Guidance for Industry and FDA Staff

Vocal Fold Medialization Devices - Premarket Notification [510(k)] Submissions

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Food and Drug Administration
Center for Devices and Radiological Health

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Division of Ophthalmic and Ear, Nose, and Throat Devices
Office of Device Evaluation

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

FDA has developed this guidance document to assist industry in preparing premarket notification submissions for vocal fold medialization devices, which are class II devices. These devices are intended to medialize a paralyzed vocal fold to improve voice quality and/or airway protection. The scope of this document is limited to vocal fold medialization devices, identified as procode MIX (system, vocal cord medialization) or KHJ [polymer, Ear, Nose and Throat (ENT) synthetic-polyamide (mesh or foil material)]. 21 CFR 874.3620.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM588914.pdf

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

2. Background

A manufacturer who intends to market a device of this generic type should conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, and obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.81 and 807.87).

This guidance document identifies the classification regulation and product codes for vocal fold medialization devices (refer to **Section 4**). In addition, other sections of this guidance document provide additional information to manufacturers on addressing risks related to these devices in premarket notifications (510(k)s).

This document supplements other FDA documents regarding the specific content requirements of a 510(k). You should also refer to 21 CFR 807.87 and "**How to Prepare a 510(k) Submission**" on FDA Device Advice at http://www.fda.gov/cdrh/devadvice/314.html.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**," http://www.fda.gov/cdrh/ode/parad510.html, a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document addressing that device. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and should briefly describe the methods or tests used. We recommend that you also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 21 CFR 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 11 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report[1] contain a:

- Description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[2]

- Description of device design requirements.

- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)

- Discussion of the device characteristics that address the risks identified in this guidance document, as well as any additional risks identified in your risk analysis.

- Brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6-10 of this guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

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[1] A Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED document) that contains the information we recommend in this guidance may suffice in place of the summary report. Please refer to **Announcement of a Pilot Program for Device Submissions (The STED Initiative)** http://www.fda.gov/cdrh/international/sted.html.

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

[3] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply

- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (Section 514(c)(1)(B) of the Act). This means that testing must be completed before you submit a declaration of conformity. For more information, refer to the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

We may request additional information about aspects of the device's performance characteristics or information to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you may submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions.

4. Scope

The scope of this document is limited to vocal fold medialization devices, identified as procode MIX (system, vocal cord medialization) or KHJ (polymer, ENT synthetic-polyamide [mesh or foil material]). 21 CFR 874.3620.

These vocal fold medialization devices include both injectable materials and other materials used in a Type I thyroplasty procedure to medialize the vocal fold through an external cervical skin incision.

The devices listed below are regulated under 21 CFR 874.3620 but are not within the scope of this guidance:

- MIB elastomer, silicone block
- NHB polymer, Ear, Nose and Throat, synthetic
- JOF polymer, ENT synthetic, porous polyethylene
- ESH polymer, ENT synthetic-PIFE, silicon elastomer, polyethylene, polyurethane.

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the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of vocal fold medialization devices addressed in this document. The information we recommend you include in your 510(k) to address these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Airway compromise	Sections 8, 10, 11
Extrusion/migration of the device	Sections 8, 10, 11
Particle migration	Sections 6, 7, 8,
Improper placement	Section 11
Infection	Section 9, 11
Adverse tissue reaction/granuloma formation	Sections 6, 10
Device breakage	Section 7, 8, 10, 11
Poor voice quality	Section 10, 11
Revision surgery	Section 10, 11

6. Biocompatibility

We recommend that you evaluate the biocompatibility of the patient contacting materials as described in the **International Standard Organization (ISO) standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing**, according to Parts 5 and 10, for tissue/bone contacting, long-term implanted devices. We also recommend that you document the results in your design history file as a part of the Quality Systems Requirements (21 CFR 820.30). If identical materials are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of performing biocompatibility testing. Generally, for devices containing new materials FDA recommends long-term animal studies (e.g., one year implantation studies at tissue sites simulating the clinical situation).

Use of injectable polytetrafluoroethylene for vocal fold medialization has been associated with migration of the material to local lymph nodes and a localized foreign body granulomatous

reaction (i.e., "Teflon granuloma") at the site of injection (Varvares,1995; Benjamin, 1987; Ellis, 1987). Teflon granulomas may lead to progressive dysphonia and airway compromise in some patients. Surgical removal of the material in affected patients has been extremely difficult and typically results in some degree of residual phonatory deficit (Billante, 2000). Animal models are useful in predicting the occurrence of this significant complication (Stein, 2000) and should be used to demonstrate lack of granulomatous inflammation in the larynx when the device consists of a material that has not been previously cleared for laryngeal use. Such a study should include appropriate control animals (e.g., injection of product vehicle, Teflon as positive control) and should be of sufficient duration to assess any possible migration and tissue interactions (at least six months to one year following injection).

7. Material and Performance Characterization

Solid silicone, solid and particulate hydroxylapatite, titanium, and certain absorbable materials have been used successfully to construct vocal fold medialization devices of this generic type. Any material selected for the design of this device should have chemical stability sufficient to withstand the intended physiological environment for the proposed duration of effectiveness (i.e., permanent vs. temporary vocal fold medialization).

You should evaluate a solid material's integrity with the appropriate *in vitro* mechanical test methods (e.g., modulus, fatigues, fracture toughness, fatigue crack propagation, flexural strength, compressive strength, sheer strength, and tensile strength for solid materials).

For injectable materials, physical and chemical analyses are used to characterize particulate materials that are suspended in a carrier gel. You should identify:

- the ingredients
- any additives in the formulation of the device, along with their respective amounts
- the time to absorption
- residual substances.

If your device includes a carrier gel, we recommend that you evaluate the carrier gel for its biocompatibility. In addition, the carrier gel should have physiological pH.

8. Bench, Animal, or Preclinical Testing

As stated in Sections 6 and 7, bench and animal studies may be used to demonstrate stability and biocompatibility of implanted materials in the acute period as well as long term. For suspended particles, animal studies are invaluable to demonstrate whether there is particle migration into surrounding or lymphatic tissues. Particles less than 65µm may migrate to regional lymph nodes as well as to distant sites (Sittel, 2000; Henley, 1995; Beisang, 1992; Allen, 1992). You should provide results from bench studies on the distribution of particle size when administered through the proposed delivery system. Animal studies should demonstrate that there is no material migration when used in the larynx.

9. Sterilization

For devices sold as sterile[5] we recommend that you provide the following information:

- the sterilization method used in the sterilization cycle (e.g., dry heat, ethylene oxide (ETO), steam, radiation)
- a description of the method that will be used to validate the sterilization cycle (but not the validation data)
- a description of the packaging that maintains the device's sterility (but not the package integrity testing data)
- the sterility assurance level specification (SAL)
- a description of the method used to make the determination, e.g., the limulus amebocyte lysate (LAL) method, if the product is labeled pyrogen free
- the maximum levels of ETO and ethylene chlorohydrin residues, if sterilized by ETO
- the radiation dose, if sterilized by radiation.

10. Clinical Information

In accordance with the Least Burdensome provisions of the Act, the agency will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most vocal fold medialization devices, FDA may recommend that you collect clinical data for devices with any one of the following:

- material formulation or designs dissimilar from material formulation or designs previously cleared under a premarket notification
- new technology, i.e., technology different from that used in legally marketed vocal fold medialization device
- indications for use dissimilar from vocal fold medialization devices of the same type.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. The Ear, Nose, and Throat Devices Branch is available to discuss any questions you may have.

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 in accordance with the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812.

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[5] If your device is labeled sterile, we recommend that you follow the guidance for devices intended for contact with intact skin in **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm109897.pdf.

FDA believes that a vocal fold medialization device addressed by this guidance document is a significant risk device as defined in 21 CFR 812.3(m).[6] In addition to the requirement of having an FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. 21 CFR 812.2(c). However, such studies must be performed in conformance with 21 CFR Part 56 and 21 CFR Part 50.

11. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.[7]

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), seethe device should have clear and concise instructions that delineate the technological features of the specific device and how the device is to be used by trained professionals on patients. Instructions should encourage use of local/institutional training programs designed specifically to familiarize users with the features of the device and how to use it in a safe and effective manner.

Surgeon's instructions should be very clear and precise and include the following:

- surgical technique to implant the device
- revision surgery
- special considerations for administration of injected materials
- airway protection/compromise
- postoperative complications
- special patient instructions
- cautions and precautions
- warnings.

[6] Refer to Blue Book Memorandum entitled "Significant Risk and Non-Significant Risk Medical Device Studies" at http://www.fda.gov/cdrh/d861.html.

[7] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a device is introduced into interstate commerce. In addition, final labeling for prescription devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801.

12. References

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5. Stein J et al. Histopathological study of alternative substances for vocal fold medialization. Ann Otol Rhinol Laryngol 109:221-6. 2000.

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8. Beisang, AA and Ersek, RA. Mammalian response to subdermal implantation of textured microimplants. Aesth. Plast. Surg. 16:83-90. 1992.

9. Allen, O. Response to subdermal implantation of textured microimplants in humans. Aesthet. Plast. Surg. 16:227-230. 1992.