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Public Regulatory Databases as a Source of Insight for Neuromodulation Devices Stimulation Parameters

Doe Kumsa, PhD^{*,†}, G. Karl Steinke, MS[‡], Gregory F. Molnar, PhD^{†,§}, Eric M. Hudak, PhD[¶], Fred W. Montague, MS^{**}, Shawn C. Kelley, PhD^{††}, Darrel F. Untereker, PhD^{††}, Alan Shi, PhD^{††}, Benjamin P. Hahn, PhD[‡], Chris Condit, MS^{‡‡}, Hyowon Lee, PhD^{§§}, Dawn Bardot, PhD[†], Jose A. Centeno, PhD^{*}, Victor Krauthamer, PhD^{¶¶}, and Pavel A. Takmakov, PhD^{*}

^{*}Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, White Oak Federal Research Center, Silver Spring, MD, USA

[†]Medical Device Innovation Consortium, Minneapolis, MN, USA

[‡]Neuromodulation Division, Boston Scientific Corporation, Valencia, CA, USA

[§]Department of Neurology, Medical School, University of Minnesota, Minneapolis, MN, USA

[¶]Department of Research & Technology, Advanced Bionics LLC, Valencia, CA, USA

^{**}Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

^{††}Medtronic Plc, Minneapolis, MN, USA

^{‡‡}Implantable Electronic Systems Division, St. Jude Medical, Plano, TX, USA

Address Correspondence to: Pavel A. Takmakov, Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, White Oak Federal Research Center, Silver Spring, MD, USA. Pavel.Takmakov@fda.hhs.gov.

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§§Weldon School of Biomedical Engineering, Birck Nanotechnology Center, Purdue University, West Lafayette, IN, USA

¶¶Division of Biomedical Physics, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, White Oak Federal Research Center, Silver Spring, MD, USA

Abstract

Objective—The Shannon model is often used to define an expected boundary between non-damaging and damaging modes of electrical neurostimulation. Numerous preclinical studies have been performed by manufacturers of neuromodulation devices using different animal models and a broad range of stimulation parameters while developing devices for clinical use. These studies are mostly absent from peer-reviewed literature, which may lead to this information being overlooked by the scientific community. We aimed to locate summaries of these studies accessible via public regulatory databases and to add them to a body of knowledge available to a broad scientific community.

Methods—We employed web search terms describing device type, intended use, neural target, therapeutic application, company name, and submission number to identify summaries for premarket approval (PMA) devices and 510(k) devices. We filtered these records to a subset of entries that have sufficient technical information relevant to safety of neurostimulation.

Results—We identified 13 product codes for 8 types of neuromodulation devices. These led us to devices that have 22 PMAs and 154 510(k)s and six transcripts of public panel meetings. We found one PMA for a brain, peripheral nerve, and spinal cord stimulator and five 510(k) spinal cord stimulators with enough information to plot in Shannon coordinates of charge and charge density per phase.

Conclusions—Analysis of relevant entries from public regulatory databases reveals use of pig, sheep, monkey, dog, and goat animal models with deep brain, peripheral nerve, muscle and spinal cord electrode placement with a variety of stimulation durations (hours to years); frequencies (10–10,000 Hz) and magnitudes (Shannon k from below zero to 4.47). Data from located entries indicate that a feline cortical model that employs acute stimulation might have limitations for assessing tissue damage in diverse anatomical locations, particularly for peripheral nerve and spinal cord stimulation.

Keywords

Electrodes; electrical stimulation; neural implants; safety of electrical stimulation; Shannon model

INTRODUCTION

Humans have used electrical stimulation for therapeutic purposes since ancient times (1). Today, neuromodulation devices are employed for numerous clinical applications including restoration of hearing, sight, and sensation; relief from tremors and obstructive sleep apnea; reduction of epileptic seizures and pain; as well as treatment for chronic depression, urinary incontinence, overeating, and morbid obesity. Further expansion of neurostimulation therapies is expected with introduction of bioelectronic medicine, where stimulation of

visceral nerves is used to modulate activity of internal organs and to target even non-neurological diseases which have been traditionally treated with drugs. DARPA ElectRx (2) program and NIH SPARC (2) common fund are supporting development of such therapies by the U.S. government. From industry, Galvani Bioelectronics has allocated a \$700 million budget (2) to develop peripheral nerve stimulation devices. Additionally, neurostimulation is expected to broaden from an exclusively therapeutic application into a method of human augmentation. A recent DARPA program, Targeted Neuroplasticity Training (TNT) (2), is funding research on the enhancement of cognitive abilities via non-invasive stimulation of peripheral nerves. Furthermore, consumer electronics for non-invasive electrical brain (3) and peripheral nerve stimulation (4) devices are already on the market.

The U.S. Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH) plays a key role in ensuring that neuromodulation devices available to US patients are safe and effective. Data collected by medical device manufacturers are submitted to CDRH to either establish a reasonable assurance of safety and effectiveness to obtain premarket approval (PMA) or to establish substantial equivalence to a predicate (legally marketed device) to obtain premarket notification (510[k]). Publicly available information regarding PMA and 510(k) decisions can generally be obtained in the form of summaries available on FDA's website. In certain cases, transcripts of public meetings (e.g., Advisory Committee meetings) may also be available. These public documents may contain significant technical information about preclinical animal studies and performance of these devices.

One of the potential hazards associated with neuromodulation devices is tissue damage due to high levels of electric current or charge. This damage may be mediated via a number of different pathways (5,6). Two broad categories for these pathways are damage from overstimulation of neural tissue (7), and damage from electrochemical products generated during neurostimulation (6), though these mechanisms are not mutually exclusive. The contribution of each of these mechanisms to tissue damage is not fully understood with only a few studies (6) adequately addressing this question. There are many factors that are important in assessing the risk of stimulation-induced tissue damage. These factors include animal species, anatomical location of a stimulating electrode, electrode material, duration of stimulation, stimulation frequency, duty cycle, charge and charge density per phase (5,6). However, historically, this complexity has been reduced to a model of tissue damage (8) that employs just two parameters, charge per phase and charge density per phase. This approach is based on studies by McCreery et al. performed in acute stimulation experiments in feline cortex (9,10) at a fixed frequency of 50 Hz and fixed biphasic 0.4 millisecond pulses. This model developed by Shannon (8) has become very popular among scholars (5,6,11–16). However, since the inception of the Shannon model, medical device manufacturers have performed a substantial number of studies to assess the safety of electrical stimulation in a number of animal models (pig, sheep, monkey, dog, goat); in different anatomical locations (deep brain structures, spinal cord, vagus nerve and other peripheral nerves); stimulation duration (several hours to years of chronic stimulation) with a range of frequencies (from 10 to 10,000 Hz); and a variety of pulse shapes and stimulation amplitudes. These data are often fragmented, unstructured, incomplete, and not available to the public; nevertheless, the

data may provide extremely important insight for the development of a comprehensive model of safe neuromodulation.

Increasing access to real-world evidence is one of CDRH strategic priorities for 2016–2017 (17). A record of what studies were performed to demonstrate a reasonable assurance of safety and effectiveness or substantial equivalence of neuromodulation devices is instrumental for device developers and the broad scientific community. Since a large portion of this data is proprietary and cannot be released in the public domain, it is hard to outline a comprehensive picture. However, a step in this direction would be to incorporate publicly available information on neuromodulation devices in a single peer reviewed document. This information will provide a substantial addition to peer-reviewed literature related to safety for neuromodulation.

In this work, we provided an overview of publicly available information on safety of electrical neuromodulation. We have mined public databases for Summaries of Safety and Effectiveness Data (SSEDs) for devices approved via the PMA pathway; 510(k) summaries for 510(k) cleared devices; and transcripts of public panel meetings to identify relevant neuromodulation devices. Next, we have selected those that have performed preclinical animal tests and reported technical details of these experiments including animal species, anatomical location of stimulating electrode, electrode material, duration of stimulation, frequency, duty cycle, charge, and charge density per phase. For PMA devices, we located SSEDs for eight neuromodulation devices satisfying these criteria: two for brain stimulators; five for peripheral nerve stimulators; one for muscle stimulators; and one for spinal cord stimulators. Out of these eight, three had enough information in the SSEDs to be plotted in Shannon coordinates. For 510(k) devices, from a review of 154 summaries, we found five that provide enough information to calculate charge per phase and charge density per phase. If plotted in the Shannon coordinates, these devices appear to be cleared to operate at stimulation levels higher than near-field Shannon model limit. This limitation in applicability of this model is outlined in Shannon's work (8), but is frequently overlooked in development of a paradigm for safe stimulation.

METHODS

Publicly available U.S. FDA databases for PMA (18), 510(k) (19) and transcripts of public panel meetings were searched for data on device neurostimulation parameters. These data sources were queried with search terms selected for device type, indication for use, or the stimulated neural target. The search was performed using the Google search engine in the following format: "*key word statement* site: fda.gov". The list of these statements is shown in Table 1 and the list of product codes is shown in Table 2. Once the entries were identified, the summaries that included preclinical animal testing with respect to output stimulation safety were selected. The selection process is illustrated in the flow chart depicted in Fig. 1. One limitation of this approach is that for some devices animal preclinical studies are performed at the Investigational Device Exemption (IDE) (20) stage and may be omitted from SSEDs and 510(k) summaries. However, all information regarding IDEs is proprietary and excluded from this consideration.

We used the coordinate system proposed by Shannon to plot stimulation parameters extracted from public regulatory databases. The Shannon equation links charge per phase (Q in μC) and charge density (D in $\mu\text{C}/\text{cm}^2$) with k , a parameter that defines a boundary between two regions of the plot where damage was or was not observed in McCreery et al. studies (9,10):

$$k = \log D + \log Q$$

Analyzing of McCreery studies provides a maximum value for k where they did not observe damage (1.70), and a minimum k value where they observed damage (1.85). Shannon chose $k = 1.50$ as a “conservative limit” “for the stimulus conditions of McCreery et al”, and suggested his model be used “as an initial framework for designing future animal safety studies” (8). Based on this difference in assignments for a boundary k value, here we have chosen a Shannon k value of 1.75 as the boundary to be used exclusively for classification purposes and we refer to this value as the Shannon limit in this work.

For PMA devices, we have calculated k -values using specified charge and charge density per phase values reported to be used during the animal studies reported in the SSEs. For 510(k) cleared devices (spinal cord stimulators), we used the maximum parameters that were listed in the 510(k) summaries. It is important to stress that maximal settings are not necessarily routinely, or ever, used clinically due to side effects (e.g., paresthesia) and other limitations. We used geometric electrode areas for all calculations (5).

RESULTS

We have identified 22 devices with PMAs. This includes three brain neurostimulators, six spinal cord stimulators (SCS), six peripheral nerve stimulators (PNS) and seven cochlear implants. We have also identified: transcripts of public panel meetings focused on deep brain stimulation (DBS) use for epilepsy (21); EnteroMedics Maestro premarket approval (22); Inspire UAS premarket approval (23); Neuropace RNS system for epilepsy (24); Cyberonics vagus nerve stimulation (VNS) for treatment-resistant depression (25); and information on premarket to postmarket shift in clinical data requirements for cochlear implant devices approved in pediatric patients (26). These transcripts did not contain neuromodulation parameters associated with studies on neurostimulation induced tissue damage.

All located brain neurostimulators are PMA devices: Medtronic Activa for Parkinson's Control Therapy (Medtronic, Minneapolis, MN, USA); St. Jude Medical (now Abbott Medical) Brio Neurostimulation System (St. Jude Medical, Plano, TX, USA); and Neuropace RNS system (Neuropace, Mountain View, CA, USA). All three (27–29) have SSEs publicly available and two (27,29) (Medtronic and Neuropace) have details of preclinical animal testing to establish neurostimulation safety (Table 3).

The peripheral nerve stimulators (PNS) identified are: Interstim Sacral Nerve Stimulation System (Medtronic, Minneapolis, MN, USA); NeuroCybernetic Prosthesis (NCP) System (Cyberonics Inc, Houston, TX, USA); Maestro Rechargeable System (Enteromedics Inc, St. Paul, MN, USA); Inspire Upper Airway Stimulation (Inspire Medical Systems, Maple

Grove, MN, USA); and NeuroControl Freehand System (Biocontrol Technology Inc, Cleveland, OH, USA). All of these devices (30–35) have publicly available SSEDs, and five (30,32–35) of them have details on preclinical animal testing for safety of electrical neurostimulation (Table 3).

The identified spinal cord stimulators that went through the PMA process are: Senza Spinal Cord Stimulation System (Nevro Corporation, Redwood City, CA, USA); Algovita Spinal Cord Stimulation system (Algostim, Blaine, MN, USA); Precision Spinal Cord Stimulator System (Boston Scientific, Valencia, CA, USA); Itrel Totally Implantable Spinal Cord Stimulation System (Medtronic, Minneapolis, MN, USA); Cordis Programmable Neural Stimulator (Cordis, Miami, FL, USA); and Genesis Neurostimulation System (St. Jude Medical, Plano, TX, USA). Four (36–39) of these devices have SSEDs publicly available, and only one (36) has details of preclinical animal testing to establish neurostimulation safety provided in SSED (Table 3).

The cochlear implants identified are: COMBI 40+ Cochlear Implant System (MED-EL, Durham, NC, USA); Clarion Multi-Strategy Cochlear Implants (Advanced Bionics, Valencia, CA, USA); Nucleus 24 Cochlear Implant System, Nucleus 22 Channel Cochlear Implant System/Children, Nucleus Hybrid L24 Cochlear Implant System, Nucleus Multichannel Implantable Hearing Prosthesis, 3M Cochlear Implant System (Cochlear Americas, Centennial, CO, USA). Five (40–44) of them have SSEDs publicly available, but none of those have details of animal preclinical neurostimulation safety testing, so cochlear implants were excluded from consideration.

Brain Neurostimulators (PMA)

Three original approved PMAs related to brain neurostimulators, two of which have conducted preclinical studies were identified (Table 3).

The preclinical studies for P960009 (27) (Medtronic Activa) were carried out in pigs, performed in two phases (acute and chronic), with two pairs of bilateral thalamic and cortical lead implants (four leads) per pig in what we presume were “a deep target intended to be the thalamus” and “under the cortical surface.” The acute phase was performed in 10 pigs under “general anesthesia,” stimulated for 7 hours, at 185 Hz in eight pigs and 130 Hz in the remaining two, at pulse widths beyond the commercial device capability (913 μ s to “nearly 2000 (μ s)”) and amplitude at the “maximum commercially available voltage (10.5 volts).” One animal was “eliminated because of seizures”. The acute phase stimulation levels correspond to phase charges of “9.5 to 42 μ C” “assuming a 500 ohm load,” yielding a range of k -values between 3.18 and 4.47. The acute phase histopathological results showed tissue damage from both stimulated and unstimulated leads. Differential damage vs. unstimulated leads was detected in three out of nine animals. A blinded pathologist correctly predicted the stimulated side for two out of these three animals showing differential damage. The chronic phase was performed in eight pigs (the summary does not specify if they were the same animals as those used for the acute study). They were stimulated continuously for 2–9 months, at 185 Hz using a 450 μ s pulse width, while “amplitude was variable depending on what the pig could tolerate”. One animal was eliminated due to hydrocephalus. Of the 14 lead pairs evaluated, 11 pairs were “judged to show different degrees of histopathology” (in

the remaining three pairs, “no pathological difference” was found between stimulation and control). In four of the 11 differential pairs, the pathologist correctly identified stimulated side (seven misclassified pairs). The summary concludes that “no additional observable effects to brain tissue over mechanical damage caused by the lead” were observed. The k -values from the chronic phase cannot be estimated, as amplitudes are not available. Using the device parameters as reported in the summary, the maximum estimated k -value is 3.17, but it is unclear whether these settings were used for actual preclinical experiments (Table 3 and Fig. 2).

The preclinical studies for Neuropace RNS system (P100026) (29,45) were carried out in sheep for period of 33–200 days with a mean of 131 days. Two depth leads were implanted into the epileptic foci and two cortical strip leads were placed on the surface of the brain near the epileptic foci for each sheep. According to the summary, longer stimulation periods were employed than what would be used in humans. According to the SSED, injury to neuronal tissue adjacent to the leads was similar between stim and control, was as expected, and did not extend into surrounding tissue. The SSED does not provide information on what specific stimulation parameters were used. The maximum limit established by the programming software (29,45) corresponds to a maximum charge density of 25 $\mu\text{C}/\text{cm}^2$ and k -value of 1.69.

Peripheral Nerve Stimulators (PMA)

There are five original PMAs (P970004, P970003, P130019, P130008, and P950035) grouped under peripheral nerve stimulation that have information on preclinical animal testing (Table 3). We should note that unlike other devices, peripheral neural implants have a variety of different geometries that can affect outcomes of the studies. Additionally, mechanical strain on nerves due to externally placed leads can be a significant contributing factor to tissue damage.

The preclinical studies for P970004 (30), Medtronic Interstim, were carried out in three pigs with two leads implanted, a stimulated electrode on the right sacral foramen and a control in the left sacral foramen. Histological examination of left and right sacral nerves and tissue surrounding the leads from each animal were performed. The SSED reports that no significant adverse effects were detected on the sacral nerve or adjacent tissue for both control and stimulated leads. The stimulation levels used in this animal studies were reported to be the same as recommended clinical stimulation parameters. Nevertheless, there is not enough information in the SSED to calculate charge per phase and charge density used for this animal study.

The preclinical animal studies that assessed safety of output parameters for P970003 (32), NeuroCybernetic Prosthesis from Cyberonics Inc, were carried out in sheep and monkeys. Out of nine sheep, histology was performed on the vagus nerve from three animals. No evidence of injury or degeneration was observed for both stimulated and control electrodes. In a chronic 14-week study, six monkeys were exposed to a total of 72 hours of stimulation with frequency of 143 Hz and 50% duty cycle. The SSED does not provide enough information to calculate charge density and charge per phase for this study.

The preclinical animal studies to assess stimulation safety for P130019 (33), Maestro from EnteroMedics Inc, were carried out on six pigs that were stimulated at 5,000 Hz for 12 hours/day for a period from 1 to 12 weeks and six pigs that were stimulated for 24 hours/day for 4–12 weeks, and one study at 24 hours/day for nine days. The abdominal anterior and posterior nerve trunks of the vagus nerve were stimulated. The SSED lists the specification for device pulse width of 90 μ s, maximum current of 8 mA and maximum charge density of 5.3 μ C/cm². This yields an electrode area of 0.14 cm² and corresponding k -value of 0.58 according to information provided in the SSED (Table 3 and Fig. 2). The SSED notes that nerve degeneration was observed in histological studies, but does not provide details for which experiments. However, it is noted that leads and the rechargeable implantable pulse generator were exteriorized due to anatomical limitations that resulted in chronic pulling forces that traumatized the nerve. Use of Maestro system in humans is more favorable than what was observed in the animal studies due to lack of issue with externalized lead pulling (33).

The preclinical animal studies assessing stimulation safety for P130008 (28), Inspire from Inspire Medical Systems, were carried out in eight dogs with stimulation of the hypoglossal nerve for 8–12 weeks. The animals tolerated chronic stimulation well, and there were no instances where therapy had to be discontinued or reduced in intensity or duration due to discomfort or problems. Histological study indicated that chronic implantation of the stimulation and sensing leads resulted in mild to moderate inflammation and fibrosis associated with the foreign body response and typical of chronically implanted devices. The SSED does not provide enough information to calculate charge density and charge per phase for this study.

The preclinical studies for P950035 (35), NeuroControl Freehand System from Biocontrol Technology Inc, were carried out in 13 dogs for 15–35 months at either 12 or 16 Hz frequency. The SSED provides details on one study with five dogs that specifically focused on effects of electrical stimulation on tissue that lasted for 15, 17, 35, 39, and 51 months. Histological evaluation showed that chronic electrical stimulation of muscle did not result in significant changes in tissue and that the tissue response was consistent with the expected mild foreign body response. The SSED does not provide enough information to calculate charge density and charge per phase for this study.

Spinal Cord Stimulators (PMA)

The preclinical studies for P130022 (36), Senza Spinal Cord Stimulation System from Nevro Corporation, were carried out in 12 goats to specifically assess safety of 10 kHz stimulation. Six were controls and six were stimulated for 24 hours/day for 10 days at 10 kHz and 100% duty cycle. The implant leads were placed at or near midline in the epidural space overlaying the L2-L3 intervertebral space. The animals were stimulated at a range of currents from 0.2 to 1.5 mA adjusted to be between stimulation perception threshold and animal's discomfort level. There were no morphologic differences between stimulated and the control groups and all morphologic changes were interpreted to be due to the placement of the implanted lead. We calculated maximum charge between 0.02 and 0.06 μ C with charge density between 0.031 and 0.47 μ C/cm² that corresponds to negative k values (Table 3 and Fig. 2).

Spinal Cord Stimulators (510(k))

There are also 154 spinal cord or peripheral nerve stimulation devices that received clearance via the 510(k) process. The main difference between spinal cord stimulation devices that have PMA approval vs. those that have 510(k) clearance is whether the power source is surgically implanted or not. For PMA SCS and PNS devices, the power source (battery) is surgically implanted; in the 510(k) case, a radiofrequency receiver is implanted and the power source is worn externally with an inductively coupled coil placed over the receiver. There are no preclinical animal studies reported in the 510(k) summaries in support of these 510(k) submissions. However, this does not mean that they were not provided in the full submissions. Among the parameters used for comparison with predicate devices, output capabilities of the stimulators along with electrode area and electrode material are provided. Out of the publicly available summaries, we selected those that revealed their cleared operating parameters. We used this information to calculate the maximum charge and charge density values listed for the 510(k) cleared devices. The following devices were included: Renew Neurostimulation System with Quattrode Lead Kit from Advanced Neuromodulation Systems Inc, K000852 (46,47); Freedom Spinal Cord Stimulator (SCS) System from Stimwave Technologies Inc, K141399 (47) and K150517 (48); Medtronic Matrix, K934065 (47,49); and Medtronic Xtrel, K883780 (47,50) (Table 4 and Fig. 2).

DISCUSSION

We employed the Shannon model (8) as a frame of reference because it is often used in peer-reviewed literature (5,6,11–16) to estimate the threshold for stimulation-induced neural tissue damage. The model is based on experiments (9,10) performed in cat cerebral cortex with 7 hours of stimulation at 50 Hz using surface disc electrodes of from 0.2 to 50 mm² under light anesthesia, which limits its translatability to cases with different conditions. Examples of such conditions include chronic stimulation in clinical applications, implantation of electrodes in locations other than the cortex, stimulation with different duty cycle and at lower or higher frequency. In this work we used existing data collected by medical device manufacturers to assess cases that are different from what was used in the pioneering studies of McCreery's group on the effect of stimulation parameters on neural tissue damage.

Brain neurostimulators represent a case that is anatomically similar to the feline studies (9,10), although deeper brain structures (non-cortical) are stimulated during DBS. Among SSEDs that we found, only the preclinical study for the Aactiva (27) had enough data to calculate *k*-values. The description of histopathological evaluation outlined in this SSEd is highly abbreviated, but it appears that a blinded pathologist could not reliably detect tissue damage from neurostimulation by examining tissue near control and stimulated leads. The study was done with acute stimulation for 7 hours at 185 Hz and *k* between 3.18 and 4.47 in a pig animal model (Table 3 and Fig. 2). This particular observation does not necessarily ensure that stimulation at this level does not lead to tissue damage since details of the specific experimental techniques and original histological data is needed to compare it to McCreery's studies (9,10). All manufacturers of brain neurostimulators recommend programming of parameters that yield a *k* value that is close to the Shannon limit. The

Medtronic Activa (27) and St. Jude Brio (28) systems display a warning when the programmed charge density would exceed $30 \mu\text{C}/\text{cm}^2$. For the 0.06 cm^2 Medtronic 3387 or 3389 electrode (27), $30 \mu\text{C}/\text{cm}^2$ corresponds to k of 1.73. For the St. Jude Brio system electrode (28), $30 \mu\text{C}/\text{cm}^2$ corresponds to k of 1.77 if the electrode area is 0.065 cm^2 (13) with the latter number being more likely to be used clinically. For the Neuropace RNS system (29,45), with electrode area of 0.08 cm^2 the software prevents programming above $25 \mu\text{C}/\text{cm}^2$, which corresponds to k of 1.69.

Placement of peripheral nerve neuromodulators is anatomically different from McCreery *et al.*'s (9,10) case on stimulation induced damage in feline cortex. The only case with enough information in the SSED was for the Maestro (33) device, which suggests that substantial damage was observed for both control and stimulated leads in a chronic study (1–12 weeks) in pigs with 12–24 hours per day stimulation at 5,000 Hz at a k -value of 0.58 (Table 3 and Fig. 2). The SSED concludes that mechanical strain due to externalized leads was a likely cause of this damage. This case correlates with McCreery's observation of tissue damage in cat sciatic nerve at much lower stimulation levels (51) than what is predicted by the Shannon model. The contributing factors might be mechanical compression induced by the cuff electrode (52) or specific peripheral nerve physiology, including the effects of electrical stimulation on blood flow (53). A better understanding of tissue damage mechanism(s) will help to explain the differences observed between brain and peripheral nerve stimulation.

Senza was the only PMA SCS device with an SSED that has sufficient details to calculate our parameters of interest on preclinical animal studies. The SSED documents no tissue damage after 10 days of continuous stimulation at 10 kHz at very low amplitude with k below zero in goat (Table 3 and Fig. 2). While this observation does not appear surprising due to small stimulation amplitude, it is valuable since it describes chronic, high frequency stimulation, not covered by classic studies in feline cortex (9,10).

The overview of 510(k) cleared SCS devices presents a more interesting case due to the high amplitudes of stimulation listed in the 510(k) summaries (Table 4 and Fig. 2). As we noted earlier, documentation of these parameters in 510(k) summaries does not mean that these SCSs are ever programmed to use this level of stimulation clinically. Additionally, there are a number of factors to consider that make SCS devices different from other neuromodulation devices.

First, SCS stimulation electrodes are located far away from target neural tissue. However, as Shannon stated in his work (8), tissue damage is linked to charge and charge density per phase via k only for cases where the distance between an electrode and stimulated tissue is either much smaller than electrode size or comparable to the electrode size. These cases are referred to as “near-field” and “mid-field” (5). This is not the case for SCSs since the stimulation electrode is far away from spinal cord with cerebrospinal fluid in between providing additional shunting of stimulation current away from nerve fibers. Computer simulations suggest that in the case of SCS, neural activation is proportional to charge per phase and does not depend on charge density and electrode size (54,55). This resembles the “far-field” case, described by Shannon (5,8), when damage is proportional to charge per

phase, but not to charge density. Of course, this correlation does not prove causal relations without additional experimental evidence.

Second, some neuromodulation devices were developed and used clinically before the Medical Device Amendments became effective in 1976 and established the regulatory framework for medical devices. Additionally, some of the devices, including SCSs (56) and cochlear implants were approved and on the market prior to development of the Shannon model in 1992 (8); namely the Itrel SCS system in 1984, Cordis stimulator in 1981, Nucleus cochlear stimulator in 1985, and the 3M cochlear stimulator in 1984.

CONCLUSION

The Shannon model for tissue damage from neurostimulation is frequently used in academic literature as a tool to assess neurostimulation safety. Medical device developers have generated a substantial body of safety data. Most of these data are kept in the non-public domain and unavailable to the scientific community for development of an understanding of stimulation induced neural tissue damage. Some of these data are available in public regulatory databases in the form of SSEDs for devices approved via the PMA process and 510(k) summaries for devices cleared via the 510(k) process. We located entries that have substantial details on preclinical experiments to establish safety of neurostimulation. We found that medical device manufacturers used pig, sheep, monkey, dog, and goat animal models in these studies. Stimulation electrodes were placed in deep brain structures, peripheral nerves (vagus, sacral), muscles and spinal cord. Stimulation protocols included acute (several hours) and chronic (several years) experiments with frequencies ranging from 10 to 10,000 Hz and magnitudes calculated according to the Shannon equation from k below zero to 4.47. Data from several entries that have sufficient information to plot results of these studies in Shannon coordinates indicated that feline cortical tissue damage model might not be relevant for assessing tissue damage for peripheral nerve stimulation and spinal cord stimulation, possibly due to difference in anatomy and electrode geometry.

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Figure 1.

Flow chart of methodology used to obtain PMA summaries of safety and effectiveness data and 510(k) summaries that list neurostimulation parameters. The search yielded 22 PMA devices out of which eight contained information about preclinical animal studies addressing tissue damage from neurostimulation. Three SSEDs contained enough information to calculate charge and charge density per phase and commented on a degree of tissue damage due to stimulation. 154 510(k) devices were identified. Out of those, five summaries for spinal cord stimulators had enough parameters to calculate charge and charge density per phase.

Figure 2.

Charge and charge density per phase for neuromodulation devices available from public regulatory databases. Charge and charge density information for approved medical devices obtained from public databases plotted along data from McCreery *et al.* (9,10) for experiments with acute stimulation in feline cortex. Open rectangles symbols correspond to experiments where no tissue damage was observed. Filled black symbols correspond to data points where tissue damage was observed. Medtronic Activa Summary of Safety and Effectiveness Data (SSED) provides details of an acute stimulation study in pigs with deep brain stimulation leads. For stimulation with k -values from 3.18 to 4.47, mechanical damage could not be reliably distinguished from electrical damage (gray filled circles). The EnteroMedics Maestro SSED for peripheral nerve stimulation (PNS) describes a study in pigs where nerve degeneration was observed after neurostimulation with $k = 0.58$, but according to the summary, it originates from mechanical strain (gray filled stars). The SSED for Nevro Corp Senza spinal cord stimulator (SCS) has details for a study in goats with stimulation at k below zero when no signs of damage were observed (gray filled diamonds). Five 510(k) summaries for SCS devices document that Medtronic Xtrel and Matrix were cleared to operate with k of 3.23 and 2.99; Renew from ANS was cleared for k of 2.65; Freedom SCSs from Stimwave were cleared for k of 2.61 (2014) and 2.51 (2015) (filled blue

semitransparent hexagons, diamonds, circles, triangles and inverted triangles, respectively). It is important to stress that SCSs do not operate in Shannon “near-field” scenario. [Color figure can be viewed at wileyonlinelibrary.com]

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Table 1

A List of Key Word Statements Used in the Search.

Key word statements	
DBS preclinical	Epilepsy PMA
PMA animal studies	Sacral nerve stimulation PMA
PMA <i>PMA number</i>	Thoracic nerve stimulation PMA
PMA brain implant	Cervical nerve stimulation PMA
<i>Company name</i> spinal cord stimulation PMA	Lumbar nerve stimulation PMA
<i>Company name</i> cochlear stimulation PMA	Coccygeal nerve stimulation
<i>Company name</i> deep brain stimulation PMA	Vagus nerve stimulation PMA
Chronic pain PMA	Sciatic nerve stimulation PMA
Parkinsonian tremor PMA	Functional electrical stimulation PMA
Bladder control PMA	

The key words statements that were used to search on the FDA.gov website. The variables in italics were replaced with the reference words.

Table 2

A List of the Product Codes for Approved Neuromodulation Devices.

Product code	Description
MCM	Implant, cochlear
PGQ	Hybrid cochlear implant
MHY	Stimulator, electrical, implanted, for Parkinsonian tremor
PFN	Implanted brain stimulator for epilepsy
GZB	Stimulator, spinal-cord, implanted (pain relief)
GZF	Stimulator, peripheral nerve, implanted (pain relief)
LHG	Electrode, spinal epidural
LGW	Stimulator, spinal-cord, totally implanted for pain relief
LYJ	Stimulator, autonomic nerve, implanted for epilepsy
EZW	Stimulator, electrical, implantable, for incontinence
PIM	Neuromodulator for obesity
MNQ	Stimulator, hypoglossal nerve, implanted, apnea
GZC	Stimulator, neuromuscular, implanted

Each device gets assigned a product code and (13 relevant product codes have been identified).

Stimulation Parameters for PMA Neuromodulation Devices Extracted From Information on Preclinical Animal Studies Found in Public Regulatory Databases.

Table 3

Device	Anatomy	Animal	f , Hz	Stim, days	P.W., ms	A , cm ²	Q , μ C	D , μ C·cm ⁻²
* Activa	Brain	8 pigs	185	0.3	0.913–2.0	0.06	9.5–42	159–700
		2 pigs	130	0.3	0.913–2.1	0.06	9.5–42	159–700
		8 pigs	185	60–210	0.415	0.06	N/A	N/A
Neuropace RNS	Brain	5 sheep	N/A	33–200	N/A	0.08	N/A	N/A
Interstim	PNS	3 pigs	N/A	N/A	N/A	0.12	N/A	N/A
Neuro Cybernetic	PNS	6 monkeys	143	3	N/A	N/A	N/A	N/A
	PNS	3 sheep	N/A	90	N/A	N/A	N/A	N/A
* Maestro	PNS	> 12 pigs	5,000	7–84	0.1	0.14	0.72	5.3
Inspire UAS	PNS	8 dogs	N/A	54–84	N/A	N/A	N/A	N/A
NeuroControl Freehand	Muscle	5 dogs	12–16	450–1530	N/A	N/A	N/A	N/A
* Senza	SCS	12 goats	10,000	10	0.02–0.05	0.127	0.004–0.06	0.031–0.47

* These summaries of safety and effectiveness data (SSEDs) had enough information to calculate charge (Q , μ C) and charge density (D , μ C/cm²) per phase.

f , stimulation frequency (Hz); Stim, length of stimulation; P.W., pulse width (milliseconds); A , electrode area; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation; N/A, data not available.

Activa (acute): damage detected in 2 out of 9 pigs (simulation vs control); Activa (chronic): damage detected in 4 out of 14 pigs; Interstim: histology showed no “significant adverse effects” for both control and stimulated; Neuro Cybernetic (monkey): no electrical or mechanical damage observed, but compression damage to large axons noted; Neuro Cybernetic (sheep): no nerve fiber damage for both stimulated and control; Maestro: nerve degeneration is observed which is attributed to mechanical stress; Senza: no signs of damage from neurostimulation. The Neuropace RNS, Inspire UAS and Neurocontrol Freehand SSEDs did not provide a clear statement on damage from neurostimulation.

Stimulation Parameters for Spinal Cord Stimulators Extracted From 510(k) Summaries Found in Public Regulatory Databases.

Table 4

Device	510(k)	Control	f, Hz	P.W., ms	A, cm ²	Q _{max} @ 500 Ω, μC	D _{max} @ 500 Ω, μC·cm ⁻²
Xirel (Medtronic)	K883780	Voltage	5–1400	0.05–1	0.1225	14.2	118.3
Matrix (Medtronic)	K934065	Voltage	5–240	0.05–0.5	0.1225	10.8	90
Renew (ANS)	K000852	Current	10–1500	0.05–0.5	0.13*	7.6	58.5
Freedom (2014, Stimwave)	K141399	Current	2–1500	0.05–0.5	0.1272	7.2	56.6
Freedom (2015, Stimwave)	K150517	Current	5–1500	0.05–0.5	0.1272	6.4	50.3

510(k), 510(k) submission number, f, stimulation frequency (Hz); Control, current or voltage control; P.W., pulse width (millisecond); A, electrode area; Q_{max}@ 500 Ω, μC; and D_{max}@ 500 Ω, μC·cm⁻², maximum charge per phase and charge density per phase calculated from device stimulation parameters listed in summaries (assuming 500 Ohm load for voltage controlled stimulation).