4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2026-N-4643]

Medical Devices; Immunology and Microbiology Devices; Classification of the Circulating Tumor Cell Enrichment Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the circulating tumor cell enrichment device 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 circulating tumor cell enrichment device. We are taking this action because we have determined that classifying the device into class II 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 May 24, 2022.

FOR FURTHER INFORMATION CONTACT: Soma Ghosh, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3316, Silver Spring, MD 20993-0002, 240-402-5333, Soma.Ghosh@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the circulating tumor cell enrichment device into class II (special controls), which we have determined will provide a reasonable assurance of 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 September 28, 2020, FDA received ANGLE Europe Ltd.'s request for De Novo classification of the Parsortix PC1 Device. 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 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 May 24, 2022, 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 866.6110.[1] We have named the generic type of device "circulating tumor cell enrichment device," and it is identified as in vitro diagnostic device used to enrich circulating tumor cells from the peripheral blood of patients diagnosed with cancer for subsequent in vitro diagnostic testing.

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 the Circulating Tumor Cell Enrichment Device

Identified Risks to Health	Mitigation Measures
Failure to identify circulating tumor cells (CTCs) that are present in the sample leading to delays in patient management.	Use of certain specimen collection devices identified in special control (1). Certain labeling information identified in special control (2), including limitations, device descriptions, training specifications, explanation of procedures, and performance information identified in special control (3). Certain design verification and validation identified in special control (3), including documentation of certain analytical studies and clinical studies.
No results obtained using downstream testing leading to delays in patient management.	Certain labeling information identified in special control (2), including limitations, device descriptions, training specifications, explanation of procedures, and performance information identified in special control (3).
Incorrect evaluation of CTCs using downstream analyses leading to associated risk of false	Certain labeling information identified in special control (2), including limitations, device descriptions, explanation of procedures, and

[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.

test results and improper patient management.	performance information identified in special control (3).
Failure to correctly operate the device leading to delays in patient management and associated risk to downstream analyses resulting in false test results and improper patient management.	Certain labeling information identified in special control (2), including limitations, device descriptions, and explanation of procedures.
Bloodborne pathogen transmission from blood waste/blood sample.	Certain labeling information identified in special control (2), including limitations, device descriptions, and explanation of procedures.

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 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.

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 circulating tumor cell enrichment devices. This device is therefore 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 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 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866—IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for part 866 continues to read as follows:

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

2. Add § 866.6110 to subpart G to read as follows:

§ 866.6110 Circulating tumor cell enrichment device.

(a) *Identification*. A circulating tumor cell enrichment device is an in vitro diagnostic device used to enrich circulating tumor cells from the peripheral blood of patients diagnosed with cancer for subsequent in vitro diagnostic testing.

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

(1) Any device used for specimen collection and transport must be FDA-cleared, -approved, or -classified as 510(k) exempt for the collection of human specimens; alternatively, the sample collection device must be cleared in a premarket submission as a part of this device.

(2) The labeling required under § 809.10(b) of this chapter must include:

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

(ii) An intended use statement that includes:

(A) The intended specimen type(s) for which acceptable, as determined by FDA, validation data has been provided (e.g., peripheral whole blood).

(B) The identification of, or the specifications for, the collection device or devices to be used for sample collection.

(C) Information on the device output(s) (e.g., circulating tumor cells (CTCs), other blood cells).

(D) The specific tumor type(s) for which the device is intended to be used.

(E) A statement for general downstream diagnostic assays and that end users need to validate use with any subsequent tests and collection devices.

(F) A statement that the standalone device is not intended for diagnostic, prognostic, or monitoring use with CTCs, including as an aid in any disease management and/or treatment decisions.

(iii) Prominent and conspicuous limiting statements clearly explaining:

(A) The use of the device is intended for the collection of CTCs from previously diagnosed cancer patients.

(B) The standalone device is not intended for cell enumeration.

(C) The users for whom the device is intended, including any training specifications.

(D) The performance characteristics of this device have not been established for general downstream diagnostic assays and that end users need to validate use with any subsequent tests and collection devices.

(E) An insufficient number of CTCs or even no circulating tumor cells may be collected.

(F) Results from the standalone device do not provide information to the patient regarding their current state of health.

(G) The standalone device does not diagnose any health conditions and is not a substitute for visits to a doctor or other healthcare professional.

(H) The device is intended only for enriching CTC content in specimens so that the enriched specimens can then be used in further processing/analysis using additional independent methods.

(I) The variability of the number of CTCs and other cells harvested by the device may impact the success of any subsequent analysis.

(iv) A troubleshooting section that includes clear instructions for resolving any common device-related issues.

(v) A description of the device mechanism of action to enrich CTCs.

(vi) A detailed summary of the analytical and clinical performance studies required under paragraph (b)(3) of this section.

(3) Design verification and validation must include the following:

(i) Documentation of studies that provide:

(A) Data demonstrating acceptable, as determined by FDA, analytical device performance using samples representative of the range of those with which the device is intended for use. The number of specimens tested must be sufficient to obtain estimates of device performance that is representative of the device performance within the full spectrum of the device's intended use.

(B) Data demonstrating acceptable precision, as determined by FDA, to adequately evaluate intra-run, inter-run, and total variability across operator, instrument, lot, day, and site, as applicable.

(C) Data demonstrating the detection limit of the device.

(D) Recovery study data demonstrating the range of the device.

(E) Data demonstrating appropriate validation of device design features and specifications such that the device reproducibly and reliably collects and isolates CTCs. At a minimum, the data must include:

(*1*) Data, as appropriate for the intended use, including estimates of within-lot, within-device, and lot-to-lot variability, demonstrating that samples collected from the intended use population using the device provide CTCs that are suitable, as determined by FDA, for the intended downstream testing.

(*2*) Data demonstrating that the device output has no contamination or minimal levels of contamination from other sources, and that any such contamination does not interfere with the recovery of CTCs.

(*3*) Data demonstrating that the presence of clinically relevant levels of potential interfering substances in the intended specimen type(s) and intended use population, including endogenous and exogenous substances, does not interfere with the recovery of CTCs.

(*4*) Data demonstrating that blood samples collected for use with the device remain stable under certain storage conditions (e.g., temperature, time) and do not impact the output of representative downstream testing.

(ii) Documentation of clinical studies using the device on intended use clinical specimens that demonstrate the device can enrich or capture an appropriate number of CTCs, as determined by FDA, to support the intended use of the device.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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