4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2017-N-5651]

Medical Devices; Immunology and Microbiology Devices; Classification of the Zinc Transporter 8 Autoantibody Immunological Test System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA or we) is classifying the zinc transporter 8 autoantibody immunological 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 zinc transporter 8 autoantibody immunological 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 August 20, 2014.

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 zinc transporter 8 autoantibody immunological 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 (the 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 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 (21 U.S.C. 360c(a)(1)). 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 (PMA) 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

For this device, FDA issued an order on May 21, 2014, finding the KRONUS Zinc Transporter 8 Autoantibody (ZnT8Ab) ELISA Assay not substantially equivalent to a predicate not subject to PMA. Thus, the device remained in class III in accordance with section 513(f)(1) of the FD&C Act when we issued the order.

On June 16, 2014, KRONUS Market Development Associates, Inc., submitted a request for De Novo classification of the KRONUS Zinc Transporter 8 Autoantibody (ZnT8Ab) ELISA Assay. 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 general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on August 20, 2014, 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 866.5670. We have named the generic type of device zinc transporter 8 autoantibody immunological test system, and it is identified as a device that consists of reagents used to measure, by immunochemical techniques, the autoantibodies in human serum samples that react

with Zinc Transporter 8 (ZnT8). The measurements aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes) in conjunction with other clinical and laboratory findings.

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.--Zinc Transporter 8 Autoantibody Immunological Test System Risks and Mitigation Measures

Identified Risks	Mitigation Measures/21 CFR Section
Inaccurate test results that provide false positive or false negative results can lead to improper patient management.	Special controls (1), (2), and (3) (21 CFR 866.5670(b)(1), 21 CFR 866.5670(b)(2), and 21 CFR 866.5670(b)(3))
Failure to correctly interpret test results can lead to false positive or false negative results.	Special controls (1)(iii), (2), and (3) (21 CFR 866.5670(b)(1)(iii), 21 CFR 866.5670(b)(2), and 21 CFR 866.5670(b)(3))

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. In order 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).

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 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 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, 360*l*, 371.

2. Add § 866.5670 to subpart F to read as follows:

§ 866.5670 Zinc transporter 8 autoantibody immunological test system.

(a) *Identification*. A zinc transporter 8 autoantibody immunological test system is a device that consists of reagents used to measure, by immunochemical techniques, the autoantibodies in human serum samples that react with Zinc Transporter 8 (ZnT8). The measurements aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes) in conjunction with other clinical and laboratory findings.

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

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

(i) A detailed description of the device that includes:

(A) A detailed description of all components in the test system, including a description of the assay components in the kit and all required ancillary reagents;

(B) A detailed description of instrumentation and equipment, and illustrations or photographs of non-standard equipment or methods if applicable;

(C) Detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software where applicable;

(D) A detailed description of appropriate internal and external quality controls that are recommended or provided. The description must identify those control elements that are incorporated into the recommended testing procedures;

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

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

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

(ii) Information that demonstrates the performance characteristics of the device, including:

(A) Device precision/reproducibility data generated from within-run, between-run, between-day, between-lot, between-operator, between-instruments, between-site, and total precision for multiple nonconsecutive days as applicable. A well characterized panel of patient samples or pools from the intended use population that covers the device measuring range must be used;

(B) Device linearity data generated from patient samples covering the assay measuring range if applicable;

(C) Information on traceability to a reference material and description of value assignment of calibrators and controls if applicable;

(D) Device analytical sensitivity data, including limit of blank, limit of detection and limit of quantitation if applicable;

(E) Device analytical specificity data, including interference by endogenous and exogenous substances, as well as cross-reactivity with samples derived from patients with other autoimmune diseases or conditions;

(F) Device instrument carryover data when applicable;

(G) Device stability data including real-time stability under various storage times and temperatures;

(H) Specimen stability data, including stability under various storage times, temperatures, freeze-thaw, and transport conditions where appropriate;

(I) Method comparison data generated by comparison of the results obtained with the device to those obtained with a legally marketed predicate device with similar indication of use. Patient samples from the intended use population covering the device measuring range must be used;

(J) Specimen matrix comparison data if more than one specimen type or anticoagulant can be tested with the device. Samples used for comparison must be from patient samples covering the device measuring range;

(K) A description of how the assay cut-off (the medical decision point between positive and negative) was established and validated as well as supporting data;

(L) Clinical performance must be established by comparing data generated by testing samples from the intended use population and the differential diagnosis groups with the device to

the clinical diagnostic standard. The diagnosis of Type 1 diabetes mellitus must be based on clinical history, physical examination, and laboratory tests, such as one or more pancreatic or insulin autoantibody test. Because the intended use population for Type 1 diabetes mellitus includes subjects less than 18 years old, samples from representative numbers of these subjects must be included. Representative numbers of samples from all age strata must also be included. The differential diagnosis groups must include, but not be limited to the following: Type 2 diabetes mellitus; metabolic syndrome; latent autoimmune diabetes in adults; other autoimmune diseases such as celiac disease (without a concomitant diagnosis of Type 1 diabetes mellitus), systemic lupus erythematosus, rheumatoid arthritis, and Hashimoto's thyroiditis; infection; renal disease; and testicular cancer. Diseases for the differential groups must be based on established diagnostic criteria and clinical evaluation. For all samples, the diagnostic clinical criteria and the demographic information must be collected and provided. The clinical validation results must demonstrate clinical sensitivity and clinical specificity for the test values based on the presence or absence of Type 1 diabetes mellitus. The data must be summarized in tabular format comparing the interpretation of results to the disease status; and

(M) Expected/reference values generated by testing an adequate number of samples from apparently healthy normal individuals.

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

(2) Your 21 CFR 809.10(a) compliant label and 21 CFR 809.10(b) compliant labeling must include warnings relevant to the assay including:

(i) A warning statement that reads, "The device is for use by laboratory professionals in a clinical laboratory setting";

(ii) A warning statement that reads, "The test is not a stand-alone test but an adjunct to other clinical information. A diagnosis of Type 1 diabetes mellitus should not be made on a single test result. The clinical symptoms, results on physical examination, and laboratory tests (e.g., serological tests), when appropriate, should always be taken into account when considering the diagnosis of Type 1 diabetes mellitus and Type 2 diabetes mellitus";

(iii) A warning statement that reads, "Absence of Zinc T8 autoantibody does not rule out a diagnosis of Type 1 diabetes mellitus"; and

(iv) A warning statement that reads, "The assay has not been demonstrated to be effective for monitoring the stage of disease or its response to treatment."

(3) Your 21 CFR 809.10(b) compliant labeling must include a description of the protocol and performance studies performed in accordance with paragraph (b)(1)(ii) of this section and a summary of the results.

Dated: October 18, 2017.

Leslie Kux,

Associate Commissioner for Policy.

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