4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2017-N-6599]

Medical Devices; Hematology and Pathology Devices; Classification of a Cervical Intraepithelial Neoplasia Test System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA or we) is classifying the cervical intraepithelial neoplasia (CIN) test system 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 the CIN test system's classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of 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 March 4, 2017.

FOR FURTHER INFORMATION CONTACT: Steven Tjoe, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4550, Silver Spring, MD 20993-0002, 301-796-5866, steven.tjoe@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the cervical intraepithelial neoplasia (CIN) test system as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. 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 as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 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 by means of the procedures for premarket notification under section 510(k) of the FD&C Act and part 807 (21 U.S.C. 360(k) and 21 CFR part 807, respectively).

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. Section 207 of the Food and

Drug Administration Modernization Act of 1997 established the first procedure for De Novo classification (Pub. L. 105-115). Section 607 of the Food and Drug Administration Safety and Innovation Act modified the De Novo application process by adding a second procedure (Pub. L. 112-144). A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 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 shall 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 21 U.S.C. 360c(f)(2)(B)(i)). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application in order to market a substantially equivalent device (see 21 U.S.C. 360c(i), defining "substantial equivalence").

Instead, sponsors can use the less-burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On May 23, 2016, Ventana Medical Systems, Inc., submitted a request for De Novo classification of the CINtec Histology. 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 safety and effectiveness, 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 21 U.S.C. 360c(a)(1)(B)). 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 March 4, 2017, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 864.1865. We have named the generic type of device the cervical intraepithelial neoplasia (CIN) test system, and it is identified as a device used to detect a biomarker associated with CIN in human tissues. The device is indicated as an adjunct test and not to be used as a stand-alone device. The test results must be interpreted in the context of the patient's clinical history including, but not limited to, prior and current cervical biopsy results, Papanicolaou (Pap) test results, human papillomavirus (HPV) test results, and morphology on hematoxylin and eosin (H&E) stained sections. This device is not intended to detect the presence of HPV.

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

Table 1.--Cervical Intraepithelial Neoplasia (CIN) Test System Risks to Health and Required Mitigations

Identified Risks	Required Mitigations/21 CFR Section
Inaccurate test results, such as false positive or false negative results	General controls and special controls (1) and (2) (21 CFR 864.1865(b)(1); 21 CFR 864.1865(b)(2))
Failure to correctly interpret test results can lead to false positive or false negative results	General controls and special controls (1) and (2) (21 CFR 864.1865(b)(1); 21 CFR 864.1865(b)(2))

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. 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 order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively 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. 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. 3501-3520). The collections of information in 21 CFR parts 801 and 809, regarding labeling, have been approved under OMB control number 0910-0485; 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 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; and the collections of information in the guidance document "De Novo Classification Process (Evaluation of Automatic Class III Designation)" have been approved under OMB control number 0910-0844.

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, 360*l*, 371.

2. Add § 864.1865 to subpart B to read as follows:

§ 864.1865 Cervical intraepithelial neoplasia (CIN) test system.

(a) *Identification*. A cervical intraepithelial neoplasia (CIN) test system is a device used to detect a biomarker associated with CIN in human tissues. The device is indicated as an adjunct test and not to be used as a stand-alone device. The test results must be interpreted in the context of the patient's clinical history including, but not limited to, prior and current cervical biopsy results, Papanicolaou (Pap) test results, human papillomavirus (HPV) test results, and morphology on hematoxylin and eosin (H&E) stained sections. This device is not intended to detect the presence of HPV.

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

(1) Premarket notification submissions must include the following information:

(i) The indications for use must specify the biomarker that is intended to be identified and its adjunct use (e.g., adjunct to examination of H&E stained slides) to improve consistency in the diagnosis of CIN.

(ii) Summary of professional society recommendations, as applicable.

(iii) A detailed device description including:

(A) A detailed description of all test components, including all provided reagents and required, but not provided, ancillary reagents.

(B) A detailed description of instrumentation and equipment, including illustrations or photographs of non-standard equipment or manuals.

(C) If applicable, detailed documentation of the device software, including, but not limited to, stand-alone software applications and hardware-based devices that incorporate software.

(D) A detailed description of appropriate positive and negative controls that are recommended or provided.

(E) Detailed specifications for sample collection, processing, and storage.

(F) A detailed description of methodology and assay procedure.

(G) A description of the assay cutoff (the medical decision point between positive and negative) or other relevant criteria that distinguishes positive and negative results, including the rationale for the chosen cutoff or other relevant criteria and results supporting validation of the cutoff.

(H) Detailed specification of the criteria for test results interpretation and reporting.

(iv) Detailed information demonstrating the performance characteristics of the device, including:

(A) Analytical specificity studies such as, but not limited to, antibody characterization (e.g., Western Blot, peptide inhibition analysis), studies conducted on panels of normal tissues and neoplastic tissues, interference by endogenous and exogenous substances as well as cross-reactivity, as applicable.

(B) Device analytical sensitivity data generated by testing an adequate number of samples from individuals with the target condition including limit of blank, limit of detection, and limit of quantification, as applicable.

(C) Device precision/reproducibility data to evaluate within-run, between-run, between-day, between-lot, between-site, between-reader, within-reader and total precision, as applicable, using a panel of samples covering the device measuring range and/or the relevant disease categories (e.g. No CIN, CIN1, CIN2, CIN3, cervical cancer) and testing in replicates across multiple, nonconsecutive days.

(D) Device robustness/guardbanding studies to assess the tolerance ranges for various critical test and specimen parameters.

(E) Device stability data, including real-time stability and shipping stability under various storage times, temperatures, and freeze-thaw conditions.

(F) Data from a clinical study demonstrating clinical validity using well-characterized prospectively or retrospectively obtained clinical specimens, as appropriate, representative of the intended use population. The study must evaluate the consistency of the diagnosis of CIN, for example, by comparing the levels of agreements of diagnoses rendered by community pathologists to those rendered by a panel of expert pathologists. Agreement for each CIN diagnostic category (e.g., No CIN, CIN1, CIN2, CIN3, cancer) and for alternate diagnostic categories (e.g., No CIN, low grade squamous intraepithelial lesion (LSIL)-histology, high grade

squamous intraepithelial lesion (HSIL)-histology, cancer) between reference diagnosis by expert pathologist and community pathologist must be evaluated, as applicable. In addition, agreements for CIN binary categories as ≥ CIN2 (i.e., CIN2 or CIN3 or cancer) and ≤ CIN1 (i.e., No CIN or CIN1) between reference diagnosis by expert pathologist with H&E staining and community pathologist with H&E staining and agreements for alternate CIN binary categories as ≥ HSIL-histology (i.e., HSIL-histology or cancer) and ≤ LSIL-histology (i.e., No CIN or LSIL-histology) between reference diagnosis by an expert pathologist with H&E+[biomarker specified in paragraph (b)(1)(i) of this section] and a community pathologist with H&E+[biomarker specified in paragraph (b)(1)(i) of this section] must be evaluated and compared, as applicable.

(G) The staining performance of the device as determined by the community pathologists during review of the study slides must be evaluated. The staining performance criteria assessed must include overall staining acceptability, background staining acceptability, and morphology acceptability, as applicable.

(H) Appropriate training requirements for users, including interpretation manual, as applicable.

(I) Identification of risk mitigation elements used by the device, including a description of all additional procedures, methods, and practices incorporated into the instructions for use that mitigate risks associated with testing.

(2) The device's 21 CFR 809.10(b) compliant labeling must include a detailed description of the protocol, including the information described in paragraph (b)(1)(ii) of this section, as applicable, and a detailed description of the performance studies performed and the summary of the results, including those that relate to paragraph (b)(1)(ii) of this section, as applicable.

Dated: December 27, 2017.

Leslie Kux,

Associate Commissioner for Policy.

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