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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA-2026-N-12212]

Medical Devices; Neurological Devices; Classification of the Prognostic Assessment Software of Mild Cognitive Impairment

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the prognostic assessment software of mild cognitive impairment 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 prognostic assessment software of mild cognitive impairment. We are taking this action because we have determined that classifying the device into class II will provide a reasonable assurance of the 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 January 11, 2024.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the prognostic assessment software of mild cognitive impairment into class II (special controls), which we have determined will

provide a reasonable assurance of the 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 29, 2022, FDA received Darmiyan, Inc.'s request for De Novo classification of the BrainSee 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 the 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 January 11, 2024, 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 882.1454.[1] We have named the generic type of device "prognostic assessment software of mild cognitive impairment," and it is identified as a prescription-only device that combines information from multiple clinical data sources to produce an output indicative of the likelihood that a patient diagnosed with mild cognitive impairment will progress to more severe forms of cognitive impairment, or will develop dementia, such as Alzheimer's disease dementia, within a specified period of time. This device is intended for adjunctive use and not intended as a stand-alone diagnostic or prognostic tool.

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 Prognostic Assessment Software of Mild Cognitive Impairment

Identified Risks to Health	Mitigation Measures
Device failure or incorrect analysis leading to: • False positives or falsely high prognostic outputs resulting in inappropriate patient treatment and delayed diagnosis of non-Alzheimer's disease conditions • False negatives or falsely low prognostic outputs resulting in delayed diagnosis and/or patient treatment	Clinical performance testing; Postmarket surveillance; Software verification, validation, and hazard analysis; and Labeling

[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.

Use error or misinterpretation of results leading to: • A false positive or falsely high prognostic outputs • A false negative or falsely low prognostic outputs • Overreliance on device output for follow-up	Human factors/usability assessment; and Labeling

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of the 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, prognostic assessment software of mild cognitive impairment is for prescription use only. Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of 21 CFR 801.109 are met.

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 prognostic assessment software of mild cognitive impairment. This device is therefore subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

We have 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 part 801 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 882

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 882 is amended as follows:

PART 882—NEUROLOGICAL DEVICES

1. The authority citation for part 882 continues to read as follows:

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

2. Add § 882.1454 to subpart B to read as follows:

§ 882.1454 Prognostic assessment software of mild cognitive impairment.

(a) *Identification*. Prognostic assessment software of mild cognitive impairment is a prescription-only device that combines information from multiple clinical data sources to produce an output indicative of the likelihood that a patient diagnosed with mild cognitive impairment will progress to more severe forms of cognitive impairment, or will develop dementia, such as Alzheimer's disease dementia, within a specified period of time. This device is intended for adjunctive use and not intended as a stand-alone diagnostic or prognostic tool.

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

(1) Data obtained from premarket clinical performance validation testing and postmarket surveillance acquired under anticipated conditions of use must demonstrate that the device performs as intended when used to analyze data from the intended patient population, unless FDA determines, based on the totality of the information provided for premarket review, that data from postmarket surveillance is not required.

(i) Data provided from paragraph (b)(1) of this section must demonstrate the accuracy, precision, and reproducibility of the device for predicting progression of patients with mild cognitive impairment to more severe forms of cognitive impairment or to dementia, such as Alzheimer's disease dementia, based on a clinically relevant reference standard for the diagnosis of such disease states or conditions. The test data set must include data acquired from a patient population that is representative of the intended patient population normally seen in clinical practice. The test data set must be independent from data used in training/development of the device.

(ii) Objective performance measures (e.g., sensitivity, specificity, positive predictive value, negative predictive value) must be reported with relevant descriptive or developmental performance measures.

(2) Software verification, validation, and hazard analysis must be provided. Software documentation must include a detailed, technical description of the model/algorithm(s) and algorithm inputs and outputs.

(3) Human factors/usability assessment must demonstrate that the intended user(s) in the intended use environment can correctly use the device and interpret the device output(s).

(4) Physician labeling must include:

(i) A detailed summary of the clinical performance testing methods, including results of the performance testing for tested performance measures/metrics, selection criteria, and the patient demographics;

(ii) A description of the patient population that was used in development or training of the device algorithm/model;

(iii) Device limitations or subpopulations for which the device may not perform as expected or for whom the device has not been validated;

(iv) A statement that the device is not a stand-alone diagnostic or prognostic tool and that the device output should only be interpreted in the context of all available clinical information, including patient history, medications, and comorbidities; and

(v) Information for interpretation of the device outputs detailing the risks associated with misinterpretation of the device outputs.

(5) Patient labeling must include information explaining the device output(s) and the associated risks if the device output is incorrect.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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