Photobiomodulation (PBM) Devices - Premarket Notification [510(k)] Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.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: Surgical & Infection Control Devices / DHT4A: General Surgery Devices at (301) 796-6970.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This draft guidance document provides draft recommendations for 510(k) submissions for photobiomodulation (PBM) devices, also known as low level light therapy (LLLT) devices, which are intended for use in applications such as aesthetics, dermatology, and other general indications. The device is designed to deliver a non-heating dose of light energy into the body to provide clinical benefit to the patient. The recommendations reflect current review practices and are intended to promote consistency and facilitate efficient review of these submissions.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. For more information regarding use of consensus standards in regulatory submissions, refer to FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[1]

In general, FDA guidance documents, including this 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.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

II. Background

For the purpose of this guidance, the term "photobiomodulation" is defined as the application of light at an irradiance that does not induce heating with the goal of altering biological activity.[2] The PBM device may use a light source that is coherent (laser) or non-coherent (filtered broadband lamps or light-emitting diodes (LED)), or a combination of both. PBM is commonly provided by using light in the visible and near infrared spectral ranges, but PBM effects are not exclusive to these ranges. PBM therapy is provided at a much lower fluence and irradiance compared to ablative or coagulating light devices such as those using high power lasers or intense pulsed light (IPL) sources. The mechanism of actions for PBM for different clinical indications is not fully understood. Outcomes are dependent on many factors such as wavelength of light, fluence, irradiance, pulsing parameters, and beam spot size.

This guidance supplements other FDA guidance documents regarding the specific content requirements and recommendations of a premarket notification (510(k)) submission. You should also refer to 21 CFR 807.87 and FDA's guidance, "Format for Traditional and Abbreviated 510(k)s."[3]

III. Scope

The scope of this document is limited to the class II PBM medical devices[4] regulated under 21 CFR 878.4810, 878.4860, 878.5400, and 890.5500 and with product codes listed in the table below:

Table 1. Product codes within the scope of this guidance.

Product Code	Regulation Number	Product Code Name
GEX[5]	878.4810	Powered laser surgical instrument
OLP	878.4810	Over-the-counter, powered, light based laser for acne
OHS	878.4810	Light based over the counter wrinkle reduction
OKJ	878.4860[6]	Light based treatment for cold sores herpes simplex virus-1

[2] *Semin Cutan Med Surg*. 2013 March; 32(1): 41–52.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-traditional-and-abbreviated-510ks-guidance-industry-and-fda-staff.

[4] Note that, as used in this guidance, "class II" refers to the medical device classification and not the laser classification as defined in 21 CFR 1040.20. Any class laser (I thru IV) can be classified as a class I, II, or III medical device depending on the intended use and technology for the specific device.

[5] Not exclusive to PBM devices. Devices that are not PBM devices under this product code are outside the scope of this guidance document.

[6] Devices in this classification are subject to special controls. See 21 CFR 878.4860(b).

OLI	878.5400[7]	Fat reducing low level laser
OAP	890.5500	Laser, comb, hair
NHN	890.5500	Powered, light based, laser, non-thermal instrument with non-heating effect for adjunctive use in pain therapy

The scope of this guidance also pertains to the PBM component of devices that combine a PBM device listed in the table above with another device(s) (e.g., electrostimulation source, mechanical massager, or ultrasound) in a single system operating simultaneously or sequentially to achieve a desired clinical effect.

Light-emitting products that are intended for only general wellness use and present a low risk to the safety of users and other persons, are not within the scope of this guidance. For details on whether or not your device is a general wellness product, refer to the guidance "General Wellness: Policy for Low Risk Devices."[8]

Some of the recommendations in this guidance may assist in complying with some of the special controls for light based treatment devices for cold sores herpes simplex virus-1 and fat reducing low level lasers. For information regarding special controls for light based treatment devices for cold sores herpes simplex virus-1, see 21 CFR 878.4860(b). For information regarding special controls for fat reducing low level lasers, see 21 CFR 878.5400(b) and "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use."

For specific questions or feedback on your proposed clinical or bench testing to show substantial equivalence of your device, we recommend that you contact the Agency through the Q-submission process to obtain further guidance. For details on the Q-Submission Program, please refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[9]

IV. Premarket Submission Recommendations

A. Device Description

We recommend you identify your device by the applicable regulation number and product code indicated in Section III above and include the information described below for devices incorporating a PBM light source with specific attention to the recommendations applicable to the indications for use (IFU) for your device. The technical parameters of the device

[7] This classification regulation is subject to special controls. See 21 CFR 878.5400(b) and "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use" available at https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/low-level-laser-system-aesthetic-use-class-ii-special-controls-guidance-industry-and-fda-staff.

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices.

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

characteristics described in recommendations 3-8 below should be measured by testing the final version of your device. The measurement or derivation methods that were used should be provided as a part of the bench testing information. Note that the technical parameters of cold sore devices, including wavelength, treatment time, treatment area, energy density, spot size, and power, must be characterized (21 CFR 878.4860(b)(1)).

(1) Anatomic Areas of Use

We recommend you provide a detailed description of the anatomic areas of use of the device, including the following information:

- The size and the shape of the anatomical site that will be illuminated by treatment light during the treatment procedure, the distance of the light source from the site during treatment, and the means by which this distance will be maintained during treatment.
- The number of treatments per session, number of sessions per week, and the total number of sessions.
- Instructions for treatment area preparation, pre- and post- procedure evaluation, and post-procedure care.

(2) Light Generation

We recommend you describe the details of the light or laser generation method. This description may include the laser gain medium, pumping source, and the technology used for pulsing, as applicable. If the light is generated without a gain medium (e.g., by broadband lamps or LEDs), we recommend providing detailed specifications and engineering drawings of the light source(s).

(3) Wavelength

We recommend you identify the individual wavelength or the range of wavelengths of light in nanometers (nm) that will be delivered to the patient's body by the device.

(4) Energy Fluence (Radiant Dose)

We recommend you identify the total energy (in J or mJ) and total fluence (or radiant dose defined as energy per area, usually in J/m^2 or mJ/cm^2), delivered at each spot on the tissue surface. If the clinical treatment procedure includes multiple steps, the submission should identify the energy delivered to a spot at each step as well as the total energy delivered to a spot.

(5) Spot Size

We recommend you describe the spot size(s) (in mm) that will be used for the procedure.

(6) Output mode

We recommend you indicate whether the light output mode is pulsed or continuous wave (CW) or another novel output mode.

(7) Radiant Power and Irradiance

We recommend you identify the radiant power (W) and irradiance (radiant power per area, usually in W/m^2 or mW/cm^2) that will be delivered to the tissue during the procedure.

(8) Pulsing Parameters (if applicable)

We recommend you describe the following parameters for pulsed lasers and light sources:

- Pulse duration (in milliseconds): The length of time during which the instantaneous laser power is at least half the peak power;
- Pulse shape: Square, Gaussian, Trapezoid, etc.;
- Energy per pulse (mJ): Energy delivered during a single pulse;
- Fluence per pulse (mJ/cm^2): Energy delivered per area per pulse during a single pulse;
- Duty cycle (%): The percentage of time the laser is on;
- Repetition rate (Hz): Number of pulses delivered at each second;
- Laser beam profile: Circle, Line, Square, Gaussian, etc.; and
- Average Power: Energy delivered per each second.

B. Predicate Comparison

For devices reviewed under the 510(k) process, manufacturers must compare their new device to a similar legally marketed predicate device to support its substantial equivalence (section 513(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR 807.87(f)). This comparison should provide information to show how your device is similar to and different from the predicate. Side by side comparisons, whenever possible, are desirable. See below for an example of how this information could be organized. This table is not intended to represent an exhaustive list of comparative parameters; ensure you provide all relevant device descriptive characteristics as outlined in the "Device Description" section, above.

Table 2. Sample predicate comparison table to outline differences and similarities between the subject and predicate devices.

Description	Subject Device	Predicate Device (Kxxxxxx)
Indications for Use		
Output wavelength(s)		
Energy fluence		
Irradiance		
Treatment regimen		
Spot size		
…		

C. Labeling

The premarket notification must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Proposed labels and labeling, sufficient to describe the PBM device, its intended use, and the directions for use must be provided.

PBM devices that are prescription devices are exempt from having adequate directions for lay use under section 502(f)(1) of the FD&C Act as long as the conditions in 21 CFR 801.109 are met. For instance, labeling must include adequate information for practitioner use of the device, including indications, effects, routes, methods, frequency and duration of administration and any relevant hazards, contraindications, side effects and precautions. (21 CFR 801.109(d).)

PBM devices that are over the counter devices must include adequate directions for use (21 CFR 801.5). The labeling (e.g., package insert) must describe the intended use of the device and include a listing of indications (21 CFR 801.5(a)). The labeling recommendations below are not intended to capture all possible limitations or instructions for all PBM devices. Therefore, when developing your labeling, it may be necessary for you to include additional limitations (e.g., contraindications, warnings, precautions, adverse reactions), and other instructions that are appropriate for your device, depending on its specific design, features, and performance characteristics, and depending on the results and conclusions drawn from a usability study (see Section G).

Note that the labeling for cold sore devices must direct end-users to contact the device manufacturer and MedWatch if they experience any adverse events when using the device (21 CFR 878.4860(b)(5)). Labeling for cold sore devices also must include specific information pertinent to use of the device by the intended patient population and the treatment regimen (21 CFR 878.4860(b)(6)). See "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use"[10] for labeling special controls for fat reducing low level lasers (21 CFR 878.5400).

In addition to the labeling requirements in 21 CFR part 801 and 21 CFR 1010.2 and 1010.3, the user manual/operator manual/package insert/box labeling should include the following information:

(1) Indications for Use

You should provide a clear statement of your device's Indications for Use. If your device consists of multiple components with different indications, we recommend that you specify this in your labeling. If your device is intended for use with another device, we recommend that you identify that device in your labeling.

(2) Warnings

We recommend you prominently display (e.g., using emphasized text) appropriate warnings in the instructions for use regarding how to avoid known hazards associated with the use of your PBM devices. We believe such warnings should include the following information:

- A statement regarding the long term effects of prolonged use of the device.
- A statement that warns against the use of non-thermal lasers during pregnancy.
- A statement that warns against using non-thermal lasers over or near cancerous lesions.

[10] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/low-level-laser-system-aesthetic-use-class-ii-special-controls-guidance-industry-and-fda-staff.

- A statement that warns of the risks of injury resulting from misuse of device.

Specific examples of warnings that follow these recommendations are provided in **Appendix B**.

(3) Precautions

We recommend you prominently display appropriate precautions (e.g., using emphasized text) for the safe and effective use of the device in the instructions for use. We believe such precautions should include the following information:

- A statement regarding the use of safety glasses by patient during treatment.
- A statement that caution should be exercised when using the device over skin area that lacks normal sensation.
- A statement that the device should be used with only manufacturer recommended accessories.
- A statement that the ingress of any liquid should be avoided.

Specific examples of precautions that follow these recommendations are provided in **Appendix B**.

(4) Overview of Clinical Studies

If applicable, we recommend including in your instructions for use an overview of the results of clinical studies conducted with the device.

D. Reprocessing

Significance: Many of the patient contacting components of PBM devices are reused and should be adequately cleaned and disinfected between uses to minimize infections while preventing device degradation.

Recommendation: You should provide instructions on how to reprocess a reusable device that is provided non-sterile to the user. Such instructions are important to ensure that the device is appropriately prepared for its initial and subsequent uses. For recommendations regarding the development and validation of reprocessing instructions in your proposed device labeling, refer to FDA's guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."[11]

Note that for cold sore devices, the cleaning and disinfection instructions for the device must be validated (21 CFR 878.4860(b)(2)).

E. Biocompatibility

Significance: PBM devices contain patient-contacting materials, which, when used as intended, (i.e., contact type and duration), may induce a harmful biological response.

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling.

Recommendation: You should determine the biocompatibility of all patient-contacting materials present in your device. If your device is identical in composition and processing methods to a PBM device with a history of successful use, you may reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to provide a reference to either a recognized consensus standard, or to a Letter of Authorization (LOA) for a device Master File (MAF). You should refer to the following FDA webpage for additional information on using device MAFs: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

If you are unable to identify a legally marketed predicate device with similar location/duration of contact and intended use that uses the same materials as used in your device, we recommend you conduct and provide a biocompatibility risk assessment. The assessment should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and identify any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks.

We recommend that you follow FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'"[12], which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

As described in ISO 10993-1: *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and Attachment A of FDA's guidance on ISO-10993-1, PBM devices are typically considered surface devices in contact with intact skin for a limited contact duration (less than 24 hours). Therefore, we recommend the following endpoints be addressed in your biocompatibility evaluation:

- cytotoxicity;
- sensitization; and
- irritation or intracutaneous reactivity.

Note that cold sore devices must be demonstrated to be biocompatible (21 CFR 878.4860(b)(3)). See "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use"[13] for special controls related to biocompatibility for fat reducing low level lasers (21 CFR 878.5400).

F. Software

Significance: Software in PBM devices ensures that appropriate energy is delivered to the patient within an appropriate timeframe. Adequate software performance testing provides assurance that the device is operating within safe parameters.

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

[13] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/low-level-laser-system-aesthetic-use-class-ii-special-controls-guidance-industry-and-fda-staff.

Recommendation: Refer to the FDA software guidance "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"[14] for a discussion of the software documentation that you should provide in your submission. The software guidance outlines the type of documentation to be provided based on the "level of concern" associated with the device. FDA generally considers the software for PBM devices to present a "minor" or "moderate" level of concern. PBM devices with software functions limited to an 'on'/'off' switch and/or 'timer function' may fall under a "minor" level of concern, in comparison to a "moderate" level of concern for devices whose software controls treatment parameters.[15] However, new indications, applications, or technological characteristics may result in a higher level of concern. If you believe that the software in your device presents either a "minor" or a "moderate" level of concern as defined in the software guidance, we recommend you provide a scientific justification that supports your rationale for the level of concern based on the possible consequences of software failure.

We recommend that you provide a full description of the software/firmware supporting the operation of the subject device following the software guidance, commensurate with the appropriate level of concern. This recommendation applies to original device/systems as well as to any software/firmware changes made to already-marketed devices. Changes to software must be re-validated and re-verified in accordance with Design Controls, 21 CFR 820.30(g)(i), and documented in the Design History File, 21 CFR 820.30(j). Some software changes may warrant the submission of a new 510(k). For further information on this topic, refer to "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."[16]

As appropriate, we also recommend you provide information on the cybersecurity aspects of your device. For more information on this topic, see FDA's guidance "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[17]

If your device includes off-the-shelf software, we recommend you provide the additional information discussed in the FDA guidance documents titled "Off-the-Shelf Software Use in Medical Devices"[18] and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software,"[19] which provide additional information regarding medical devices utilizing off-the-shelf software.

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[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices.

[15] Note that the "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use" indicates that FDA believes that the software used to operate a low level laser for aesthetic use (21 CFR 878.5400) presents a "moderate level of concern" because a failure or latent design flaw could directly result in minor injury to the patient or operator.

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices-0.

[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices.

[19] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-networked-medical-devices-containing-shelf-ots-software.

Overall, we recommend that the documentation related to the software contained in your device provide sufficient evidence to describe the role of the software included in the device, and performance testing to demonstrate that the software functions as designed.

G. Usability Study Considerations for Over the Counter (OTC) Home Use PBM Devices

To support a marketing submission for an OTC PBM device, we recommend that you perform three usability studies to 1) demonstrate that lay users can correctly self-select themselves as being appropriate users of the device for the stated indication by reading the box labeling, 2) demonstrate that lay users can correctly and safely use the device after reading and following the instructions for use, and 3) assess the understanding and comprehension by lay users of the patient labeling including all indications, contraindications, warnings and precautions. Note that for cold sore devices, simulated use testing must include information from a usability, label comprehension and self-selection study to demonstrate that the device can be used by the intended patient population without any assistance (21 CFR 878.4860(b)(7)).

We recommend that the following points be considered when conducting these studies:

- The studies can be conducted individually or can be combined. One or more of the usability studies can also be combined with a clinical study designed to assess safety and effectiveness of the device.

- The subjects enrolled for the usability studies should be representative of the intended use population.

- We recommend you initially test the patient labeling in a group of a few subjects. If needed, the labeling should be revised based on the outcome of a small study. This process should be repeated using small studies until there is no need for significant modifications to the labeling. Then, the final draft of the labeling should be tested in a larger study.

- Whenever the patient labeling is modified, the final version should be tested to demonstrate the revised labeling is effective in providing instructions to the intended patient population for the specific intended use.

- When applicable, changes made on one part of the labeling should be incorporated to the rest of the labeling. For example, changes to the box label should be incorporated in the instructions for use and vice-versa.

- We recommend you include important safety instructions and warnings (e.g., eye safety) on the box labeling to inform the self-selection and in case a layperson does not choose to read the instructions for use.

A study protocol can be submitted to FDA in a Pre-Submission to obtain FDA's feedback prior to conducting the study. For more information on the Q-submission program, refer to the following guidance document: "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[20]

Alternatively, you can provide a justification for why only a part or none of the three recommended usability studies should be provided to support a marketing submission for a PBM device intended to be marketed OTC. For cold sore devices, if a different approach was used to satisfy the special control for simulated use testing (21 CFR 878.4860(b)(7)), this information must be provided in your submission.

Devices used in the home or other non-clinical environments are associated with unique risks created by the interactions among the user (often a layperson), the use environment, and the device. Refer to the following guidance for factors that should be considered during home use device design and development: "Design Considerations for Devices Intended for Home Use"[21] Additional recommendations on patient labeling can be found in the FDA guidance "Guidance on Medical Device Patient Labeling"[22]

H. Electrical Safety and Electromagnetic Compatibility (EMC)

Significance: PBM devices are medical electrical equipment and therefore may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance.

Recommendation: PBM devices should be tested to demonstrate that they perform as anticipated in their intended use environment. We recommend that this testing be performed as described in the currently FDA recognized versions of the following standards for medical electrical equipment safety and electromagnetic compatibility:

- ANSI/AAMI ES60601-1: *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*

- ANSI/AAMI IEC 60601-1-2: *Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests*

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[21] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use.
[22] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-medical-device-patient-labeling.

Note that for cold sore devices, performance testing must validate electromagnetic compatibility (EMC) and electrical safety of the device (21 CFR 878.4860(b)(4)). See "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use"[23] for special controls related to electrical safety and electromagnetic compatibility for fat reducing low level lasers (21 CFR 878.5400). If submitting a declaration of conformity to the above standards, we recommend that appropriate supplemental information be provided, such as an assessment of the results and how conformity was determined, and information regarding test methods used. This is because the above series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria or address assessment of results. For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance, "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices."[24]

I. Wireless Technology

Significance: In the design, testing, and use of wireless medical devices, the correct, timely, and secure transmission of medical data and information is essential for the safe and effective use of both wired and wireless medical devices and systems.

Recommendation: If your PBM device incorporates radiofrequency wireless technology such as Bluetooth, IEEE 802.11 (Wi-Fi™), or radio frequency identification (RFID) technology, we recommend testing beyond what is specified in the IEC 60601 standards to demonstrate that the wireless device functions will perform as intended in environments with other wireless products. For additional recommendations for home use devices with wireless technology, please refer to FDA's guidance "Design Considerations for Devices Intended for Home Use".[25]

We recommend that you consult FDA's guidance, "Radio Frequency Wireless Technology in Medical Devices"[26] for additional recommendations on this topic.

J. Thermal Safety

Significance: PBM devices are not intended to raise skin or body temperature as the mechanism of action. However, it is possible for some PBM devices with relatively higher irradiances or devices that cover certain parts of the body (e.g., masks and helmets) to increase the tissue temperature to dangerous levels if used for long periods of time and/or in close contact.

[23] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/low-level-laser-system-aesthetic-use-class-ii-special-controls-guidance-industry-and-fda-staff.
[24] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/information-support-claim-electromagnetic-compatibility-emc-electrically-powered-medical-devices.
[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use.
[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/radio-frequency-wireless-technology-medical-devices-guidance-industry-and-fda-staff.

Recommendation: For PBM devices that can unintentionally increase the tissue temperature, the risk of burning the patient should be mitigated. We recommend that you demonstrate that no tissue damage will be caused by your device, using appropriate technological comparisons or performance testing data, such as skin temperature measurements. If your device is likely to induce tissue damage due to inadvertent overuse, we recommend placing built-in time limits in the software or firmware of your device, especially for an over-the-counter device. We also recommend using tissue temperature sensors to detect any potential harmful temperature rise and shut off device output, when needed.

K. Eye Safety

Significance: PBM devices pose a risk for ocular tissue damage as they may deliver energy and irradiance values greater than the maximum permissible exposure for the patient's or user's eyes.

Recommendation: When a PBM device has the potential to harm the eyes of an operator or a treated individual, safety measures, such as the use of safety eyewear and/or skin contact sensors, should be included in the instructions for use to mitigate the risk. We recommend that you measure the energy and irradiance output values of your device to determine which safety measures, if any, would be appropriate. Note that cold sore devices performance testing must validate ocular safety of the device (21 CFR 878.4860(b)(4)).

L. Clinical Performance Testing

Significance: In some cases, non-clinical evaluation does not fully characterize all clinical experience, outcomes, and risks. In such cases, we recommend that you conduct *in vivo* (i.e., clinical) studies to evaluate device safety and effectiveness for new and modified PBM devices. Compared to the predicate device, changes in indications for use, output parameters, or treatment regimen may warrant clinical studies to assess the clinical benefit of the PBM device.

Recommendation: We recommend you conduct *in vivo* (i.e., clinical) studies to determine the safety and effectiveness for new and modified PBM devices when the device is operated by the intended user, on the target population, and as instructed in the labeling. In order to provide this information, we recommend that clinical studies of the PBM device be designed to reflect the use in the intended populations as closely as possible. Note that for cold sore devices, clinical data must show adequate reduction in time to healing and assess risks of redness, discomfort, burns, and blisters (21 CFR 878.4860(b)(8)). See "Class II Special Controls Guidance Document: Low Level Laser System for Aesthetic Use"[27] for special controls related to clinical testing of fat reducing low level lasers (21 CFR 878.5400).

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. Generally, we believe PBM devices

[27] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/low-level-laser-system-aesthetic-use-class-ii-special-controls-guidance-industry-and-fda-staff.

within the scope of this guidance are non-significant risk devices; therefore, the study would be subject to the abbreviated requirements of 21 CFR 812.2(b). However, if your PBM device is intended to treat a disease or condition in a way that would alter the standard of care (e.g., trauma treatment) then the device could be considered a significant risk device subject to all requirements of 21 CFR 812. See the FDA Guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[28] In addition to the requirements of 21 CFR Part 812, sponsors of such trials of a device conducted in the United States must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

When data from clinical investigations conducted outside the United States are submitted to FDA for these devices, the requirements of 21 CFR 812.28 may apply.[29] 21 CFR 812.28 outlines the conditions for FDA acceptance of clinical data from investigations conducted outside the United States when submitted to support premarket submissions. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."[30]

In some cases, "real-world data" (RWD) can be used to support expansion of the indication for a device for which 510(k) clearance has already been obtained as long as the intended use of the device remains the same. Whether the collection of RWD for a legally marketed device requires an IDE depends on the particular facts of the situation. Specifically, if a cleared device is being used in the normal course of medical practice, an IDE would likely not be required. For additional information regarding this topic, please refer to the FDA Guidance entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[31]

FDA encourages you to seek early feedback on your proposed study design using the Q-submission process. For information on the Q-submission process see FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[32]

(1) Purpose/Objective

We recommend that the study objectives be defined to support the performance of the device as described in the proposed indication for use. Performance assessments should generally address both the desired outcome(s) (i.e., effectiveness) and potential undesired effects, to support benefit-risk analysis. The outcomes of the study should be evaluated in the context of performance previously demonstrated for the predicate device(s); therefore, the objectives of the

[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

[29] This applies to data from clinical investigations that began on or after February 21, 2019, and are submitted to support a premarket submission, including IDEs, premarket approval (PMA) applications, and 510(k)s.

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked.

[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

study should be designed to facilitate comparative analysis. For example, a device for hair growth could be designed with an objective to determine the increase in number of terminal hairs per centimeter. To demonstrate substantially equivalent performance, the mean increase in hair density of the subject device would then be compared to the increased density when using the predicate device in its clinical studies.

(2) Controls

For most indications treated with PBM devices, control arms will aid in distinguishing device-induced effects from background effects, such as placebo or natural history of the condition. Depending on the indications for use, appropriate strategies may include contralateral control, sham treatments, or other control designs that allow the investigator to compare the changes in areas exposed to PBM with the changes in a matched body area that was not exposed to PBM. We recommend that treatment and control assignments be blinded from the study subjects and from the investigator(s) performing the post-treatment evaluations.

(3) Inclusion/Exclusion Criteria

We recommend that selection of study subjects include all subjects for whom a device is intended, with qualifying criteria for minimum or maximum severity of the condition to be treated, when appropriate. However, some subjects whose condition would warrant their inclusion in the study may not be appropriate candidates due to safety concerns related to their health, age, skin type, co-existing or prior conditions or treatments, or other factors that might be negatively impacted by the test treatment or the control treatment.

When developing your clinical study, we recommend you consider the following parameters or characteristics in your inclusion and exclusion criteria, including but not limited to:

Inclusion:

- Age: The age range should reflect that of the expected population for the proposed indication for use. Studies that involve pediatric or geriatric patients may warrant additional considerations to address potential for variable performance in these populations. For more information regarding the evaluation and reporting of age, race, ethnicity and sex-specific data in medical device clinical studies, see FDA's guidances "Evaluation of Sex-Specific Data in Medical Device Clinical Studies"[33] and "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies."[34]

- Sex: For certain indications, sex may impact the natural history of the condition being treated as well as the response to treatment. In such circumstance, studies could be designed to limit enrollment based on sex. You should note that, in these cases, subsequent labeling should reflect the study population sex.

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug.

[34] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies.

- Skin type: Different Fitzpatrick skin phototypes may have different treatment-emergent risks with energy-based treatment. In designing the study and the inclusion/exclusion criteria, we recommend you consider whether your device would be applied differently for individuals with darker or lighter Fitzpatrick skin phototypes. This consideration may affect whether you include a separate treatment protocol (e.g., different energy output) for a subgroup of subjects or whether the subgroup should be excluded from the study. Due to increased risk of adverse events in certain skin types, the labeling should reflect the skin types evaluated in the conducted clinical studies.

- Body site: Certain Indications for Use statements may specify body sites. In such cases, performance testing on the specific body sites may be needed. For an indication for use for the whole body, data obtained from three or more discrete anatomic locations justified to be representative of the entire body may sufficiently represent the entire body of the patient.

- Subtype and/or severity: For some disorders, you may choose to exclude very mild or very severe disease due to benefit-risk considerations, or to limit enrollment to subjects with specific subtypes of the disorder. When studies are performed in a subtype- or severity-restricted population, labeling should reflect the range of severity for which performance testing data is available.

Exclusion:

- General health considerations for safe participation in a study.

- Photosensitivity disorder to light in the spectrum delivered by the device.

- Photosensitizing medication use.

- Pregnant; planning pregnancy before the end of the study; of childbearing potential and not using birth control; or lactating.

- Active infection, wound, or skin lesion in the area to be treated (unless the indication being assessed is treatment of an active infection, wound, or skin lesion).

- Skin cancer or history of skin cancer at the treatment site.

- Active or recurrent cancer of any organ, or current chemotherapy and/or radiation treatment.

- States of immune compromise.

- Collagen vascular or autoimmune disease.

- Co-existing medical conditions or treatments that may increase the risk of complications, reduce the response to treatment, confound the interpretation of results, or which necessitates an intervention with demonstrated effectiveness rather than experimental intervention.

- Emotional or mental health concerns.

- Elements of lifestyle such as smoking, physical activity, sun exposure, certain food/beverage consumption or restrictions that may impact the safety or effectiveness of the intervention.

Further inclusion and exclusion criteria should be determined by the study design and technological characteristics of the device.

(4) Radiant Dose Selection

As with any energy delivery device, proper dose selection should be justified with testing or derived from known safety and effectiveness attributes given a specific wavelength or wavelengths of light energy. Dose selection should encompass irradiance, pulse width, pulse frequency, and duration of exposure. Dose selection may also be impacted by the subject's Fitzpatrick skin phototype disease severity, etc. We recommend that the choice of output settings and treatment schedule be justified and, when warranted, confirmed in pilot studies prior to initiation of pivotal studies. However, some dose selection could be attempted via use of adaptive design elements in the proposed clinical study. For more information, refer to FDA guidance "Adaptive Designs for Medical Device Clinical Studies."[35]

(5) Study Endpoints

The study endpoints should be identified prior to study initiation. We recommend the following be considered when selecting your study endpoint(s):

- The characteristic that will be assessed (e.g., hair growth, reduction in acne, improvement in periorbital wrinkles, reduction in circumference at a pre-specified location).

- The metric that will be used, employing objective quantitative data when possible (e.g., hairs/cm^2 or lesion count). Validated scales and patient reported outcomes can be used in conjunction with objective measures and as endpoints.[36] For endpoints that involve observable changes, endpoints should quantify the change. The primary data, including physical measurements and photographs upon which the endpoints rely, are an integral part of the evaluation process and should be provided in your submission or made available for review.

[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies.

[36] FDA guidance "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation" can be found at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use.

- Criteria for success, per subject and per study (e.g., the increase in hair count that will define a subject as a responder, and the percent of responders that will define study success).

- The time at which endpoints are assessed. The time points at which evaluation is performed should be determined by the proposed indications for use, expected timeline for response, and known history of the target disorder.

- A measurement of safety as well as effectiveness. Safety endpoints will vary with the mechanism of the device. Since devices may be operated at variable parameters, both safety and effectiveness endpoints should be assessed across the spectrum of parameters that is expected to be employed in clinical use of the device.

- Device parameter ranges. Energy-based device treatments may produce dose-related responses. The inclusion of a range of treatment parameters may affect the choice or definition of endpoints, as well as the statistical analysis plan, the number of subjects enrolled, and the labeling.

- When endpoints include subjective outcomes, we strongly recommend that external observers who are blinded to the history of the treatment are utilized. We recommend the inclusion of three observers as it strengthens the data validity by reducing equivocal or contradictory scores. If proposing a study design that varies from this recommendation (e.g., fewer number of observers), we recommend you consult with the FDA.

(6) Study Duration and Follow-Up Schedule

The duration of follow-up will depend on the indications for use. We recommend that the study duration and follow-up schedule be based on the anticipated interval needed to assess the durability of the response, as well as the duration and consequent effects of any adverse events, and the incidence of delayed adverse events.

In the analysis of safety, follow-up schedules are best designed to detect both early (acute) and delayed adverse events. In the analysis of effectiveness, the duration and frequency of follow-up assessments depend on the known and/or expected tissue effects.

Devices that are intended for ongoing or maintenance use may warrant different follow-up timelines for monitoring.

(7) Statistical Considerations

We recommend that clinical studies for PBM devices be well designed with valid statistical analysis plans. The statistical analysis plan should be developed in conjunction with the study design to ensure the data set will be robust. For more information on design of statistical analysis

plans, we recommend you refer to FDA guidance titled "Design Considerations for Pivotal Clinical Investigations for Medical Devices."[37]

(8) Adverse Event Monitoring

We recommend that all adverse events related to PBM device procedures be recorded during the clinical study and reported in your submission in order to develop an accurate understanding of the risks and benefits of these devices.

M. Modifications

In accordance with 21 CFR 807.81(a)(3), a change or modification to a device in commercial distribution "that could significantly affect the safety or effectiveness of the device" or represents "a major change or modification in the intended use of the device" requires a new 510(k). The changes or modifications listed below would likely require submission of a new 510(k). Note that this list is not exhaustive but provides examples of modifications that FDA believes will generally require submission of a new 510(k). For additional details, see FDA guidances "Deciding When to Submit a 510(k) for a Change to an Existing Device"[38] and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."[39]

Such changes or modifications include:

- Changes to the light source, circuitry, or power supply of the device – FDA considers these changes to be modifications in design and energy source. FDA has determined that these changes could significantly affect safety of the device by changing laser safety, thermal safety (if the modified device is generating heat), electrical safety, and EMC.

- Change in light output or treatment regimen – FDA considers this change to be a modification in design. FDA has determined that this change could significantly affect both safety and effectiveness of the device by altering light induced tissue effects.

- Changing from prescription use to OTC use – FDA considers this change to be a significant change. FDA has determined that this change could significantly affect both safety and effectiveness of the device by changing the use environment and intended user.

FDA believes that the following changes or modifications would likely not require submission of a new 510(k):

- Cosmetic changes to the appearance of the device.

[37] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.
[38] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.
[39] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

- Changes to the labeling that do not affect the intended use, indications for use, or conditions of use.

Appendix A. Glossary of Terms

The definitions listed here are for the purposes of this guidance:

Coherent: Waves that are in-phase with one another.

Fluence: Light energy received by a surface per unit area.

Gain Medium: The solid, liquid, or gaseous medium that is usually placed between two mirrors which is called an optical cavity. Gain medium is used to convert the energy from the pumping source to a laser beam.

Irradiance: Light power received by a surface per unit area.

Melanin: Natural pigments in the skin.

PBM: Photobiomodulation, also known as low level light therapy (LLLT), is a therapeutic technique that uses low energy light to alter the function of the body.

Periorbital: Around the orbit of the eye.

Pulsed Laser: Any laser that delivers energy in pulses instead of a continuous wave.

- **Pulse duration (in milliseconds):** The length of time during which the instantaneous laser power is at least half the peak power.
- **Pulse shape:** Square, Gaussian, Trapezoid, etc.
- **Energy per pulse (mJ):** Energy delivered during a single pulse.
- **Fluence per pulse (mJ/cm^2):** Energy delivered per area per pulse during a single pulse.
- **Duty cycle (%):** The percentage of time the laser is on.
- **Repetition rate (Hz):** Number of pulses delivered at each second.
- **Laser beam profile:** Circle, Line, Square, Gaussian, etc.

Pumping Source: The energy source used to amplify light in the gain medium.

Skin Type: A scientific classification of human skin such as Fitzpatrick Skin Scale.

Wavelength: The distance between two successive wave crests; determines the color of the light in the visible spectrum.

Appendix B. Labeling Examples

The following provide examples of warnings and precautions for PBM devices that follow the recommendations provided in Section C. Labeling.

(1) Warnings

- The long term effects of prolonged use of non-thermal laser exposure are unknown.
- Safety of non-thermal lasers for use during pregnancy has not been established.
- Laser treatment should not be applied over, or in proximity to, cancerous lesions as conclusive tests have not been conducted.
- Misuse of the device might lead to injury.

(2) Precautions

- To eliminate any possible danger to the eyes, safety glasses must be worn by the patient during treatment.
- Caution should be used over areas of skin that lack normal sensation.
- Use only with accessories recommended by manufacturer.
- Avoid the ingress of any liquid.