

Guidance for Industry and FDA Staff

Implantable Middle Ear Hearing Device

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

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

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket No. 02D-0228. Comments may not be acted upon by the Agency until the document is next revised or updated.

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TABLE OF CONTENTS

| | |
|---|-----------|
| 1. INTRODUCTION | 1 |
| 2. DEVICE DESCRIPTION | 2 |
| 3. MANUFACTURING | 3 |
| <i>Software Validation</i> | 3 |
| <i>Sterilization</i> | 4 |
| 4. PRECLINICAL INFORMATION | 5 |
| <i>Design Characteristics of IMEHD</i> | 5 |
| <i>System Output and Response</i> | 5 |
| <i>Biocompatibility</i> | 6 |
| <i>Animal Studies</i> | 6 |
| <i>Environmental Testing</i> | 7 |
| <i>Stress, Fatigue, and Wear</i> | 9 |
| <i>Reliability</i> | 9 |
| 5. INVESTIGATIONAL DEVICE EXEMPTIONS | 10 |
| <i>Clinical Protocol</i> | 10 |
| 6. CLINICAL RESULTS | 14 |
| 7. DEVICE MODIFICATIONS | 16 |
| APPENDIX A INFORMED CONSENT | 17 |
| APPENDIX B LABELING | 18 |

Guidance for Industry and FDA Staff

Implantable Middle Ear Hearing Device

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

This guidance document is intended for manufacturers of implantable middle ear hearing devices (IMEHD) for use in adults 18 years of age and older. IMEHD require premarket approval applications (PMA). The product code is MPV.

This guidance is based on current scientific knowledge, clinical experience, and recommendations made by the Ear, Nose, and Throat Advisory Panel at panel meetings held on June 18, 1999 and August 16, 2002. This guidance provides specific recommendations about IMEHD and is an adjunct to the Code of Federal Regulations (CFR) such as 21 CFR Part 814-Premarket Approval of Medical Devices, 21 CFR Part 801-Labeling, and other FDA guidance documents for the preparation of premarket approval applications, such as the **Premarket Approval Manual**, <http://www.fda.gov/cdrh/dsma/pmaman/front.html>. It does not supersede those publications.

Wherever possible, you should follow the recommendations in this guidance document and provide explanations of any deviations or omissions in your PMA. PMAs that contain all the necessary information recommended in this guidance ordinarily can be reviewed more expeditiously than those that do not.

For the nonclinical laboratory studies, you should state whether each nonclinical study of each final human prototype and the supporting documentation is in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58. If not, you should state the reasons for noncompliance.

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.

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The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to 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 comply with 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: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

2. DEVICE DESCRIPTION

You should provide a description of the device and its functional components, including:

- pictorial representations
- engineering drawings
- block diagrams of circuits.

The block diagrams of the circuits should trace signal flow, processing, and logic of operation at the transducer level and the circuit level, as appropriate. You should describe each of the functional components and, for each, provide:

- complete set of electrical schematics
- complete set of mechanical drawings
- detailed drawings and descriptions of all components including material composition
- electrical specifications and, where appropriate, references to laboratory testing that established these specifications
- mechanical specifications and, where appropriate, references to laboratory testing that established these specifications

Transducer

You should describe the type of transducer utilized to provide stimulation to the middle ear. Describe the size and frequency response characteristics of the transducer, and its effect on middle ear physiology (e.g., residual hearing). Describe the attachment and any mounting mechanism(s) necessary for adequate surgical placement of the transducer.

Attachment

You should describe the means of attachment of any external connector, transmitter or charging apparatus and the effects of hair and varying skin thickness, as appropriate. Include the effects on “normal” use activities (i.e., work environment, walking, running, swimming, etc.).

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Radiopacity

You should describe the radiopacity of the device components or other means of localizing the implanted components.

Finite Element Modeling

You should describe parameter values used to model the normal middle ear system and the changes to the same as a consequence of implanting their device. Describe any Finite Element Modeling (FEM) of the middle ear, if possible.

Device Accessories

You should describe all device accessories, such as user controls, programming interface(s), software, cables, connectors, and audiological equipment provided and designed exclusively for your device. You should describe the type of battery used in the device and indicate the projected battery life. You should describe the battery, including whether or not it is rechargeable, and how it would be replaced. You should also provide detailed description of any surgical procedure required for replacing batteries for a totally implantable IMEHD.

3. MANUFACTURING

For guidance additional to that noted here, please refer to the **Premarket Approval Manual**, <http://www.fda.gov/cdrh/dsma/pmaman/front.html>.

Software Validation

Please refer to **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**, <http://www.fda.gov/cdrh/ode/software.pdf>, for a discussion of the software documentation that you should provide. As discussed in the *Software Guidance*, the "level of concern" is related to the possible consequences of software failure, and may be minor, moderate, or major. The software for IMEHD is generally considered a "moderate level of concern." If you believe that the software in your IMEHD should be considered a minor level of concern, you should provide a clear scientific justification that discusses the possible consequences of a software failure.

We encourage you to take advantage of any FDA-recognized software standards and provide statements or declarations of conformity. A standard that may be used is ISO/IEC 12207: Information technology software life cycle processes (Software), Information Technology - Software Life Cycle Processes.

If the device includes off-the-shelf software, you should provide the additional information as recommended in the **Guidance for Industry, FDA Reviewers and Compliance on Off-the-Shelf Software Use in Medical Devices**, <http://www.fda.gov/cdrh/ode/guidance/585.html>

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Sterilization

You should submit the following information for devices sold as sterile:

- 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;
- a description of the packaging that maintains the device's sterility;
- the sterility assurance level specification (SAL); FDA recommends 10^{-6} for implanted components labeled sterile;
- a description of the method used to make the determination, e.g., the limulus amoebocyte lysate (LAL) method, if the product is labeled pyrogen free;
- the maximum levels of EtO and ethylene chlorohydrin residues, if sterilized by EtO; and
- the radiation dose, if sterilized by radiation.

IMEHDs labeled sterile should have expiration dating. Determination of expiration dating involves assessing the barrier properties of the packaging to assure sterility. In addition, we recommend testing to assure that storage and shipping conditions do not alter their function and that they will function the same as when manufactured.

All preclinical testing (chemical, toxicology, or mechanical) should be performed on the final sterilized product or components thereof. You should provide the type of information below for an IDE, PMA, or PDP application or an adequate rationale.

The following is a partial list of sterilization standards. There may be other standards that are useful. If you use a FDA-recognized standard, you may submit a declaration of conformity in lieu of performance data. See **Recognition and Use of Consensus Standards; Final Guidance for Industry and FDA Staff** <http://www.fda.gov/cdrh/ost/guidance/321.html> See also CDER guidance: Guideline on validation of the Limulus Amoebocyte Lysate Test as an end-product endotoxin test for human and animal parenteral drugs, biological products and medical devices <http://www.fda.gov/cder/guidance/old005fn.pdf>.

- ANSI/AAMI/ISO 11134 - Sterilization of health care products-Requirements for validation and routine control of industrial moist heat sterilization
- ANSI/AAMI/ISO 11135 - Sterilization of medical devices -Validation and routine control of ethylene oxide sterilization
- ANSI/AAMI/ISO 10993- 7 - Biological evaluation of medical devices - part 7: Ethylene oxide residuals
- ANSI/AAMI/ISO 11137 Sterilization of medical devices -Validation and routine control - radiation sterilization

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- ANSI/AAMI/ISO 11607 Packaging for terminally sterilized devices
- USP 24:2000 (85) Biological Tests and Assays, Bacterial Endotoxin Test (LAL) or USP 24:2000 (151) Pyrogen Test (USP Rabbit Test)

4. PRECLINICAL INFORMATION

Design Characteristics of IMEHD

Design safety mechanisms

You should describe specific design provisions that limit or prevent excessive stimulation of the subject's middle and inner ear structures.

Surgical placement

You should describe the design provisions that accommodate anatomical variations. You should also describe the implant site and the design characteristics that have been incorporated to facilitate surgical placement.

Implant stability

You should describe the design provisions that promote long-term implant stability and prevent device movement (e.g., during pressure changes, tympanometry, impact, or injury). You should include pull testing parameters, data, and analyses to demonstrate that the force of detachment of the device from an ossicle is lower than the force required for disarticulation.

Biomechanical function

You should describe the design provisions that facilitate the normal biomechanical function of the middle ear(s) after implantation.

System Output and Response

The design of an IMEHD may limit your access to system component output measures for your use during final testing. Pre- and post-implant test methods should provide objective test data within practical limits of the design of the device. Similarly, you should describe the contribution of the transducer to the overall system response. You should describe the middle ear transfer function of each system component, including potential effects on overall system response due to attachment to a complex mechanical load (i.e., the middle ear system).

When possible, you should measure vibration of the middle ear using a fresh human temporal bone, which approximates the in-vivo system. You may use, for example, laser vibrometry to completely describe the system responses of the human ear. You should directly compare the

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vibration data to equivalent mechanical vibrations induced by sound input to the ear [i.e., decibel (dB) output from the device referenced to equivalent decibel sound pressure level (dB SPL)]. You should describe the characterization of the level and duration of stimulation with evidence of the safety of this level.

Pre-implant testing

You should conduct design verification and validation activities so that there is assurance that components meet established requirements. The evaluations should ensure that the external and internal implant systems, as well as any accessories, operate within defined specifications on an assembly level and on an overall system level. You should provide the results as a graph, table or text, as appropriate. You should provide a discussion of the results including conclusions.

For semi-implantable IMEHDs, you should describe methods of testing external and internal unit performance against your input/output specifications.

For totally implantable IMEHDs, you should describe methods of testing unit performance against your input/output specifications.

Biocompatibility

You should evaluate the biocompatibility of the materials used in your device. Please refer to the guidance document entitled **Blue Book Memo, G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"** <http://www.fda.gov/cdrh/g951.html>.

You should select biocompatibility tests appropriate for implant device; tissue/bone contacting; intended for permanent duration. See ANSI/AAMI/ISO 10993-1 - Biological Evaluation for Medical Devices Part 1, Evaluation and Testing. If you use an FDA-recognized standard, you may submit a declaration of conformity in lieu of performance data. See **Recognition and Use of Consensus Standards; Final Guidance for Industry and FDA Staff** <http://www.fda.gov/cdrh/ost/guidance/321.html>

Animal Studies

Depending on the design of your device, animal studies may be necessary to support the safety and effectiveness of your device. If you conduct animal studies, the reports should include:

- protocol
- objective of the study
- experimental design (including type and number of animals used)
- method of performing the study
- auditory evoked response testing
- histology with particular attention to regions of device attachment

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You should provide an analysis of the data and a description of any modifications made to the device as a result of this testing. If conducted, animal studies should be of sufficient length to allow for evaluation of tissue remodeling.

Environmental Testing

You should demonstrate the reliability and performance of external components, as appropriate, under various operating and storage conditions (e.g., temperature, vibration, handling, and electrostatic discharge). You should provide test information demonstrating the longevity of external components, including battery-powered components.

You should provide results of environmental tests (e.g., dry heat, cold temperature, hermeticity, free fall, thermal cycling, vibration impact shock, weld tests, lead stretch and flex test, failure mode analysis).

Standards that address environmental testing for your device include:

- IEC 68: Basic environmental testing procedures
- EN 45502-1: Active implantable medical devices-Part 1: General requirements for safety, marking and information to be provided by the manufacturer
- ISO 6474: Implants for Surgery – Ceramic materials based on high purity alumina.

Electromagnetic Compatibility (EMC) Testing

You should use the test methods that apply to your device in ANSI/IEEE C63.19-2001 American National Standard for Methods of Measurement of Compatibility between Wireless Communications Devices and Hearing Aids. Testing should include magnetic field immunity to electromagnetic fields emitted from anti-theft systems and security systems (Electronic Article Surveillance Systems, Walk-Through Metal Detectors, and Hand-Held Metal Detectors).

Other EMC testing should be done in accordance with accepted electromagnetic immunity standards such as IEC 60601-1-2 Medical Electrical Equipment - Part 1: General Requirements for Safety; Electromagnetic Compatibility – Requirements and Tests (General). If you use an FDA-recognized standard, you may submit a declaration of conformity in lieu of performance data. See **Recognition and Use of Consensus Standards; Final Guidance for Industry and FDA Staff** <http://www.fda.gov/cdrh/ost/guidance/321.html> EMC testing should demonstrate reasonable assurance that use of the device with everyday electrical products results in neither serious bodily injury nor device malfunction or failure.

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Magnetic Resonance Imaging (MRI) Compatibility Testing

If you intend that your device be safe for MRI, you should evaluate its compatibility with MRI. You should perform all MRI compatibility testing on finished devices. You should also assess the magnetically induced forces and torques on the device during imaging. You should also address any potential risk to the patient due to induced electrical currents and functional disruption of the operation of your device caused by its presence in a magnetic field.

You should determine the magnetically-induced deflection force for a paramagnetic material at the location where the product of the magnitudes of the magnetic field and the spatial gradient of the magnetic field, $|\mathbf{B}| |\nabla\mathbf{B}|$, is at a maximum. You should also determine the magnetically-induced deflection force for a saturated ferromagnetic object at the location where the spatial gradient in the magnetic field is a maximum. It is possible that these locations are off the central axis of the bore of the scanner. The magnetically-induced torque is a function of the field strength; therefore, you should measure it where the static magnetic field is the greatest within the bore of the magnet. We expect that the physical location of the maximum torque and displacement force be different.

You should assess the heating of the device produced by the magnetic and radio frequency (RF) fields during imaging. You should also assess gradient-induced voltages and image artifacts. Final testing should use sequences that will produce maximal distortion in the image and maximal heating to evaluate the worst case conditions for both. Please provide copies of the images showing the distorted regions.

Because MRI technology is changing rapidly and systems with larger magnetic fields are being introduced on the market, any claims for compatibility of the device with the MR environment should include a description of the field conditions under which it was tested.

Standards that address MRI safety and compatibility are:

- ASTM F2052-00: Standard Test Method for Measurement of Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment
- ASTM F2119-01: Standard Test Method for Evaluation of MR Image Artifacts From Passive Implants
- IEC 60601-2-33 - Medical Electrical Equipment - Part 2: Particular requirements for the safety of magnetic resonance equipment for medical diagnosis.

Electrical Testing

The device should meet the electrical safety requirements of IEC 60601-1, Medical Electrical Equipment Part 1: General Requirement for Safety, (General); Amendment 1, Amendment 2. EN 1441: Medical Devices Risk Analysis (General) may also apply.

Stress, Fatigue, and Wear

You should evaluate the stress, fatigue, and wear properties of your device (as a system) and its materials. You should also evaluate the flexure performance of any implanted leads that connect system components. You should select engineering tests appropriate for the design of your device and describe the rationale for your selection. If you use an FDA-recognized standard, you may submit a declaration of conformity in lieu of performance data. However, if you have modified a test method, used a test method from a standard that is not recognized, or developed your own test method, you should provide a complete description of the test method and the data.

Reliability

You should evaluate the physical properties of the implanted device after prolonged exposure to the biological environment. *In vitro* physiological model testing may serve in place of an animal study, provided that you have already demonstrated the biocompatibility of the materials in the implanted device. Alternately, you may conduct an animal study that includes a sufficient number of devices (one per animal) implanted into the middle ear of suitable animal models for sufficient lengths of time to provide reasonable assurance of safety and effectiveness as a long term implant.

You should assess the system reliability both predictively and retrospectively. Note: predictive techniques include tolerance analysis, fault tree analysis (FTA), failure mode, effect, criticality analysis (FMECA), and mean time between failure (MTBF) prediction. Retrospective techniques include demonstrations of reliability through environmental and accelerated stress tests as well as FTA and FMECA of actual *in vivo* and *in vitro* failures. You should discuss design revisions that result from the system reliability analyses. Particular attention should be given to failures that could injure the patient, create excessive noise or discomfort, or require revision surgery. Software system(s) and safety should be discussed in detail.

You should discuss the techniques for predicting and testing the *in vivo* reliability and stability of implanted components. You should provide the rationale and test data supporting your selection of:

- electronic components
- attachment materials
- lead materials
- joining methods and sealing techniques.

The reliability analysis should address predictive analyses as described above. You should provide special emphasis on:

- methods and data used in FMECA
- tolerance analysis

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- determination of FMECA categories.

You should provide retrospective methods with special emphasis on:

- methods and data used to evaluate *in vitro* and *in vivo* reliability of implanted components
- environmental test methods and results for nonimplanted components.

A standard that addresses reliability of the device as a result of shipment is ASTM D4169: Standard Practice for Performance Testing of Shipping Containers and Systems.

5. INVESTIGATIONAL DEVICE EXEMPTIONS

Studies involving these devices must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50). See also Appendix B Informed Consent. In addition, because FDA has determined this device is a significant risk device as defined in 21 CFR 812.3(m), these studies should have an FDA-approved IDE (21 CFR Part 812).

Clinical Protocol

You should conduct a within-subject, repeated measures clinical trial, designed to demonstrate safety and effectiveness of the IMEHD. One example of such a design is a non-inferiority study where IMEHD is compared to an appropriately fit conventional acoustic hearing aid(s). The subject (i.e., experimental unit) serves as his/her own control. Alternatively, you may consider a randomized (independent group) study to compare the IMEHD with another surgical intervention.

The sample size should be sufficient to provide a power of .80 or greater, with a two-sided $\alpha = .05$ or less or a one-sided $\alpha = .025$ or less. By increasing the power of your statistical test, an adequate sample size increases the likelihood that you will achieve statistical significance in your clinical trial, if a significant difference exists in the population. Refer to the Clinical Results Section below for additional information. FDA recommends that the study have at least three investigators at different locations, each with a sufficient number of subjects to support the study design.

Investigators

The Principal Investigator at each study site should be a licensed physician who has training and experience in middle ear surgery and has received training regarding the surgical implantation of your device. Co-investigators should include audiologists who have knowledge and experience with current air conduction (acoustic) hearing aid technology.

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Subject selection criteria

You should specify the hearing loss degree, range and type indicated for the IMEHD. You should describe hearing impairment in each ear as determined by objective hearing tests. This should include pure-tone procedures including the test frequencies: 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz.

You should include a description of aided performance assessment: soundfield audiological evaluation (see **Preimplant and Postimplant Assessments** section below), i.e., functional gain testing, real ear probe microphone testing, tolerance levels, and speech perception measures, as appropriate. Specify aided performance for each test measure of subjects selected for the study.

You should measure and describe the subject's self-assessment with conventional acoustic amplification using a validated scale appropriate for the intended patient population.

Describe any subject's inability to use conventional hearing aid(s) due to medical contraindication (e.g., external otitis).

You should not include subjects who are contraindicated for undergoing implantation surgery (e.g., active infectious process, lesion of the acoustic nerve or central auditory pathway).

You should specify whether or not you have included any subjects with an IMEHD in the non-surgical ear or any subjects undergoing revision (explanting previously implanted IMEHD with implantation of your device).

If any deviations occurred, you should include a description of, and rationale for, the deviations from the subject inclusion criteria.

Study Sample

You should include the distribution of relevant variables:

- hearing aid use-e.g., current hearing aid user, previous user
- number of subjects in experimental and, when used, control groups
- age distribution
- etiology of hearing impairment, if known
- other pertinent variables, e.g., audiological history, age at onset of hearing impairment (including manner of determining age of onset).

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Device Safety

You should discuss and analyze the following information when determining device safety:

- all residual-hearing changes in detail, including air and bone conduction threshold measures and speech perception testing results
- each adverse event and complication
- device failures, including a definition for device failure and a complete failure analysis report for each device failure.

Effectiveness measures and control conditions

You should describe in detail the pre-surgical aided condition for each subject. Pre-operative measures obtained without the use of hearing aids, or with hearing aids whose fitting and operational status is not optimized for the patient, may provide inadequate assessment of the control condition. You should define and justify your criteria for establishing that the fitting and operational status are optimal.

The basic recommended study design compares the IMEHD to appropriately fit conventional acoustic hearing aids. Direct device comparisons (i.e., conventional hearing aid vs. IMEHD) are necessary to establish the benefit side of the risk/benefit comparison. You should conduct baseline tests that document the benefit associated with appropriately fit conventional acoustic hearing aids. You should incorporate the same or similar methods of fitting and signal processing with the conventional hearing aids as the IMEHD, if possible. In addition, we recommend that you perform comparisons to the unaided condition.

Preimplant and Postimplant Assessments

For both preimplant and postimplant assessments, you should conduct the following:

Presurgical medical examination – you should include a preoperative history, including whether tinnitus is present and an otologic evaluation with temporal bone radiology, if indicated. You should state the clinical criteria used to diagnose tinnitus.

Audiological assessment – you should measure and determine pure-tone air and bone conduction thresholds for each ear, tolerance levels, acoustic immittance measurements, speech reception thresholds and speech perception testing, including monosyllabic word material, sentence material and/or spondee (two syllable word) material. You should include the following frequencies for pure-tone air conduction testing: 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz.

Soundfield assessment – You should include masking for the non-test ear during soundfield assessments.

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Soundfield audiological assessment – you should include both aided and unaided conditions, e.g., warble-tone thresholds at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, and 6000 Hz, including tolerance levels.

Soundfield speech perception testing – you should include verification of the intensity of the stimuli at the subject's ear. This is especially important when data are collected from several investigational sites having varying size sound suites containing varying numbers of objects. Speech perception testing should include more than one norm-referenced, standardized test, and should be conducted in quiet and in noise. Various intensity levels, such as average conversational speech level and PB-Max (Phonetically Balanced Maximum) level should be included. Estimates of test-retest reliability and alternate form equivalency should be addressed.

Monaural vs. binaural assessment – you should describe how you will address binaural benefit or lack thereof; and describe any variables or potential bias from the aided non-implant ear.

Self-assessment of communicative performance should be measured in several conditions, such as untreated and with current means of treatment (e.g., conventional hearing aid, implant + conventional hearing aid, implant only, etc). You should include self-report inventories of subject satisfaction, attributes of satisfaction, use, or benefit in daily life in order to assess those properties outside of the laboratory setting. You should use test instruments that have been validated and for which normative data are available. You should provide the rationale for the instruments you select.

Counseling – you should include a detailed explanation of realistic expectations of the implant and how you will incorporate them into the investigational plan.

In addition to the above, **during the preimplant assessment**, you should conduct real ear measurements with reference to a normed target. You should include a prescriptive target formula that is appropriate for the hearing aid circuitry used with a given subject.

Post-implant testing

You should evaluate output of the device after implantation. You should provide actual system and subsystem data to show that the IMEHD system is functioning within your defined specifications. You should conduct this testing as a part of the post-implant assessment of each subject in the clinical trial.

You should describe the overall system vibrational output as a function of sound input including gain, phase, and frequency responses. The data should show the response characteristics of the transducer or transduction mechanism (i.e., vibrational output as a function of electrical input.)

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Standards that may partially apply to device function include:

- ANSI S3.22: Specification of Hearing Aid Characteristics
- ANSI S3.42: Testing Hearing Aids with a Broad-Band Noise Signal

Surgical concerns

You should describe the incision type, the surgical approach (e.g., facial recess, mastoidectomy) to be used, how the device is attached to the appropriate vibratory structure of the ear, how anchoring assemblies (if required) are utilized. You should detail the critical technical portions of the surgery (i.e., device placement). Include an estimate of the required surgical time required for device installation. You should describe any device-specific requirements regarding anesthesia for the procedure.

You should describe pre-surgical and post surgical care that will be required for each subject.

You should describe any limits or considerations for the use of standard surgical and otologic instruments (e.g., monopolar electrocautery after placement of the implant).

Monitoring

Clinical investigators should monitor patients closely with 100 percent follow-up or with a detailed explanation for any loss of follow-up.

You should specify the minimum length of follow-up postimplant. You should describe how dropouts or lost to follow up will be counted in the analysis.

6. CLINICAL RESULTS

You should present and thoroughly describe the results of the statistical analyses of the clinical investigation in the PMA. You should include the statistical methodology and rationale for each test. Include references and formulas for each methodology. You should describe and explain any deviations from the methodology.

The primary endpoint of a study design should be directly related to the statements regarding device safety and effectiveness. You should state the study hypothesis and describe how the endpoint either supports or rejects the hypothesis. You should include a sufficient number of patients and complete follow-up at regular intervals in order to determine the safety and effectiveness of the device.

You should determine the sample size based on a power analysis and you should set the sample power to 0.8 or greater and a two-sided alpha to 0.05 or less. You may also consider a one-sided alpha of 0.025 or less. You should analyze the data to describe the success or failure rate and the complication rate.

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You should provide a statistical analysis that is based on a subject serving as his/her own control. The analysis should use appropriate characteristics and measurement endpoints. You may use traditional parametric, non-parametric or Bayesian analyses.

You should define the level of improvement that constitutes a clinically significant change in the study. You should describe and justify the method used to determine this level.

You should also provide the following information as part of this section:

- summary table specifying duration of follow-up for each subject in the investigation
- statement as to why a study was discontinued, if it was, or a statement that it is continuing, if such is the case
- tabulations of data from all individual subject report forms
- patient complaints
- methods used to eliminate bias on the part of the subjects or investigators.
- copies of case report forms for each subject who did not complete the investigation
- any interim analyses that were performed with adjustment of alpha, if indicated.

All tables and graphs should be accompanied with appropriate text so that they are able to stand alone in the submission. You should provide a detailed index of tables and graphs to facilitate review. The following are examples of tables, which may be helpful in presenting results and facilitating clinical review.

Demographics

| Subject ID | Age | Sex | Degree of Hearing Loss | Hearing aid(s) Make & Model | Binaural or Monaural fitting | Years experience with amplification |
|------------|-----|-----|------------------------|-----------------------------|------------------------------|-------------------------------------|
| | | | | | | |
| | | | | | | |

Unaided Audiological Results, Air Conduction

| Subject ID | 250 Hz | 500 Hz | 1.0 kHz | 2.0 kHz | 3.0 kHz | 4.0 kHz | 6.0 kHz | 8.0 kHz |
|-------------------|--------|--------|---------|---------|---------|---------|---------|---------|
| Pre-Op Threshold | | | | | | | | |
| Post-Op Threshold | | | | | | | | |
| Difference | | | | | | | | |

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Unaided Audiological Results, Bone Conduction

| Subject ID | 250 Hz | 500 Hz | 1.0 kHz | 2.0 kHz | 3.0 kHz | 4.0 kHz |
|-------------------|---------------|---------------|----------------|----------------|----------------|----------------|
| Pre-Op Threshold | | | | | | |
| Post-Op Threshold | | | | | | |
| Difference | | | | | | |

7. DEVICE MODIFICATIONS

A PMA Supplement is required for a change affecting the safety or effectiveness of an approved device, unless FDA has advised you that an alternate type of submission is appropriate for a particular change. You should refer to the regulation on PMA Supplements 21 CFR §814.39. You should also see PMA Supplements and Amendments on CDRH's Internet Device Advice <http://www.fda.gov/cdrh/devadvice/pma/supplement.html>

FDA believes that a PMA supplement may be necessary when you:

- change the design of the audio processor or implant
- change the circuitry, such as changing from analog to digital,
- add new accessory devices
- modify the indication for use.

The FDA review division staff is available to discuss whether your changes may require you to submit a supplement.

APPENDIX A INFORMED CONSENT

Subject informed consent must comply with 21 CFR Part 50. You should describe any reasonably foreseeable risks or discomforts 21 CFR 50.20(a)(2). For an IMEHD, these should include:

Short term risks/discomforts

- loss of any residual hearing in the implanted ear as a result of the surgery
- injury to the facial nerve
- meningitis
- perilymph or cerebrospinal fluid leakage
- electrical or mechanical failure of the device requiring its removal
- revision/reinsertion
- infection
- blood or fluid collection at the site of surgery
- vertigo
- tinnitus
- facial twitch
- taste disturbances
- a numbness or stiffness about the ear
- a lump behind the ear

Long term risks/discomforts

- necrosis
- disarticulation of the ossicular chain
- bone growth with potential damage to the auditory system
- calcification
- adhesions
- other potential unknown long term effects on the auditory system.

You should also include these reasonably foreseeable risks for an IMEHD:

- The possibility that it may be necessary to remove the device and/or utilize other methods in an attempt to regain hearing, such as reconstructive surgery and use of Total Ossicular Replacement Prostheses (TORPs) or Partial Ossicular Replacement Prostheses (PORPs). Include risks of revision procedure(s).
- A statement that MRI is contraindicated after implantation, if applicable.
- The necessity for an external speech processor, if applicable (i.e., with semi-implantable device).
- Surgical removal of the battery, if applicable (i.e., with totally implantable device).

You must disclose appropriate alternative procedures or treatments 21 CFR 50.20(a)(4). For an IMEHD, you should discuss other implantable middle ear hearing devices and other recognized communicative systems and devices, such as conventional acoustic hearing aids.

APPENDIX B LABELING

General Information

General labeling requirements for medical devices are described in 21 CFR 801. Additional labeling information may be obtained from the guidance, **Device Labeling Guidance #G91-1** <http://www.fda.gov/cdrh/g91-1.html>. You must submit all proposed labeling 21 CFR 814.20(b)(10). These should include package labels, a package insert, a Surgeon's Manual, an Audiologist's Manual, a Patient Information Brochure, and a Patient Identification Card. When developing the patient labeling, you should refer to **Guidance on Medical Device Patient Labeling** which is available at <http://www.fda.gov/cdrh/ohip/guidance/1128.html> and our information regarding plain language at <http://www.plainlanguage.gov>.

Package Labels

The outer package label(s) for IMEHD should include, at minimum, the following information:

- device name, model
- name and address of manufacturer
- quantity
- material
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date.

The label of the device packaging must bear the prescription device statement in accordance with 21 CFR [801.109](#)(b)(1) "CAUTION: Federal law restricts this device to sale, distribution, and use only upon the lawful order of a physician."

Package Insert

The package insert for IMEHD should contain the following information:

- package contents
- device name, model, etc.
- indications for use
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- name and address of manufacturer
- contact information for customer service inquiries
- brief device description of all implanted and external components (if any)

Contains Nonbinding Recommendations

- indications for use
- individualization of treatment section outlining specific patient selection criteria.

Contraindications

You should list the contraindications appropriate to your IMEHD. Contraindications should include any patient populations where evidence demonstrates that the IMEHD should not be implanted. For the IMEHD, this section may include patients with:

- conductive hearing loss
- retrocochlear or central auditory disorder
- active middle ear infections
- tympanic membrane perforations associated with recurrent middle ear infections.

Additional or different contraindications may apply depending on the specific design or intended use of the device.

Warnings

We recommend that you include the warnings below, if applicable to your device. We have provided examples of statements for each warning.

MRI or strong magnetic fields: Implanted patients should not be subjected to MRI and should not enter an MRI Suite or come into close proximity to other sources of strong magnetic fields.

Electrosurgery: Electrosurgical instruments are capable of producing radio frequency voltages that can directly couple the instrument tip with the implant. Monopolar electrosurgical instruments must not be used within the vicinity of the implant because the induced currents could cause damage to the implant or the patient's hearing.

Diathermy: Do not apply diathermy over the device because the high currents induced into the implant could cause damage to the implant or the patient's hearing.

Electroconvulsive therapy: Do not use electroconvulsive therapy because it may damage the implant or the patient's hearing.

Other procedures: A statement that the effects of cobalt treatment, PET scans, transcranial diagnostic ultrasound, and linear acceleration techniques on the implant are unknown.

Contains Nonbinding Recommendations

Precautions

Precautions alert the reader to exercise special care necessary for the safe and effective use of the IMEHD. We recommend that you consider including the following labeling precautions, if appropriate, for your device:

Damage: You should list activities or conditions that could damage or affect the performance of the device including contact sports, extremes in temperature (e.g., blow dryers), moisture, and hair care products.

Theft and Metal Detection Systems: You should include a precaution that the IMEHD may activate the detector alarm of theft and metal detection systems and that patients should therefore carry their Patient Identification Card with them at all times.

Ingestion: You should include precautions against ingestion any part of the IMEHD system. In particular, button cell batteries are harmful if swallowed. You should include instructions for immediate consultation with a physician and/or the National Button Battery Hotline (1-202-625-3333).

Fitting: You should also include any specific precautions related to fitting of the device (e.g., earmold impression).

Clinical Considerations

This section should include a general description of evaluation procedures (e.g., audiometric tests, questionnaires, and conventional hearing aid evaluations) to determine candidacy for the IMEHD. Additionally, you should include the following sections:

Adverse and Potential Adverse Events - You should include a table listing the type and number of adverse events. You should report the total number of patients implanted (i.e., the denominator) and the time period covered for the adverse events listed.

Clinical Study Summary - This section briefly summarizes the safety and efficacy results of the clinical trials.

Clinical Study Results - You should include a detailed presentation of the clinical study results including descriptive statistics, figures, and tables.

Information for Use and Recommended Training

You should describe the surgical expertise (e.g., experience in middle ear surgery, stapedectomy) and any other specific training required for the implantation procedure.

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Surgeon's Manual

The Surgeon's Manual should include all information contained in the Package Insert (indications for use, contraindications, warnings, precautions, etc.) unless the two are in a combined manual. Additionally, you should include the following items within the Surgeon's Manual:

- a clear description of all device components, accessories, and surgical tools used for implantation.
- procedures for preoperative preparation of the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and troubleshooting procedures.
- instructions for implantation, including placement of incision and thickness of skin flap, surgical approach (e.g., mastoidectomy, facial recess approach), proper seating and securing of the implantable device components into position, and any specific wound closure instructions.
- warnings regarding potential surgical hazards associated with the implantation procedure and suggested measures to avoid/minimize them.
- warnings, if applicable, regarding the use of monopolar cautery during the procedure to avoid damage to the implant or injury to the patient.
- intraoperative test procedures to ensure implant integrity and proper placement (if necessary).
- instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period and during any subsequent surgical procedures, post-operative patient care, etc.
- patient counseling instructions for device handling, maintenance, and storage (external components).

Audiologist's Manual

The Audiologist's Manual should include all information contained within the Package Insert (indications for use, contraindications, warnings, precautions, etc.) unless the two are in a combined manual. Additionally, you should include the following items within the Audiologist's Manual:

- a clear description of all device components, accessories, and fitting instruments/kits
- suggested timetable for initial post-operative visits for fitting and programming audio processor and subsequent visits for adjustments and monitoring

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- stepwise instructions on programming of the audio processor (e.g., setting the frequency ranges, gain, and compression ratios for individual channels)
- assessment of patient's aided performance and adjustments for optimization of programming
- troubleshooting
- patient counseling instructions regarding device handling, maintenance, and storage
- information on device registration warranty, repairs, and technical assistance

Patient Information Brochure

The Patient Information Brochure should not exceed the eighth grade reading comprehension level so that it is easily read and understood by most patients. You should keep technical terms to a minimum and define them if they must be used.

The Patient Brochure should include, at minimum, the following information:

- device name, style, etc.
- brief device description with material information
- indications for use
- detailed description of the operation of the external processor (if applicable) including operation of all controls and checking/exchanging batteries
- troubleshooting
- relevant contraindications, warnings, and precautions as described in the "Package Insert" section above (should be placed in the front of the brochure)
- potential complications, including the possible methods of resolution
- anticipated benefits and risks (to give patients realistic expectations of device performance)
- a statement that conventional acoustic hearing aids and other IMEHD are available and that patients should discuss these alternatives with their physicians and/or audiologists
- postoperative care, including what to expect after surgery, symptoms to tell doctor about immediately, length of recovery, physical limitations, etc.

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- additional information related to the device such as registration and warranty, loss and damage provisions, and information regarding repairs
- study safety and effectiveness results.

Patient Identification Card

Patient Identification Card are carried by patients and allow them to share accurate information about their device with others when required. You should construct the card of a material durable enough to last for the anticipated life of the device. The card should include the following information:

- device name, model and serial number
- brief device description
- patient name, address, telephone number
- name and contact information for the implanting surgeon and hospital
- manufacturer name and contact information
- information regarding theft and metal detection systems that may be activated by the IMEHD
- medical precautions including warnings against MRI, electrosurgery, diathermy, and electroconvulsive therapy as outlined in the “Package Insert” section above.