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Clinical Considerations for Investigational Device Exemptions (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes

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Guidance for Industry and Food and Drug Administration Staff

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For questions about this document, contact the Neurostimulation Devices Branch at 301-796-6610.



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Preface

Public Comment

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Clinical Considerations for Investigational Device Exemption (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The U.S. Food and Drug Administration (FDA) recognizes the value of medical device innovation to address unmet clinical needs and improve patient care, particularly, when novel treatments may revolutionize how neurological diseases or conditions are treated. FDA developed this guidance to assist sponsors that intend to submit an investigational device exemption (IDE) to the FDA to conduct clinical trials on medical devices targeting neurological disease progression and clinically meaningful patient centered outcomes.

Medical devices intended to slow, stop, or reverse the effects of neurological disease (neurological devices) face challenges with regard to collecting safety and efficacy data in a clinical study, when less invasive pharmacotherapy approaches may be better understood or more-well accepted in the clinical community. The Center for Devices and Radiological Health (CDRH) is issuing this guidance for Industry and FDA staff to assist in considering the benefits and risks of medical devices that target either the cause or progression of the neurological disorder or condition such as Alzheimer's disease, Parkinson's Disease, or Primary Dystonia, rather than their symptoms, and importantly, address an unmet medical need of the patient.

FDA believes that neurological devices intended to slow disease progression and improve clinical outcomes that are meaningful to patients may represent a revolutionary option for patients. This guidance provides considerations for the research and development of such devices, as well as FDA review considerations to aid in the promotion of this innovative sector of technology.

We recommend that you use this document to help determine the types of data that may be needed to support an IDE application and to help in the design of clinical trials. The clinical considerations mentioned in the guidance represent FDA's current thinking based on the information available at this time. For this reason, we strongly suggest that sponsors who wish to conduct such studies submit a Pre-Submission to facilitate discussion of pre-clinical test protocols, clinical trial designs, and proposed indications for use. For additional information, please see the guidance document, *Request for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

This guidance is intended to apply to neurological medical devices that are designed to slow, stop, or reverse the progression of disease and result in clinically meaningful patient outcomes. This guidance provides general study design considerations for clinical trials that investigate neurological devices using biological markers and clinical outcome assessments.

III. Clinical Study Considerations

The use of intermediate clinical endpoints, surrogate endpoints, and/or biomarker tests can contribute to device development, regulatory evaluation, and ultimately, an assessment of the benefits and risks associated with a device on a shorter time scale. For purposes of this guidance, CDRH defines intermediate clinical endpoints, surrogate endpoints and biomarkers as follows:

> An intermediate endpoint is itself a clinical endpoint concerning a symptom or measure of function that is not the ultimate outcome of the disease. Improvement according to an intermediate endpoint is of value to patients even if this does not lead to reduced morbidity or mortality. An intermediate endpoint may also be a clinical endpoint measured at an earlier time point than has historically been accepted. A treatment effect shown by an intermediate endpoint may also be taken as reason to expect a favorable ultimate outcome; in this sense, the intermediate endpoint plays the role of a surrogate.
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> A surrogate endpoint is a measurement used in trials as a substitute for a clinical endpoint, and is expected to reflect clinical outcomes based on epidemiologic,

therapeutic, pathophysiologic, or other scientific evidence. For example, blood pressure measurements are sometimes used as endpoints in trials of antihypertensive therapeutics, and as a surrogate for clinical endpoints of stroke, myocardial infarction, or mortality.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or responses to a therapeutic intervention. A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that relates to an aspect of normal or abnormal biologic function or process.

However, challenges remain with use of these metrics. Identifying meaningful endpoints that measure the rate of progression of a neurological disease such as Alzheimer's disease, Parkinson's Disease, or Primary Dystonia, especially over short periods of time (e.g., on the order of weeks or months) such as during a clinical trial can be subtle and difficult to assess. Similarly, biological markers may not be accompanied by clinically meaningful observable changes. These considerations become especially important when patients forgo currently approved treatments in earlier stages of disease, and in some cases undergo a more invasive treatment, when less invasive pharmacotherapy treatments exist and may be better understood.

This guidance is intended to leverage advances in the state of science and facilitate more efficient device development and regulatory evaluation to promote innovative devices to market that are reasonably safe and effective.

A. Biological Markers and Clinical Endpoints

Biomarker tests that rely on biological imaging assessments (e.g., MRI) have been proposed as candidates for measuring disease progression. However, changes in any specific imaging modality alone may not represent a fundamental change in the underlying cause or progression of a given disease because anatomical changes do not always correlate with neurological disease progression or more importantly, clinically meaningful benefits to the patient. Nevertheless, clinically meaningful outcomes may require longer periods of time to evaluate (e.g., years). Therefore, both could provide important evidence for medical devices that target neurological disease cause or progression and address an unmet clinical need.

1. Biomarker Tests

Biomarker tests can objectively measure and evaluate normal biologic processes, pathogenic processes, or responses to a therapeutic intervention. Neurological biomarkers may include biological proteins, neurotransmitters, amino acids and metabolites in the blood, cerebrospinal fluid, or brain parenchyma. In the context of neurological disease, a biomarker test would measure the physiologic response (i.e., neurological biomarkers) to a therapeutic intervention. When biomarkers are chosen as a metric, there should be well established evidence and agreement in the clinical community that the chosen biomarker test reflects a characteristic that is important to

the underlying disease process and that it is associated with a clinically meaningful outcome measure. It is therefore important that supporting studies for the validation of biomarker tests used in previous clinical trials be included in the proposals submitted. The FDA's Medical Device Development Tools (MDDT) program is one way to qualify tools (e.g., biomarker test) that medical device sponsors can use in the development and evaluation of medical devices (http://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/default.htm). The context of use depends on the product area, the stage of medical device development, and the role of the tool in device evaluation.

2. Clinical Outcome Assessments

Clinical outcome assessments should consist of direct quantitative measurement of the effect of a treatment upon disease progression and its impact upon the patient. Clinical outcome assessments include patient-reported, clinician-reported, and observer-reported outcomes such as symptom reduction, decreased need for medication, or improvement in functional and quality of life measures. However, changes in the clinical features of a neurological disease may only represent the symptomatic effect of an intervention and this should be considered when designing a study (e.g., concurrent use of biomarker tests to objectively measure and evaluate a treatment may also be appropriate). The patient population, the nature of the underlying condition, and how they will be studied over time should be considered when developing clinical effectiveness endpoints. Any rationale for use of a specific clinical outcome assessment should address the above points. Additionally, investigational treatment approaches should incorporate standard care regimens or evaluate the investigational device compared to standard care regimens, including trials designs that involve symptomatic treatment so patients may continue to treat their underlying conditions. The labeling of the device should be consistent with the manner in which it was studied.

B. Trial Designs: Study Approaches and Limitations

Distinguishing between symptomatic and disease-altering treatments may be challenging, since a positive outcome in one (symptomatic benefit) may or may not be related to the other (treatment of the underlying disease or condition). Study designs should aim to distinguish between symptomatic benefit(s) and disease-altering benefit(s) that slow disease progression and quantify the magnitude of such benefits in terms of biomarkers and clinical outcome assessments. In some cases, studies may be prolonged due to the desire to understand disease progression in the target patient populations where other therapies exist and have proven effectiveness.

Depending on the study objectives, trial designs may be considered for determining whether or not a device can slow the progression of a neurological disease by using biomarker tests and providing clinical outcome assessments for patients. FDA advises early engagement with CDRH through the Pre-Submission process to obtain more detailed feedback for a particular device and related trial designs intended to target disease progression and clinical outcomes.

C. Investigational Plans

An IDE application must include the complete investigational plan or, where appropriate, a summary of the investigational plan (21 CFR 812.20(b)(2)). Investigational plans must also include a description of the device and its important components (21 CFR 812.25(d)).

A written overview describing all anticipated phases of the clinical investigation (e.g., feasibility and pivotal study stages) should be included, outlining the studies planned at each phase and describing any plans to pool data from more than one phase. Specifically, a detailed description of the initial feasibility study (i.e., study to define clinical metrics or device design) should be provided, including an overview of later phase studies, if these studies are already in the planning stages.

For each planned clinical study, the following should be provided:

- the proposed indications for use, which should include the target population;
- the study type (e.g., pivotal, expansion [i.e., continuation of a feasibility or pivotal study], or feasibility trial);
- the design of the study, including objectives, any masking, randomization, and controls (e.g., best medical management, delayed time-to-treatment in the control arm in comparison to active treatment);
- the total time planned for subject follow-up;
- the number of subjects you plan to enroll (sample size);
- the number of investigational sites, both inside and outside the U.S.;
- the subject inclusion and exclusion criteria;
- primary safety and effectiveness endpoints described as specific objective clinical targets;
- a study plan detailing tests and testing methodologies you plan to test in the subjects;
- a schedule/time table of all clinical tests to be performed for pre- and post-operative evaluation of the subjects. We recommend you evaluate subjects at intervals that are appropriate for distinguishing between symptomatic and disease progression effects; and
- the participating investigators, if known.

D. Safety

Due to the potential risk of participating in a medical device study evaluating disease progression and related clinical outcome assessments, examining patient safety is particularly important. Surgical complications (if any) and perioperative as well as longer-term adverse events should be captured. The choice of a primary safety endpoint and tracking potential adverse events will depend on the device design and the patient population for which the device is indicated. Furthermore, there should be a clearly delineated protocol of reporting and adjudicating adverse events, including mortalities related or not related to the study's treatment and/or procedure, to the Data and Safety Monitoring Board (DSMB), Institutional Review Board (IRB) and/or FDA. In cases where a medical device may already be currently marketed, when possible, safety information should be leveraged when studying the device for a new indication.

A risk analysis should also be part of any study, including steps to mitigate risks as well as identify the most likely types of adverse events and acceptable levels for the most probable and the most serious adverse events.

E. Benefit-Risk Considerations

FDA recommends using a benefit-risk framework to facilitate the incorporation of evidence and knowledge from different domains—clinical, nonclinical, and patient perspective —to support a comprehensive, balanced decision-making approach. The framework should focus on device technology, relevant facts, uncertainties, and key areas of judgment to add clarity and predictability to the regulatory process.

FDA may approve an IDE application where only a subset of the eligible study subject population would accept the risks as weighed against the benefits, provided there is enough information and an adequate informed consent process in place for study patients to make informed decisions.

It is important to acknowledge that individual patient preferences vary, and that a patient may not assign the same values to various risks and anticipated benefits as their physician, family member, or other individual. Furthermore, patient preferences vary, both in preferred modality of treatment/diagnostic procedure (often devices are one option to be considered in a treatment care path which may include surgery or medication), as well as in risk tolerance. Some patients are willing to take on higher risks to potentially achieve a small benefit, whereas others are more risk averse. In certain circumstances, some patients may be willing to participate in clinical studies that offer no or limited direct benefit to subjects, but have anticipated societal benefits in advancing medical science.

FDA may disapprove an IDE application if there is reason to believe that the risks to the subjects outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained.[1] Assessment of benefits and risks should not necessarily be made in comparison to the most technologically advanced alternative but rather to commonly used therapies and treatments.

The factors considered when making benefit-risk determinations of medical device submissions seeking premarket approval or *de novo* classification are detailed in *Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM517504.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery). FDA reviews these submissions to determine whether "the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device."[2] FDA staff review this information and determine whether the probable benefits of the device outweigh its probable risks. In the context of medical devices targeting neurological disease progression, the potential long term benefit of using a neurological device to slow the progression of disease is a significant factor to consider. At the same time, patients who forgo currently approved treatments in earlier stages of disease, and in some cases undergo a more invasive treatment, when less invasive pharmacotherapy treatments exist and may be better understood, potentially take on greater risk(s) in managing their disorder or condition. FDA recognizes that patient tolerance for risk for potential benefit will vary depending on a number of factors, including the nature of their disease or condition and the availability of existing treatments, as well as the risks and benefits of the proposed intervention. FDA encourages any sponsor that is considering developing such devices to have early interaction with the appropriate FDA review division. Assessing probable benefits and probable risks is an essential part of FDA's evaluation of devices targeting neurological disease progression and clinical meaningful patient centered outcomes.

IV. Informed Consent Documents

Clinical investigations are required to comply with 21 CFR parts 50 and 56 regarding informed consent and IRB review when the data support applications or submissions to FDA. Informed consent documents provide potential participants adequate information to consider when deciding whether or not to participate. FDA believes that, in most cases, neurological devices targeting the progression of disease are significant risk devices as defined in 21 CFR 812.3(m).

[1] 21 CFR 812.30(b)(4).
[2] Section 513(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Sponsors intending to study the safety and effectiveness of these devices in a clinical investigation in the United States must therefore submit an IDE application to FDA and obtain IRB approval for their studies (21 CFR 812.2). Your IDE application must include a copy all information to be provided to subjects to obtain informed consent (21 CFR 812.20(b)(11)). In your application, we recommend that you explain your method of administering the informed consent documents.

Your informed consent documents must contain the elements specified in 21 CFR 50.25. We recommend that an informed consent document for a neurological device targeting the progression of a disease describe:

- the possibility that the proposed treatment may have little or no effect upon halting or delaying the progression of the disease, or could increase rate of progression;
- options for discontinuing participation in the study should the subject be dissatisfied with the study; and
- the potential need for long-term follow up to evaluate the effect of the treatment.

V. Labeling

Investigational plans are required to include copies of all labeling, including patient information, for the device (21 CFR 812.25(f)). Labeling of investigational medical devices must comply with 21 CFR 812.5.

A. Indications for Use

The labeling should be consistent with the indications for use statement that identifies the intended patient population. For neurological devices targeting the progression of a disease and clinical outcomes, the target population should be a disease population that may substantially benefit from using the device and early onset disease populations may present one population of candidates to study disease progression and its impact on patients.

B. Warnings and Precautions

The labeling must describe all relevant hazards, adverse effects, interfering substances or devices, warnings, and precautions (21 CFR 812.5(a)). For example, your labeling should alert users to potentially injurious outcomes associated with use or misuse of the device, including a lack of clinical benefit, and should describe actions users should take to avoid potentially injurious events.