas of the image with clinical implications. Information from this device is intended to assist the user in rendering a cytology 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 August 27, 2021, FDA received your De Novo requesting classification of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Genius Digital Diagnostics System with the Genius Cervical AI algorithm 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, FDA has determined that, for the previously stated indications for use, the Genius Digital Diagnostics System with the Genius Cervical AI algorithm 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:

Risks to Health	Mitigation Measures
False negative and false positive results due to device errors in presenting abnormal cells in the digital image gallery	Certain design verification and validation, including certain studies and risk mitigation analysis.

Risks to Health	Mitigation Measures
	Certain labeling information, including limitations, device descriptions, methodology and protocols, and performance information.
False negative and false positive results due to incorrect interpretation of digital images or incorrect operation of the device by the user	Certain design verification and validation, including certain studies and risk mitigation analysis. Certain labeling information, including limitations, user training, device descriptions, methodology and protocols, and performance information.

In combination with the general controls of the FD&C Act, the digital cervical cytology slide imaging system with artificial intelligence algorithm is subject to the following special controls:

(1) The labeling required under 21 CFR 809.10(b) must include the following:
  (i) The intended use must include the specimen type (e.g., Pap test or conventional Pap smear), information on the device input (e.g., Pap test glass slides) and output(s) (e.g., whole slide image (WSI) of cytology glass slides or cell spot), information on the AI algorithm output(s) (i.e., format of the information provided by the device to the user, e.g., objects of interest (OOI) found on the WSI, which is presented in a gallery for the user to review), and intended users.
  (ii) A detailed description of the intended patient population;
  (iii) Detailed instructions for use, including the intended image review and interpreting protocol for use of the device, and how to resolve device-related issues (e.g., cybersecurity or device malfunction issues.
  (iv) A detailed description of the device, including the following:
    (A) Necessary input/output devices (e.g., scanner, imager, management server, review station, viewing software, software algorithm);
    (B) Necessary infrastructure, platform, and/or software application services, and configuration(s) (e.g., storage, network architecture, cloud services, etc.);
    (C) Compatible scanning hardware and scanning protocols;
    (D) Interaction with input/output devices,and necessary third-party software;
    (E) Recommended training for intended users for safe use of the device;
  (v) A detailed summary of the performance testing required by paragraphs (2)(i), (2)(ii), (2)(iv), and (2)(v)(A), including test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders, i.e., 3D characteristics of cells and cell clusters in cytology samples, patient demographics, medical history, user experience, sites, and scanning equipment, etc., as applicable;
  (vi) Intended user screening time data to provide information about daily slide screening workload limits, as determined by the performance testing in paragraph (2)(v)(B);
  (vii) Limiting statements, including the following:
    (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 due to the dataset used to train, test, and tune the algorithm during device development;

(B) That review of the entire gallery (i.e., OOIs with clinical implications, etc.), should be performed by the user prior to rendering a diagnosis;
(C) That users should use the device in conjunction with the standard of care, an assessment of patient history and other risk factors, and professional screening and management guidelines to guide patient care; and
(D) That users should employ appropriate procedures and safeguards (e.g., daily quality control measures, deferral to glass slide review, cybersecurity, etc.), including when the device is used for remote review of images, to assure the validity of the interpretation of images obtained using this device.

(2) Design verification and validation must include:
(i) A detailed description and the technical performance assessment of each component in the device, including the following, as appropriate:
(A) Slide feeder;
(B) Light source;
(C) Imaging optics;
(D) Z-focal plane acquisition, including a detailed description of methods used to ensure that the complete depth of the cellular material is captured (e.g., Z-plane merging, Z-stacking), when applicable;
(E) Mechanical scanner movement;
(F) Digital imaging sensor;
(G) Image processing software;
(H) Image composition techniques;
(I) Image file formats;
(J) Image review manipulation software;
(K) Computer environment; and
(L) Display system.
(ii) Detailed technical performance assessment at the system level, including for the following, as appropriate:
(A) Coverage of Z-depth to represent the 3D aspects of cells and cell clusters in cytology samples;
(B) Color reproducibility;
(C) Spatial resolution;
(D) Focusing accuracy;
(E) Whole slide cell spot or specimen material coverage;
(F) Stitching error;
(G) Turnaround time.
(iii) 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) The study protocols (e.g., OOI reproducibility study, imaging reproducibility study, cell count validation study, etc.) and results used to assess the device output(s) (e.g., image overlays, image heatmaps, image location, total number of cells, etc.);
(B) The training dataset, including cases representing different pre-analytical variables representative of the conditions likely to be encountered when used as intended (e.g., fixation type and time, cytology slide processors, challenging diagnostic cases, multiple sites, patient demographics, etc.);

(C) An appropriate number of digital cytology images in an independent validation dataset to demonstrate device accuracy in detecting OOI on scanned cytology images, which must include subsets clinically relevant to the intended use of the device; and

(D) A 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.

(iv) Detailed documentation of studies demonstrating acceptable, as determined by FDA, analytical device performance using samples that are representative of the entire spectrum of challenging cases likely to be encountered when the device is used as intended. 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) Testing to assess device outputs (e.g., OOI reproducibility study, cell count validation study, etc.); and

(B) Precision and reproducibility study(ies) that demonstrate device performance when used with multiple input devices (e.g., digital cytology scanners) to assess total variability across images, operators, within-scanners, between-scanners and between-sites, using a comprehensive set of representative clinical specimens with defined, clinically relevant features and challenging characteristics likely to be encountered when the device is used as intended. Precision and reproducibility must be assessed by agreement between replicates.

(v) Data demonstrating acceptable, as determined by FDA, clinical validation by conducting studies with clinical specimens to demonstrate that screening and diagnosing digital images of cervical cytology slides with the assistance of the device's software algorithms, is non-inferior to using a comparator method that FDA has determined to be appropriate, (e.g., optical microscope). 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 AI algorithm [i.e., unassisted (manual microscope read) and device-assisted reading of scanned digital images of cervical cytology slides]. The study dataset must contain sufficient numbers of cytological slides for each diagnostic category and processed by representative processing instruments such that the performance estimates and confidence intervals for these individual subsets can be appropriately characterized. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., sensitivity, specificity, predictive value, diagnostic likelihood ratio, etc.);

(B) Intended user screening time data obtained from the clinical study, to characterize and set recommended daily maximum workload screening limits for intended users. The study dataset must contain sufficient 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.). The reader population must be comprised of

the intended user population in terms of clinical training, certification, years of experience, etc.

(vi) Human factors study data to evaluate the usability and user experience of the device with representative users.

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 digital cervical cytology slide imaging system with artificial intelligence algorithm 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 Parts 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,

Donna M. Roscoe -S

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