


Workshop Materials



Discussion Paper: “Brain-Computer Interface (BCI) Devices for Patients with Paralysis and Amputation”



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I. Introduction

The FDA is releasing this discussion paper in preparation for the “Brain-Computer Interface (BCI) Devices for Patients with Paralysis and Amputation” public workshop, which will be at FDA’s White Oak Campus in Silver Spring, Maryland on November 21, 2014.

It’s important to the FDA to help stakeholders (e.g., manufacturers, health care professionals, patients, patient advocates, academia, and other government agencies) navigate the regulatory landscape for medical devices. The agency is holding this workshop to open discussion and obtain public feedback on scientific and regulatory considerations associated with BCI devices for patients with paralysis or amputation.

The workshop is open to all stakeholders to address challenges in the development of BCI devices. The FDA hopes that open discussion will help successfully advance this rapidly evolving product area. The FDA will use information and feedback from the workshop to develop an overall strategy that will promote advances in the technology while maintaining appropriate patient protections. This strategy will identify advances in regulatory science and the development of FDA guidance on premarket submissions for BCI technologies.

For the purposes of this workshop, the FDA defines BCI devices as neuroprostheses that interface with the central or peripheral nervous system to restore lost motor or sensory capabilities. Investigational studies of BCI devices have underscored the potential utility for patients as well as the challenges in translating scientific knowledge to clinical benefit.

Moving BCI devices from the laboratory to U.S. patients can be impeded by gaps in scientific and clinical knowledge, questions concerning long-term effectiveness, reliability and safety, and uncertainty in the regulatory and marketing pathways.

This discussion paper provides background information and questions for workshop attendees to consider in advance, and will help facilitate discussion. While the information and questions provided represent FDA’s focus, we look forward to hearing other considerations and questions at the workshop.

The information and questions contained in this document are not binding and do not create new requirements or expectations for affected parties, nor is this document meant to convey FDA’s recommended approaches or guidance. Rather the information contained in this document offers background and the basis for discussions at the Public Workshop.

II. Advancing Regulatory Science for BCI Devices

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health. One component of CDRH's vision is to assure that patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world. One step towards achieving our mission and vision is to facilitate medical device innovation by advancing regulatory science.¹

Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.² In the last few years, rapid advances in innovative science have provided new technologies to discover, manufacture, and assess novel medical devices—the FDA must keep pace with and utilize these new scientific advances in order to accomplish our mission.

Advances in regulatory science supporting BCI technologies will help make the evaluation and approval process more efficient, fueling the delivery of safe new products to patients faster and strengthening the ability to monitor product use and improve performance.

Regulatory science can help guide the types of preclinical and clinical testing that may be important to support potential clinical studies or marketing approval for BCI technologies. Regulatory science can improve the efficiency of product evaluation by identifying non-clinical testing that can substitute for or complement clinical testing.

Regulatory science is often used to help provide recommendations for non-clinical testing and clinical study measurements (e.g., appropriate outcome measures, patient preferences, and benefit-risk considerations) that may be incorporated into FDA guidance documents. For example, a guidance document may contain the scientific basis for evaluating device modularity and interoperability of devices. Two important goals of this public workshop are clarifying the regulatory science research needs for this field and to present and discuss the regulatory elements that can be evaluated to provide a predictable path to market for the devices.

The field of regulatory science—the knowledge generated in developing new tools as well as the tools themselves—can inform a range of health-related advances in treating numerous diseases and conditions. An example of this is the FDA partnership with the Medical Device Innovation Consortium (MDIC), for the purpose of developing and promoting medical device regulatory science with a focus on speeding the development, assessment, and review of new medical devices.³

Questions for Consideration

With regard to advancing regulatory science for BCI devices, we recommend that the following questions be considered in preparation for the workshop:

1. What are the key design characteristics for BCI technologies? For example, what are the best approaches to evaluating patient usability information, examining control of

¹ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/ucm300639.htm>

² <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf>

³ <http://mdic.org/>

motor functions and sensory feedback, and modularity and interoperability with multiple platforms?

2. What are approaches to examining BCI sustainability and long-term safety and effectiveness? For example, how should one assess long-term reliability of implanted microelectrode arrays, structural changes from implanted arrays, including neural and vascular structures, long-term functionality of neural elements in brain, evaluation of motor and sensory function, and behavioral changes; and the development of common platforms for reliable non-clinical testing?
3. In what ways can technical solutions be sought with non-clinical data? For example, how should animal test platforms for safety, reliability, and function be assessed and what are the important functional biomarkers for human studies?
4. What are the most productive mechanisms by which federal and non-federal entities can work together in pursuit of common regulatory science goals?

III. Regulatory Considerations for BCI Devices

The field of BCI devices is progressing rapidly from fundamental neuroscience discovery and proof-of-concept to clinical application. The FDA recognizes the value of supporting medical device innovation to address clinical needs that improve patient care, particularly when alternative treatments are unavailable, ineffective, or associated with substantial risks to patient safety. As a starting point, the workshop will consider regulatory issues associated with BCI devices in the following areas:

- A. Non-Clinical Considerations for Evaluating BCI Devices;
- B. Clinical Study Considerations for Human Investigations with BCI Devices; and
- C. Device Modularity.

During the workshop, and through an open public docket (available to collect public comments starting August 19, 2014), the feedback we collect will inform our development of a guidance document for BCI devices. Although the recommendations for some aspects of clinical studies of BCI devices may vary with the specific patient population and the type of IDE study performed (See Appendix A), we recognize non-clinical, clinical, and modularity of a device as important common factors in developing this technology. *As part of the workshop discussion paper, a brief overview of device regulation is also provided (Appendix A).*

A. Non-Clinical Considerations for Evaluating BCI Devices

Non-clinical device testing is important to mitigate risk and to support potential clinical studies or market approval. As with all medical devices, it is important to perform a thorough risk analysis and implement adequate risk mitigations. In addition to standard device testing such as biocompatibility, sterility, and electrical safety, BCI technologies may have unique testing considerations, for example:

- BCI technologies may measure signals from the brain or peripheral nerves; so important factors to consider include electrode reliability, signal-to-noise ratio, artifact removal (e.g., eye or muscle movement), and battery longevity.
- The signal of interest may vary among and within subjects over time, making the quality of BCI input signal for a specific individual at a specific time very difficult to predict. As a result, most BCI systems require training or adjustment to each subject individually.
- If the device provides stimulation to the nervous system, determining maximum safe levels of stimulation that can be applied to brain tissue or peripheral nerves is important.
- In “real world” use, BCI systems may need to perform reliably in complex and unstable environments that often contain sources of electronic noise.

Questions for Consideration

With regard to regulatory preclinical considerations, we recommend that the following questions be considered in preparation for the workshop:

1. What are the key areas of non-clinical testing that should be addressed for BCI technologies? For example, what test methods and metrics should be presented to demonstrate long-term reliability of implanted electrodes in the central or peripheral nervous systems? Can new methods/metrics be developed to more accurately assess the long term reliability?
2. When should animal studies be performed prior to implantation into humans (e.g., to determine device reliability or stimulation safety) and what general study design principles (and results) should be examined to determine whether preclinical data supports moving to human study?

B. Clinical Study Considerations for Human Investigations with BCI Devices

BCI devices have the potential to benefit people with severe disabilities by increasing their ability to interact with their environment. This could increase their independence by enabling them to operate prostheses, wheelchairs, communications devices, and other assistive devices using signals recorded from the brain or peripheral nerves. BCI devices also present additional risks compared to conventional prostheses due to technology, such as the use of implanted components. Implantation carries potential risks such as neural tissue damage that can result in additional functional or sensory deterioration. The development of adequate clinical study designs for BCI devices that are intended to support marketing authorization in the U.S. is essential to the successful translation of BCIs from concept to patient access.

Patient Populations

Patients with limb amputations and neurological conditions such as spinal cord injury (SCI), stroke, and neuromuscular disorders may benefit from BCI devices that augment their ability to interact with their environment as well as to communicate with others. Towards this goal, it is important to identify initial and future target populations for BCI devices. Different patient populations are likely to have different functional impairments and benefit-risk considerations. For example:

- The functional impairments of a person with an amputation may differ from those of a person with a SCI; and the needs of people with SCI may differ depending on the level of injury. Additionally, persons with progressive disorders, such as amyotrophic lateral sclerosis (ALS), will have impairments that change over time.
- Patients with SCI, ALS, amputations, and stroke may all have some type of motor impairment, but they may require different device outputs relevant to their clinical condition. The available device inputs and signal processing required may also differ.
- Patients may vary as to what type of BCI technology may work best given their level of functioning. For example, a cortical implant may be optimal for a patient with SCI but may not work well in patients with ALS or stroke due to brain abnormalities. The patient's level of amputation may also impact the level of functioning.
- The risk tolerance may vary depending on the severity of the disability. For example, a patient with quadriplegia may be more willing to undergo a brain implant than a patient

with a single limb amputation. Other patients may be more willing to tolerate a higher rate of adverse effects associated with BCI device.

- Comorbid conditions, such as phantom limb pain, post-traumatic stress disorder, depression, impaired cognition, and loss of sensation within a specific patient population may affect acceptance and successful integration of BCI devices.

Clinical Metrics

Clinical metrics or endpoints are important for defining the benefits and risks of medical devices. Metrics should be clinically meaningful, measure how a patient functions or feels or both, and ideally be validated for the indicated patient population. Unfortunately, there are few clinically meaningful endpoints that have been validated for assessing BCI devices and there is a need for defining and developing such metrics. Under these circumstances, feasibility studies can be used to help develop metrics and determine clinically relevant changes in performance.

The following may be important to consider when developing metrics for evaluating study success for BCI device clinical studies:

- The patient population for which the device can be used and the type and level of benefit achieved through use of the device. For example, a patient with an amputation may primarily benefit from control of a prosthetic limb, a patient with SCI may primarily benefit from control of a motorized wheelchair or control of their bowel and bladder function, while patients with ALS may have needs related to communication
- The level of benefit needed to outweigh the risks associated with the BCI device may depend on the level of disability as well as the risk tolerance of the patient population.
- Activities of daily living and quality of life are often important to patients.

Home Use

It is important to study BCI devices in realistic home-use environments since lab conditions may not adequately reflect where a patient will actually use the device. For home use, it may also be necessary to have a caretaker who is willing, able, and available to manage the BCI (attach electrodes, start the system, etc.) when necessary, monitor patient progress, and contact the physician and thus, considerations for caretakers may be important when developing clinical endpoints.

Questions for Consideration

With regard to clinical considerations, we recommend that the following questions be considered in preparation for the workshop:

1. Can different disease states or conditions such as patients with SCI and patients with amputations be served by the same BCI technology?
2. How should one consider the level of functional loss in designing BCI technologies versus targeting particular diseases or conditions?

3. Comorbid conditions, such as phantom limb pain, post-traumatic stress disorder, depression, cognitive disability, and loss of sensation may occur within specific patient populations and may affect acceptance and successful integration of BCI technologies. How these considerations should be incorporated into clinical studies and what clinical metrics exist to measure these phenomena?
4. What are important activities of daily living and quality of life factors to measure in a clinical study for various populations? What are important patient-oriented clinical metrics for daily living and quality of life? And what patient-oriented metrics are available to assess the risk tolerance of the device as well as the added benefit over a state-of-the-art device?
5. What individual subjects consider most important for their quality of life may not only vary between patient populations, but also between individuals. How should this be assessed in clinical studies?

C. Device Modularity

There are typically four main components to most BCI systems. As depicted in Figure 1 below these include:

- A component for signal acquisition (e.g., electrodes);
- A component for signal processing that includes software for decoding and encoding signals and associated hardware;
- An assistive device (e.g., a prosthetic limb or wheelchair); and
- An operating protocol to control functions such as turning the device on and off and switching between various outputs and programs.

A thorough understanding of how various components interact with one another, with the user and patient, and with the environment, is essential to the safety and efficacy of medical devices. While each component of the system has characteristics that can introduce risk on their own, new risks can arise when the components interact to perform as a system.

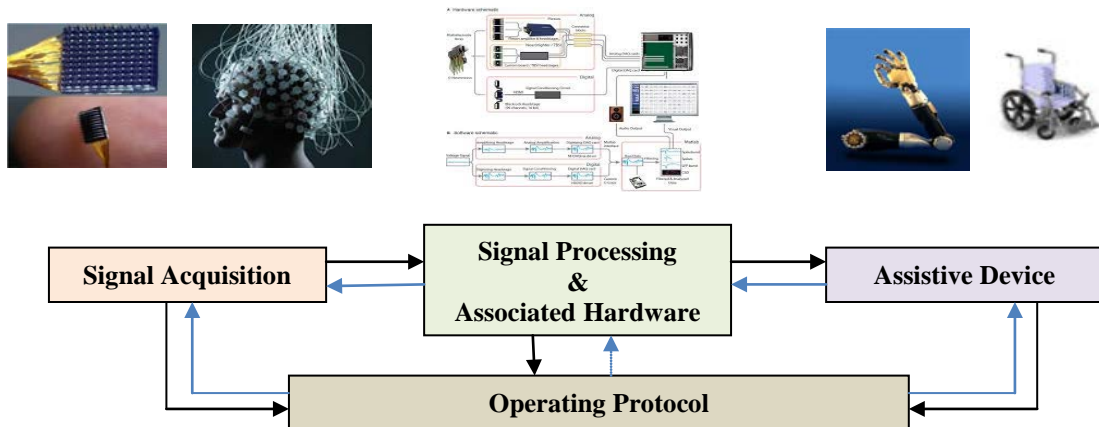


Figure 1: Main Components of a BCI System

Often individual components are manufactured by different manufacturers and then combined into a system. In order to help facilitate this process, while preserving the trade secrets of the various manufacturers and facilitate the sound scientific evaluation of medical devices, FDA established the device master file (MAF) system (See Appendix A).

It is also recognized that, given the variability of individual patient needs, it may be desirable for individual components to be manufactured by different manufacturers and to “mix and match” compatibility across several manufacturers. One potential solution is the development of standardized BCI systems, for example, standardized connectors and data protocols or standards development for components or interconnections of a BCI device/system.

Questions for Consideration

With regard to device modularity, we recommend that the following questions be considered in preparation for the workshop:

1. What are the important technology elements to standardize for BCI technologies? Apart from standardization, what are other potential solutions to addressing modularity concerns?
2. What are the major translation challenges for BCI technologies and how can they be practically addressed?
3. Timing of standardization relative to technology development is important in terms of enabling and speeding innovation and standardization is a key element in assuring safe and effective adoption of modular BCI devices. Is the time right for standardization of inter-connections of modular BCI devices or is it still premature to do so?

IV. Submitting Public Comments

Regardless of attendance at the public workshop, if you have information related to this workshop that you wish the FDA to consider, please post your material to Docket Number FDA-2014-N-1130 at <http://www.regulations.gov>. Instructions for posting material can be found at: <http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm> or in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Docket ID: FDA-2014-N-1130). Both individuals and groups may submit materials.

Please note that the docket will be public, and not appropriate for addressing individual confidential medical device concerns.

V. **Appendix A: A Backgrounder on Medical Device Regulation**

For general information on how to market a medical device please refer to the following FDA website: <http://www.fda.gov/training/cdrhlearn/default.htm>. This is a link to the CDRH web page for multimedia industry education that includes learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics.

Additional resources are provided as follows:

A. **Medical Device Classification**

There are three classes of devices: Class I (general controls), Class II (special controls), and Class III (premarket approval), with the level of regulatory control increasing from Class I to Class III based on the types of regulatory controls considered necessary to provide reasonable assurance of safety and effectiveness⁴. For more information on device classification please refer to the following FDA website:

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/default.htm>

B. **Marketing Applications**

Information on the various types of marketing applications can be found on the following FDA websites:

- **Premarket Notification (510(k)):**
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketnotification510k/default.htm>
- **Premarket Approval (PMA):**
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketapprovalpma/default.htm>
- **Humanitarian Device Exemption (HDE):**
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm>
- **Evaluation of Automatic Class III Designation (*De Novo* Classification Process):**
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf>

C. **Investigational Device Exemptions (IDEs)**

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)⁵ establishes a framework for FDA to study medical devices for investigational use. This provides an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their devices' safety and effectiveness. This exemption is known

⁴ 21 Code of Federal Regulations (CFR) 860.3(c)

⁵ 21 U.S.C. § 360j(g)

as an Investigational Device Exemption (IDE). The FDA considers implanted BCI devices to be “significant risk devices” because they are “intended as an implant and present a potential for serious risk to the health, safety, or welfare of a subject.”⁶ In order to study a significant risk device in human subjects, a sponsor (defined here as the person responsible for initiating the investigation) must receive approval of an investigational device exemption (IDE) application prior to beginning the investigation.⁷ Investigational BCI devices (as defined above for purposes of this workshop) are generally evaluated by the Division of Neurological and Physical Medicine Devices (DNPMD), one of seven divisions in CDRH’s Office of Device Evaluation (ODE).

A number of pathways exist to study BCIs including:

- **Early Feasibility Study (EFS)**: a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application).⁸
- **First in Human (FIH) Study**: a type of study in which a device for a specific indication is evaluated for the first time in human subjects.
- **Traditional Feasibility Study**: a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study.
- **Pivotal Study**: a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.

D. Benefit-Risk Evaluation

In making decisions regarding premarket submissions, the FDA weighs benefits and risks. There are a multitude of factors to consider assessing benefits and risks and some of these are listed in Table 1 below.⁹

E. Medical Device Master Files (MAFs)

Often a sponsor submitting a premarket submission (i.e., an applicant) needs to use another party's product (e.g., ingredient, subassembly, or accessory) or facility in the manufacture of the device. In order that a sound scientific evaluation may be made of the premarket medical device submission, the review of data and other information related to the other party's product, facility, or manufacturing procedures is required. The other party, while willing to allow FDA's confidential review of this information, may not want the applicant to have direct access to the information. To help preserve the trade secrets of the ancillary medical device industry and at the same time facilitate the sound scientific evaluation of

⁶ 21 CFR 812.3(m)

⁷ 21 CFR 812.20

⁸ <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

⁹ Please refer to the FDA guidance documents referenced at the end of this discussion paper for additional information regarding benefit-risk evaluations in premarket submissions.

medical devices, FDA established the device master file system. Please refer to the following FDA webpage for additional information on device master files:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm>

Table 1 – Factors to Consider when Evaluating Benefits and Risks

<p align="center"><u>Considerations for Assessing Benefits</u></p> <ul style="list-style-type: none"> • Type • Magnitude • Probability of patient experiencing one or more benefit • Duration of effect(s) 	<p align="center"><u>Considerations for Assessing Risks</u></p> <ul style="list-style-type: none"> • Severity, type, number and rates of harmful events associated with the device • Probability of harmful event • Duration of harmful event
<p align="center"><u>Additional Benefit-Risk Considerations</u></p> <ul style="list-style-type: none"> • Type of submission • Stage of Device Development • Uncertainty • Characterization of Disease • Patient tolerance for risk and perspective on benefit • Availability of alternative treatments • Risk Mitigation 	

VI. Appendix B: FDA Guidance Documents

The following is a list of current FDA guidance documents that may of interest when developing premarket submissions:

Benefit-Risk

- “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>

IDE

- “Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies”
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>
- “Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff”
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf>
- “Design Considerations for Pivotal Clinical Investigations for Medical Devices”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf>

510(k)

- “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>

PreSubmission

- “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

Technical

- “Recognition and Use of Consensus Standards”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf>

- “Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment”
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm>
- “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>
- “Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077272.pdf>
- “Off-The-Shelf Software Use in Medical Devices”
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf>

Developing Guidance Documents

- “Food and Drug Administration Report on Good Guidance Practices”
<http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf>

VII. Appendix C: Glossary of Acronyms and Abbreviations

510(k): Premarket Notification

ALS: Amyotrophic Lateral Sclerosis

BCI: Brain Computer Interface

CDRH: Center for Devices and Radiological Health

EFS: Early Feasibility Study

FDA: U.S. Food and Drug Administration

FIH: First in Human

HDE: Humanitarian Device Exemption

HUD: Humanitarian Use Designation

IDE: Investigational Device Exemption

MAF: Master File

ODE: Office of Device Evaluation

PMA: Premarket Approval

PTSD: Post Traumatic Stress Disorder

SCI: Spinal Cord Injury