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4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2026-N-12384]

Medical Devices; Hematology and Pathology Devices; Classification of the Digital Cervical Cytology Slide Imaging System with Artificial Intelligence Algorithm

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the digital cervical cytology slide imaging system with artificial intelligence algorithm into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for classification of the digital cervical cytology slide imaging system with artificial intelligence algorithm. We are taking this action because we have determined that classifying the device into class II will provide a reasonable assurance of the safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on January 31, 2024.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the digital cervical cytology slide imaging system with artificial intelligence algorithm into class II (special controls), which we

have determined will provide a reasonable assurance of the safety and effectiveness of the device. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified into, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) modified the De Novo classification process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a premarket notification (510(k)) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On August 27, 2021, FDA received Hologic Inc.'s request for De Novo classification of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see section 513(a)(1)(B) of the FD&C Act). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on January 31, 2024, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 864.3900.[1] We have named the generic type of device "digital cervical cytology slide imaging system with artificial intelligence algorithm," and it is identified as 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 artificial intelligence (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.

FDA has identified the risks to health associated with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Risks to Health and Mitigation Measures for Digital Cervical Cytology Slide Imaging Systems with Artificial Intelligence Algorithm

Identified Risks to Health	Mitigation Measures

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

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. 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.

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of the safety and effectiveness of the device. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this final order.

At the time of classification, digital cervical cytology slide imaging systems with AI algorithm are for prescription use only. Therefore, these devices are subject to the prescription labeling requirements for in vitro diagnostic products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)).

Under the FD&C Act, submission of a premarket notification under section 510(k) is required to reasonably assure the safety and effectiveness of class II devices unless FDA determines that the device type should be exempt under section 510(m) of the FD&C Act. At this time, FDA has not made this determination for digital cervical cytology slide imaging systems with AI algorithm. This device is therefore subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not normally have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 regarding quality management system regulation have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR parts 801 and 809 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 864

Blood, Medical devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 864 is amended as follows:

PART 864--HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for part 864 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Add § 864.3900 to subpart D to read as follows:

§ 864.3900 Digital cervical cytology slide imaging system with artificial intelligence algorithm.

(a) *Identification*. 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.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) The labeling required under § 809.10(b) of this chapter 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, such as 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);

(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 (b)(2)(i), (b)(2)(ii), (b)(2)(iv), and (b)(2)(v)(A) of this section, including test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders, i.e., three-dimensional (3D) characteristics of cells and cell clusters in cytology samples, patient demographics, medical history, user experience, sites, and scanning equipment 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 (b)(2)(v)(B); and

(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) 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), 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; and

(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) and results used to assess the device output(s) (e.g., image overlays, image heatmaps, image location, total number of cells);

(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);

(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). The analytical studies must include:

(A) Testing to assess device outputs (e.g., OOI reproducibility study, cell count validation study); 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). 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); and

(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, subsets defined by image scanning characteristics). The reader population must be comprised of the intended user population in terms of clinical training, certification, and years of experience.

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

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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