Q220469
Openwater
Prabhu Raghavan

Re: Written Feedback for Openwater LOFU Therapy System

This document is being communicated via e-mail as an attachment. The date on which the Food and Drug Administration (FDA) sent this e-mail is the official date of this correspondence.

This document contains the FDA's written feedback to your Pre-Submission request. This feedback represents our best advice based on the information provided in the Pre-Submission and other information currently known. While our review of your Pre-Submission does not imply that your future submission will necessarily be approved or cleared, FDA intends that this feedback will not change, provided that the information submitted in a future IDE or marketing application is consistent with that provided in this current Pre-Submission and that the data in the future submission do not raise any important new issues materially affecting safety or effectiveness.

If you requested a meeting and this feedback satisfies your needs, you may cancel our upcoming meeting by contacting the lead reviewer. If you still wish to meet, please provide us with your agenda of items and any slides you wish to present no later than two business days prior to the scheduled meeting date per the Pre-Submission Guidance https://www.fda.gov/media/114034/download. If that agenda or presentation contains significant new information, FDA may not be prepared to discuss it. As a reminder, you are expected to submit draft meeting minutes as an amendment to this pre-submission within 15 days of the meeting.

Our feedback to your pre-submission questions is provided below.

Sponsor Question

1. **Does FDA agree that the proposed regulatory pathway is appropriate for OLTS? Specifically,**
   a. **Does the FDA agree that based on the regulatory strategy provided and the device's risk profile, the subject device may be classified as a Class II device?**
   b. **Does the FDA agree that based on the regulatory strategy provided that a de novo pathway would be appropriate?**

Official FDA Response

According to 201(h) of the Federal Food, Drug and Cosmetics (FD&C) Act a medical device is defined as:

- *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*

- *intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."*

It appears that the device, as described in the submission, has no specific "intended use" or "indication for use" for diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals. However, the device does appear to be intended to affect the function of the body of man, per the information provided in the submission. Although you have proposed an indication for use, the indication for use does not provide sufficient specificity for the FDA to determine the appropriate regulatory pathway for your device. Hence, the De Novo pathway may not be the appropriate regulatory pathway for your device at this time. If your intent is to study the device for a specific indication for use, the FDA recommends the submission of an investigational device exemption. For more information regarding IDE submissions, we recommend you review the information found in the FDA "IDE Guidance" landing page at: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-guidance. Also, see our response to Sponsor Question three. Per our response to Sponsor Question five of this submission, you may wish to consider the submission of a Masterfile. Alternatively, if you would like an official determination regarding an appropriate future marketing submission, the FDA recommends you submit a 513(g) request. Please refer to our December 16, 2019 guidance "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act" (https://www.fda.gov/media/78456/download) for additional information regarding the 513(g) process.

Sponsor Question

2. **Does the Agency have any comments on the proposed special controls for the subject device discussed in Section 6?**

Official FDA Response

You have provided a set of proposed special controls based on special controls for transcranial ultrasound diagnostic devices and transcranial magntic stimulation devices (TMS). However, it is unclear how the proposed special controls provide a reasonable assurance of safety and effectiveness for any potential indication for use, any potential environment of use, or any potential use case of the device. As the device has no specific indication for use nor specific preclusions, the potential range of risks is broader than those of either TMS or transcranial ultrasound diagnostic devices. Therefore, we do not believe the proposed special controls could adequately establish safety and effectiveness over a wide range of conditions and diseases associated with various brain targets and that have highly variable risk profiles. If you intend to propose special control, the FDA recommends you do so in consideration of the result of your specific indication for use and safety data collected from your clinical trials.

Sponsor Question

3. **When the OLTS device has successfully has been granted a de novo by the FDA, Openwater intends to market the device for neuromodulation clinical research without requiring an IDE. When such clinical research can establish efficacy for specific claims (e.g., treatment of mood disorders), Openwater would approach the Agency for a premarket submission for these efficacy claims.**

For efficacy claims similar to TMS devices that are regulated as Class II devices, could Openwater use the OLTS de novo as a predicate to expand the indications for use in a 510(k) premarket submission or would the efficacy claims require a de novo premarket submission? Does the FDA have any comments on the regulatory approach for future LOFU-based neuromodulation efficacy submissions using the OLTS device?

Official FDA Response

As stated previously the device as intended for clinical research will not be appropriate for a De Novo submission. Furthermore, granting, clearing, or approving a device for interstate commerce in the United States via a De Novo, 510(k), or PMA submission does not necessarily circumvent the need for or requirements of an investigational device exemption (IDE). As stated previously, it appears that the appropriate pathway for use of your device for clinical research is the IDE. For an official decision on the need for an IDE when studying a device for a specific indication for use, the FDA has established the Study Risk Determination (SRD) Q-Submission process. As such, the FDA recommends the submission of an SRD prior to initiating a clinical study with your device. For additional information regarding SRD submissions, please review the FDA guidance document published on January 6, 2021, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" (https://www.fda.gov/media/114034/download). Additionally, please refer to the January 2006 FDA information sheet guidance, "Significant Risk and Nonsignificant Risk Medical Device Studies" (https://www.fda.gov/media/75459/download) for information regarding how to determine the differences between significant and non-significant risk medical device studies. Please note that significant risk medical devices do require an approved IDE before conducting research involving human subjects.

Sponsor Question

4. **Does the FDA have any comments on the proposed testing plans to assess device performance, as described in Section 7, for a future device submission?**
   a. **Does the FDA have any comments on the proposed bench testing plan for the OLTS? Are there any specific considerations that Openwater should additionally include in its test plans?**
   b. **Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that animal performance testing data is not needed to support a future device submission?**
   c. **Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that clinical performance testing data is not needed to support a future device submission?**
   d. **Does FDA agree that the OLTS software is a "Moderate" level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA's recommendations provided in FDA's guidance entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" as part of the premarket device submission?**

Official FDA Response

You have requested feedback on your intended testing plan. However, your testing plan appears to preclude any animal or clinical investigations with the subject device. It is important to note that it is incumbent upon the submitter of a pre-market submission to demonstrate the safe and effective use of the device for its intended use, which may include bench testing, animal investigations, and clinical investigations. After review of the information provided, the Agency has the following feedback:

a. Thermal testing could provide valuable safety data, particularly on the outer surface of the skull. It is recommended that you place the thermocouples between the skull and a skin mimicking phantom. Depending on the type of thermocouples used, it is advised you correct for viscous artifacts (see, Investigation of the viscous heating artefact arising from the use of thermocouples in a focused ultrasound field, https://iopscience.iop.org/article/10.1088/0031-9155/53/17/020/meta) to avoid potential over-estimation of temperature.

   Ultrasonic output testing and reporting that follows IEC 62555 and IEC 61161 is generally appropriate. It is important that the device output under maximum output conditions is specified (See Additional Feedback below).

   Additionally, *Standard Operating Mode (SOM)* will use a numeric model to predict the acoustic pressure in the brain. Acoustic output would then be increased to compensate for the predicted level of attenuation, up to an mechanical index (MI) of 1.9. However, if the model were to over-predict attenuation, the actual MI in the brain could exceed this value. While simulations (including k-wave) have been relatively successful in predicting skull induced scattering and diffraction, there is little data to show they accurately predict the overall attenuation of an ultrasound field. This is due, in part, to the large natural variation in acoustic properties between skulls. It will be important to provide data showing that MI cannot exceed 1.9 in the brain. Otherwise, it may be necessary to provide additional data demonstrating safety under maximum output conditions.

b. Per the feedback addressed in previous questions, the FDA does not believe Openwater's regulatory strategy is appropriate. A future pre-market or Investigational Device Exemption submission may require animal data depending on the claimed intended use of the device, the associated risks for the intended population, and the results of available nonclinical safety data.

c. Per the feedback addressed in previous questions, the FDA does not believe Openwater's regulatory strategy is approipriate. A future pre-market submission may require clinical data depending on the intended use of the device and the associated risks for the intendeded population.

d. The FDA does not agree with the assertion that the software for the device is of a "moderate" level of concern. Although you assert that failure of the OLTS device "cannot result in the delivery of potentially harmful energy that could result in death or serious injury", you have provided no evidence to demonstrate the validity of this assertion. There is the potential to instigate tissue damage or other severe adverse events when stimulating the brain with ultrasonic energy. Furthermore, it is unclear the potential injuries that may occur if the OLTS planning software were to indicate inappropriate treatment parameters or locations. Thus, as there is the potential for death or serious injury to patients who may use the device due to failure of the software to perform as intended, the device is a "major" level of concern.

Sponsor Question

5. **Does the FDA have any other concerns or topics they would like Openwater to consider for OLTS premarket device submission?**

Official FDA Response

From the information provided it appears that Openwater has the impression that the availability of a device for interstate commerce precludes the need of IDE submissions for investigational use. However, devices that have been cleared, granted, or approved through a pre-market submission are still subject to the requirements of 21 CFR 812 and other human subject protection regulations as described in 21 CFR 50 when such device is a signicant risk device and is being studied for an intended use for which is has not been cleared, granted, or approved. In addition, a significant risk device that has not been cleared, granted, or approved through a pre-market submission is subject to 21 CFR 812 and other human subject protection regulations as described in 21 CFR 50 . If you intent is to streamline your clinical studies by reducing redundant submission of information or to maintain trade-secrets, the FDA offers Master File submissions for devices. The Master File does not grant authorization to introduce your device into interstate commerce in the United States, but does allow for a single reference point for IDE submissions and other marketing submission. For example, a Master File may be submitted that includes all nonclinical and animal test protocols and results that support the safety of the device for a clinical study that will be conducted under and IDE. As such, the FDA recommends you review the Master File submission process. Additional information regarding the Master File can be found on the Master File landing page at the following link: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

Although our review focused on addressing the questions you asked, in the course of reviewing your pre-submission, we also noted the following. This is not intended to be an exhaustive list of issues.

1. Eventual FDA submissions should include all relevant information about the acoustic characteristics and parameters to be used in the clinic, as determined from your planned test results. This would minimally include:

    a. A full description of the transducer surface geometry and any relevant matching or standoff materials.
    b. The instantaneous and time-averaged acoustic output power (or operational range of powers) of the transducer.
    c. The output frequency (or frequencies).
    d. Calibrated plots of the acoustic pressure field in water (without a skull or other tissues).
    e. The peak pressure of the underated field (in water) while operating at maximum clinical-level powers.
    f. The duty cycle, and any other pulse parameters that may be used during operation of the device.
    g. The maximum total sonication time(s) to be used clinically.

    This information is necessary for FDA to make a full assessment of the ultrasonic and thermal safety of the device.

2. Due to variations in terminology used to describe ultrasound neuromodulation sequences, a table with clear definitions and a schematic of ultrasound sequences would be helpful in any planned future submissions. Figure 1 and Table one from Blackmore, et al, Ultrasound in Med. & Biol.45(7) 1509:2019, is a useful guide. This information is necessary for FDA to make a full assessment of the ultrasonic and thermal safety of the device.

3. In several sections your submission states: **“**the theoretical threshold for bubble nucleation or inertial cavitation is 3.9MPa,” with reference to the AIUM Statement on Biological Effects of Ultrasound in Vivo. This reference does not provide a theoretical threshold. Part 2 of the Statement asserts:

   > **Experimental** values for the inertial cavitation threshold in vivo lie at or above approximately 3.6 MPa for frequencies of 0.5 MHz or greater.

   This value is taken from an experiment performed at ~0.56 MHz, with the understanding that the cavitation threshold varies inversely with frequency. Theoretical peak negative pressure thresholds are much lower than 3.9MPa. See, for example, Church, et al Ult Med Bio 41, P472, 2015 https://doi.org/10.1016/j.ultrasmedbio.2014.09.012. Please be advised that cavitation may occur in tissue at pressures below 3.9 MPa.

This notification is being sent in lieu of a formal written letter. If you have any questions, please contact Francisco Delgado at 301-796-0084 or Francisco.Delgado@fda.hhs.gov.