4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2026-N-5725]

Medical Devices; Hematology and Pathology Devices; Classification of the Von Willebrand Factor Assay

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the von Willebrand factor assay 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 von Willebrand factor assay. 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 September 29, 2022.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the von Willebrand factor (VWF) assay 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 October 28, 2020, FDA received Siemens Healthcare Diagnostics Products GmbH's request for De Novo classification of the INNOVANCE VWF Ac 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 September 29, 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 864.7293.[1] We have named the generic type of device "von Willebrand factor assay," and it is identified as a prescription device intended for the measurement of von Willebrand factor activity or von Willebrand factor size distribution in human plasma. This device is indicated to aid in the diagnosis and management of patients being evaluated for von Willebrand factor disorders in conjunction with other clinical and laboratory findings.

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 Von Willebrand Factor Assays

Identified Risks to Health	Mitigation Measures
Falsely elevated VWF activity results may lead to delayed diagnosis and delayed patient management of von Willebrand disease (VWD). Patients with delayed diagnosis and resulting delayed patient management of VWD are at increased risk of bleeding due to the withholding of appropriate treatment.	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations and performance information identified in special control (1).
Falsely depressed VWF activity results may lead the physician to suspect VWD in patients who do not have the disease. As a result, the patients may receive unnecessary follow-up testing and unnecessary treatment as well as delays in receiving a correct diagnosis and	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations

[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.

appropriate patient management. In addition, affected patients may experience mental anxiety because of the erroneous diagnosis.	and performance information identified in special control (1).
No results may lead to delayed patient management.	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations and performance information identified in special control (1).

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.

At the time of classification, von Willebrand factor assays are for prescription use only. Therefore, these devices are subject to the prescription labeling requirements for in vitro diagnostic (IVD) 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 von Willebrand factor assays. 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 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 § 864.7293 to subpart H to read as follows:

§ 864.7293 von Willebrand factor assay.

(a) *Identification*. A von Willebrand factor assay is a prescription device intended for the measurement of von Willebrand factor activity or von Willebrand factor size distribution in human plasma. This device is indicated to aid in the diagnosis and management of patients

being evaluated for von Willebrand factor disorders in conjunction with other clinical and laboratory findings.

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

(1) Design verification and validation must include:

(i) Detailed documentation of studies demonstrating acceptable, as determined by FDA, analytical performance, including, as applicable, precision, linearity, assay interference, detection capability, specimen and reagent stability, and hook effect, with a sufficient number of specimens tested in order to obtain unbiased estimates of analytical performance. For devices measuring multiple analytes, the detailed documentation must include studies demonstrating the analytical performance of the device in regard to each individual analyte, including precision, linearity, assay interference, cross-reactivity, detection capability, specimen and reagent stability, and hook effect, as applicable.

(ii) Detailed documentation of a comparison study of clinical samples demonstrating performance relative to clinically relevant and appropriate, as determined by FDA, clinically validated laboratory tests. Further, the studies must meet all of the following criteria:

(A) All eligible subjects must meet appropriate study inclusion and exclusion criteria that define the intended use population. Specimens must be representative of the intended use population(s) and must representatively cover the full range of the device output and any clinically relevant decision points, as appropriate;

(B) The study must be conducted at a minimum of three external sites representative of the intended use setting by operators representative of the intended user population;

(C) For all intended pediatric patient populations, clinical outcome validation studies must study those populations in accordance with paragraphs (b)(1)(ii)(A) and (B) of this section; and(D) Expected (reference) values for test output must be demonstrated by testing a statistically appropriate number of samples from apparently healthy normal individuals in all relevant

subpopulations (i.e., blood group O and non-O, male and female, and, if applicable, pediatric and adults), as applicable to the intended use of the device.

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

(i) Limiting statements indicating, as applicable:

(A) This device should always be used in conjunction with the patient's medical history, clinical presentation, and other laboratory findings.

(B) Identification of any known interferents, including all endogenous, exogenous, technology-specific, and patient population-specific interferents, specific to the test outputs. The information must include the concentration(s) or level(s) of the interferent at which clinically significant interference was found to occur, and the concentration range or levels at which interference was not found to occur.

(ii) A detailed summary of the performance testing results of analytical and clinical performance testing, including results of concordance evaluation (overall agreement, positive percentage agreement and negative percentage agreement) as required under paragraph (b)(1) of this section.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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