Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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Table of Contents

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Draft Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

When finalized this guidance will provide industry with an assessment paradigm for radiofrequency (RF)-induced heating on or near multi-configuration passive medical devices in the magnetic resonance (MR) environment, including multi-component and single-component device types with various dimensions and shape. Multi-component passive devices, such as orthopedic fixation devices, may result in a very large number of possible device configurations and combinations of individual components. Single-component devices, such as cardiovascular stents, are also frequently available in multiple sizes or configurations. For these multi-configuration passive devices, it is typically not possible to leverage RF-induced heating testing from one device configuration or combination to other device configurations or combinations because the geometry or configuration of the device can affect heating in a non-linear manner. As a result, the total number of possible configurations or combinations that need to be assessed for RF-induced heating of some passive devices can be very large. This document provides an approach to reduce the number of possible device configurations or combinations to a manageable number for the testing of RF-induced heating in the MR environment. Additionally, this document provides guidance on how to assess RF-induced device heating for multi-

configuration passive medical devices. The information provided in this guidance is intended to be used to support MR conditional labeling claims in conjunction with the information provided in FDA's current guidance document for *Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment* (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.pdf).

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances 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 document provides guidance on a recommended method to select device configurations or combinations to be tested for RF-induced heating in the MR environment. Additionally, this document provides guidance on how to assess RF-induced device heating for multi-configuration passive medical devices.

This guidance applies to multi-configuration passive devices consisting of multiple components, as well as single-component devices, which can be used in multiple configurations. A passive device is one that functions without the supply of electrical power. These devices may be completely implanted (e.g., cardiovascular stents, spinal fixation devices) or partially implanted in the patient's body (e.g., external fracture fixation devices), or used entirely externally (e.g., head fixation frames). This document is applicable to all electrically conductive multi-configuration passive medical devices intended to be used in the MR environment that include MR Conditional labeling, regardless of their size, or number of components.

Active devices, or devices that require use of internal or external electrical power, are not within the scope of this guidance. In addition, this guidance document does not establish a heating acceptance criterion in general or for any specific medical device.

III. Overview of Heating Assessment

The methodology recommended below describes one way to reduce a large number of possible device configurations or combinations to a manageable number (i.e., test set) for the assessment of RF-induced heating in the MR environment, and one way to conduct an assessment of RF-induced heating for the devices within the identified test set.

1. Define and describe the proposed scan conditions: magnetic field strength, Specific Absorption Rate (SAR) levels, landmark position (e.g., position of the device relative to the MR bore), and scan area.

2. Use a scientific rationale, animal data, and/or published literature to establish the heating acceptance criterion (i.e., the maximum heating allowed for your medical device). The intended use and benefit-risk profile of the device should also be considered when establishing the acceptance criterion.

3. Define and describe all possible device configurations and combinations (CC_{all}) in which your device is intended to be used in clinical practice, using tables, lists, and/or drawings. The description should include device size and geometry, in addition to all materials used and their electrical properties (i.e., the electrical conductivity and the permittivity at the frequency of interest). While it is not necessary to describe each individual configuration/combination, the limits in dimensions, geometry, and the total number of configurations/combinations should be clearly identified; preferably in a tabular or matrix format.

4. Use a scientific rationale or a scientific method, such as those described in section IV below, to reduce CC_{all} to a subset of potential worst-case device configurations and combinations (CC_{test}) for heating assessments. The scientific method used to reduce CC_{all} to CC_{test} should include a detailed description of the algorithm and parameters used. The scientific rationale should note any clinically relevant information and known worst-case factors for RF-induced heating.

   Factors influencing RF-induced heating include, but are not limited to, the following:

   a. Device Dimensions and Resonant Effects: The half-wavelength of the electromagnetic field inside a patient for 1.5T systems is about 25 cm, and for 3.0T systems about 12 cm.[1] For implants with dimensions on the order of a half-wavelength to a wavelength (i.e., 25 to 50 cm or 12 to 24 cm), resonant effects between the device and electromagnetic field can lead to significant high heating. RF-induced heating can change significantly if the device dimensions change by about one-tenth of a wavelength. Therefore, device heating for dimension increments of about one-tenth of the wavelength should be assessed (i.e., approximately 5 cm for 1.5T and 2.4 cm for 3.0T).

   b. Device Geometry: The RF-induced heating can depend on: 1) shape of the device, 2) cross-section of the device, and 3) the length of the device along the MRI bore direction.

[1] Kainz W., (2007), MR Heating Tests of MR Critical Implants, Journal of Magnetic Resonance Imaging, vol. 26, pp. 450–451.

c. Device Components (e.g., Screws): All possible component configurations should be considered. For example, for screws aligned in parallel with the MRI bore direction, longer screws typically lead to higher heating for the entire construct. However, when screws are oriented perpendicular to the MRI bore, shorter screws can lead to higher heating for the entire construct. Therefore, all screw lengths and screws in all possible openings/holes of the device, and all possible directions, should be considered.

d. Device Configuration: Sub-components connected to each other can significantly change the RF-induced heating. Therefore, devices should be studied as the entire construct rather than individual sub-components.

e. Surface Properties: Devices with smoother surface typically heat less, while devices with sharp edges tend to heat more.

5. The minimum number of configurations/combinations within CC_{test} depends on the number of CC_{all}, the proposed scan conditions, the device size and geometry, and the electrical properties of the materials used.

6. Once an appropriately justified CC_{test} has been defined, you should assess the RF-induced heating for each device configuration/combination in CC_{test} and within each MR environment in which you intend the device to be used. RF-induced heating can be assessed by:

   a. *in vitro* temperature measurements according to ASTM F2182,[2]
   b. computer modeling to determine temperature,
   c. computer modeling to determine Specific Absorption Rate (SAR), or
   d. a combination of a, b, and/or c.

   Note that all results using computer modeling should be validated including a detailed uncertainty analysis.

   Using one of the above methods, the location of the maximum heating on the device surface should be determined for all devices in CC_{test}. The heating at this location for a specified local SAR should then be determined. The local SAR should be measured before performing the heating tests.

   With the exception of simple elongated structures (e.g., stents), the location of the maximum heating on the device surface should not be estimated using a scientific

[2] ASTM F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging. The current edition recognized by the FDA is listed on the FDA Recognized Consensus Standards Database Website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm)

rationale. In general, an experimental or computational method should be used to assess the location of the maximum heating on the device surface. Also, if the geometry of your device is highly irregular and has geometrical features orientated in more than one direction, testing of all devices in CC_{test} in all three exposure orientations (i.e., alignment of the three major axis of the device relative to the tangential induced electric field) should be performed. If the device is located outside of the patient, you should determine the heating for a specified electric field in air. If the device is partially outside and partially inside of the patient, you should determine the heating for both a specified local SAR, and for a specified electric field in air.

For all testing, you should report the heating for a 15 minute RF exposure and a typical local SAR (e.g., 10 W/kg) or a typical electric field (e.g., 100 V/m). You should also report the location on the device surface where heating was assessed.

The scope of ASTM F2182 is limited to devices entirely implanted inside the body. However, for medical devices with other implantation conditions (e.g., external fixation devices, catheters), RF-induced heating can be evaluated experimentally and/or computationally using a method similar to that described in ASTM F2182, with modifications for the specific medical device and the context of use. ASTM F2182 should not be used to assess the worst-case MRI-induced RF-induced heating for medical devices used in multi-channel transmit RF coils.

7. Provide an estimate of the accuracy of the results (i.e., an uncertainty analysis for all measured or computed results). In addition, validation data for all computational models should be provided.

8. If the observed worst-case *in vitro* heating exceeds the specified heating acceptance criterion, you should estimate the expected worst-case *in vivo* heating to demonstrate the safety of your device in the MR environment. Since *in vitro* testing outlined in ASTM F2182 does not consider the actual *in situ* electric fields, *in vitro* heating results may be substantially higher than the actual *in vivo* heating. The estimated *in vivo* assessment should consider the patient population for which your device is indicated and should include all possible scan conditions.

We strongly recommend that you submit a pre-submission to obtain feedback on your plan for identifying and assessing CC_{test} and your plan for conducting *in vitro* RF-induced heating measurements before conducting the assessments, especially for complex multi-component devices. Please refer to FDA's Guidance *Requests 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).

IV. Recommended Methods to Reduce the Number of Configurations and Combinations for Testing

The number of possible device configurations can become very large for RF-induced heating testing if multiple parameters vary between configurations or if each parameter has a range of options. For example, if a device is defined by three parameters (e.g., length, width, and thickness), and each of these parameters has 100 different options there will be $100^3 = 1{,}000{,}000$ possible combinations for CC_{all}. Since many combinations or configurations within CC_{all} will be very similar to neighboring combinations or configurations, statistical or stochastic sampling of the same parameter set can significantly reduce the number of devices to be tested to a smaller subset (CC_{test}), while still providing an accurate representation of CC_{all}.

To reduce CC_{all} to CC_{test}, first perform a sensitivity analysis to assess the effect of each parameter on RF-induced heating. One simple type of sensitivity analysis is the minimum-maximum differentiability. Using this method, the sensitivity of RF-induced heating to each parameter can be assessed by testing its maximum and minimum value while other parameters are set at their mean values. Once the critical parameters are determined, a selection method such as, but not limited to, those outlined below, should be used to identify device configurations and combinations for heating assessments:

1. Constant Value Justification: If many parameters are varied between design configurations, it is possible that some parameters have little or no influence on RF-induced heating and may justifiably be set at a constant value to reduce CC_{all}. The maximum-minimum approach outlined above may be an appropriate sensitivity analysis to support this justification.

2. Sampling Methods: CC_{all} can often be reduced substantially, while providing a comprehensive response evaluation, by using a non-deterministic, pseudo-random sampling technique such as a Monte-Carlo analysis (e.g., Haldar and Mahadevan, 2000[3]). A Monte-Carlo analysis generally consists of the following components:

   a. Creating a deterministic model which can reliably reach a solution for the range of random distribution of device parameters in the problem.

   b. Defining the appropriate probabilistic characteristics of each random parameter. These could take the form of distribution parameters (e.g., the mean and standard deviation of a normal distribution), or as a set of cumulative distribution quantiles (without a named distribution). For the purpose of identifying worst-case devices for RF-induced heating tests, a uniform distribution may provide an effective parameter sweep. For a design parameter with a specific set of nominal values (e.g., length = 10, 15 or 20

[3] Haldar, A. and Mahadevan, S., (2000). Probability, reliability and statistical methods in engineering design. New York: John Wiley & Sons, Inc., ch. 9.

mm) a discrete random variable, with equal likelihood for each nominal value, may be most effective.

c. Generating samples of these random parameters for testing (to identify devices for CC_{test}). Several sampling methods are commonly used: a) random sampling, b) Latin hypercube sampling, and c) importance sampling (Helton et al., 2006[4]).

In random sampling, the input parameters are sampled according to their probability density functions, with each sample independent of the others. This approach offers the advantage of conceptual simplicity and the ability to easily add new samples if sufficient accuracy has not been achieved (see item 'f' below).

The Latin hypercube method may increase sampling efficiency relative to random sampling. In this method, the number of samples (N) must be selected at the outset. Each parameter is stratified into N, i.e., the number of samples, equally likely intervals, each of which is randomly sampled only once (Helton et al., 2006[5]). The relative efficiency of this method arises from the stratification that prevents overlapping samples and guarantees more complete parameter space filling than random sampling.

Importance sampling concentrates sampling near parameter values that are most likely to induce higher levels of RF-induced heating. This method can be used to focus tests towards those combinations of parameters to which RF-induced heating is most sensitive. The disadvantage of this approach is that it requires distortion of the sampling distributions which should be justified and corrected for, when evaluating the system results. In generating samples, it is first necessary to estimate the number of samples needed to achieve the required accuracy. An estimate can be calculated from

$$N=4 / \varepsilon^2$$

where N is the estimated number of samples and ε is the uncertainty of the mean RF-induced heating; e.g., <10% (Haldar and Mahadevan, 2000[6]).

d. Solving the deterministic model for all samples.

e. Combining the individual model solutions into probabilistic system information. In the present application, the maximum expected level of RF-

[4] Helton, J. et al., (2006). Survey of sampling-based methods for uncertainty and sensitivity analysis. Reliability, Engineering and System Safety, vol. 91, pp. 1175–1209.
[5] Ibid.
[6] See footnote 2 above.

induced heating is quantified. In practice, the maximum heating identified from all tests will depend on the number of tests, such that a higher maximum will be likely when more samples are taken. Therefore we recommend reporting a consistent quantile of RF-induced heating, such as the 99th percentile.

f. Evaluating the accuracy of the simulation study and the necessity of additional analyses. As noted in item 'e' above, the observed RF-induced heating results will depend upon the number of samples, with uncertainty remaining about intermediate, un-sampled cases. Therefore, we recommend that you evaluate the degree of convergence of the RF-induced heating results to ensure the conclusions are not dependent upon the specific sample used. In random sampling, each sample point is independent of the others and additional random points can be added until a stopping criterion is converged upon.

   A recommended stopping criterion could be when the standard deviation of the mean RF-induced heating (taken from bootstrapped datasets of, e.g., 25 sub-samples) converges within a pre-defined uncertainty of the mean RF-induced heating (e.g., <10%). Note that this criterion can be applied to evaluate a completed Latin hypercube analysis; however, a post-hoc addition of sample points will disturb the original scheme and result in a non-Latin hypercube sample.

   An alternative approach, often used with Latin hypercube sampling, is to run multiple, equally-sized, sample sets (e.g., two or three sets of 100 samples). Once the analyses are completed, the results of the samples can be compared (e.g., t-test) to confirm that the mean RF-induced heating from the different samples is statistically equivalent. Once this is confirmed, the data from the different samples can be combined into one dataset (Helton et al., 2006[7]).

V. Hypothetical Example

A fracture fixation system contains 10 plates of the same thickness, but different lengths (50mm to 250mm in 5mm increments) and two widths (8mm and 12mm). The plate can be used with 5 to 20 screws. There is only one compatible screw diameter, but a continuously variable screw length (15-25mm), and the screws can be angled in any direction up to 30 degrees.

First, a sensitivity analysis of parameters reveals that RF-induced heating does not change significantly (less than 5%) with the plate width, with the direction angle of the screws, or with various contouring (plate bending to fit the fracture) of the plate. Therefore the plate width is kept constant at 12mm (which showed slightly higher heating than the 8mm width), the screw direction angle is kept constant at 0 degrees, and the plate is kept unbent.

[7] See footnote 3 above.

Next, the number of samples is estimated to give approximately 10% uncertainty in the mean RF-induced heating. Using the equation in Section IV, 2.c. above (i.e., $N = 4/\varepsilon^2 = 4 / 0.1^2$) 400 random models ($CC_{test}$) of the fracture fixation system are created for different combinations of plate length, screw number, and screw length. Plate length is defined as a discrete random variable with equally likely possible values at intervals of 5mm from 50-250mm. Screw number is defined as a discrete random variable with equally likely possible values at intervals of 1 from 5-20 screws. Screw length is defined as a uniform distribution with minimum and maximum values of 15mm and 25mm, respectively. A random sampling method is used for each parameter to generate the 400 models to be solved.

After all 400 models are solved, the stopping criterion is evaluated to confirm that the mean RF-induced heating calculated does not vary by more than 10% regardless of the addition of more samples. This is done in five steps:

1. The mean RF-induced heating of the 400 results is calculated (e.g., 3.5°C);

2. the 400 heating results are randomly resampled into sub-samples (e.g., 25 sub-samples), each containing 16 results;

3. the mean of each sub-sample is calculated as 25 different values;

4. the standard deviation of the 25 sub-sample means is calculated (e.g., 0.31°C); and

5. the standard deviation from the mean of all 25 sub-samples is less than 10% of the mean RF-induced heating of the 400 results (i.e., 0.31°C < 10% of 3.5°C), indicating that the stopping rule has been satisfied.

The device configurations/combinations that result in the highest heating are identified from all 400 models tested. The highest device heating is calculated as the 99th percentile of the distribution of RF-induced heating observed in all 400 tested models.