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Evaluation of Thermal Effects of Medical Devices that Produce Tissue Heating and/or Cooling

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

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For questions about this document, contact OHT4: Office of Surgical and Infection Control Devices/DHT4A: Division of General Surgery Devices at 301-796-6970.

When final, this guidance will supersede "Guidance Document for the Preparation of Premarket Notification [510(k)] Applications for Heating and Cooling Devices," issued on July 26, 1995.

FDA U.S. FOOD & DRUG ADMINISTRATION
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U.S. Department of Health and Human Services
Food and Drug Administration
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Preface

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Evaluation of Thermal Effects of Medical Devices that Produce Tissue Heating and/or Cooling

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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The Food and Drug Administration (FDA) is issuing this draft guidance document to describe relevant information that should be provided in a premarket submission (i.e., premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, premarket notification (510(k)) submissions, investigational device exemption (IDE) applications and De Novo requests) to support the evaluation of thermal effects of medical devices that produce local, regional, and/or systemic changes in tissue temperature (i.e., heating and/or cooling) due to their use. The recommendations in this guidance reflect current review practices and are intended to promote consistency and facilitate efficient review of thermal effects data for these devices. Where available, device-specific guidance documents and/or standards may include additional technical recommendations on thermal effects evaluation that should be considered.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database. If submitting a Declaration of Conformity to a recognized standard, we recommend you include the appropriate supporting documentation. For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. Scope

The scope of this guidance is limited to evaluating thermal effects of medical devices that produce tissue temperature change (i.e., heating and/or cooling) as an intended or unintended consequence of device use. Examples of such devices include, but are not limited to, devices that deliver radiofrequency, microwave, light, or other forms of electromagnetic energy, devices that deliver ultrasound, electroporation devices, devices that produce temperature change (e.g., hyperthermia, high temperature ablation, hypothermia, cryoablation) by contact, and devices where electrical components (e.g., batteries, generators, chargers, leads, electrode contacts) can potentially heat surrounding tissue during use.

III. Evaluation of Thermal Effects

When a change in tissue temperature happens because of device-induced heating and/or cooling, regardless of whether it is an intended or unintended consequence of device use, there is a potential for adverse health consequences, such as tissue damage and/or a negative impact on physiological functions, to occur. Assessing thermal effects is an important aspect of the FDA's review of premarket submissions for these devices.

An evaluation of thermal effects should include verification of device parameters and an assessment of tissue effects (e.g., thermal damage, tissue appearance, tissue/organ function) and related spread of thermal energy. An assessment of tissue effects and thermal energy spread may be performed experimentally (i.e., using phantoms, *ex vivo* animal tissue models, and/or *in vivo* animal testing), computationally, and/or clinically.

More information on how such evaluations should be conducted and presented in premarket submissions are detailed in the sections below. When developing a strategy for the thermal effects evaluation of your device, we encourage you to engage with the Agency through the Q-Submission Program to obtain early feedback on your approach and study design. For additional information regarding the Q-Submission Program, refer to FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program." We recommend you submit a Pre-Submission (a type of Q-Submission) if you have specific questions on aspects of your study design, such as the following:

- The use of phantoms, *ex vivo* tissue, or *in vivo* animal models.
- Selection of appropriate model parameters for your intended clinical application.
- Questions related to induced spatial temperature distribution over time (i.e., "temperature-time history") needed to support to a claimed tissue effect.
- Design of clinical studies, when needed, to support the device's indications for use.
- Questions regarding scenarios where the recommendations below may not apply.

A. Verification of Device Parameters

FDA recommends that you provide bench testing data to verify that the device meets labeled parameters (including all energy-related parameters) for the full range of device specifications. Testing should have pre-defined acceptance criteria relevant to the conditions of use. If the testing results in deviations from the acceptance criteria, you should provide a scientific rationale to support device safety and effectiveness for the specific use conditions. This verification testing is important to demonstrate that the data generated on tissue effects and thermal energy spread are appropriately representative of the final finished device's performance. Therefore, we recommend that verification of device parameters be conducted prior to conducting the assessment of tissue effects and thermal energy spread.

B. Experimental Assessment of Tissue Effects and Thermal Energy Spread

(1) Experimental Models

Experimental assessment of tissue effects and thermal energy spread can be conducted using phantoms, *ex vivo* animal tissue models, and/or *in vivo* animal testing, as applicable to the intended use. The suitability of each method for a given device depends on the magnitude and distribution of the heating and/or cooling, as well as the availability of appropriate experimental models. For example, tissue temperature changes may be local (confined to a small volume of tissue or a portion of a specific anatomical structure), regional (affecting the majority or all of a given anatomical structure and potentially one or more immediately surrounding structures), or systemic (affecting multiple diffuse anatomical structures or all body). While it may be feasible to develop a suitable phantom model or *ex vivo* animal tissue model for devices with local tissue temperature changes, it may be more challenging to do so for devices with regional or systemic effects, where the impact of blood flow on the development of tissue effects would need to be accounted for.

Each experimental model is discussed in more detail in the following sections.

a. Phantom Testing

Phantoms are often suitable for characterizing tissue effects and thermal energy spread for devices that raise local tissue temperature minimally (e.g., a maximum, absolute, local temperature change of ≤ 6 °C resulting in the expected absolute *in vivo* temperature of ≤ 43 °C) for a short duration and for which local-, regional-, and systemic-level effects related to such temperature change are well characterized in the literature. The use of phantoms may also be appropriate for the assessment of certain cryotherapy devices and certain diagnostic devices.

For certain cryotherapy devices, based on the risk of the intended use, when the goal of thermal evaluation is to demonstrate the formation of comparable ice-ball dimensions between devices that have comparable parameters, gel phantoms and/or water bath phantoms of appropriate tissue-mimicking properties and comparable initial and boundary conditions may be appropriate.

When device parameters (e.g., probe dimensions, coolant temperature, target cooling temperature, application time, number of cycles) and/or intended tissue are significantly different between the compared devices, additional *ex vivo* tissue testing, *in vivo* animal testing, and/or clinical studies may be needed.

Phantom testing verifying energy output and accompanying rationale or results from appropriately validated computational models (refer to Section III.C. below) may also be appropriate for the characterization of diagnostic devices (e.g., MRI systems, ultrasound imaging systems) that may raise local, regional, and/or systemic tissue temperature minimally as an unintended consequence of device use, since well-established relationships between power output (or specific absorption rate (SAR)) and safe use to ensure patient safety can be also leveraged. In such cases, phantom testing may be used to demonstrate that the output energy limitations of the device are adequate to ensure that the energy deposition does not raise concerns about adverse thermal effects consistent with product specific guidances and FDA recognized standards.[1]

When using a phantom, the phantom used should consist of geometry, dimensions, and material properties (e.g., thermal, mechanical, electromagnetic, acoustic, optical) that are representative of the *in vivo* conditions of use for the intended clinical application(s). The phantom should be exposed to initial and boundary temperature conditions relevant to the intended clinical application(s) and the full range of device parameters. As part of your premarket submission, you should provide the following:

i. a scientific rationale to justify how your phantom model is adequately representative of the tissues relevant to your device's specific indications for use (i.e., the target and surrounding tissues);
ii. discussion on how the results generated by the phantom translate to the *in vivo* environment; and
iii. discussion on how your measured thermal energy spread helps your device achieve its intended use without adversely affecting patient safety.

Phantom testing may not be suitable when an established phantom with the relevant properties is not available, *in vivo* translation of the test results is not clear, and/or when associated tissue effects are not well characterized in the literature. In these cases, *ex vivo* tissue testing, *in vivo* animal testing, and/or clinical studies may be needed.

b. *Ex Vivo* Animal Tissue Testing

Ex vivo animal tissues are often suitable to characterize tissue effects and thermal energy spread for devices that raise local tissue temperature over 43 °C for a short duration and for which local-, regional-, and systemic-level effects related to such temperature change are well characterized

[1] See FDA's guidances, "Marketing Clearance of Diagnostic Ultrasound Systems and Transducers," "Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices," and IEC 60601-2-33 Edition 4.0. *Medical electrical equipment - Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis*.

in the literature. *Ex vivo* animal tissue testing are often suitable for use for certain cryotherapy devices when testing in phantoms is insufficient.

We recommend that the *ex vivo* animal tissue model consist of geometry, dimensions, and properties (e.g., thermal, mechanical, electromagnetic, acoustic, optical) that are representative of the *in vivo* conditions of use for the intended clinical application(s). The *ex vivo* animal tissue model should be exposed to suitable initial and boundary conditions and the full range of device parameters. As part of your premarket submission, you should provide a scientific rationale to justify how your *ex vivo* animal tissue model is adequately representative of the tissues relevant to your device's specific indications for use. Your rationale should include a discussion on the following:

i. why the geometry, dimensions, initial conditions, and boundary conditions of your tissue sample are clinically relevant and support an accurate assessment of tissue effects and thermal energy spread;
ii. a comparison of the properties of your tissue sample and your tissue of interest and an explanation of why any differences would not adversely affect your assessment of tissue effects and thermal energy spread; and
iii. how your measured tissue effects and thermal energy spread helps your device achieve its intended use without adversely affecting patient safety.

Ex vivo animal tissue testing may not be sufficient when *ex vivo* evaluations indicate that the dimensions of the thermal energy spread and/or thermally affected tissue region (the size (i.e., length, width, depth, and volume) of tissue with damage and/or adverse effects resulting from device use) are likely to approach or exceed the distance to critical tissue structures from the application site and/or when the effect of such spread is not well characterized in the literature. In such cases, additional *in vivo* animal testing and/or clinical studies may be needed.

Additional recommendations on tissue testing methodology for thermal effects evaluations are provided in Section III.B.(2), below.

c. *In Vivo* Animal Tissue Testing

In vivo testing in clinically relevant animal models[2] may be needed to characterize tissue effects and thermal energy spread when:

- testing in phantoms and *ex vivo* tissue is expected or found to be insufficient;
- devices raise local tissue temperature for a prolonged duration;
- devices raise regional or systemic tissue temperature;
- local-, regional-, and/or systemic-level effects related to the device-induced temperature change are not well characterized in the literature; or

[2] FDA supports the principles of the "3Rs" to replace, reduce, and/or refine animal use in testing, when feasible. We encourage sponsors to consult with the Agency if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if a proposed alternative method could be assessed for equivalency to an animal test method.

- new scientifically relevant information related to tissue effects and/or its impact on patient safety becomes available.

The *in vivo* animal model should consist of geometry, dimensions, and properties (e.g., thermal, physiological, mechanical, electromagnetic, acoustic, optical) that are representative of the *in vivo* conditions of use for the intended clinical application(s). The *in vivo* animal model should be exposed to suitable initial and boundary conditions and the full range of device parameters. As part of your premarket submission, you should provide a scientific rationale to justify how your *in vivo* animal model is adequately representative of the tissues relevant to your device's specific indications for use. Your rationale should include a discussion on the following:

i. why the geometry, dimensions, blood flow, initial conditions, and boundary conditions in your *in vivo* animal model are clinically relevant and support an accurate assessment of tissue effects and thermal energy spread;
ii. a comparison of the properties of your *in vivo* tissue and your tissue of interest and an explanation of why any differences would not adversely affect your assessment of tissue effects and thermal energy spread;
iii. how your measured tissue effects and thermal energy spread helps your device achieve its intended use without adversely affecting patient safety; and
iv. why use of anesthetics is not likely to adversely affect your assessment of tissue effects and thermal energy spread.

For information on FDA's recommendations for animal studies intended to evaluate medical devices, see FDA's guidance titled "General Considerations for Animal Studies Intended to Evaluate Medical Devices." Additional recommendations on tissue testing methodology for thermal effects evaluations are provided in Section III.B.(2), below.

(2) Tissue Testing Methodology

a. Selection of Tissues

Ex vivo tissue testing and *in vivo* animal testing should be performed in tissues relevant to the specific indications for use to provide the most clinically applicable thermal data. In some cases, other tissue type(s) with comparable tissue properties can be considered for testing if accompanied by adequate scientific rationale. To support a general soft tissue indication of producing thermal damage, testing should include at least three tissue types. We recommend testing liver, kidney, and muscle tissue to cover a range of soft tissue densities, but other tissue types may be appropriate based on the indicated treatment location and sufficient justification.

The tissue under test should allow the flow of energy such that the development of tissue effects is not impeded by test conditions. For example, when measuring thermal damage in *ex vivo* tissue, if the tissue sample is too small or too thin, then the tissue would not be large enough for the thermal damage to fully develop. Also, when the *ex vivo* tissue is kept at baseline temperature using a water bath, but the flow rate in the water bath is set too high, then the flow may impede the development of thermal damage by removing the energy reaching the tissue boundaries faster

than what is typically anticipated *in vivo*. Likewise, while assessing thermal damage *in vivo* using animal models, care should be taken to make sure that the tissue under test is representative of the clinical conditions of use (e.g., there should not be structures, such as, but not limited to, major blood vessels, nearby that are otherwise absent in clinical conditions and may impede the development of thermal damage).

b. Test Methods

Tissue effects are a function of spatial temperature distribution over time (i.e., "temperature-time history"), which involves temperature change (i.e., heating or cooling) as well as returning of the temperature to baseline value. Therefore, testing should be performed such that the tissue is exposed to the minimum, average, and worst-case temperature-time history. The tissue should be maintained at the baseline temperature relevant for the indications for use (e.g., core body temperature for internal tissues) prior to application of the device. After application of the device, the tissue should be allowed to return to the baseline temperature as it would under clinical conditions of use and energy flow in order for the tissue effects to fully develop. Some tissue effects may take hours to days, or longer in some cases, to fully evolve after the thermal exposure. For example, assessment of electroporation-induced lesions should take into account that the full extent of tissue damage may not be evident immediately after the electroporation procedure, and visible fibrotic lesions may take days or weeks to form. For questions regarding specific time points to study a tissue effect, we recommend you submit a Pre-Submission to obtain early feedback.[3]

Tissue testing should be performed, at a minimum, in triplicate. If the device treatment may be applied using a range of power settings, then testing should at least be performed in triplicate at the minimum, default, and maximum energy and power settings to demonstrate thermal safety for the full range of device specifications.

For devices that include temperature sensing as a device function, you should provide temperature measurements in your submission to demonstrate that this feature works as intended. Although the methods may vary based on the device design, your testing should demonstrate that the temperature sensing under simulated conditions meets your device performance requirements for the full range of device settings. For more on thermometry, refer to Section III.B.(2)c.

For aesthetic devices intended to create fractional effects (i.e., the device induces discrete zones of damage with healthy tissue in between and the damage heals within 14 days), the complex interplay of the various parameters of the fractional devices makes it difficult to validate this effect. Therefore, when evaluating a subject device against a comparator device with similar, but not identical, technical parameters, testing in appropriate *ex vivo* tissue can be conducted to show comparable or smaller thermal damage and comparable or larger healthy tissue in between two nearby damage zones for the worst-case energy and power specifications of the devices. When the technical parameters of the subject device are significantly different from the technical

[3] For more information, see "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

parameters of a comparator device, we recommend you provide histological data from use of the device in tissues of interest in humans or an appropriate animal model to support fractional effects claims. For devices that are intended to create fractional effects on the skin, porcine abdomen skin has been shown to be an appropriate animal model of the human skin. *In vivo* treatments and evaluations should occur in at least 3 different subjects/animals, should utilize treatment parameters representing the full range of device specifications (e.g., lowest, medium, and highest power), and should be performed at various time points (i.e., immediately post-treatment, within 3 days after treatment, and then 10-14 days after treatment) to show initial damage and healing. Comparison of thermal damage should include comparison of the dimensions (e.g., depth and diameter) of the vaporized tissue (ablation zone) as well as the dimensions of the damaged tissue around the vaporized tissue (thermal damage zone). *In vivo* testing should also identify the time to complete healing based on the histological analysis. If you use less than 3 subjects/animals, you should provide a scientific rationale to support why such evaluation allows you to adequately characterize your device for your intended population.

For some electroporation devices, unmeasurable (i.e., could not be measured using traditional temperature probes due to the response time or dimensions of the probes), but significant, heating may occur due to the induction of excessive power density distribution. Therefore, we recommend that you provide a measurement of the size (length, width, and depth) of the affected tissue region using appropriate animal models, tissue types, and histology to demonstrate thermal safety for the full range of device specifications. Additionally, electroporation-based ablation has been associated with induction of cardiac arrhythmias.[4] If you believe that your device induces electroporation effects (reversible or irreversible), we recommend submitting a Pre-Submission to request feedback on your study design, to ensure it is capable of adequately addressing all potential tissue effects.[5]

For electrosurgical devices used in general surgery, refer to FDA guidance "Premarket Notification (510(k)) Submissions for Electrosurgical Devices for General Surgery" for device-specific recommendations on assessing thermal effects using *ex vivo* animal tissue.

c. Assessing Thermally Affected Tissue Region

For *ex vivo* tissue testing and *in vivo* animal testing, you should provide an assessment of the thermally affected tissue region and related thermal energy spread. The thermally affected tissue region is the size (i.e., length, width, depth, and volume) of tissue with damage and/or adverse effects resulting from device use. The related thermal energy spread is determined by measuring the temperature-time history, or the spatial temperature distribution over time. Recommended measurement methods for thermally affected tissue region and thermal energy spread are discussed in more detail below.

[4] A Deodhar, T Dickfeld, G W. Single, W C Hamilton, Jr., R H. Thornton, C T. Sofocleous, M Maybody, M Gónen, B Rubinsky, and S B. Solomon, "Irreversible Electroporation Near the Heart: Ventricular Arrhythmias Can Be Prevented With ECG Synchronization" AJR Am J Roentgenol. 2011 Mar; 196(3): W330–W335.

[5] For more information, see "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

Measuring Thermally Affected Tissue Region

i. Using Histological Methods

We recommend assessing the thermally affected tissue region using histological stains. Your choice of stain(s) should be appropriate to fully assess the extent of the thermally affected tissue region and margins (i.e., depth, thickness, width, and volume). In some cases when the extent of affected tissue is likely to approach or exceed distance to critical structures, histological evaluations performed using a single stain such as Hematoxylin-Eosin (H&E) may not be sufficient, and additional stains, such as viability stains, may be needed to appropriately characterize the full extent of the thermally affected tissue region. You should provide data and/or a scientific rationale to show that your choice of stain(s) enables accurate quantification of the full extent of the thermally affected tissue region.

ii. Using Change in Properties Based Methods

Alternatively, you can assess thermally affected tissue region by measuring changes in tissue properties (e.g., electrical properties such as electrical impedance, mechanical properties such as elastic modulus, optical properties such as birefringence loss, properties related to magnetic resonance imaging such as relaxation times T1 and T2, properties related to computed tomography such as Hounsfield Unit, perfusion loss, or collagen shrinkage). Your choice of method should be capable of fully assessing the extent of the thermally affected tissue region and margins (i.e., length, width, depth, and volume). You should provide data and/or a scientific rationale to show that your choice of method(s) enables accurate quantification of the full extent of the thermally affected tissue region.

Measuring Thermal Energy Spread

i. Using Probe Based Thermometry

The temperature-time history should be measured using temperature probes that are calibrated and that have appropriate accuracy, precision, and response time to be able to measure the temperatures in the intended environment of use (e.g., radiofrequency environment, laser environment). You should provide data and/or a scientific rationale regarding the appropriateness of the temperature probes in measuring the full range of temperatures that could be produced due to the device (i.e., minimum to maximum) with sufficient accuracy, precision, and spatial and temporal resolution in the intended environment of use.

ii. Using Image Based Thermometry

The temperature-time history can alternatively be measured using imaging (e.g., magnetic resonance imaging, ultrasound imaging, computed tomography, infrared imaging) that are calibrated and have appropriate accuracy, precision, and response time to be able to measure the temperatures for the purpose of the measurement. You should provide data and a scientific rationale, alongside the complete set of imaging parameters, regarding the appropriateness of the method in measuring the full range of temperatures

that could be produced due to the device (i.e., minimum to maximum) with sufficient accuracy, precision, and spatial and temporal resolution. Since image-based thermometry methods measure temperature in a 'voxel' (i.e., a three-dimensional volume) or 'pixel' (i.e., a two-dimensional area), the effect of the spatial and temporal temperature gradients on the accuracy of the thermometry method should be provided.

(3) Reporting Results

You should provide the complete experimental protocol and final report as part of the premarket submission. We recommend providing dimensions of the thermally affected tissue region and graphs of temperature vs. time at relevant locations, as applicable. Your results should include discussion of why such results, when translated *in vivo*, help your device achieve its intended use without adversely affecting patient safety.

If the device treatment was applied using a range of power settings, we recommend providing the results in a chart and/or graph that indicates the dimensions of the thermally affected tissue region and related temperature-time history in relation to the power setting, and duration of activation for relevant tissue types.

C. Computational Evaluation of Tissue Effects and Thermal Energy Spread

Tissue effects and thermal energy spread can alternatively be evaluated using computational methods. Evaluation should be performed in computational models of tissues relevant to the specific indications for use to provide the most clinically applicable thermal data. In some cases, computational models of other tissue type(s) with comparable thermo-physiological properties could be considered for evaluation if accompanied by adequate scientific rationale. Computational models should be validated to predict tissue effects and thermal energy spread in your intended tissue of interest for the full range of spatio-temporal temperature distribution. See FDA guidance "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions" for detailed recommendations on conducting a model credibility assessment, which includes validation.

As noted earlier in this guidance, tissue effects are a function of spatial temperature distribution over time (i.e., "temperature-time history"). Therefore, computations should be performed such that the tissue is exposed to relevant (minimum, average, and worst-case) temperature-time history. Imposed computational initial and boundary conditions (e.g., ambient conditions) should mimic clinically relevant conditions of use. You should provide the details and rationale for how the control volume (i.e., computational tissue volume) was developed, such as imaging method, imaging parameters, tissue segmentation, types of tissue, tissue geometry, dimensions, properties, and initial and boundary conditions. Once the tissue temperature is altered due to the application of the device, the tissue should be allowed to return to the baseline temperature as it would under clinical conditions of use before assessing the thermally affected tissue region and thermal energy spread. You should provide evidence (e.g., data from relevant scientific

literature, direct measurements) to support that the simulated spatio-temporal temperature distribution is comparable to the temperature distribution expected in clinical conditions of use.

Tissue effects may be estimated using temperature thresholds or thermal dose thresholds validated for the tissues of interest. We recommend you provide the estimation for the size (i.e., length, width, depth, and volume) of the thermally affected tissue region and related temperature distribution in space and time (i.e., temperature-time history) depicting the spread of thermal energy for the full range of device settings. For additional information on estimating the thermally affected tissue region and related spread of thermal energy, refer to Section III.C.(1) and Section III.C.(2), below.

We recommend you report details of the implementation of the computational models (e.g., governing equations, initial condition, boundary condition, assumptions, discretization, numerical convergence, verification, validation) per the FDA guidance titled "Reporting of Computational Modeling Studies in Medical Device Submissions."

We recommend providing dimensions of the thermally affected tissue region and graphs of temperature vs. time at sufficient locations in the tissue of interest to show that the dimensions of the thermally affected tissue region were computed in response to the temperature-time history relevant to the clinical conditions of use and to depict related thermal energy spread. If the device treatment was applied using a range of power settings, we recommend providing the results in a chart and/or graph that indicates the dimensions (i.e., length, width, depth, and volume) of the thermally affected tissue region and related temperature-time history in relation to the power setting and duration of activation for different tissue types.

(1) Estimating Thermally Affected Tissue Region

a. Using Temperature Thresholds

The thermally affected tissue region can be assessed using temperature thresholds. You should provide data (e.g., histology) and/or scientific rationale to show that the chosen temperature threshold(s) is sufficient to accurately quantify the full extent of the thermally affected tissue region for the full range of temperature-time histories that could be produced due to your device in the tissue of interest.

b. Using Thermal Dose Models

Tissue effects can alternatively be assessed using thermal dose models (e.g., Cumulative Equivalent Minutes at 43 °C (CEM43),[6] Arrhenius equation-based models,[7,8,9] or other weighted temperature-time integral based models[10]) with thresholds relevant to the target and surrounding tissue. You should provide data (e.g., histology) and scientific rationale, alongside your choice of the model, model assumptions, model parameters, and thresholds, to show that the model and threshold(s) are applicable to your chosen clinically relevant end point and sufficient to accurately quantify the full extent of the thermally affected tissue region.

Temperature-time data, needed to compute the dimensions of the thermally affected tissue region can be obtained experimentally, as elaborated in Section III.B.(2)c. above, or computationally, as noted in Section III.C.(2) below.

(2) Estimating Thermal Energy Spread

a. Using Bioheat Transfer Models

The temperature-time history can be obtained by solving first principles based or empirical/semi-empirical bioheat transfer models[11,12,13] that are validated to accurately predict spatio-temporal temperature distribution for your indications for use and tissue of interest in humans and/or clinically relevant animal model(s). You should provide validation data[14] and/or rationale regarding the appropriateness of your bioheat transfer model in predicting temperatures with sufficient spatial and temporal resolution.

b. Using Empirical Thermal Models

The temperature-time history can also be obtained using empirical thermal models that are appropriately validated to accurately predict spatio-temporal temperatures for your indications

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[6] Sapareto SA, Hopwood LE, Dewey WC, Raju MR, Gray JW, "Effects of Hyperthermia on Survival and Progression of Chinese Hamster Ovary Cells," Cancer Research 1978, Vol. 38, pp. 393-400.
[7] J. Pearce and S. Thomsen, Rate Process Analysis of Thermal Damage, Plenum Press, New York (1995).
[8] F.C. Henriques and A.R. Moritz, "Studies of Thermal Injury I. The Conduction of Heat to and through Skin and the Temperatures Attained Therein: A Theoretical and Experimental Investigation," American Journal of Pathology, vol. 23, (no. 4), pp. 531-549, 1947.
[9] A.R. Moritz and F.C. Henriques, "Studies in Thermal Injury II: The Relative Importance of Time and Surface Temperature in the Causation of Cutaneous Burns," American Journal of Pathology, vol. 23, (no. 5), pp. 695-720, 1947.
[10] A.R. Moritz, "Studies of Thermal Injury III. The Pathology and Pathogenesis of Cutaneous Burns: An Experimental Study," American Journal of Pathology, vol. 23, (no. 6), pp. 915-934, 1947.
[11] Shrivastava D, Vaughan JT, "A Generic Bioheat Transfer Model for a Perfused Tissue", 2009, J. of Biomechanical Engineering, Vol 131, 074506-1:074506-5.
[12] H. Arkin, L. X. Xu and K. R. Holmes, "Recent developments in modeling heat transfer in blood perfused tissues," in IEEE Transactions on Biomedical Engineering, vol. 41, no. 2, pp. 97-107, Feb. 1994, doi: 10.1109/10.284920.
[13] Caleb K. Charny, Mathematical Models of Bioheat Transfer, Editor(s): Young I. Cho, Advances in Heat Transfer, Elsevier, Volume 22, 1992, Pages 19-155, https://doi.org/10.1016/S0065-2717(08)70344-7.
[14] See FDA guidances "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions," and "Reporting of Computational Modeling Studies in Medical Device Submissions."

for use and tissue of interest in humans and/or relevant animal model(s). You should provide validation data and/or scientific rationale regarding the appropriateness of your thermal model in predicting temperatures with sufficient spatial and temporal resolution.

D. Clinical Evaluation of Tissue Effects and Thermal Energy Spread

Clinical data may be needed when results from non-clinical and animal thermal effects evaluation studies are found insufficient to support the safety and effectiveness of the device when used as intended. Clinical studies should be designed to test the full range of device parameters and proposed conditions of use in the intended patient population. The study design should include safety measures to provide reasonable assurance of safety of subjects undergoing the study. The results should include a complete account of the thermally affected tissue regions including, but not limited to, thermal injury to vital structures, skin burns (if applicable), as well as the corresponding temperature-time history depicting the thermal energy spread, including real-time temperature monitoring of target and non-target critical organs.

IV. Labeling

In addition to labeling requirements and recommendations from any relevant regulations or statute, and device-specific guidances, we recommend that you include a chart and/or graph in your labeling that provides the dimensions (i.e., length, width, depth, and volume) of the thermally affected tissue region in relation to the power setting, and duration of activation for different tissue types. This information is important to inform users of the expected damage and to facilitate safe use.