U.S. FOOD & DRUG ADMINISTRATION

April 13, 2020

Anthony R. Ignagni
Synapse Biomedical, Inc.
300 Artino Street
Oberlin, OH 44074

Dear Mr. Ignagni:

This letter is in response to your request that the U.S. Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for the emergency use of the TransAeris Diaphragmatic Pacing Stimulator System[1] (hereafter "TransAeris Diaphragm Pacing System") to assist in weaning patients determined by their healthcare provider to be at high risk of weaning failure[2] off of breathing assistance machines requiring patient intubation (hereafter referred to as "ventilators," described in Section II), in healthcare settings during the Coronavirus Disease 2019 (COVID-19) pandemic for no more than 30 days[3].

On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[4] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that

[1] This EUA includes the emergency use of the TransAeris Diaphragmatic Pacing Stimulator Model 20-1000-EUA (Denotes base product model, deliverable kit configurations denoted by 20-10xx). In general, Diaphragmatic Pacing Simulator Systems function by means of either phrenic nerve stimulation, or by stimulation of the diaphragm using surgically implanted temporary electrodes to prevent Ventilator Induced Diaphragm Dysfunction (VIDD). These systems include any surgical tools needed for implantation, as well as all of the components of the system that are needed for proper operation of the product (e.g., electrodes, power cord/supply, etc.).

[2] Patients at high risk of weaning failure include COVID-19 patients requiring ventilation and patients being mechanically ventilated for other high-risk conditions including post-cardiac and post-thoracic surgical procedures and medical ICU patients requiring prolonged ventilation. For these populations, transitioning patients off ventilators, when appropriate, may increase the availability of ventilators for use by patients during the COVID-19 pandemic. Modeling indicates that 30% of patients hospitalized will require critical care (invasive mechanical ventilation or ECMO). In those patients, the ventilator and bed demand will be 10 days in the ICU. If 40% of the time on ventilation is spent trying to wean off (4 days in this case) and the 64.5% reduction of that time with diaphragm pacing is applied, then this would mean that TransAeris Diaphragm Pacing System could shorten those 4 days to 2.6 days. This would effectively reduce the ventilator burden by 26% in the COVID-19 patients. Less time on the ventilator also decreases the risk of secondary pneumonia.

[3] Based on a review of the available scientific evidence, FDA believes that this authorized product may also help address concerns about ventilator availability in addition to helping treat patients.

[4] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. 85 FR 7316 (February 7, 2020).

circumstances exist justifying the authorization of emergency use of medical devices, including alternative products used as medical devices, during the COVID-19 outbreak, subject to the terms of any authorization issued under that section.[5]

There are no FDA approved, licensed, or cleared device treatments to assist in weaning patients off of ventilators. Based on bench testing and reported clinical experience, FDA has concluded that the TransAeris Diaphragm Pacing System may be effective at treating patients during COVID-19 by helping wean patients off ventilators in healthcare settings, thereby reducing their risks of prolonged mechanical ventilation and increasing the availability of ventilators during the COVID-19 pandemic. Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act are met, I am authorizing the emergency use of the TransAeris Diaphragm Pacing System, as described in the Scope of Authorization (Section II) and pursuant to the Conditions of Authorization (Section IV) of this letter.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the TransAeris Diaphragm Pacing System as described in the Scope of Authorization (Section II) of this letter for emergency use to assist in weaning patients off ventilators in healthcare settings during the COVID-19 pandemic meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

A. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the TransAeris Diaphragm Pacing System may be effective for emergency use to treat patients by assisting in weaning patients off ventilators in healthcare settings during the COVID-19 pandemic, and that the known and potential benefits of the such products, for such use, outweigh the known and potential risks of such product; and

C. There is no adequate, approved, and available alternative to the emergency use of the TransAeris Diaphragm Pacing System for treating patients during the COVID-19 pandemic.[6]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the TransAeris Diaphragm Pacing System for emergency use to assist in weaning patients determined by their healthcare provider to be at high risk of weaning failure

[5] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 17335 March 27, 2020.

[6] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

off of ventilators in healthcare settings during the COVID-19 pandemic for no more than 30 days.

Under this EUA, "ventilators" include any breathing assistance machine requiring patient intubation that are cleared, approved, or authorized[7] under the Act or are otherwise distributed and used consistent with FDA policy.[8]

Authorized Product

The TransAeris Diaphragm Pacing System is a temporary percutaneous intramuscular diaphragm stimulator intended for patients at risk of or on prolonged positive pressure mechanical ventilation. TransAeris is indicated for use in the prevention and treatment of VIDD. The TransAeris System includes four TransLoc intramuscular diaphragm electrodes, the TransAeris external stimulator, and the FrictionLoc connectors which provides the interface between the TransLoc electrodes and the TransAeris stimulator. Placement of the diaphragm electrodes can be performed in conjunction with another surgical procedure or as the primary procedure. TransAeris is used to provide neuromuscular electrical stimulation to the diaphragm while the patient is on mechanical ventilation to prevent, slow, or reverse diaphragm disuse atrophy and, more generally, to treat VIDD. Once the patient is successfully extubated after mechanical ventilation, the electrodes are removed from the patient.

The primary components of the TransAeris System are described below. The TransLoc electrode consists of a stainless steel helically wound lead with a distal deinsulated segment. Up to two electrodes are inserted into each, right and left, hemidiaphragm. The distal segment is inserted into the diaphragm with the curved needle, which is subsequently cut off. The proximal portion of the lead is brought out of the abdominal or chest wall with the straight percutaneous access needle, which is also subsequently cut off. The proximal leads are then inserted into the right and left FrictionLoc connectors. The TransAeris stimulator is then connected, via the right and left color-coded jacks, to the FrictionLoc connectors for use.

Once the patient is successfully extubated after mechanical ventilation, the electrodes are removed from the patient, through a simple retraction pull – as is done with temporary percutaneous epicardial leads. To avoid any transfer of nosocomial infections in the ICU environment, the entire system is disposed of after single patient use.

The external control box of the TransAeris System generates stimulation. The front panel of the TransAeris provides channel selection and parameter settings. Individual channels can be turned on/off or selected for changing stimulation intensity. The stimulation outputs are independent, capacitively coupled charge balanced waveforms that range

[7] On March 24, 2020, FDA issued an EUA authorizing certain ventilators, anesthesia gas machines modified for use as ventilators, and positive pressure breathing devices modified for use as ventilators. Devices authorized by this EUA at https://www.fda.gov/media/136423/download can be found in Appendix B at https://www.fda.gov/media/136528/download.

[8] Available at https://www.fda.gov/media/136318/download

from a minimum (0.1μC) to a maximum (5μC). The stimulus intensity and channel status is displayed above each channel selection button.

TransLoc Electrode

The TransLoc electrode is a unipolar temporary diaphragm stimulation and sensing lead. It consists of a de-insulated multi-filament 316LVM stainless steel electrode, that continues as an insulated multi-filament lead and terminates in a crimped pin at the proximal end. A blue monofilament extends through the length of the electrode and lead and terminates distally in an atraumatic curved needle and proximally in an atraumatic percutaneous access needle. The curved needle provides insertion of the electrode into the diaphragm muscle. The percutaneous access needle permits exiting the lead through the abdominal or chest wall. To remove the lead, gentle traction should be applied. No part of the lead remains in the body.

The pacing wires are for temporary use and are to be removed prior to hospital discharge. Wires are removed with gentle transcutaneous retraction with a slow steady pull in a straight, non-oblique line. It may be necessary to release dermal adhesions prior to performing the transcutaneous retraction.

FrictionLoc Connector

The FrictionLoc Connector provides the connection interface between the TransLoc electrodes and the TransAeris stimulator. Following the placement of all the electrodes in the diaphragm and percutaneous exit from the skin, the proximal end connector pin is inserted into the FrictionLoc connector. The slide switch on the connector locks the pin in place, making electrical connection to the TransAeris connector and cable. If the TransLoc electrode needs to be removed from the connector, the release button can be pressed and the slide switch moved to unlock the connector pin. Excess lead from the TransLoc electrode can be wrapped around the cletes on the side. A commercially available snap connect surface electrode (see accessories, below) is snapped onto the bottom of the FrictionLoc connector to hold it on the skin and provide the electrical path for anodic current return. If desired the surgeon can fasten the FrictionLoc connector to the skin, using the integral suture loops on the corners of the connector.

Accessories

Surface Electrode

A commercially available self-adhering surface electrode commonly used in neuromuscular electrical stimulators (NMES) is used as the anodic return path. The FrictionLoc connectors have an integral snap to attach the surface electrode on the bottom of each. An example suitable electrode would be the Axelgaard UltraStim 2” x 2” electrode (Model SN2020).

Diaphragm pacing with the TransAeris System works at neuromuscular junctions and with propagation of action potentials to surrounding motor end-plates. The TransLoc intramuscular electrodes are placed at locations on the surface of the diaphragm called the “motor point”. The motor points are the locations in the diaphragm in proximity to where the phrenic nerve axons enter and branches into many subsequent axon terminals.

Each axon terminal synapses with muscle sarcolemma for individual fiber contraction. By placing two TransLoc electrodes in each hemi-diaphragm at motor points, the greatest number of motor end-plates may be stimulated to create a diffuse contraction of the diaphragm. The proximity of the TransLoc electrodes to the motor point allows the spread of the electrochemical reaction and propagating action potentials induced by the stimulus charge to recruit the desired contraction strength without the risk of axonal degeneration or demyelination from contact with the phrenic nerve. The level and coordination of stimulus to each electrode is controlled by the external stimulator to provide a smooth and sufficient inspiration. Electrical activation of the diaphragm through motor point stimulation conditions the muscle to mitigate VIDD.

The above described product, when labeled consistently with the labeling authorized by FDA, entitled "TransAeris System User Manual" and "Surgical Procedures for Implantation of TransLoc Electrodes (for TransAeris System)" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations) is authorized to be distributed under this EUA, despite the fact that it does not meet requirements otherwise required by applicable federal law.

In addition, the authorized TransAeris Diaphragm Pacing System must be accompanied by the following information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Providers: Emergency Use of TransAeris Diaphragm Pacing System During the COVID-19 Pandemic
- Fact Sheet for Patients: Emergency Use of TransAeris Diaphragm Pacing System During the COVID-19 Pandemic

The "TransAeris System User Manual," "Surgical Procedures for Implantation of TransLoc Electrodes (for TransAeris System)" and two fact sheets are referred to as "authorized labeling." Synapse Biomedical, Inc. may request changes to the authorized labeling. Such requests will require concurrence of the Office of Health Technology 1, Office of Product Evaluation and Quality, Center for Devices and Radiological Health (OHT1/OPEQ/CDRH).

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized TransAeris Diaphragm Pacing System, when used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of such products.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized TransAeris Diaphragm Pacing System may be effective for emergency use in treating patients by assisting in weaning patients off ventilators in healthcare settings during the COVID-19 pandemic when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the authorized TransAeris Diaphragm Pacing System, when used for emergency use to assist in weaning patients off ventilators in healthcare settings during the COVID-19 pandemic (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized TransAeris Diaphragm Pacing System under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of DHS's determination described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the TransAeris Diaphragm Pacing System is authorized to be used and distributed as set forth in this EUA.

This EUA will cease to be effective when the HHS declaration that circumstances exist to justify the EUA is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving applicable current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the authorized TransAeris Diaphragm Pacing System that is used in accordance with this EUA.

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

Synapse Biomedical, Inc. as Sponsor of Authorized Product

A. Synapse Biomedical, Inc. will make the TransAeris Diaphragm Pacing System available with authorized labeling. Synapse Biomedical, Inc. may request changes to the authorized labeling. Such changes require review and concurrence from OHT1/OPEQ/CDRH.

B. Synapse Biomedical, Inc. may request changes to the Scope of Authorization (Section II in this letter) of the authorized TransAeris Diaphragm Pacing System. Such requests will be made by Synapse Biomedical, Inc., in consultation with OHT1/OPEQ/CDRH, and require concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and OHT1/OPEQ/CDRH.

C. Synapse Biomedical, Inc. must comply with the labeling requirements under 21 CFR 801 Subpart A (general labeling provisions) and 21 CFR 801.109 (labeling for prescription devices), as well as those described in Section II of this letter, Scope of Authorization.

D. All descriptive printed matter relating to the use of the authorized TransAeris Diaphragm Pacing System shall be consistent with the authorized labeling. No descriptive printed matter relating to the use of the authorized TransAeris Diaphragm Pacing System may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

E. Synapse Biomedical, Inc. will have process in place for reporting adverse events of which they become aware to FDA under 21 CFR Part 803.

F. Synapse Biomedical, Inc. will notify FDA of any authorized distributor(s)[9] of the TransAeris Diaphragm Pacing System, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA and any updates.

G. Synapse Biomedical, Inc. may request changes to any components or materials. Such requests will be made in consultation with and require concurrence of OHT1/OPEQ/CDRH.

Synapse Biomedical, Inc., and any Authorized Distributor(s)

H. Synapse Biomedical, Inc., and authorized distributors will distribute the authorized TransAeris Diaphragm Pacing System with the authorized labeling only to healthcare facilities with healthcare providers who are adequately equipped, trained, and capable of using the TransAeris Diaphragm Pacing System according to the criteria set forth by Synapse Biomedical, Inc.

I. Synapse Biomedical, Inc., and authorized distributors will make authorized labeling available on their websites.

J. Authorized distributors will make Synapse Biomedical, Inc. aware of any adverse events of which they become aware.

K. Through a process of inventory control, Synapse Biomedical, Inc. and authorized distributors will maintain records of the healthcare facilities to which they distribute the TransAeris Diaphragm Pacing System and the number of each product they distribute.

L. Synapse Biomedical, Inc., and authorized distributor(s) are authorized to make

[9] Currently, Synapse Biomedical, Inc. is the sole distributor. "Authorized Distributor(s)" are identified by Synapse Biomedical, Inc. in an EUA submission as an entity allowed to distribute the device.

available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

M. Synapse Biomedical, Inc. and authorized distributors will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

Healthcare Facilities

N. Healthcare facilities using the authorized TransAeris Diaphragm Pacing System must make available to patients the accompanying Patient Fact Sheet, and make available to healthcare providers the accompanying Healthcare Provider Fact Sheet.

O. Healthcare facilities using the TransAeris Diaphragm Pacing System must make Synapse Biomedical, Inc. aware of any adverse events.

P. Healthcare facilities will ensure healthcare providers using the TransAeris Diaphragm Pacing System are adequately equipped, trained, capable, and will maintain records of device usage.

Conditions Related to Advertising and Promotion

Q. All advertising and promotional descriptive printed matter relating to the use of the authorized TransAeris Diaphragm Pacing System shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

R. No advertising or promotional descriptive printed matter relating to the use of the authorized TransAeris Diaphragm Pacing System may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

S. All advertising and promotional descriptive printed matter relating to the use of the authorized TransAeris Diaphragm Pacing System shall clearly and conspicuously state that:

- The TransAeris Diaphragm Pacing System has neither been cleared or approved for the indication to assist in weaning patients off ventilators in healthcare settings during the COVID-19 pandemic.

- The TransAeris Diaphragm Pacing System has been authorized for the above emergency use by FDA under an EUA;

- The TransAeris Diaphragm Pacing System has been authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the TransAeris Diaphragm Pacing

System under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures