On June 14, 2023, FDA issued a guidance titled "Content of Premarket Submissions for Device Software Functions."[1] This final guidance supersedes the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued on May 11, 2005. The final guidance issued on June 14, 2023, provides information regarding the recommended documentation sponsors should include in premarket submissions for FDA's evaluation of the safety and effectiveness of device software functions. In particular, the final guidance includes information to help determine a device's Documentation Level (formerly known as Level of Concern). The purpose of the Documentation Level is to help identify the minimum amount of information that would support a premarket submission that includes device software functions.

Within the framework of the superseded guidance, implanted Brain-Computer Interface devices were considered a device with a Major Level of Concern. Based on the device's risk in the context of the device's intended use, as discussed in the final guidance "Content of Premarket Submissions for Device Software Functions," implanted Brain-Computer Interface devices should generally address the recommendations for an Enhanced Documentation Level. The actual Documentation Level for your device may vary based on the specifics of your device. For more information about the Documentation Level and recommended documentation for a premarket submission, sponsors are encouraged to review the guidance "Content of Premarket Submissions for Device Software Functions."

[1] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.

Contains Nonbinding Recommendations

Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations

Guidance for Industry and Food and Drug Administration Staff

Document issued on May 20, 2021.

The draft of this document was issued on February 22, 2019.

For questions about this document, contact the OHT5: Office of Neurological and Physical Medicine Devices/DHT5B: Division of Neuromodulation and Physical Medicine Devices/Acute Injury Devices Team at (301) 796-6610.



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

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2014-N-1130. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1500045 and complete title of the guidance in the request.

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Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation – Non-clinical Testing and Clinical Considerations

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance document provides recommendations for Q-Submissions and Investigational Device Exemptions (IDEs) for implanted Brain-Computer Interface (BCI) devices for patients with paralysis or amputation. The field of implanted BCI devices is progressing rapidly from fundamental neuroscience discoveries to translational applications and market access. Implanted BCI devices have the potential to bring benefit to people with severe disabilities by increasing their ability to interact with their environment, and consequently, providing new independence in daily life. For the purposes of this guidance document, implanted BCI devices are neuroprostheses that interface with the central or peripheral nervous system to restore lost motor and/or sensory capabilities in patients with paralysis or amputation.

FDA's Center for Devices and Radiological Health (CDRH) believes it is important to help stakeholders (e.g., manufacturers, health-care professionals, patients, patient advocates, academia, and other government agencies) navigate the regulatory landscape for medical devices. Towards this goal, on November 21, 2014, CDRH held an open public workshop on its White Oak, MD campus with the aim of fostering an open discussion on the scientific and clinical considerations associated with the development of BCI devices.[1] FDA considered the input provided during this workshop to develop the recommendations provided in this guidance document for implanted BCI devices.

This guidance document provides non-clinical testing and clinical study design recommendations associated with implanted BCI devices. Non-clinical device testing can be used to demonstrate

[1] http://wayback.archive-it.org/7993/20170112091055/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm410261.htm

that potential risks have been mitigated prior to initiating a clinical study. Proper design of clinical trials is essential to provide a reasonable assurance of safety and effectiveness necessary to support a regulatory submission, and translation of BCI devices from concept to assisting device users.

This guidance is a leapfrog guidance, a type of guidance that serves as a mechanism by which the Agency can share initial thoughts regarding emerging technologies that are likely to be of public health importance early in product development. This leapfrog guidance represents the Agency's initial thinking and our recommendations may change as more information becomes available.

The Agency strongly encourages manufacturers to engage with CDRH through the Q-Submission process to obtain more detailed feedback for BCI devices. For more information on Pre-Submissions, see "Requests for Feedback on Medical Device Submissions: The Q-Submission Program."[2]

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[3] For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff."[4]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

The scope of this document is limited to implanted BCI devices that interface with the nervous system to restore motor and/or sensory capabilities in patients with paralysis or amputation. This guidance provides general recommendations for non-clinical testing and study design considerations for IDE feasibility and pivotal clinical studies.

Non-clinical testing methods may not be available or may not sufficiently provide the information needed to advance to a final version of an implanted BCI device under development. Therefore, if your device is still under development, we recommend that you consider

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

[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

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

performing an early feasibility study through an IDE to collect an early clinical evaluation of your device to provide proof of the principle and initial clinical safety data. As with all clinical studies, initiation of an early feasibility study must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures. Refer to FDA guidance document "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies"[5] for information on performing a device evaluation strategy as part of your risk analysis.

Non-implanted BCI devices are outside the scope of this guidance, as the regulatory considerations for non-implanted BCI devices may differ from those recommended in this guidance document, depending on various aspects, such as but not limited to the technical characteristics and indications for use/patient population. For feedback on regulatory considerations for non-implanted BCI devices, we recommend following the Q-submission process.

If your implanted BCI device incorporates technological characteristics, components, or indications for use/patient population that are not described or referenced in this document, we also recommend that you submit a pre-submission to seek FDA feedback.

III. Pre-Submission & IDE Recommendations

A. Device Description

We recommend that you include the device descriptive information listed below.

1. A complete description of every module of the device. For example, BCI systems typically consist of several modules including but not limited to the following modules:

    a. Signal acquisition (e.g., leads and recording electrodes);

    b. Signal processing that includes software for decoding and encoding signals and providing stimulation (in some cases) and associated hardware;

    c. Stimulation delivery (internal/external stimulator and stimulating electrodes);

    d. Assistive effector component (e.g., a prosthetic limb, wheelchair, functional electrical stimulators applied to intact limbs, exoskeletons or robotic systems, or communication devices and computers);

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including

e. Sensor component for neural feedback (e.g., sensors for restoring touch or reporting other information), if applicable; and

f. Programming module that consists of an operating protocol to control functions, such as turning the device on and off and switching between various outputs and programs.

2. A general overview of the BCI device as a whole system including a description of how the different modules are configured to comprise the whole system and if applicable, a description of the different system configurations (e.g., programming, calibration, or testing configurations).

3. A complete description of key components of the device including its function, relevant model numbers, materials, location (implanted or external component) and dimensions or sizes that a user would need to know to use the device properly. If previously cleared or approved, the premarket submission number (i.e., 510(k), PMA number) with a description of modifications to the cleared or approved device(s) should be provided. The following information is recommended for specific key components:

   a. Leads and connection cables: The following descriptive information should be provided for leads and connection cables:

      (i) Number of leads and cables;
      (ii) Insulation and conductor materials;
      (iii) Length(s);
      (iv) Diameter;
      (v) Impedance;
      (vi) Connectors;
      (vii) Number and orientation of the conductors within the lead/cable (e.g., parallel to lead body, coiled within lead body); and
      (viii) Method of fixation and strain relief.

   b. Electrodes: The following descriptive information should be provided for electrodes:

      (i) Material (including any coatings or surface treatments);
      (ii) Length;
      (iii) Diameter;
      (iv) Electrode geometry (e.g., cuff, flat, depth) and the electrode contact surface area;
      (v) Number of electrodes/electrode contacts;
      (vi) Electrode spacing;
      (vii) Electrode span (from most proximal edge of proximal electrode to distal edge of distal electrode);
      (viii) Implant location (brain region, specific peripheral nerve, muscle group, spinal cord, external); and
      (ix) Sensor and/or stimulation location (intracortical, subdural, cutaneous).

c. Connectors: A description of the connectors intended to be used for joining leads to the other components such as assistive effector components, signal processing hardware or programing modules. The description should include the materials, the diameter, the number and type of contacts, and how the connections are secured (e.g., male-female connection, clip).

d. Processing/Stimulation Hardware: The following descriptive information should be provided for the processing/stimulation hardware:

(i) Description of whether the hardware is implanted or external;
(ii) Power source/method (e.g., battery, inductive coupling, radio frequency);
(iii) Description of the signal filters (processing hardware);
(iv) Number of output and recording channels; and
(v) Description of output specifications (see Appendix A for more information on output modes).

e. Assistive effector and/or sensor component: A description of the assistive effector and/or sensor component(s) (e.g., a prosthetic limb, computer, sensors), including the following:

(i) Model Number;
(ii) Description of modifications to the cleared or approved device(s) (e.g., addition of sensors);
(iii) Degrees of freedom (i.e., the total number of independent displacements or aspects of motion); and
(iv) Description of how the assistive effector or sensor component(s) is controlled (e.g., sequential or simultaneous control of the arm joints).

f. Programmers/Control Unit: The following information for both the physician and patient system for programming and control (if available) should be provided:

(i) Description of device and user interface, including all buttons, switches, etc.;
(ii) Description of all outputs that are controlled;
(iii) Description of data readout (including, if relevant, details such as number of channels, rate of digitization, bit size and duration of recording) and/or stimulator output (e.g., frequency, pulse width, intensity, electrodes, polarity);
(iv) Description of any special programming features;
(v) Description of hardware and software platforms;
(vi) Method of communication with other components (e.g., wired, wireless);
(vii) Power source;
(viii) Any additional settings; and
(ix) All alerts and circumstances in which they are communicated to the user.

g. Algorithms: We recommend that you provide a description of any algorithms used in your device. We recommend the use of flow charts (and/or other visual or

organizational aids) to highlight the input parameters and their sources and the output parameters and their implementation (e.g., control of end-effector, for offline data analysis).

h. Wireless Function: We recommend that you describe the ability of your wireless medical device, as applicable, to function properly in the intended use environments where other RF wireless technologies will likely be located. In the design, testing, and use of wireless medical devices, the correct, timely, and secure transmission of medical data and information is important for the safe and effective use of both wired and wireless medical devices and device systems.

i. Battery: A complete description of all batteries used in the system by the various components should be provided, including chemistry and performance characteristics (e.g., usable battery amp-hour capacity, shelf life, and life testing under worst-case usage).

4. A thorough description (e.g., drawings, flow charts) of interactions between the various components, the user and patient, and the environment.

5. For a device that must be assembled or can be adjusted prior to use, an "exploded" view of the individual components relative to each other. The various components should be clearly labeled.

6. For a device that includes software, a brief description of the software, including the various functions, prompts, user inputs, etc.

7. For a device that incorporates radio frequency (RF) wireless technologies, a complete description of the exact wireless technology used, its characteristics, performance, risk management, and functions, including alarm conditions. See the FDA guidance document, "Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff"[6] for additional recommendations for evaluating and documenting wireless technologies in premarket submissions.

8. A description of all safety features built into the device.

9. For a device that applies electrical current to the muscle or nerves, the output stimulation characteristics provided in Appendix A should be provided.

10. All devices intended to be used in conjunction with the implanted BCI device (e.g., implantation tools, clips or belts for body-worn components), and whether the devices are packaged or sold with the implanted BCI device, should be described. We recommend that you include a detailed description of all the devices packaged with the implanted BCI device, including:

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/radio-frequency-wireless-technology-medical-devices-guidance-industry-and-fda-staff

(i) Model number;
(ii) Design drawings;
(iii) Materials; and
(iv) Similarity to all devices intended to be used in conjunction with the implanted BCI device that may have been approved/cleared with other leads or electrodes.

B. Risk Management

We recommend that you apply accepted risk management principles, such as those described in the currently recognized version of ISO 14971: *Medical devices – Application of risk management to medical devices*, while conducting the risk analysis as part of your design controls required in 21 CFR 820 during the development of your device. We recommend you submit risk management information that identifies hazardous situations, estimates the risks (e.g., risks of device malfunction, adverse tissue reaction, infection, use error, extravasation), and describes risk control measures and overall residual risk specific to your device. Certain verification and validation testing performed as a result of these activities should be provided (as described in Sections D to L below).

We recommend that the risk analysis detail qualitative examination of the potential hazards (e.g., hardware, software, non-clinical-related, and clinical-related hazards) of the device from the perspective of the user. We also recommend identification of hazards caused by single-fault conditions to ensure that the failure of any single component of the implanted BCI device does not cause an unacceptable risk during use.

The risk analysis should be provided in a tabular format and should analyze all potential causes for the identified risks. All mitigating strategies or corrective actions should also be identified, with a detailed analysis on how the corrective actions reduce the clinical risk to acceptable levels. You should provide a rationale for why the levels are acceptable.

C. Software

Significance: Software in implanted BCI devices ensures that various components of the implanted BCI system, such as the signal processing modules, controllers, stimulation hardware, and assistive device, operate as intended and provide software mitigations when appropriate. Adequate software performance testing provides assurance that the device is operating within safe parameters.

Recommendation: Refer to the FDA software guidance "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"[7] for a discussion of the software documentation that you should provide in your submission. The software guidance outlines the type of documentation to be provided based on the "level of concern" associated with the device. We generally consider the software for implanted BCI devices to present a "major" level of

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

concern. If you believe that the software in your device presents either a "minor" or a "moderate" level of concern as defined in the software guidance, you should provide a scientific justification that supports your rationale for the level of concern based on the possible consequences of software failure.

We recommend that you provide a full description of the software/firmware (including programming languages, hardware platforms, operating system and use of Off-the-Shelf software, if applicable) supporting the operation of the subject device following the software guidance, commensurate with the appropriate level of concern. This recommendation applies to original device/systems as well as to any software/firmware changes made to already-marketed devices. Changes to software must be revalidated and reverified in accordance with Design Controls, 21 CFR 820.30(g)(i), and documented in the Design History File 21 CFR 820.30(j).

For early feasibility studies, we recommend that you provide adequate software performance testing to provide assurance that the system operates within safe parameters. Overall, the documentation related to software should provide sufficient evidence to describe the role of the software included in the device, risks associated with the device, and performance testing to demonstrate that the software functions as intended. In the case of software that will control various assistive effector components (i.e., motorized wheelchairs, computer software, upper limb prosthetics), we recommend that you account for any software-related hazards, and associated changes due to algorithm updates, in your risk-analysis plan.

As appropriate, you should also provide information on the Cybersecurity aspects of your device. For more information on this topic, see FDA's guidance "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[8]

If the device includes off-the-shelf software, you should provide the additional information as recommended in the FDA documents titled "Off-the-Shelf Software Use in Medical Devices"[9] and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software"[10], which provide additional information regarding medical devices utilizing off-the-shelf software.

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

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

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

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

D. Human Factors

Significance: Use-related hazards are hazards resulting from failure modes tied to the use of implanted BCI devices by end users (e.g., patients, surgeons, prosthetists, caregivers). They are a unique form of hazard in that use-related hazards can exist even if the device operates according to specifications. They generally do not involve specific failure modes associated with mechanical, electrical, and software components that are previously known or reasonably anticipated. These hazards might result from aspects of the user interface design that cause the user to fail to adequately or correctly perceive, read, interpret, understand or act on information from the device. Use-related hazards may vary in severity of potential harm to the user, ranging from hazards that lead to user annoyance to hazards that result in death. Regardless of the severity of potential harm from a use-related hazard, it is important to understand and identify these hazards to ensure that you have designed a safe and usable device.

Recommendation: To understand and identify the use-related hazards associated with the use of an implanted BCI device, it is important to have an accurate and complete understanding of the specific behaviors required of users when using the device, the environment(s) in which the device will be used, the intended users of the device, and how environmental conditions and intended user characteristics could impact device use. With this information, you should be able to incorporate use-related hazards into the early stages of your risk management process to ensure user safety and satisfaction are integrated into device design and development. Additional recommendations on risk management can be found in Section III.B of this guidance document.

Many implanted BCI devices are likely to undergo early feasibility studies. Human factors validation and evaluation is typically not needed to support feasibility study approvals; however, human factors data may be needed to support your future marketing submission to the Agency. If your device is still under development and you intend to pursue an early feasibility study through an IDE, the early feasibility study could be conducted to obtain initial insights into human factors (e.g., difficulties in comprehending procedural steps, insufficient training).[11] Prior to implementing your early feasibility studies for implanted BCI devices, we recommend following Section 6 of FDA guidance, "Applying Human Factors and Usability Engineering to Medical Devices," [12] to take into account human factors considerations.

We recommend identifying a plan in your investigational protocol to capture usability information during the course of the early feasibility study. This information can be used to modify the procedures or device as necessary. In order to address and mitigate use-related hazards in final device designs, we recommend conducting usability evaluations (e.g., cognitive-walk throughs, simulated-use testing, satisfaction surveys) early in the device design process and iteratively throughout the device development and evaluation process.

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[11] See FDA guidance, "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including.

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices

E. Biocompatibility

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

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

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

We recommend that you follow FDA's guidance "Use of International Standard ISO-10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"[13], which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

The type of tests that are applicable to your device may depend on whether the electrodes interface with the central or peripheral nervous system. Additionally, devices intended to be used in conjunction with the implanted BCI device (e.g., components, surgical tools) may contact the patient in different ways and durations. Using ISO 10993-1: *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and Attachment A of FDA's guidance on ISO-10993-1, the following biocompatibility categories may be applicable to your implanted BCI device system:

Category 1: Implant in permanent contact (>30 days) with neural tissue/bone, cerebrospinal fluid (CSF), and blood (indirect contact with blood through CSF as CSF is reabsorbed into the venous system)

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

Intracortical electrodes (i.e., electrodes implanted in the cortex of the brain) or other subdural electrodes are examples of an implanted BCI device component in this category. The following endpoints should be addressed in your biocompatibility evaluation:

- cytotoxicity
- sensitization
- irritation or intracutaneous reactivity
- acute systemic toxicity
- material-mediated pyrogenicity
- subacute/subchronic toxicity
- genotoxicity
- implantation
- neurotoxicity
- hemocompatibility (extract hemolysis test)
- chronic toxicity
- carcinogenicity testing

Category 2: Implant in permanent contact (> 30 days) with neural and non-neural tissue/bone (i.e., muscle, not intended directly or indirectly to contact CSF or blood)

Electrodes implanted in peripheral nerve or muscle tissue or percutaneous connectors on the skull (i.e., pedestals) are examples of an implanted BCI device component in this category. The following endpoints should be addressed in your biocompatibility evaluation:

- cytotoxicity
- sensitization
- irritation or intracutaneous reactivity
- acute systemic toxicity
- material-mediated pyrogenicity
- subacute/subchronic toxicity
- genotoxicity
- implantation
- neurotoxicity
- chronic toxicity
- carcinogenicity testing

Category 3: External communicating device with limited (≤ 24 hours) tissue/bone contact

A tunneling tool used to create a pathway in the body for leads is an example of an implanted BCI device tool in this category. The following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous Reactivity

- Acute Systemic Toxicity
- Material Mediated Pyrogenicity

Category 4: Surface device with limited (≤ 24 hours) / prolonged (> 24 hours – 30 days) / permanent (> 30 days) contact with intact skin

External transmitters used as programmers/control units and assistive effector component (i.e., prosthetic limbs) are examples of implanted BCI device system components in this category. The following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous Reactivity

F. Sterility

Significance: Implanted BCI devices should be adequately sterilized to minimize infections and related complications.

Recommendation: For implanted BCI components and surgical tools labeled as sterile, we recommend that you provide the information outlined below.

1. For the sterilization method, the sponsor should provide the following:
   a. a comprehensive description of the sterilization method/process;
   b. a description of the sterilization chamber if not rigid, fixed (e.g., flexible bag);
   c. the sterilization site;
   d. in the case of radiation sterilization, the radiation dose;
   e. for chemical sterilants (e.g., Ethylene Oxide (EO), H_2O_2), the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

      In the case of EO sterilization, CDRH has accepted EO residuals information based on the currently recognized version of the standard, ANSI/AAMI/ISO 10993-7: *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*.

2. For the sterilization method, you should provide a description of the method used to validate the sterilization cycle (e.g., the half-cycle method) as well as the sterilization validation data. The submission should also identify all relevant consensus standards used and identify any aspects of the standards that were not met. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.

3. You should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile unless the device is intended only for contact with intact skin. FDA recommends a SAL of 10^{-3} for devices intended only for contact with intact skin.

We recommend that you describe the sterilization process validated for each sterile configuration. If you are only planning to sterilize a limited number of devices using EO for the purposes of an IDE, you may want to consider a single lot sterilization process. For specifications on the single lot sterilization process, see Annex E: Single Lot Release in ISO-11135: 2014: *Sterilization of health care products — Ethylene oxide — Requirements for development, validation and routine control of a sterilization process for medical devices*.

G. Pyrogenicity

Significance: Pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to gram-negative bacterial endotoxins and/or chemicals that can leach from a medical device (e.g., material-mediated pyrogens).

Recommendation: To address the risks associated with the presence of bacterial endotoxins, implanted BCI devices should meet pyrogen limit specifications. You should also follow the recommendations in "Pyrogen and Endotoxins Testing: Questions and Answers."[14] To address the risks associated with material-mediated endotoxins, follow the recommendations in FDA's guidance "Use of International Standard ISO-10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."[15]

Additionally, we recommend providing your routine batch release Limulus Amebocyte Lysate (LAL) monitoring procedures. For guidance, refer to FDA's Guidance for Industry "Pyrogen and Endotoxins Testing: Questions and Answers" and the USP Endotoxin Reference Standard (USP Chapter <161> Medical Devices – Bacterial Endotoxin and Pyrogen Tests). You may also refer to ANSI AAMI ST72: *Bacterial endotoxins – Test methodologies, routine monitoring, and alternatives to batch testing* for endotoxin testing on your device.

For devices intended to be labeled as "non-pyrogenic," we recommend that both bacterial endotoxins and material-mediated pyrogens be addressed.

H. Shelf Life and Packaging

Significance: Shelf life testing is conducted to support the proposed expiration date through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to device performance or functionality.

Recommendation: With respect to package integrity for maintaining device sterility, you should provide a description of the packaging, including how it will maintain the device's sterility, the protocol(s) used for your package integrity testing, the results of the testing, and the conclusions drawn from your results. We recommend that a package validation study include simulated

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pyrogen-and-endotoxins-testing-questions-and-answers

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

distribution and associated package integrity testing, as well as an aging process (accelerated and/or real-time) and associated seal strength testing, to validate package integrity and shelf life claims. We recommend you follow the methods described in the current edition of the FDA-recognized consensus standards ANSI/AAMI/ISO 11607-1: *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging* systems and ANSI/AAMI/ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes.*

With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties to ensure it will perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality, we recommend that you assess each of the bench tests described in Sections L(1)(a), L(1)(b), L(2)(a-g), L(3)(a-d) and repeat all tests that evaluate design components or characteristics that are potentially affected by aging using aged devices.

We recommend that you provide the protocol(s) used for your shelf life testing, the results of the testing, and the conclusions drawn from your results. If you intend to extend the shelf-life of the implanted BCI device after initial approval of your IDE study, we recommend that you provide the protocol(s) and results to support the extension in an IDE supplement. We recommend all test samples undergo real-time aging to determine definitively the effects of aging on the maintenance of sterility and device performance. If you use devices subjected to accelerated aging, we recommend that you specify the way in which the device was aged and provide a rationale to explain how the results of shelf life testing based on accelerated aging are representative of the results if the device were aged in real time. We recommend that you age your devices as per the currently FDA-recognized version of ASTM F1980: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and specify the environmental parameters established to attain the expiration date. We recommend that the accelerated aging shelf life testing protocol include a concurrent real-time aging study protocol to confirm the results obtained from the shelf life studies on aged samples.

I. Electrical Safety and Electromagnetic Compatibility (EMC)

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

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

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

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

- ISO 14708-1: *Implants for surgery – Active implantable medical devices — Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

  ISO 14708-3: *Implants for surgery – Active implantable medical devices - Part 3: Implantable neurostimulators*.

For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance, "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices."[16]

J. Wireless Technology

Significance: In the design, testing, and use of wireless medical devices, the correct, timely, and secure transmission of medical data and information is essential for the safe and effective use of medical devices and systems. BCI systems may utilize wireless connections to transfer neural signals, to control assistive technologies or to drive electrical stimulation.

Recommendation: If your implanted BCI device incorporates radiofrequency wireless technology such as Bluetooth, IEEE 802.11 (Wi-Fi™), RFID (radio frequency identification) technology, or other wireless functionalities needed to perform the clinical function of your device, we recommended assessing the risk as described in the FDA-recognized version of AAMI TIR69: *Technical Information Report Risk management of radio-frequency wireless coexistence for medical devices and systems.*

The selection of RF wireless operating frequency and modulation should take into account other RF wireless technologies and users that might be expected to be in the vicinity of the wireless medical device system. These other wireless systems can pose risks that could result in medical device signal loss or delay that should be considered in the risk management process. If the risk management evaluation of the wireless function is found to be critical to the clinical function of the device, FDA recommends that you address your device's environmental specifications and needs as outlined in the current FDA-recognized version of ANSI/IEEE C63.27: *American National Standard for Evaluation of Wireless Coexistence.*

For additional recommendations for home use devices with wireless technology, refer to FDA's guidance "Design Considerations for Devices Intended for Home Use."[17]

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[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/information-support-claim-electromagnetic-compatibility-emc-electrically-powered-medical-devices

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use

We recommend that you consult FDA's guidance, "Radio Frequency Wireless Technology in Medical Devices"[18] for additional recommendations on this topic.

K. Magnetic Resonance (MR) Compatibility

Significance: MR imaging of patients with implanted BCI device poses the following potential hazards:

- Heating of the tissue adjacent to the implanted device produced by gradient and RF fields;
- Tissue damage caused by vibration of the device produced by gradient fields;
- Tissue damage caused by movement of the device from displacement force from the static magnetic fields;
- Tissue damage due to torque of the device produced by static magnetic fields;
- Unintended stimulation and tissue damage due to extrinsic electric potential produced by gradient field-induced lead voltage;
- Tissue damage due to rectification produced by RF field-induced lead voltage; and/or
- Device malfunction specific to MR-environment induced by B_0, RF, and gradient fields.

Recommendation: We recommend that you address the issues affecting safety and compatibility of your implanted BCI device in the MR environment as described in the FDA guidance, "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."[19]

L. Non-Clinical Bench Testing

We recommend that the non-clinical bench testing outlined below be addressed in your IDE. In general, the typical duration of implantation should be considered when determining appropriate test methods for characterizing durability (e.g., mechanical and electrical) of the components. Testing should ensure that the device meets appropriate specifications that represent a clinically relevant, worst-case *in vivo* conditions during device implantation and the expected life of the device. When appropriate, we recommend that the testing simulate the effect of any body fluids on the device components that come in contact with such fluids (e.g., after soaking in saline and before drying). We also recommend that you specify clinically-justified acceptance criteria for testing.

We recommend that you include relevant information on the non-clinical bench testing provided in the form of test report summaries, test protocols and complete test reports, as described in the

[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/radio-frequency-wireless-technology-medical-devices-guidance-industry-and-fda-staff

[19] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishing-safety-and-compatibility-passive-implants-magnetic-resonance-mr-environment

guidance document "Recommended Content and Format of Non-clinical Bench Performance Testing Information in Premarket Submissions."[20]

(1) Electrodes

Electrodes can be used to measure physiological signals or provide stimulation to the brain, spinal cord, and/or peripheral nerves or muscles for eliciting movement and/or sensation. If the implanted BCI device includes electrodes, we recommend testing the following characteristics:

a. Dimensional verification and visual inspection

Significance: Accurate dimensions are important to ensure that the electrodes meet the specifications that are relevant to the intended use of your device with justification. Additionally, if your device is intended to provide stimulation, the dimensions of your electrode can influence charge and current density, which can affect the safety and effectiveness of your stimulation parameters.

Recommendation: We recommend that you provide dimensional specifications and tolerances for your electrode as manufactured. We recommend that the specified tolerances should be based on your risk analysis and intended use of the electrodes (i.e., stimulation or recording). In order to provide accurate and consistent measurements, we recommend the use of a calibrated tool.

b. Impedance

Significance: Impedance measurements are important to ensure that the electrode has conductive properties appropriate for the intended use of the device.

Recommendation: We recommend that you record and provide the impedance specifications and tolerances for your electrode as manufactured. We recommend that the specified tolerances be based on your risk analysis and intended use of the electrodes (e.g., stimulation for restoring sensory or motor function or recording physiological signals).

c. Accelerated Lifetime Testing

Significance: To ensure long-term performance of the device, electrode materials should be stable and resist physical and chemical breakdown in the intended implant location for the expected duration.

Recommendation: We recommend that you assess the device functionality (e.g., impedance spectroscopy, cyclic voltammetry, voltage transients) or image the device integrity (e.g., scanning electron microscopy) following exposure to aging protocols,

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket

both in the context of recording and stimulating, in a simulated physiological environment and over a range of environmental conditions.

(2) Leads and Connectors

Leads are used to connect electrodes to multiple components in an implanted BCI system, such as but not limited to processing hardware and power modules. It is important that they function appropriately in the implanted BCI device system. We recommend testing to characterize the following attributes:

a. Dimensional verification and visual inspection

Significance: Accurate device dimensions are important to ensure that the leads and connectors meet the specifications.

Recommendation: We recommend that you provide dimensional specifications and tolerances for your leads and connectors as manufactured. Visual inspection and electrical evaluation should be conducted after non-clinical testing. We recommend that the specified tolerances should be based on your risk analysis and intended use of the lead connection (i.e., stimulation or recording). In order to provide accurate and consistent measurements, we recommend the use of a calibrated tool.

b. Leakage Current

Significance: Leakage current from the enclosures of the various implanted BCI device components during use of the implanted BCI device system may result in unintended electrical shock and potential tissue damage or the loss of recorded neural signal.

Recommendation: We recommend that the leakage current be measured after soaking and before drying to simulate the effect of any body fluids on the lead body. We also recommend that you measure the leakage current during full operation (i.e. voltage application) and when the device is energized and in stand-by condition. The leakage current during voltage application should be within acceptable range (see ISO 14708-3:2017 *Implants for neurosurgery – Active implantable medical devices – Part 3: Implantable Neurostimulators, clause 16*).

c. Lead Body and Connector Flex Fatigue Testing

Significance: Failures in the lead due to flexural fatigue can result in unintended electrical shock and potential tissue damage or the loss of recorded neural signal.

Recommendation: We recommend flex fatigue testing of the lead body and connector. We also recommend that the fatigue test protocol include subjecting different areas of the lead to different stresses (e.g., near or at connector joints and lead anchor points) during fatigue testing.

d. Tensile Strength of Lead

Significance: Failures in the lead due to tensile forces can result in unintended electrical shock and potential tissue damage or the loss of recorded neural signal.

Recommendation: We recommend that you conduct tensile testing that simulates the worst-case forces that the lead or extension could experience during the implantation procedure as well as after implantation.

e. Connector Insertion and Withdrawal Forces

Significance: Lead connectors should have a proper fit into the device header cavity to form the necessary electrical contacts and to ensure that the seals are in the correct location and function as designed. Connectors should be able to tolerate the forces associated with insertion and withdrawal.

Recommendation: We recommend that you ensure that lead and extension connectors meet appropriate specifications representing physiologic conditions experienced by the device, including the appropriate minimum and maximum withdrawal forces. During testing, you should evaluate that leads or extensions are fully inserted, electrical connections are made, and that seals between the generator and lead/extension are intact after repeated insertions and withdrawals. If repeated connection and disconnection is expected to occur, we recommend that you evaluate whether seals between the generator and lead/extension are intact after repeated insertions and withdrawals.

f. Particulate Matter Hazards

Significance: The release of particulate matter from any part of an implanted system that is intended to be in contact with body fluids during normal use is hazardous.

Recommendation: We recommend that you use test methods described in ISO 14708-3: *Implants for neurosurgery – Active implantable medical devices – Part 3: Implantable Neurostimulators.*

g. Corrosion Resistance

Significance: Lead materials should be stable and resist physical and chemical breakdown to demonstrate that the lead can withstand the environment of the human body and ensure long-term performance.

Recommendation: We recommend that the corrosion resistance be evaluated on the finished leads and connectors. Appropriate signal and stimulation parameters (e.g., signal to noise ratio, pulse rate, amplitude, and pulse width) should be chosen to evaluate the functionality of the leads and device system following exposure to corrosive environments that simulate the physiological environment of the device. This should include testing the lead in saline, using the smallest electrode surface area.

h. Compliance with 21 CFR 898.12

Significance: Accessible connectors from percutaneous leads or other cables in contact with the patients may be connected to the incorrect components or mains power in error, resulting in unintended electrical shock and harm to the patient.

Requirement: Percutaneous leads or other cables having a conductive connection to a patient must comply with the performance standard in 21 CFR 898.12, which states that any connector in a cable or electrode lead wire having a conductive connection to a patient shall be constructed in such a manner as to comply with subclause 56.3(c) of the following standard: International Electrotechnical Commission (IEC) 601-1: *Medical Electrical Equipment Part 1 – General requirements for safety (1988, amendment No.1, 1991, amendment No. 2, 1995).* However, FDA believes conformance to applicable subclauses in the currently FDA-recognized version of the IEC 60601-1: *Medical Electrical Equipment Part 1 – General requirements for basic safety and essential performance* (2005, MOD) standard would provide the same level of or improved protection of the public health and safety from unintended electrical shock as the FDA performance standard in 21 CFR 898.12, and that conformity to this currently FDA-recognized standard would be sufficient to meet the performance standard in 21 CFR 898.12. Therefore, firms may submit a declaration of conformity to this currently FDA-recognized standard.[21]

(3) Implanted Casing and Electronics

Electronics are often implanted, covered in a can or similar casing, which serve to process signals received from the leads and/or to provide electrical stimulation signals to the leads. We recommend you provide the following testing:

a. Hermeticity Testing

Significance: A high level of moisture enclosed inside a hermetic casing can lead to device failure.

Recommendation: We recommend conducting hermeticity testing for integrity of all joints, bonds, etc., to verify that the implanted casing is leak-proof.

b. Environmental Testing

Significance: The implanted casing and electronics should be subjected to a sequence of mechanical and environmental tests to ensure that the device will meet its specifications after being subjected to conditions that adequately capture stress that the device would encounter during worst case handling, shipping, storage, surgery and clinical use conditions.

Recommendation: We recommend tests evaluating the following be conducted:

a. Temperature changes (including temperature cycling);

b. Atmospheric pressure changes; and

c. Mechanical forces.

We recommend that you use methods described in ISO 14708-3: *Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators or equivalent methods*.

[21] See Section 514(c) of Federal Food, Drug and Cosmetic Act.

c. Header Adhesion Testing

Significance: If a header is attached to the casing for the purposes of connecting leads to the casing, header adhesion testing should be performed to ensure that the header does not separate from the casing and ensure the continuity of the current path for stimulation, recording, or powering.

Recommendation: The header cavity should have a proper fit with the lead and extension connectors to form the necessary electrical contacts, and to ensure that the seals are in the correct location and function as designed. We recommend that the lead ports and header connection be tested to ensure that the lead can withstand suitable force without being pulled out of the connector block.

d. Battery

Significance: If a battery is a part of the implanted casing and electronics, testing to evaluate the suitability and performance of the battery for use in the implanted device should be performed to ensure it operates as intended and risks (e.g., overheating) associated with battery failures (e.g., short circuiting) are appropriately mitigated to minimize harm to the patient.

Recommendation: The tests should assess the characteristics and general reliability of the battery when subjected to stresses anticipated under normal usage and clinically relevant worst-case conditions. Testing should also demonstrate how the batteries are protected from over discharge and overcharge and measure the battery and device's surface temperatures in the event of a battery short circuit.

See the following voluntary consensus standards for additional battery-related safety information:

- UL 2054: *Household and Commercial Batterie*s;
- UL 1642: *Lithium Batteries*;
- IEC 60086-4: *Primary batteries – Part 4: Safety of lithium batteries*; and
- IEC 60086-5: *Primary batteries – Part 5: Safety of batteries with aqueous electrolyte.*

(4) Output Stimulation Measurements

Significance: For devices that deliver electrical stimulation, it is important that the output stimulation delivered by the device and stimulation output limitations are appropriately characterized.

Recommendation: We recommend using methods described in ISO 14708-3: *Implants for surgery - Active implantable medical devices - Part 3: Implantable neurostimulators*. For each output mode, we recommend that you provide an oscilloscope trace describing the electrical output waveform of the individual pulse output waveform under physiologic loads that may be encountered. Additionally, one tracing should be provided showing a series of

pulses under a 500 Ω load. We recommend that you provide the following information with each trace:

- Name of the output mode;
- Clearly labeled amplitude and time axes;
- Identification of the amplitude baseline; and
- Listing of all output parameter settings (e.g., amplitude, pulse width, frequency).

Traces should demonstrate ability to achieve maximum stimulation settings in each trace and remain within specification. Results can be recorded in the format recommended in Appendix A.

(5) Output Stimulation Safety

Significance: For devices that deliver electrical stimulation to the nervous system and muscles, it is important that the output stimulation delivered to the tissue be safe for the intended use and stimulation duration. Excessive stimulation can produce tissue damage that could result in serious injury or death, depending on the stimulation location.

Recommendation: We recommend that you provide a scientific rationale (e.g., from literature and/or animal studies as outlined in Sections III(N)(1) and III(N)(2) to support the safety of the stimulation output parameters (e.g., maximum current, charge density, current density, charge per phase, frequency, and duration). An analysis of the safety of the output stimulation parameters provides assurance that the risk of tissue damage is minimized during use of the device.

(6) Programmers/Control Unit

Significance: Hardware used to program stimulation parameters or select different device modes are often called programmers/control units and may present risks to the patients if they do not operate as intended.

Recommendation: We recommend that programmers/control units be subjected to verification testing to assess electrical safety, functional, environmental, EMC, software, and reliability performance. This testing should be designed to ensure that the system level operation is verified in accordance with specifications. The testing should also verify that the system performance is maintained under specified, expected environmental conditions, as well as in storage, shipping and handling. For programmers/control units that communicate with implanted electronics, testing demonstrating that the programmer/control unit is capable of communicating with and programming the implanted electronics should be provided. If applicable, the transmitting and receiving antennae, transmitting distance, reed switch, and magnet should be tested to ensure that they function as intended.

(7) Radiofrequency (RF) Transmitter and Receiver

Significance: Radiofrequency (RF) communication through a transmitter and receiver (e.g., inductive coupling) is sometimes used for programming/controlling implanted components or recharging implanted batteries. RF transmitters and receivers may present risks to the patients if they do not operate as intended. For example, inductive coupling may lead to tissue heating or tissue damage.

Recommendation: Testing for the RF transmitter should include information outlined for the programmer/control unit as described in Section L(6) above. In addition, we recommend that you provide the following testing for the RF transmitter:

1. Mechanical testing;
2. Electrical testing; and
3. Transmission distance and orientation between the external emitting antenna and the antenna inside the receiver.

Testing for the transmitter and receiver should consider the testing recommendations for wireless technology outlined in Section J above. To adequately demonstrate protection from heating and ionizing radiation during the RF energy transfer, we recommend referring to the currently recognized version of ISO 14708-3: *Implants for surgery - Active implantable medical devices - Part 3: Implantable neurostimulators*.

(8) System Level Testing

Many BCI device technologies have multiple components that may be interchangeable to achieve different and configurable clinical uses (i.e., a modular approach). For example, a system may include an implanted electrode that acquires neural signals. These signals are then sent to another system component where they are processed (i.e., decoded and encoded) and used to control an assistive effector component. Additionally, a separate programmer may be used to control functions such as turning the device on and off and switching between various outputs and programs.

Given the variability of individual patient needs, manufacturers may choose to develop BCI systems with individual components manufactured by different manufacturers, which allows "mix and match" compatibility across several manufacturers. Such individual components can be produced by different manufacturers and subsequently combined to make a complete system. For example, a cortical electrode may be developed and manufactured by Company A and used to record neural signals to be acquired, processed, and transferred by an acquisition system and software developed by Company B. The data transferred from Company B's acquisition system is then used to control an assistive technology developed by Company C.

Significance: A thorough understanding of how various components interact with one another, with the user and patient, and with the environment is essential to demonstrate the safety and effectiveness of implanted BCI systems. While each component of the system has characteristics that can introduce risk individually, new risks can arise when the components interact to perform as a system.

Recommendation: To verify all system components operate together as set forth by the system specifications, FDA intends to evaluate the entire system and associated performance testing of the system. Electrical safety, EMC, and wireless coexistence testing should be performed on the full complete system for the proposed intended use. In addition, you should identify specific criteria that demonstrate compatibility of the component with other device components and provide scientific or clinical justification for the criteria. However, if

system-level testing is not feasible, a rationale for the exclusion of system-level testing and description of how risks will be mitigated should be provided. In this event, we also recommend that you provide a rationale for how malfunctions in system operation can be traced back to the modular component in which the malfunction occurred and how the malfunction was resolved and mitigated. All devices intended to be used in conjunction with the implanted BCI device (e.g., implantation tools, clips or belts for body-worn components, components from another marketed medical device) should be compatible. Incompatibility can result in device damage or other clinical adverse events. Therefore, we recommend that you identify and provide specifications needed to ensure compatibility between all modular components of the system in the protocol and any labeling provided to the operators/investigator.

M. Referencing Master Files (MAF) and other FDA Premarket Submissions

Often a sponsor submitting an IDE needs to use another party's product (e.g., material, subassembly, or component) from another marketed medical device (i.e., modular component, see Section III(L)(8) or use another party's facility in the manufacture of the device. In this circumstance where a sponsor chooses to leverage information related to the other party's product, facility, or manufacturing procedures in their submission, a device master file (MAF) may be referenced as part of the submission to FDA with a Letter of Authorization (LOA). You should refer to the following FDA webpage for additional information on using device MAFs: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

N. Non-Clinical Animal Testing

Significance: Non-clinical animal testing is generally recommended to evaluate the *in vivo* safety of implanted BCI devices, particularly for new designs, significant device modifications, and new indications.

Recommendation: Animal testing of implanted BCI devices should address factors that cannot be evaluated through bench tests or in a clinical study. The study design and endpoints should be based upon the mechanism of action of the device and mitigation of risk.

FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. You should consider the best practices for the development, conduct and presentation of these animal studies while incorporating modern animal care and use strategies. In addition, we encourage you to consult with FDA if you wish to use a non-animal testing method that you believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method. For details on the

Q-Submission Program, refer to the guidance "Requests for Feedback on Medical Device Submissions: The Q-Submission Program."[22]

We encourage manufacturers to take advantage of the Q-Submission Program to ensure that the animal study protocol addresses safety concerns and contains the appropriate elements (e.g., the study should be performed under Good Laboratory Practice (GLP) regulations as stated in 21 CFR 58 at an animal study facility with appropriate licensure and accreditations).

In most cases, we recommend that you conduct animal testing on a final, finished device to support the assessment that the risks to the subjects do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained, in a human clinical trial. For devices evaluated in early feasibility studies, an animal study using a final, finished device may not be needed if an adequate rationale is provided. See FDA guidance, "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies"[23] for more details on the device evaluation strategy and how leveraged information may support your rationale.

(1) General Considerations for Animal Studies

Implanted BCI devices encompass a variety of device designs, neural targets, and mechanisms of action. For example, they can include recording or stimulation actions, penetrating or surface electrodes, or components from another marketed medical device (i.e., modular design, see Section III(L)(8)), and central or peripheral nervous system targets. They also offer a variety of therapeutic and restorative benefits to patients. Each of these variables may affect the types of risks and benefits posed to the patient, and consequently, the non-clinical information needed to support use in human subjects. Therefore, you may need to customize your animal protocols to establish the data needed to support a future clinical study. Prior to initiating your animal study, we strongly recommend that you submit a Pre-Submission to obtain FDA feedback on your animal model and study design. General factors to consider for animal study protocols are provided below.

1. Purpose of the animal study – The main purpose for conducting an animal study is to provide evidence of device safety. Animal studies may also provide evidence of device performance that cannot be adequately obtained from bench testing, including *in vivo* reliability over time. However, alternative methods may be needed in situations in which animal studies may be inappropriate, such as cognitive assessments.
2. Study protocol and reported results – When designing the study protocol, specific determinations of study variables (such as the number of animals studied, the study duration, the type of animal model, the choice of controls) depend on both the risks of the device and the currently available scientific information that can be leveraged to mitigate expected risks. An understanding of device risks includes device attributes and mechanisms of action, anatomical target, and surgical implementation. Examples

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

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including

include the way in which the device interfaces with the target tissue (such as penetrating vs non-penetrating), the device location and the corresponding biological and mechanical stress inflicted on the device, the robustness of the device mechanisms of action (e.g., neural stimulation may be more robust to tissue responses than neural recording), and the expected device lifetime. Existing scientific information with sufficient rationale may be leveraged to lower the burden associated with conducting animal studies (e.g., smaller number of animals, short duration of animal study) or justify why additional animal studies may not be needed. Such scientific information includes the use of the device or device components in clinical studies, prior studies in animals using the device or device prototypes, bench testing of device performance, and published literature with direct relevance to the device attributes.

Many BCI devices involve implanted, multi-component systems designed for long-term use in human patients. For these devices, animal studies that address chronic *in vivo* evaluation of the final device system provide a greater degree of understanding of device safety than acute studies or chronic investigations of partial systems. A full evaluation of device risks and available scientific evidence will allow for the determination of the appropriate protocol for a given BCI system.

When describing the results of conducted animal studies, we recommend that you include a discussion of how the findings support preliminary safety of the device for your proposed clinical study.

3. Good Laboratory Practices – Good Laboratory Practices (GLP) for animal care and study conduct as specified in 21 CFR Part 58 ensure the quality and integrity of animal data to support IDE applications. Non-GLP study data may be used to support an IDE application only if the deviations from GLP are identified and justified[24] and do not compromise the validity of the study results. See FDA guidance, "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies"[25], for more information on when non-GLP animal study data may be used to support an IDE study.

(2) Animal Study Protocols

We recommend that animal study evaluations include macroscopic and microscopic effects on tissue and evaluation of the explanted device components. The animal study test protocols should include, but are not limited to, the following items:

- Study objective;
- Study design including the species, strain (if applicable to the proposed animal model) and number of animals used, study duration, as well as the rationale for the design;
- Details regarding the device to be tested and a rationale for any difference between the study device and the device intended for clinical use; recording and/or stimulation

[24] See 21 CFR 812.27(b)(3).

[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including

location; and stimulation intensities, including stimulation type (voltage or current), amplitude, pulse mode (monophasic, biphasic), duration, frequency, charge density, charge per phase, electrode surface area and material (if applicable);
- Stimulation evoked response testing (if applicable);
- Recording signal quality at both acute and chronic timepoints (if applicable); and
- Histopathology of the surrounding tissues.

Some recommendations for an animal study design evaluating BCI devices include:

1. Choice of animal models: The choice of animal models depends on the BCI device and may vary based on device type, indication, and implant site. We believe that the animal and its related environmental and physiologic attributes should provide a test system that offers a best attempt at simulating the clinical setting. Animal models that can accommodate human-sized devices may be preferable, although the use of scaled devices might be acceptable in some circumstances if appropriate scientific justification is provided.

2. Number of animals: We recommend inclusion of a sufficient number of animals with justification.

3. Controls: Appropriate controls should be identified in the study protocol. In some studies, non-implanted contralateral tissue is an appropriate control. For evaluation of stimulation safety only, implanted but non-stimulated contralateral tissue may be used.

4. Study duration: Study duration is dependent upon the profile of expected device risks. We recommend that you provide a justification of the length of your animal study.

5. Safety tests: We recommend histopathological or histomorphological evaluation of implanted tissue, including both structural analysis and evaluation of injury markers that are relevant for the neural tissue. Such markers might include necrotic neurons, neural processes, astrocytes and microglia/macrophages in central nervous system tissue, or an analysis of axons, Schwann cells and myelin in peripheral nervous system. We recommend that you justify the use of specific histological markers and provide evidence that the histological protocol is adequate to capture major adverse reactions. Histopathological results should be quantified (e.g., the volume of necrotic tissue) by an independent veterinary pathologist who is blinded to study groups. In order to better predict clinical adverse effects, behavioral and functional assays are recommended.

   For devices involving a stimulation component, we also recommend that you provide experiments to establish the safety of stimulation. The exact stimulation protocol varies depending on the application of the device. If the device is designed for continuous activation, both acute and long-term tests are recommended. If the device is intermittently active, long-term testing should be performed. See below for acute and long-term stimulation testing recommendations.

6. Reliability test: For devices designed for chronic implantation, long-term device performance should be established in a biological environment, unless scientific evidence for device performance *in vivo* has already been collected (e.g. prior animal studies and/or published literature using the same or similar electrode configuration). For devices involving recording components, periodic recording should be performed over the lifetime of device implantation and evaluated with a quantitative metric, such as signal to noise ratio and spike amplitudes. *In vivo* impedance of electrodes may be acquired to demonstrate the functionality of the device. For devices involving stimulation components, impedance measurements should be performed to characterize the functionality of the device, although care should be taken to assure that measurement protocol does not affect interpretation of data from control animals. Microscopic evaluation of explanted devices should be used to identify physical damage or other failure modes to device components (i.e., electrode conductor or insulation, leads and connectors).

7. Acute stimulation test: To test stimulation safety, electrode stimulation at the maximal limits should be applied for durations of up to 24 hours. The animal may be sedated during the stimulation protocol. After testing, histological evaluation of tissue responses should be performed.

8. Long-term stimulation test: Periodic stimulation at maximal limits, or the highest stimulation intensity that is acceptable for the welfare of the animal, should be applied for a period that is reflective of your clinical protocol, with justification. After explantation, tissue around the implant should be examined to identify any histological or pathological response. We also recommend that you evaluate the explanted device at a magnification sufficient to detect any failure mechanisms such as corrosion or insulation degradation. A detailed comparison of animal study and clinical IDE study stimulation parameters should be included. If the stimulation charge delivered in animal studies is less than the maximal proposed limit for human studies, we recommend providing a scientific justification discussing why this is an accurate representation of the safety risk posed to patients.

9. Surgical Approach – A detailed description of the implantation approach should be provided along with its translatability to human implantation. Included in this section should be a rationale for the anatomical device target, with justifications for any differences from the intended human implantation site. Whenever possible, the surgical tools designed for human implantation should be used for animal surgery. If the clinical plan involves explantation of the device, incorporate surgical device removal strategies into the surgical approach of the animal study.

O. Clinical Performance Testing

(1) Report of Prior Investigations

For an Investigational Device Exemption (IDE), a summary of any prior clinical studies of the device used for the proposed intended use must be provided in the report of prior

investigations.[26] For early feasibility studies, although clinical data may not be available with the subject device for its proposed intended use, any relevant background clinical information should also be provided. Relevant information includes data or publications on:

- similar or related devices utilized for the proposed intended use; or
- the subject device or similar devices used for a different use.

This information may come from clinical use outside of the United States (OUS) and may be used to support proof of principle and/or to address the likelihood of potential failure modes that may be observed during an IDE study. If such information is available, it should be summarized in a format appropriate for the type of information (e.g., clinical study reports, summaries of publications with copies of the citations, individual experience with the device or prototype outside of a clinical study).

A narrative description of the other clinical study or studies should be provided in this section. The narrative should be brief, and should include the following information for each study:

- the purpose of the study (e.g. proof of concept, patient perspective study)
- whether the study was a pivotal, supporting, or feasibility study
- the design of the study, including any randomization, blinding, and the control(s) used
- the number of patients enrolled
- the number of investigational sites both inside the United States (US) and OUS
- the primary study endpoint(s)
- the amount of available follow-up
- a summary of results/conclusions

(2) Clinical Study Considerations

The recommendations for some aspects of a clinical study for implanted BCI devices may vary with device development stage and the type of IDE study (e.g., Early Feasibility, Traditional Feasibility, Pivotal) being performed. If an Early Feasibility Study is submitted, the study type should be clearly stated as such in the IDE. The following FDA guidance documents describes the Agency's current thinking on clinical study design for early feasibility studies and Pivotal IDE studies:

- Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies[27]

[26] See 21 CFR 812.27.

[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including

- Design Considerations for Pivotal Clinical Investigations for Medical Devices[28]

Generally, we believe implanted BCI devices addressed by this guidance document are significant risk (SR) devices subject to all requirements of the IDE regulation, 21 CFR Part 812. For studies that are not exempt from the IDE regulation, sponsors are responsible for making the initial risk determination (SR or nonsignificant risk (NSR)) and presenting it to the Institutional Review Board (IRB). For more information, see the Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors, "Significant Risk and Nonsignificant Risk Medical Device Studies."[29] In addition to the requirements of 21 CFR 812, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50). Certain components of the clinical study design are especially important, when designing a clinical study intended to evaluate the performance of a BCI system. For each clinical study design component, scientifically supported and justified descriptions are essential to provide clarity and facilitate understanding. In addition, adaptive trial designs, when properly implemented, can reduce resource requirements and/or increase the chance of study success.[30] The following design components should be considered and supported with a justification in your IDE submission when developing the clinical study protocol:

a. Patient Populations

A variety of patient populations may benefit from BCI devices whose function is to augment their ability to interact with their environment and improve communication. Such populations include patients with limb amputations or diseases and conditions such as spinal cord injury (SCI), stroke, paralysis, and neuromuscular disorders. For an IDE approval, the potential benefit to the patient for any device should outweigh the potential risks.[31] Patients with different medical conditions may have different needs and different risk tolerance for a BCI system; therefore, sponsors should consider a subject population with needs that are appropriately addressed by the device, so that the potential benefits and risks are appropriately considered.

b. Home Use

It is important to study BCI devices in realistic, home use environments since lab conditions may not adequately reflect the possible risks and/or benefits that the patients will experience during actual use in the environments in which the patient will be using

[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices

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

[30] See FDA Guidance "Adaptive Designs for Medical Device Clinical Studies", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies.

[31] See FDA Guidance "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device.

the device. Additionally, for home use, it may be necessary to have a caretaker who is willing, able, and available to perform essential tasks related to the BCI system such as:

- manage startup and maintenance of the BCI: attach electrodes, start the system;
- monitor patient progress, if applicable; and
- can contact the physician when necessary.

Therefore, it is important to incorporate assessment of caregiver safety and their ability to assist the user (i.e., time, attention and physical ability) in the clinical study metrics. To ensure safe use of your device in the home setting, we recommend that you specifically describe in your clinical protocol how subjects and caregivers will be trained to use the device at home. We also recommend that you describe how you plan to assess the effectiveness of your training program.

Refer to the FDA guidance titled "Design Considerations for Devices Intended for Home Use"[32] for recommendations on minimizing the risks associated with home use devices.

c. Investigational Plan

The following information is intended to clarify how the investigational plan can be developed for IDE studies for implanted BCI devices.[33]

i. Purpose/Objective

The clinical protocol should begin with clearly defined objective(s) and hypothesis(es). There should be an overall statement of the purpose/objective of conducting the study (e.g., to evaluate the safety and effectiveness of the BCI device in the treatment of a specific condition as compared to a control). In addition, the purpose should include a precise, medically accepted definition of the condition to be treated and a scientifically sound rationale for the proposed clinical study. For pivotal clinical studies, the null and alternative hypotheses for the proposed study should be stated in terms of the specific study endpoints, outcomes, and parameters used to measure the success/failure of the system. The study should then be designed to test these hypotheses.

ii. Study Design

Your study design description should include, but not be limited to, the following basic elements:

- whether it is randomized or non-randomized;

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use

[33] See 21 CFR 812.25

- whether it is controlled or uncontrolled and, if controlled, the type of control(s);
- whether the study results will be compared to a performance goal[34] and, if so, how the performance goals were derived;
- a description of the study success criteria (e.g., superiority or non-inferiority when compared to the control) and a description of patient-level success/failure if a responder analysis is being used; and

Studies may include more than one treatment group such as SCI, stroke, or other conditions with proper justification as to why the different populations can be pooled. See FDA's Guidance for Industry, "E9 Statistical Principles for Clinical Trials"[35] for more details on how to effectively incorporate and analyze multiple subject populations in a single study.

iii. Study Duration and Follow-up Schedule

In order to assess all safety and primary effectiveness outcomes sufficiently, the proposed study should include a sufficient amount of safety and an appropriate level of effectiveness data. A long-term follow up period of at least 1 year is recommended due to the current lack of data regarding the long-term effectiveness of implanted electrodes and to identify any long-term safety signals. Long-term clinical durability and reliability are important factors to long-term efficacy of the implanted BCI device; for example, over time, implanted electrodes can lose their ability to detect signals from physical or biological processes. Although some information on electrode durability and reliability can be obtained from animal studies (see Animal Study Protocols in Section III(N)(2)), animal studies may not accurately predict long-term clinical performance in humans.

iv. Inclusion/Exclusion Criteria

Adequate inclusion and exclusion criteria are essential to define the appropriate patient population for the proposed device, and eventually the intended use population for a marketing submission. The criteria for enrollment into any clinical study of an implanted BCI system will differ depending on the population targeted for the proposed treatment and the type of the disease process (e.g., SCI, Amyotrophic Lateral Sclerosis (ALS), amputations, and stroke).

Regardless of the indication being investigated for any implanted BCI system, the following general inclusion criteria should be considered:

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

[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials

- Range of patient ages (skeletally mature, if applicable)
- Spinal injury levels involved (e.g., C2-C7, L2-S1, if applicable)
- Type of clinical condition (i.e., diagnosis) and level of paralysis/impaired function (measurement depending on the type of neurologic condition)
- Clinical conditions for patient entry (e.g., preoperative function score, preoperative neurological score)
- Description with suggested time frame of any prior, unsuccessful, non-operative or conservative treatment (e.g., physical therapy, medication trials)
- Ability of patient to understand and sign the informed consent
- Ability of patient to communicate verbally or via typing on a computer
- Ability of patient to meet the proposed follow-up schedule
- Ability of patient to follow the postoperative management program
- Willingness and ability of caregiver to monitor for surgical site complications and behavioral changes of the patient on a daily basis

Regardless of the indication being investigated for any BCI system, the following patients should be considered for exclusion from the clinical study:

- History of seizure
- Intellectual impairment
- Presence of clinically relevant memory problems
- Psychotic illness or chronic psychiatric disorder, including major depression if untreated (diagnosis of Axis I or Axis II)
- Active wound healing or skin breakdown issues
- History of poorly controlled autonomic dysreflexia
- Medical contraindications for general anesthesia, craniotomy, or surgery
- Diagnosis of acute myocardial infarction or cardiac arrest within the last 6 months
- Any type of destruction and/or damage to the primary motor cortex region as determined by magnetic resonance imaging (MRI)
- Other active implantable devices such as cardiac defibrillator, pacemaker, vagal nerve stimulator, spinal cord stimulator, etc.
- Reliance on ventilatory support
- Co-morbid conditions that would interfere with study activities or response to treatment, which may include:
    - Severe chronic pulmonary disease
    - Local or systemic acute or chronic infectious illness
    - Life threatening cardiac arrhythmias
    - Severe collagen vascular disorder
    - Kidney failure or other major organ systems failures
- History of a neurological ablation procedure

- Labeled contraindication for MRI
- History of hemorrhagic stroke
- History of HIV infection or ongoing chronic infection
- Pregnant or of child-bearing potential and not using contraception
- Concurrent participation in another device or drug trial

If you believe any of the above inclusion/exclusion criteria does not apply to your proposed clinical study or intend to propose new or alternative inclusion/exclusion criteria, we recommend providing a clinical justification.

v. Patient Demographics

Characteristics of the planned patient population that could affect the results of the study should be described, including:

- Characteristics such as age, race, sex, disease;[36,37] and
- If performing a study that includes non-US study sites OUS, any differences between US and non-US populations that may be expected, based on specific population characteristics, disease progression or treatment paradigms.

Your description should also explain how expected differences (if any) will be accounted for in the clinical study design or analysis of the results.

vi. Treatment Parameters/Protocol (including post-operative regimen)

The clinical study protocol should include sufficient information regarding the implantation procedure, the post-surgical recovery period and regimen, the treatment duration, any other surgical procedures anticipated such as device removal.

vii. Endpoints and Other Outcomes

1. Primary safety endpoint(s): The study safety endpoints should include a characterization of all adverse events (AEs) for all subjects, including, but not limited to, subjects in both the treatment and control groups (if applicable), and adverse events related to the implant surgical procedure, the implantable device, and the assistive effector component. In addition to identifying safety endpoints, we recommend that you include in your protocol a description of your plan for addressing adverse events when they occur and safety criteria in

[36] See FDA guidance "Evaluation of Sex-Specific Data in Medical Device Clinical Studies," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug.

[37] See FDA guidance, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies.

your study that would require device removal or subject discontinuation in the study.

2. Primary effectiveness endpoint(s) and second effectiveness endpoints, (if applicable): In addition to identifying the primary and secondary effectiveness endpoints, you should include how the primary effectiveness endpoint was validated (if applicable) for the intended use population/subjects, the minimal clinically important difference, and how the timing of the assessments is appropriate and clinically meaningful. Although validated endpoints are recommended, FDA realizes that feasibility studies may be used to validate desired clinical metrics and may not require *a priori* validated clinical endpoints. Likewise, early feasibility studies may use clinical endpoints not validated due to the type of data that are often pursued during device development. For non-validated endpoints that may be used in early feasibility studies and other feasibility studies, similar information (other than validation methods), as well as justification for their clinical utility, should be included.

3. Patient Input (patient engagement, patient preference information, patient-reported outcome measures):

   Patient engagement during clinical trial design may positively impact how an implanted BCI study is designed and conducted. Patients may provide recommendations to improve the patient experience of the trial, and improve the relevance, quality, and impact of the study results.

   Patient preference information (PPI) may be an important factor in the design and benefit-risk evaluation of a medical device, including implanted BCI devices. Ideally, a BCI technology should be comfortable, easy to don and doff (i.e., put on and take off, if applicable), user friendly, reliable, and aesthetically neutral or appealing, so patients are willing to accept and use the device. Factors such as requirements for daily calibration, fatigue with use, and inconsistent performance may affect the benefit-risk tradeoff patients are willing to make when deciding among treatment options. Additionally, risk tolerance may vary depending on the severity of the disability. For example, a patient with quadriplegia may be more willing to accept risks associated with a brain-implanted device than a person with a single limb amputation. FDA recommends early discussion on a potential PPI study to ensure its regulatory relevance; note that PPI studies are generally conducted separate from an IDE clinical study, although it is possible to integrate them into the overall study plan. Refer to the FDA guidance titled "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and

Inclusion in Decision Summaries and Device Labeling"[38] for more information on incorporating PPI into a study or submission.

A patient-reported outcome measure (PROM) can be used when the outcome of interest and desired intended use are best measured from the patient's perspective, (e.g., pain reduction). In such cases, it is important to select a scoring assessment that is validated for the appropriate "context of use,"[39] in this case: subject population and condition being treated, and desired intended use. For this reason, early discussion with FDA during the study design phase is important. These measures are often used in conjunction with other clinical outcome assessments (COAs) as part of a composite endpoint. When using PROMs in multinational trials, sponsors should make sure that the PROMs are interpretable, measure the same concept, and valid across cultures and languages. See the FDA guidance titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[40] for more information on incorporating a PROM into a study or submission.

d. Informed Consent Document

The informed consent document (ICD) must include all required elements and be worded appropriately.[41] We recommend ensuring that the document only contains words and terms that the average patient would be able to understand. The ICD should not include language that could lead subjects to overestimate the chance of personal benefit.

e. Statistical Analysis Plan (SAP) Considerations

The statistical analysis plan (SAP) will vary based on upon the type of clinical trial. For example, a feasibility study may have a small number of subjects and the clinical study protocol may be designed to lead to an understanding of the new therapy. Therefore, the statistical plan may be limited to descriptive statistics.

For a clinical study designed to demonstrate effectiveness (e.g., pivotal study), the study protocol should include a detailed, pre-specified SAP that includes plans to evaluate, to the extent possible, key assumptions that were made in the design of the study (e.g., pooling analysis across clinical sites or geographic regions, assessment of carry-over effects in a crossover study design, or proportionality of hazards in a survival analysis). The predefined SAP should be adhered to in analyzing the data at the completion of the study to support the usefulness of the

[38] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications

[39] Context of Use: a statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use. (https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-C)

[40] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

[41] See 21 CFR 50.25.

evidence generated by the study.[42] Advanced analysis techniques such as Bayesian statistics can also be used to accommodate adaptive trial designs, analyze complex models, or perform sensitivity analyses.[43]

[42] See FDA guidance, "Design Considerations for Pivotal Clinical Investigations for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

[43] See FDA guidance entitled, "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-use-bayesian-statistics-medical-device-clinical-trials-pdf-version.

APPENDIX A
Stimulation Output Specifications

An output mode is defined (for reporting purposes) as a version of a waveform produced by the unit. For example, biphasic symmetrical and biphasic asymmetrical would be considered separate output modes. If multiple values are available for a given parameter within the output mode, then the manufacturer should provide the range and identify the different steps that may be selected in that range if not continuous. The following table provides an example of how this information may be organized for each output mode. This table is not intended to represent an exhaustive list of parameters; ensure you provide all relevant device descriptive characteristics, as outlined in Section III(A) and Section III(L) above.

Output Characteristic	Device Output
Number of Output Channels[1] - Synchronous, alternating - Method of channel isolation	
Waveform[2] (e.g., charge balanced biphasic symmetrical, biphasic asymmetrical)	
Pulse Shape (e.g., rectangular, sinusoidal)	
Current/voltage regulated? Compliance voltage (if current source)?	
Maximum Output Voltage (specify units) (+/-_____%) [voltage should be reported at 500 Ω and at impedances covering the minimum, typical, and maximum range of physiologic impedances for the location being stimulated]	
Maximum Output Current (specify units) (+/-_____%) [current should be reported at 500 Ω and at impedances covering the minimum, typical, and maximum range of physiologic impedances for the location being stimulated]	
For multiphasic waveforms[2]: - Symmetrical or Asymmetrical phases? - Phase Duration[3] (include units) (state range, if applicable) (both phases, if asymmetrical)	
Pulse Duration[2, 4] (specify units)	
Frequency (Hz)[5]	
Method of Balancing Charge[6]	
Are charge balancing cycles always completed?[7]	
Net Charge (μC per pulse) @ 500 Ω	
Leakage Current[8] (nA) @ 500 Ω	

Output Characteristic	Device Output
Net DC Current[9] (μA) at maximum pulse rate @ 500 Ω	
Maximum Phase Charge (μC) @ 500 Ω	
Maximum Charge Density[10] (μC/cm²/phase) @ 500 Ω	
Maximum Phase Power (W/phase) @ 500 Ω	
Maximum Phase Power Density (W/cm²/phase) @ 500 Ω	
Pulse Delivery Mode (continuous/bursts (pulse trains))	
Burst Delivery[11]: a. Pulses per burst; b. Bursts per second; c. Burst duration (seconds); and d. Duty Cycle [Line a X Line b]	
ON Time[12] (seconds)	
OFF Time[12] (seconds)	
Current Path Options[13] (bipolar, unipolar, multipolar)	
Additional Features, if applicable	

Notes:

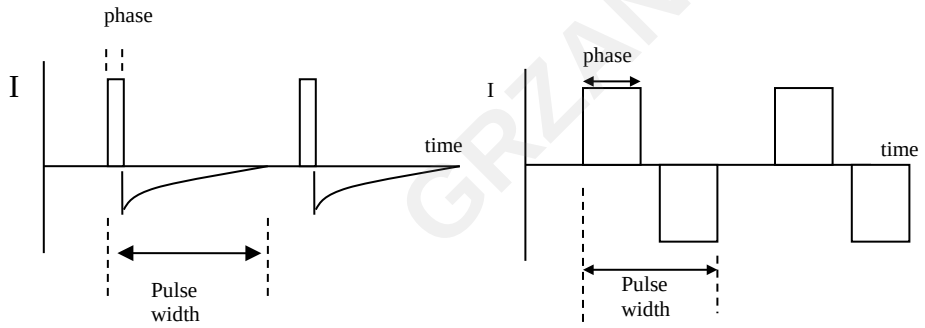
Variable Parameters: For continuously variable parameters, specify the full range; for parameters with discrete settings, specify all available selections.

Density Measurements: Maximum density values should be calculated using the conductive surface area of the smallest electrode and worst-case current path option available; sample calculations should be provided. The maximum power density should be based on the maximum duty cycle and should be averaged over an appropriate timeframe.

Output Mode: An output mode is defined as a version of a waveform produced by the unit (e.g., biphasic symmetrical and biphasic asymmetrical).

[1]Output Channels: The number of independently controlled circuits. For example, two leads that are independently controlled would be two channels and 8 electrodes that are independently controlled would be 8 channels. Synchronous channels both operate on the same on/off cycle. Alternating channels alternate between on and off states. Interleaved channels are generated by gating the outputs of a single-channel generator. If more than one channel is available, the method of channel isolation should be provided.

[2]Waveforms:



Biphasic Asymmetric Biphasic Symmetric

[3]Phase Duration: A phase is the current flow in one direction for a finite period of time. The phase duration is the time elapsed from the beginning to the end of one phase of a pulse or cycle.

[4]Pulse Width: The time elapsed from the beginning to the end of all phases plus the interphase interval within one pulse. Note that for monophasic waveforms pulse and phase are synonymous.

[5]Frequency: The number of pulses per second for pulsed current.

[6]Charge Balance Method: Charge may be balanced passively through capacitive coupling or actively by delivering pulse phases of equal and opposite charge. Both methods may also be combined.

[7]Completion of Charge Balancing Phases: If charge is balanced only by means of balanced pulse phases, pulse cycles may not be completed if a burst is terminated before the delivery of a charge balancing phase. With repeated bursts a net charge imbalance can occur. Operating parameters that can result in charge imbalance and resulting local pH changes, electrode corrosion, and/or tissue damage, should be mitigated through design of the output circuitry or through programming ability to prevent these effects.

[8]Leakage Current: current that is not functional.

[9]Net DC Current: Current due to charge imbalance or incomplete charge recovery when the device is delivering pulses.

[10]Maximum Charge Density per Phase: Note that the maximum charge density per phase should be safe for the site of stimulation.

[11]Pulse Delivery Mode: The mode is continuous if there is a continuous repetitive sequence of pulses. A burst is a finite series of pulses delivered for an identified duration.

[12]ON/OFF Time: ON time is the time during which trains of pulses are delivered. OFF time is the time between trains of pulses.

[13]Current Path Options: Bipolar involves the activation of one positive (anode) and one negative electrode (cathode) in close proximity to one another. Unipolar involves the activation of one or more negative electrodes and typically the IPG case as a positive electrode. Multipolar involves the activation of more than two electrodes (e.g., two positive and one negative, two positive and two negative). If more than one channel is included, a discussion of current flow between leads should be provided. Since output characteristics such as current density may be affected by different current paths, the worst case available current path should be used in such calculations.