Guidance for Industry and Food and Drug Administration Staff

Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems

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Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices
Neurodiagnostic and Neurotherapeutic Devices Branch

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Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers lane, rm. 1061, (HFA-305), Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

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1. Introduction

This guidance document was developed as a special controls guidance to support the classification of Repetitive Transcranial Magnetic Stimulation (rTMS) systems for the treatment of Major Depressive Disorder (MDD) into class II (special controls). A rTMS system is an electromagnetic device that non-invasively delivers a rapidly pulsed magnetic field to the cerebral cortex in order to activate neurons within a limited volume without inducing a seizure. The device is intended to be used to treat patients meeting clinical criteria for MDD as defined in the Diagnostic and Statistical Manual of Mental Illnesses, Fourth Edition (DSM-IV). This guidance is issued in conjunction with a Federal Register notice announcing the classification of rTMS systems for the treatment of MDD.

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of rTMS systems for the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. Thus, persons who intend to market a device of this generic type must (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with repetitive transcranial magnetic stimulation systems identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification regulation and product code for rTMS systems (Please refer to **Section 2. Scope**). In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, when followed and combined with the general controls, will generally address the risks associated with rTMS systems for the treatment of MDD and lead to a timely 510(k) review. This document supplements other FDA documents regarding the content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87 and the guidance, **Format for**

Traditional and Abbreviated 510(k)s;[1]

Designation of this document as a special control means that any firm currently marketing or intending to market, repetitive transcranial magnetic stimulation (rTMS) systems for the treatment of MDD will need to address the issues covered in this special controls guidance. The firm will need to show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provide equivalent assurances of safety and effectiveness.

2. Scope

The scope of this document is limited to the repetitive transcranial magnetic stimulation (rTMS) system, (21 CFR 882.5805 and product code OBP) described below.

21 CFR 882.5805 Repetitive Transcranial Magnetic Stimulation (rTMS) System

A repetitive transcranial magnetic stimulation (rTMS) system is an external device that delivers repetitive pulsed magnetic fields of sufficient magnitude to induce neural action potentials in the prefrontal cortex to treat the symptoms of major depressive disorder (MDD) without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.

3. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the rTMS system addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device and include the results of this analysis in your 510(k). If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, then you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Mitigation Measures
Failure to identify correct patient population	Section 10. Clinical Testing Section 11. Labeling
Ineffective treatment	Section 5. Nonclinical Analysis and Testing Section 9. Software Life Cycle and Risk Management

[1] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm

Identified Risk	Mitigation Measures
	Section 10. Clinical Testing Section 11. Labeling
Seizure	Section 5. Nonclinical Analysis and Testing Section 10. Clinical Testing Section 11. Labeling
Scalp discomfort, scalp burn, or other adverse effects	Section 5. Nonclinical Analysis and Testing Section 9. Software Life Cycle and Risk Management Section 10. Clinical Testing Section 11. Labeling
Magnetic field effects on functioning of other medical devices	Section 5. Non-clinical Analysis and Testing Section 11. Labeling
Adverse tissue reaction	Section 6. Biocompatibility
Hazards associated with electrical equipment	Section 7. Electrical Equipment Safety Section 11. Labeling
Hazards caused by electromagnetic interference and electrostatic discharge hazards	Section 8. Electromagnetic Compatibility Section 11. Labeling
Hearing loss	Section 11. Labeling

4. Device Description

We recommend you identify your device using the regulation and product code described in **Section 2. Scope**, and provide a complete description of your rTMS system. You must provide information to show how the new device is similar to and different from the legally marketed predicate device ("predicate device") (21 CFR 807.87(f)). Side by side comparisons, whenever possible, are desirable; for example, we recommend you use a tabular format such as shown below in **Table 1. Example of a Device and Predicate Comparison**. We also recommend that you describe how any differences between your device and the predicate device may affect the comparative safety and effectiveness of your device.

Table 1. Example of a Device and Predicate Comparison

DESCRIPTIVE INFORMATION	DEVICE	PREDICATE DEVICE
Area of brain to be stimulated		
Applicator: Configuration Diameter		

DESCRIPTIVE INFORMATION	DEVICE	PREDICATE DEVICE
Core material		
Output Stimulation Parameters: Amplitude in Standard Motor Threshold (SMT) units Pulse width (± accuracy) Frequency (± accuracy) Pulse train duration (± accuracy) Inter-train interval (± accuracy) Trains per session Maximum number of pulses per session (cumulative exposure)		
Physical unit of amplitude setting (e.g., coil current, peak magnetic field) at coil and its relation to the SMT unit		
Magnetic Field: Peak magnetic field strength at 2 cm Maximum dB/dt		
Temperature on surface at maximum output		

The Maximum Safe Train Duration Limits for Avoiding Seizure, described in Table 2, are based on literature articles by Wassermann[2] and Rossi[3]. Pulse train durations that are above certain limits increase the risk of seizures.[3] The recommended maximum train duration (in seconds) for healthy adults for the intensity (% of Motor Threshold) levels and frequencies are shown in Table 2. See Appendix A for discussion of terms used in Table 2. Note that the paper by Wassermann[3] and this guidance document address safe limits for the use of rTMS when used as a stand alone therapy.

You should indicate whether your device falls within the limits listed in Table 2. If your device does not fall within these parameters, FDA may recommend that you provide data from a clinical study to demonstrate that your device's output parameters are as safe as those of the predicate device. See **Section 10. Clinical Information**.

[2] Wassermann, E, et al. "Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996," *Electroencephalography and clinical Neurophysiology* 108 (1998) 1–16.

[3] Rossi S et al. "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research", *Clinical Neurophysiology* 120 (2009) 2008–2039.

Table 2. Maximum Safe Train Duration (seconds) Limits for Avoiding Seizure

Freq (Hz)	**INTENSITY** (% of Motor Threshold)													
	80-100	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Your device description should also include:

- the area of the brain to be stimulated (e.g., motor cortex);
- an illustration or photograph that shows the positions and orientations of the stimulating coil when stimulating the identified location; and
- a complete listing and description of all of the device components and accessories (e.g., console, treatment coil, user interfaces, data management systems, cables).

In addition, you should include the following information describing your device.

Coil Positioning

You should describe the features of your device intended to ensure the repeatable delivery of rTMS treatment. You should discuss the design features that are used for positioning the coil and patient for rTMS treatment. This discussion should also describe how you have ensured positioning consistency and repeatability.

You should describe the method used for determining the strength of the magnetic field flux needed for therapy. If your device relies on motor threshold (MT) for determining the magnitude of the output, you should describe the design features that are used for positioning the coil for locating the MT position and how you have ensured its positioning repeatability. The procedure for determining MT location should result in a reproducible and accurate MT location in order to ensure reliable MT level setting and, if used to identify the treatment location, to provide repeatable navigation for treatment when performed by different clinicians. Moreover, the setting for your device should be traceable to a reproducible physical parameter (see Magnetic Field Characteristics, below).

You should also describe the method used to ensure that the coil is in proper position and contact with the patient's head during MT and rTMS treatment procedures. This should

include a description of any design features (e.g., sensors, alarms) used to ensure proper contact and position. This should be included in the device labeling. The magnetic field decreases quickly with distance from the face of the treatment coil, therefore any loss of contact may result in changes in effectiveness.

Magnetic Field Characteristics

We recommend you describe the physical characteristics of the magnetic field produced by your device and compare them to those of the predicate device. You should also include a description of the method used for these measurements and how they have been validated. If the physical characteristics (including differences in spatial and temporal characteristics) of your device's magnetic field differ from the predicate's magnetic field, you should provide valid scientific evidence that these different technical characteristics do not affect the safety or effectiveness of your device, as compared to the predicate device. You should provide a description and comparison of the following to the predicate device:

- pulse shape, timing, width, and amplitude;
- spatial distribution of the output level; and
- linearity of the output level.

Output Waveform

We recommend you provide oscilloscope tracings of the signal magnetic output waveform (with the applicator attached) over the device's range of output settings (including minimum, maximum, and a sampling of intermediate settings). You should identify all salient features of the waveform (e.g., pulse width) and specify the horizontal and vertical oscilloscope gain settings. In addition, you should supplement the oscilloscope tracings with a graphical representation of the output waveform with all stimulation parameters and temporal characteristics clearly labeled. In addition to graphical representations, a tabular format that summarizes the output specifications is desirable.

Magnetic Field Spatial Distribution

We recommend you provide the dimensions of the treatment target stimulation volume and its location relative to the applicator. If the spatial distribution differs from that of the predicate device, you should explain how your device is as safe and as effective as the predicate device despite the difference. Field spatial distribution measurement should include a 3-dimensional array of points using a calibrated test fixture that measures either the electric or magnetic field for clinically relevant locations. You should include the rationale supporting your selection of sample locations and grid spacing. Testing should include the magnitude of the field in the area of the stimulation volume, near the coil surfaces, and areas where there may be local field maxima outside the intended stimulation volume. You should define your stimulation volume as the region within the Standard Motor Threshold (SMT) set at 1.0.

Magnetic Field Strength Gradient

You should provide a measurement of the ratio of the maximum dB/dt (time rate of change of the magnetic field strength) at the surface of the scalp versus dB/dt at an appropriate reference point in the brain.

Scalp stimulation may result in cutaneous pain and could affect the tolerability of the rTMS procedure. rTMS devices may mitigate the surface field using differing methods. A ratio of peak dB/dt on the scalp relative to peak dB/dt at the selected reference point below the scalp may help to characterize resulting differences in performance. We recommend you measure this ratio and compare it to the predicate device. In addition, we recommend that you provide a calibration curve between the settings on your device and measure the magnetic field strength at an appropriate standard location and compare this to the predicate device.

Device Compatibility

If your device is labeled as compatible with other medical devices (including active and passive implants), you should provide data to establish the safety of using your device with those devices. The pulsed rTMS magnetic field has the potential of interacting with pacemakers and other active implanted devices, potentially causing their malfunction and subsequent patient injury.

Safety Features

We recommend that you describe the safety features of your device as follows.

You should include a description of the design features and components incorporated into the device to prevent overheating. Your description should discuss the potential for the applicator to become overheated during treatment, which presents a risk of burns to the patient.

You should describe any alarms included to ensure safe operation; provide the default alarm limits; and indicate whether limits can be adjusted by the user.

You should describe the method used by your device to recall treatment history, such as prior patient treatment settings. rTMS treatment may require several sessions with the treatment coil located at the same position on the head and with stimulation at the same level as at previous sessions. The determination of MT level and treatment location is typically not repeated at every session. Therefore, recall of previous treatment settings is important for delivery of the appropriate rTMS treatment at the correct location.

You should also describe features and quality measures included in your system to ensure proper system output for each treatment and from unit-to-unit. rTMS system output could change over time due to component failure or drift, which may be difficult for the user to detect. The inability to detect component failure or drift may affect the safety or

effectiveness of rTMS treatment. Therefore, we recommend the device include a means to validate the delivery of the magnetic field at each treatment session and from unit-to-unit to reduce the chance of inadequate treatment.

The consensus concerning the limits of safe rTMS in terms of the risks of seizure induction (Wassermann, 1998[3]) is cited in **Section 4. Device Description**. The limits depend upon the amplitude of stimulation, pulse frequency, and duration of the pulse train. See **Appendix A. Definitions and Units of Measurement** for more details regarding known safe limits of rTMS. If the output parameters (amplitude, frequency, train duration) of your device exceed these established limits and exceed those of the predicate device, you should provide further evidence of safety that may include clinical data. Note that the paper by Wassermann[3] and this guidance document addresses safe limits for the use of rTMS when used as a stand alone therapy.

5. Non-Clinical Analysis and Testing

For each test, you should provide:

- a description of the test methodology;
- the test objective;
- equipment used;
- number of samples tested;
- test specifications;
- standards to which conformance is demonstrated;
- pass/fail criteria;
- a rationale for the appropriateness of any consensus standards used;
- a summary of the results (including generated data), including an analysis explaining how the testing results demonstrate that the device performs as intended; and
- a description of test failures.

If any test failures were identified and samples of the device modified as a result, you should provide the results from the new testing with the modified samples.

You should also provide a summary of the testing that you performed, tabular format is desirable. We recommend you include the following:

- the test (e.g., electrical characterization, electromagnetic compatibility (EMC));
- the test method;
- the mode of device operation during the test;
- acceptance criteria;
- the standard to which conformance was demonstrated; and

- the location of the test report in the submission.

6. Biocompatibility

You should select biocompatibility tests appropriate for the duration and nature of contact with your device. We recommend you conduct biocompatibility testing on any patient contacting materials used in your device as described in the FDA guidance, **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**[4] for external devices in contact with the skin for a limited duration (i.e., less than 24 hours). If you use materials in your device that are *identical* to your predicate device and have the same body contact classification (e.g., surface, external communicating, implant) and duration of patient contact (e.g., limited, prolonged, permanent), you may identify the predicate device and leverage previous biocompatibility data in lieu of performing new biocompatibility testing. FDA recognizes that it is difficult to document that materials in your device and a predicate device are identical with respect to composition and manufacturing processes. Therefore, if you have documentation to support the identical nature of the materials, we recommend the following statement for biocompatibility certification of previously used materials:

> *The [polymer/metal/ceramic/composite name] [component name] of the [subject device name] is identical to the [component name] of the [predicate device name] as it was approved/cleared in [PMA/510k/IDE number, approval date] in formulation, processing, and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.).*

7. Electrical Equipment Safety

We recommend that you demonstrate the electrical and mechanical safety of the device by performing electrical and mechanical safety testing as described in the FDA-recognized standard, IEC 60601-1, Medical Electrical Equipment – Part 1: General Requirements for Safety or by an equivalent method.

8. Electromagnetic Compatibility (EMC)

You should perform testing for electromagnetic compatibility for all device output modes. The testing should include:

- a clear summary of all EMC testing (emissions and immunity) of this device with the test results and data to support any claims for immunity to electromagnetic interference (EMI);

- a brief explanation of how each EMC test was performed and how the testing for each

[4] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm

mode addresses the risks for EMI and demonstrates EMC to the claimed levels;

- a brief explanation of how the testing addresses the timing of the device for therapy delivery;
- references to appropriate EMC testing standards (e.g., FDA-recognized, IEC 60601-1-2:2001 Standard for Medical Electrical Equipment) along with explanations and justifications for any deviations from the referenced standards or modifications to the device tested;
- pass/fail criteria for each EMC tests, how these were quantified and measured, and justifications for these criteria.

Wireless Technology

If the device incorporates Radio-Frequency (RF) wireless technology to perform some of its functions, you should address safety and effectiveness concerns involving the wireless technology.

9. Software Life Cycle and Risk Management

We recommend that you submit the information for software-controlled devices described in **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices** (the Software Guidance).[5] The kind of information we recommend you submit is determined by the "level of concern," which is related to the risks associated with software failure. The level of concern for a device may be minor, moderate, or major. FDA believes that the software used to operate a rTMS device presents a "moderate level of concern" as described in the Software Guidance because a failure or latent design flaw could either directly result in minor injury to the patient or operator or could indirectly result in minor injury to the patient or operator through incorrect or delayed information or through the action of a care provider..

10. Clinical Testing

Clinical testing will generally be needed for new devices, unless the proposed device is sufficiently similar to the predicate device in terms of indications, device specifications, and energy output, such that reliance on bench and/or animal testing may be sufficient. In cases where clinical testing is needed, FDA recommends that the clinical study be designed to demonstrate the substantial equivalence of safety and effectiveness of your device when used as described in the Indications for Use statement. Sponsors must conduct clinical studies in compliance with 21 CFR parts 50, 56, and 812. Recommendations for a clinical study are

[5] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf

provided below.[6]

The clinical trial design should address the concerns discussed below.

Indication for use: The indication for use should identify the patient population for whom the device is indicated, including the DSM-IV diagnosis, treatment severity, and medication resistance.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria should characterize the population for the proposed indication for use. Your inclusion and exclusion criteria should specify the DSM-IV diagnosis, medication resistance and treatment severity. Due to safety concerns, we recommend you exclude subjects who have any metal implanted in the head (except the mouth), e.g., subjects with cochlear implants, implanted brain stimulators, ocular implants, aneurysm clips or stents. In addition, you should address other subject characteristics, including:

- age,
- comorbid psychiatric and neurological disorders,
- pregnancy,
- length of current episode, single or recurrent episode,
- baseline depression severity, based on validated depression scale,
- risk of suicide, based on a validated suicide severity scale,
- prior treatment with antidepressant therapies. Dose and duration of antidepressant trials should be documented using an antidepressant treatment history form (ATHF),
- cardiac pacemakers, cardioverter defibrillators, or neurostimulators,
- implanted medication pumps or intracardiac lines,
- significant heart disease, cerebrovascular disease, or hearing loss,
- history of epilepsy, cerebrovascular disease, dementia, head trauma, increased intracranial pressure, or central nervous system (CNS) tumors.

Treatment parameters: Treatment parameters should be standardized and should be specified in detail in your protocol. You should include a description of the method and timing of motor threshold determinations, identification of treatment location (e.g. dorsolateral prefrontal cortex), and the specific technical parameters for stimulation. You should specify the number and frequency of treatments and overall duration of treatment exposure. Treatment parameters that exceed those prescribed in Table 2 will require adequate justification and risk assessment. FDA recommends you provide details about whether treatment sessions will be individualized (i.e., whether treatment parameters will be adjusted based on the study subject response). Subjects should be required to wear earplugs during the treatment sessions.

[6] We recommend that you request the Agency's review of your protocols prior to initiating clinical studies for your device. This process may help ensure that any issues are addressed prior to submitting your premarket submission. To request the Agency's review of your protocols, you can submit a pre-submission to the Agency.

Study design: FDA recommends a prospective randomized double blind sham-controlled multicenter study, since the specific parameter of the rTMS signal that is correlated with the beneficial clinical effect has not been determined. Due to placebo effects in depression studies, the control group condition should be designed such that unblinding does not occur due to stimulation induced side effects.

Due to clinical variations in the severity of depression, we recommend that you incorporate a baseline phase, prior to the randomized phase of the study. When withdrawing subjects from antidepressant therapies, you should follow the drug manufacturer's labeling regarding the time period that is necessary to assure that the antidepressant medications has been washed out. Multiple baseline depression assessments should also be performed to assure that the subject's depression has stabilized.

Since depression is a chronic disease, the length of the randomized phase of the trial and the follow-up phase should be of sufficient duration to demonstrate a clinically meaningful effect on depression and be consistent with standard of care. FDA also recommends that the adequacy of blinding be assessed.

Device effectiveness: You should specify the primary and secondary effectiveness endpoints for the study. Endpoints should be chosen to assure a clinically meaningful effect.

Validated depression assessment scales should be used as the primary endpoint. FDA recommends that a comparison of the proportion of subjects who meet the criteria of response and remission in both the active and control groups be performed. In addition, FDA recommends that you assess a patient reported outcome such as quality of life as one of your secondary endpoints. Additional outcome measures should include patient global impression of improvement and clinician global impressions of improvement and severity.

Device safety: Clinical studies conducted in the US must comply with the applicable reporting requirements of 21 CFR 812.150(b). For clinical studies of rTMS devices, device safety data should include the incidence of serious adverse events, e.g., worsening depression, suicidal ideation, suicide attempt, suicide, switching to hypomania/mania, seizure, death, and device malfunction resulting in patient or operator injury. FDA recommends that the protocol includes a suicide severity rating scale, such as the Columbia Suicide Severity Rating Scale[7], to assess both suicide intent and behavior.

You should also collect incidence of common adverse events such as headache, application site pain, and discontinuation rate due to adverse events. We recommend that you collect targeted safety outcomes for auditory threshold, such as pre- and post- audiograms, and cognitive function. You should also determine the severity and duration of each adverse event. Data on each adverse event should include information about the intervention that was performed and whether the event was resolved.

[7] See http://www.cssrs.columbia.edu

Training: You should describe any training provided to study investigators, including both training on the use of the device and on any assessment tools. Supporting information to substantiate an adequate level of training should be provided, such as a pre-study reliability certification program and reliability assessment for clinical raters during the study.

Reporting of Statistical Outcomes for Clinical Study Results

The following study design features should be stated clearly in the study protocol document.

Sample Size Estimation

You should provide a sample size calculation that specifies an acceptable type I error and power, the anticipated minimum detectable treatment difference for superiority studies, and the anticipated control and treatment results and an agreed-upon non-inferiority margin for non-inferiority studies.

Hypotheses

You should specify your null and alternative hypotheses. Your statistical hypothesis should describe the specific statistical model proposed for the main analysis and any relevant secondary analyses.

Randomization and Blinding

You should describe an *a priori* method of randomization and provide a method to ensure integrity of the study blind in detail. We recommend that you assess the adequacy of blinding, by asking patients to guess their treatment group and the reason for their guess. In addition, we recommend that you perform sensitivity analyses, such as examining the correlation between adverse events and the observed treatment effect to examine the possibility of unblinding due to adverse events.

Effectiveness Assessments

You should include an overall assessment of safety and effectiveness. In your assessment you should report:

- the primary efficacy endpoint which should be based on a validated assessment tool;
- the secondary efficacy endpoints which should also be based on validated assessment tools and should assess any benefits for which you plan to claim effectiveness; and
- the standardized effect size for continuous outcome measures and/or the number-needed-to-treat (NNT) for categorical endpoints.

Statistical Analysis Plan

Analysis populations: The preferred analysis population for a superiority study is the intent-to-treat population, consisting of all subjects as originally randomized. For non-inferiority studies

with an active control, you should base the determination of effectiveness on the intent-to-treat populations. In addition, supporting analyses should include per-protocol and as treated analyses. A per-protocol population refers to patients with no protocol violations and complete follow-up. As-treated, although similar to intent-to-treat, refers to all patients, but is grouped according to the treatment actually received not the randomization assignment.

Primary and secondary endpoints: You should report the primary and secondary endpoints, comparing the results of the active group to the control group. For depression studies, we recommend that you report change as a continuous measure, as well as the rate of response, defined as a 50% reduction on the assessment scale, and also the rate of remission.

If you wish to make any labeling claims based on your secondary endpoints, you should prespecify a statistical method to control multiplicity, such as a hierarchical testing order or the step-down method of Holm.

Missing data: Your study analysis plan should include methods for handling missing data. This includes imputation methods, such as multiple imputation, and sensitivity analyses, such as imputing various proportions of missing outcomes (of a binary endpoint) as "successes" or "failures."

Covariate Analysis: We recommend you specify methods for handling significant covariates in the statistical model. For any covariate term included in the proposed statistical model to evaluate effectiveness, we recommend you investigate a treatment group by covariate interaction. If such an interaction term is found to be statistically significant, your statistical summary should include a discussion of the implication of the statistically significant interaction on the overall interpretation of the study results.

Treatment by site interactions: Multicenter studies should include a measure to assess any significant treatment by center interaction on the primary effectiveness measure. We recommend both treatment and control groups be studied at the same site(s). We also recommend you apply an appropriate randomization blocking procedure to balance the number of subjects in each participating center between control and treatment groups in order to facilitate an assessment of the poolability of data across centers. In addition, your statistical analysis section should include a discussion of the importance of any statistically significant treatment-by-site interaction to the overall interpretation of the study results.

Reporting Results from Journal Articles or Meta-analyses

If applicable, safety results obtained with the rTMS device that were reported in the medical literature should be summarized and included in the premarket notification. In addition, effectiveness data for your rTMS device for your indications for use that are available from journal articles or meta-analyses may be submitted as supportive information.

11. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the applicable requirements of 21 CFR Part 801.[8] For the rTMS system, such labeling includes patient labeling (described below) with instructions to the physician to provide the patient labeling to the patient so that the practitioner who is licensed by law to administer the device can use the device safely and for the purpose for which it is intended (21 CFR 801.109(c)).

Directions for Use

The labeling should include an operator's manual with clear and concise instructions that delineate the technological features of the specific device and how the device is to be used. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Coil Positioning

Labeling should describe how to determine the rTMS treatment location in sufficient detail for the user to understand how to identify, transition to, and record any coordinates needed for reproducible positioning from session to session.

Safety Instructions

You should describe any safety features included to address the risk of seizure. We recommend that the rTMS device have features that allow:

- rapid access to the patient;
- immediate termination of pulsing;
- rapid removal of the coil from the patient; and
- the ability to place the patient in a safe position for seizure management.

Users of the device should monitor patients for seizures by:

- electromyography (EMG) monitoring of contralateral abductor pollicis brevis or first dorsal interosseous activation; or
- electroencephalography (EEG) monitoring for after-discharges during rTMS sessions; or
- visual and/or video monitoring for signs of seizures or muscle twitching.

[8] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

Instructions for seizure management procedures should include:

- presence of physician or nurse trained in seizure management;
- presence of or ready access to, life-support equipment (oxygen, suction, blood pressure monitor, intravenous equipment, CPR equipment); and
- access to anti-seizure medications.

Indication for Use

The labeling should include an indication for use that is consistent with that described in 21 CFR 882.5805 (see Section 2. Scope). The labeling should also contain a description of the clinical trial population that identifies the study population according to treatment severity and duration of disease.

Contraindications

The contraindications section of the labeling should address the concerns related to implanted electronic devices and electrical conductive objects as described below. Each contraindication in the labeling should describe the consequences of contraindicated use.

Metallic Objects in or near the Head

rTMS devices are ***contraindicated*** for use in patients who have conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death.

Implanted Stimulator Devices in or near the Head

rTMS devices are contraindicated for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death.

Warnings

The warnings section of the operator's manual should address the concerns described below.

Worsening Depression or Suicidality

Labeling should include a warning, presented in bold text, regarding the risk of worsening depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior during treatment. Labeling should also warn that patients undergoing treatment should be observed closely for clinical worsening and suicidality

and, if worsening of symptoms continues, physicians should consider discontinuing rTMS treatment.

Risk of Ineffective Therapy

The labeling should include appropriate warnings (consider using bold text) for use in patient populations where efficacy has not been established and where treatment may represent a risk to the patient.

The therapeutic effects of rTMS are known to require several treatments over a period of time, therefore we recommend labeling warning against use in response to acute cirumstances.

Implants Controlled by Physiological Signals

The labeling should include a warning regarding the possible effects of the rTMS device when used in patients who have implanted devices that are activated or controlled in any way by physiologic signals, irrespective of the distance from the treatment coil. This includes patients with pacemakers and implantable cardioverter defibrillators (ICDs), as well as patients using wearable cardioverter defibrillators (WCDs), even if the device is removed, due to the potentially unstable cardiac condition of such patients. Use could result in serious injury or death.

Medical Devices Containing Electronics or Ferromagnetic Material

The labeling should include a warning regarding the possible effects of the rTMS device on devices implanted or located in areas of the body near the magnetic field if they contain electronics or ferromagnetic materials. The warning should describe the appropriate distance between the rTMS device and other devices, so the magnetic field does not cause movement, heating, or dysfunction of these other devices.

Wearable/Removable Medical Devices, Conductive Objects and Other Devices

The labeling should include a warning that wearable/removable medical devices, other devices or conductive objects (including personal items) that may be affected by the magnetic field should be removed from the patient area before treatment to prevent possible injury to the wearer or damage to the device. Examples of these types of products include wearable monitors, bone growth stimulators, earrings and other jewelry, hearing aids, eyeglasses, cell phones, and MP3 players.

The warning section of the labeling should include a table that lists all devices that are known to be adversely affected by the rTMS device. The labeling should instruct the prescribing physician to screen each patient for the presence of these devices.

In addition, the warnings should summarize the compatibility requirements for each

device and electrically conductive object in the vicinity of the rTMS device treatment coil. These requirements should indicate whether the device's proximity to the treatment coil is contraindicated, should be kept at a safe distance from the magnetic coil, or should be removed from the patient area. The warning should also note that this list is for guidance in screening a patient for magnetic field compatibility and is non-comprehensive, so prudent judgment should be applied for cases not listed, including contacting the device manufacturer if compatibility is uncertain.

Risk of Seizure

The labeling should indicate that seizure is a potential risk of treatment with rTMS devices. A summary of the number of seizures reported with the use of the rTMS device in clinical studies should be included; the patient populations should also be described since, for example, use of rTMS as an adjunct to certain medications may increase the likelihood of a seizure. The labeling should state that patients who have a history of seizure, or potential alteration in seizure threshold, should be closely monitored when the device is used. This includes patients with a history of seizure or epilepsy, stroke, head injury, high intractranial pressure, severe headaches, or presence of other neurologic disease that may be associated with an altered seizure threshold, or concurrent medication use as such as tricyclic antidepressants, neuroleptic medications or other drugs that are known to lower the seizure threshold, secondary conditions that may significantly alter electrolyte balance or lower seizure threshold, or where a quantifiable motor threshold cannot be accurately determined.

Labeling should also cite relevant guidelines (e.g., 1998 National Institute of Neurological Disorders and Stroke (NINDS) Workshop) for rTMS stimulation parameters[3] which are also summarized in **Section 4. Device Description**, intended to reduce the potential risk of seizure. In addition, labeling should recommend use of the device within any guidelines cited.

Precautions

The following precautions should be provided, unless otherwise justified.

Lack of Evidence for Efficacy or Safety in Specific Patient Populations

Labeling should include precautions for the use of rTMS devices in the treatment of patients with depressive or related conditions where safety and efficacy has not been established. This may include patients with these characteristics:

- age less than 22;
- suicide plan or recent suicide attempt;
- varying degrees of medication resistance in either the current or previous episode;
- on concurrent antidepressant medication, i.e., cannot tolerate discontinuation of current antidepressant medication;

- history or concurrent use of electroconvulsive therapy or vagus nerve stimulation;
- depression secondary to a general medical condition or substance-induced;
- seasonal affective disorder;
- history of substance abuse, obsessive compulsive disorder or post-traumatic stress disorder;
- a psychotic disorder, including schizoaffective disorder, bipolar disease, or major depression with psychotic features;
- neurological disorders, including a history of seizures, cerebrovascular disease, primary or secondary tumors in CNS, cerebral aneurysm, dementia, or movement disorders;
- history of increased intracranial pressure or head trauma;
- cadiac pacemakers, implantable cardioverter defibrillators, occular implants, deep brain stimulators, vagus nerve stimulators, implanted medication pumps, intracardiac lines, or significant cardiac disease; or
- pregnant or nursing.

Hearing Protection

Labeling should include a precaution that hearing protection is required during the use of rTMS devices. Patients and those operating the device should always wear earplugs or similar hearing protection devices with a rating of 30dB of noise reduction during rTMS treatment.

Long-Term Effects

Labeling should include a precaution that describes the limitations of available information on the safety and effectiveness of long term treatment with the rTMS device.

Labeling should state the known long term effects and indicate that other long terms effects may be unknown.

Procedure Precaution

Labeling should include a precaution to address the risk of explosion due to the presence of flammable materials, risk of electrical shock, risk of overheating of the magnetic coil, and discontinuation of treatment for any patient who has a continued significant adverse reaction or discomfort during or immediately after use. A sample of such a precaution that may be considered is as follows:

> "To avoid the risk of explosion, do not use this device in the presence of flammable anesthetics"

Adverse Events

A specific section of the operator's manual should present a summary of adverse events that occurred with the rTMS device in clinical trials. Reports of headache and application site pain should be cited in number and severity as these are frequently associated with rTMS treatment. In addition, the number and incidence of deaths, suicides, seizures or worsening of depression should be provided. Effects on cognitive function or auditory threshold using targeted measures of analysis should be reported.

Electrical Safety

Electrical safety requirements for the rTMS device should be stated clearly in the product labeling. A list of technical standards to which the device has been tested and shown to meet specifications as indicated in **Section 8. Electromagnetic Compatibility** also should be provided.

Electromagnetic Compatibility

Electromagnetic compatibility safety requirements for the rTMS device should be clearly stated in the product labeling. A list of technical standards to which the device has been tested and shown to meet specifications as indicated in **Section 9. Software Life Cycle and risk Management** should also be provided.

User Training

We recommend that a clinician training program be developed that includes information on the characteristics of the intended patient population and how to differentiate these patients from patients for whom evidence of efficacy is not available. It should also cover the design features of the rTMS device, methods for training in the use of the device and appropriate methods to describe the safety and risks of the device in the treatment of patients with major depression. The training should ensure operator competency and uniform, optimal treatment technique to safely and effectively use the device for the purposes described in the indication.

Patient Labeling

Physician labeling should include patient labeling with instructions to the physician to provide such labeling to the patient. Patient labeling should provide a prospective patient information that will assist the patient in understanding who may benefit from the treatment with the device, what those potential benefits are, relevant contraindications, warnings, precautions, adverse effects/complications, and alternative treatments. Providing such information to the patient prior to scheduling treatment should help ensure effective communication between the patient and practitioner concerning the safe use of the device and the purposes for which it is intended. Each patient should have realistic expectations of the treatment, the potential complications, and understand what types of feedback, e.g., headache, worsening depression, may be important to provide the practitioner. The patient

labeling should use terminology that is well known and understood by the average lay person.

We recommend you follow the relevant principles discussed in the CDRH guidance document entitled, **Guidance on Medical Device Patient Labeling**.[9] For rTMS systems, we recommend physicians provide patients with the patient labeling that includes the following information.

Information on Treatment

Describe how the device operates to achieve its effects and the course of treatment. Patient labeling for rTMS systems should state the following:

- A course of rTMS traditionally requires multiple treatments.
- Patients should discuss the number of treatments and treatment schedule with their physicians.
- rTMS treatment effects in reducing depression are temporary, and patients may need to continue other forms of depression therapy.
- Relapse into depression is likely without follow-up treatment.

Candidates for Treatment

Based upon the information from your clinical trial, describe the patient population for the device.

Benefits

Describe the potential benefits of your device and probability of such benefits based upon your clinical trial.

Risks

Describe the known risks from your device and rTMS in general.

Alternative Treatments

Patient labeling should describe the alternative treatments such as medications, psychotherapy, and electroconvulsive therapy.

[9] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm

Appendix A. Definitions and Units of Measurement

For the purposes of this guidance document, the following definitions and recommendations for measurement are used:

Frequency: The number of pulses per second expressed in Hertz (Hz).

Magnetic Field Strength: Magnetic field strength is expressed as B, the magnetic flux density, in units of Tesla. The time rate of change of B determines the current density level induced in the cortex; therefore, dB/dt is used to express the strength of the field induced by the magnetic field at a given point. The units for magnetic field flux (i.e., dB/dt) are Tesla/second. Magnetic field strength is determined by measuring the voltage induced across a small pickup loop placed at the location of interest.

Motor Threshold (MT)/MT Intensity: The motor threshold level is the minimum stimulator setting, in Standard Motor Threshold (SMT) units, that induces an observable motor response by the patient in 50% of the applied pulses, usually as observed by movement of the thumb. "MT level" is determined with the rTMS treatment coil positioned over a specific location within the motor strip, called the motor threshold location (MT location).10 The MT location may be used as an anatomic reference point for navigating the coil to the rTMS treatment location. The MT level is used as a reference point for setting the rTMS treatment intensity, usually expressed as a percent multiple of the MT level, e.g. 120% MT.

Pulse Width: When your rTMS output is a damped sinusoidal wave, the pulse width is defined as the time (duration) from the initial peak to next peak of the wave; it is also described as the period of the sinusoidal wave. For monophasic pulse shapes, we recommend reporting pulse width as the time between the rising phase and falling phase of the wave measured at a standard amplitude (e.g., 10% of total amplitude). The pick-up loop for making this measurement should be located at the same distance from the coil as the target tissue in the brain.

SMT Unit: So that measurement of stimulator magnetic field output may be standardized, the SMT unit is suggested. 1.0 SMT is the output setting of a rTMS device that corresponds to an

[10] Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W, Magnetic stimulation: motor evoked potentials. Electroenceph Clin Neurophysiol Supp 1999; 52:97-103.

induced electric field of 130V/m at a point located at the fixed distance of the target along the central axis of the coil from the surface of the scalp into the cortex. This induced electric field is measured with a pick-up loop with the dipole oriented along the front-to-back (i.e., normally anterior-posterior) axis of the treatment coil.

Stimulation Volume: Stimulation volume defines the region of cortical tissue within the magnetic field that is above the threshold of cortical stimulation, i.e., the 3-dimensional volume within which the induced electric field achieves a value greater than or equal to 80% of the electric field at the 2.0 cm reference point. For example, for a treatment at the 120% MT level, the field at the boundary of the stimulation volume is equivalent to the MT level and all tissue within the stimulation volume is above the MT level.