4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2026-N-3930]

Medical Devices; Immunology and Microbiology Devices; Classification of the Alzheimer's Disease Pathology Assessment Test

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is classifying the Alzheimer's disease pathology assessment test 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 Alzheimer's disease pathology assessment test. 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 4, 2022.

FOR FURTHER INFORMATION CONTACT: Woosung (David) Cho, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3461, Silver Spring, MD 20993-0002, 301-796-5998, Woosung.Cho@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the Alzheimer's disease pathology assessment test 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 November 20, 2020, FDA received Fujirebio Diagnostics, Inc.'s request for De Novo classification of the Lumipulse ***G*** β-Amyloid Ratio (1-42/1-40) 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 4, 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 866.5840.[1] We have named the generic type of device "Alzheimer's disease (AD) pathology assessment test," and it is identified as an in vitro diagnostic device intended to measure one or more analytes in human specimens to assess whether a patient presenting with cognitive impairment and being evaluated for AD and other causes of cognitive decline would test positive or negative for amyloid plaques or neurofibrillary tangles at the time of testing, as measured by FDA-approved positron emission tomography imaging agents. The device is intended to assess the underlying AD-associated pathology in conjunction with clinical assessment to increase diagnostic certainty.

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 Alzheimer's Disease Pathology Assessment Test

Identified Risks to Health	Mitigation Measures
Failure to correctly interpret test results can lead to false positive results (leading to workup and anxiety regarding a serious diagnosis that is incorrect) or false negative results (leading to delays in getting treatment and delays planning early in the course of this progressive disease)	Special controls (1) and (2)
Incorrect test results that provide false positive results (leading to workup and anxiety	Special controls (1) and (2)

[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.

regarding a serious diagnosis that is incorrect) or false negative results (leading to delays in getting treatment and delays planning early in the course of this progressive disease)	

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) (21 U.S.C. 360(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 Alzheimer's disease pathology assessment tests. 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 § 866.5840 to subpart F to read as follows:

§ 866.5840 Alzheimer's disease pathology assessment test.

(a) *Identification*. An Alzheimer's disease (AD) pathology assessment test is an in vitro diagnostic device intended to measure one or more analytes in human specimens to assess whether a patient presenting with cognitive impairment and being evaluated for AD and other causes of cognitive decline would test positive or negative for amyloid plaques or neurofibrillary tangles at the time of testing, as measured by FDA-approved positron emission tomography (PET) imaging agents. The device is intended to assess the underlying AD-associated pathology in conjunction with clinical assessment to increase diagnostic certainty.

(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 analytical performance, including precision, linearity, assay interference, cross-reactivity, detection capability, specimen and reagent stability, and hook effect, as applicable. 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 studies demonstrating clinical performance in the intended use patient population. All eligible subjects must meet the appropriate study inclusion and exclusion criteria that define the intended use population. Relevant demographic and patient characteristics must be documented, including the time from specimen collection for testing with the subject device to PET imaging acquisition; patient cognitive, neurological, and psychiatric assessments; Apolipoprotein E (APOE) carrier status; and patient education level. All specimens must be tested with the users of the subject device blinded to the disease status and PET scan results of the subject from whom the specimen was obtained. Each PET scan must use an FDA-approved PET tracer and must be independently evaluated in a blinded manner and interpreted according to the FDA-required labeling for the PET tracer. For banked specimens, details on storage conditions and storage period must be documented. In addition, documentation must include evidence to support the stability of the archived specimens for the duration of storage.

(iii) Detailed documentation of studies, which are performed using specimens from persons established to be cognitively normal, that establish the upper and lower limits of reference intervals for the output provided by the device. For banked specimens, the detailed documentation must include details on storage conditions and storage period. In addition, the detailed documentation must include evidence to support the stability of the archived specimens for the duration of storage.

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

(i) An intended use that provides a description of the measurand(s) (i.e., AD pathology biomarker(s)) the device measures in the specified human specimens, the results provided to the user (including information to facilitate clinical interpretation of all device outputs), the clinical

indications appropriate for test use, and the specific population(s) for which the device is intended.

(ii) Limiting statements indicating that:

(A) This device is not intended to be used as a stand-alone test and the test results must be interpreted in conjunction with other diagnostic tools and clinical information.

(B) The safety and effectiveness of the device have not been established for predicting development of dementia or other neurologic conditions or for monitoring the effect of any therapeutic product.

(C) A positive result is associated with the presence of amyloid plaques or neurofibrillary tangles in the brain but does not establish a diagnosis of AD as would be established by neuropathological examination.

(iii) A detailed summary of the performance testing, including results, required under paragraph (b)(1) of this section.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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