ANS

June 11, 1999

Food and Drug Administration
Center for Devices and Radiological Health
Office of Standards and Regulations (HFZ-84)
5600 Fishers Lane
Rockville, Maryland 20857

Re: Section 513(f) Reclassification Petition

Dear Sir/Madam:

The undersigned submits the enclosed petition in accordance with Section 513(f) of the Federal Food, Drug, and Cosmetic Act, (the "FDCA"), 21 U.S.C. § 360c(f) and regulations appearing in 21 C.F.R. § 860.123 to reclassify the device "Totally implanted spinal cord stimulator for pain relief" from class III into class II.

Since 1978 the device "Implanted spinal cord stimulator for pain relief" as identified in 21 C.F.R. § 882.5880 has been classified into class II (performance standards). This classification was accomplished in accordance with procedures described in Section 513 of the FDCA. No performance standards have been identified for application to this device. Prior to and at the time of classification, the direct current generator power source for this device was external to the implanted portions of this device. Subsequently, implanted generators were developed. Because implanted generator devices for spinal cord stimulators were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, Section 513(f) of the FDCA required classification into class III (premarket approval).

The only difference between "Implanted" and "Totally implanted" spinal cord stimulator devices is the location of the generator power source. Therefore, the petitioner believes that reasonable assurance of safety and effectiveness can be maintained through the application of special controls as authorized for class II devices since passage of the Safe Medical Devices Act of 1990.

The attached document is formatted in numerical order to address the specific reclassification content and form requirements outlined in 21 C.F.R. § 860.123.

Sincerely,

Drew Johnson
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RECLASSIFICATION PETITION

FOR

TOTALLY IMPLANTED SPINAL CORD STIMULATOR

FOR PAIN RELIEF

INTRODUCTION

This petition is submitted in accordance with Section 513 (f) of the Federal Food, Drug, and Cosmetic Act (the "FDCA"), 21 USC § 360c(f) to reclassify the above referenced type of device from class III (premarket approval) to class II (special controls). This type of device is presently classified into class III by application of Section 513 (f) of the FDCA, because the implanted pulse generator (IPG) was not in commercial distribution prior to May 28, 1976, the effective date of this section of the FDCA.

(1) SPECIFICATION OF THE TYPE OF DEVICE FOR WHICH RECLASSIFICATION IS REQUESTED

Stimulator, Spinal Cord, Totally Implanted for Pain Relief

(2) ACTION REQUESTED

It is requested that Stimulator, Spinal Cord, Totally Implanted for Pain Relief device(s) be reclassified from class III to a class II under Section 513 (f) of the FDCA.

(3) SUPPLEMENTAL DATA SHEET

See attachment 1D

(4) COMPLETED CLASSIFICATION QUESTIONNAIRE

See attachment 1E

(5) BASIS FOR DISAGREEMENT WITH THE PRESENT CLASSIFICATION STATUS

Implanted spinal cord stimulators have been in commercial distribution since 1966 and formally classified into class II through notice and comment rulemaking by the Food and Drug Administration (FDA). Although the 1978 classification of the implanted spinal cord stimulator utilizing an external generator power source specified promulgation of a performance standard, no performance standard was ever proposed. Consequently the regulatory controls applicable to this type of device consisted of all the restrictions applicable to class I devices plus the requirement for biennial inspection. Review of the FDA experience associated with commercial distribution and use of these devices supports that the pervasive controls applicable to class II devices have been sufficient to provide the public with reasonable assurance of device safety and effectiveness.

The "totally implanted" spinal cord stimulator differs from the existing class II device identified in 21 C.F.R. 882.5880, because the generator power source is implanted rather than external. At least one totally implanted device has been in commercial distribution as a class III device for over 10 years. The safety and effectiveness performance of the totally implanted device as reflected by FDA documents available to the public and in the published literature support that the controls applicable to class II devices are adequate to provide reasonable assurance of safety and effectiveness.

While petitioner is required by regulation to express a statement of disagreement with the present classification as it is mandated by the FDCA, petitioner believes that representatives of the FDA and the public would agree that the pervasive regulatory controls applicable to class II devices when supplemented by appropriate special controls will provide reasonable assurance of safety and effectiveness. Finally, the authority vested in the FDA through the premarket notification requirement under section 510(k) of the FDCA represents the barrier to commercial distribution of any totally implanted device that is not substantially equivalent to the type of class II device identified and subject to special controls.

Since 1990, the 510(k) notification order has become the functional equivalent of a premarket approval (PMA) for certain devices. Unless the FDA issues an "order" of substantial equivalence, no totally implanted spinal cord stimulator can be lawfully made available in interstate commerce. Consequently, the "order" issued by the FDA for a class II device represents a premarket clearance by the FDA that is adequate to the needs of the public and facilitates the need for subsequent beneficial improvements to the device and competition.

(6) FULL STATEMENT OF REASONS

Devices that are used for pain relief through spinal cord stimulation require the surgical implantation of a receiver with electrodes. There are acceptable risks associated with any surgical procedure, but the benefit to the patient justifies the risk. Likewise, there are risks associated with the implantation of any device into the human body; and, some device implants such as prosthetic heart valves or cardiac pacemakers are intended to support or sustain life. Thus the benefit clearly outweighs any foreseeable risk.

The implantation of a spinal cord stimulator for the relief of pain is not undertaken to support or sustain life, but it is essential to the quality of life for a patient. Moreover, as established by the 1978 classification into class II of implanted spinal cord stimulators, there is neither a potential unreasonable risk of illness or injury nor a use which is of substantial importance in preventing impairment of human health associated with the use of these devices. The implantation of the generator power source neither affects the intended use of the device nor alters the risk to the patient. The surgical risks associated with implantation of the receiver and electrodes is the same whether the generator power source is implanted or external. Spinal cord stimulation using both an IPG device or a radio frequency system has been proven to be safe and effective in treating a variety of chronic pain conditions. These include tumors, brachial plexus injuries, cord injury, phantom limb pain, reflex sympathetic dystrophy, ischemic limb pain, multiple sclerosis, peripheral vascular disease arachnoiditis, and pain after failed spine surgery (De la Porte and Siegfried, 1983; Kumar et al., 1986; Long and Erickson, 1975; Meglio et al., 1989; Ray et al., 1992; Siegfried and Lazorthes, 1982; Young, 1978).

Consequently, the special controls applicable to class II devices are abundantly sufficient to provide reasonable assurance of the safety and effectiveness of the spinal cord stimulator for which the generator power source is also implanted.

Consistent with the criteria for safety and effectiveness as described in 21 C.F.R. § 860.7, the petitioner has identified the benefits and risks associated with the implantation and use of all spinal cord stimulators irrespective of whether the generator is implanted or external. This information as described below was derived from data maintained by the FDA and the published literature.

Spinal Cord Stimulation (SCS) History

SCS Background

The use of electrical stimulation as a clinical tool has had a long history, which predates any apparent understanding of its mechanism of action. The first documented use of electrical stimulation was for the relief of pain from headaches and arthritis. Dioscorides, in 1559, reported that the marine torpedo could be applied on the skin to relieve prolonged headache (for review see Licht, 1996). Despite this long history, it wasn't until 1965 that Melzack and Wall first proposed a theory to explain the suppression of pain by electrical stimulation (Melzack and Wall, 1965). This theory, called the "gate control theory", proposed that the activation of low-threshold myelinated primary afferent fibers decreases the response of dorsal horn neurons to unmyelinated nociceptors (Melzack and Wall, 1965). Shealy et al., were the first to apply this theory in practice when they electrically stimulated the dorsal columns to treat chronic, intractable pain (Shealy et al., 1967). Since the first implant, dorsal column stimulation (or spinal cord stimulation, SCS) has been applied to a wide variety of painful disorders. These include tumors, brachial plexus injuries, cord injury, phantom limb pain, reflex sympathetic dystrophy, ischemic limb pain, multiple sclerosis, peripheral vascular disease arachnoiditis, and pain after failed spine surgery (De la Porte and Siegfried, 1983; Kumar et al., 1986; Long and Erickson, 1975; Meglio et al., 1989; Ray et al., 1992; Siegfried and Lazorthes, 1982; Young, 1978). It has been estimated that 12,000 SCS systems are sold every year world-wide (Linderoth and Myerson, 1995).

Possible Mechanisms

Although, first inspired by the gate theory (Melzack and Wall, 1965), spinal cord stimulation is now linked to several other mechanisms. It has been found to activate spinal pain inhibitory

circuits, mainly those concerned with the GABAergic and adenosine transmission (Lundeberg, 1996; Cui et al., 1997; 1998). After peripheral nerve injury, levels of excitatory amino acids (EAA), mainly glutamate and aspartate, have been found to increase in the dorsal horn (Al-Ghoul et al., 1993; Castro-Lopes et al., 1993). Experiments performed on rats have found that SCS induces a decreased release of the EAA, associated with an increase in the release of GABA and adenosine (Cui et al. 1997; 1998). This SCS induced response can be transiently abolished by local perfusion with a $GABA_b$-receptor or an adenosine A_1 receptor antagonist. Cui and colleagues have proposed that the effect of SCS on neuropathic pain and allodynia may be due to an activation of local GABAergic mechanisms inhibiting the EAA release. More recently, they have found that SCS treatment in patients previously found to be non-responders can be enhanced by combining SCS therapy with the infusion of either baclofen **(a GABA agonist)** or adenosine. Other theories have suggested that electrical stimulation of the spinal cord may produce analgesia through a frequency-related conduction block (Campbell et al. 1981).

SCS has also been shown to have an affect at the cerebral level (Hosobuchi 1985; Hautvast et al., 1997). Hautvast et al. found that SCS increased regional cerebral blood flow in the left ventrolateral periaqueductal grey, the medial prefrontal cortex, the dorsomedial thalamus bilaterally, the left medial temporal gyrus, the left pulvinar of the thalamus, bilaterally in the posterior caudate nucleus, and the posterior cingulate cortex. In both experimental animal studies and human studies SCS induces peripheral vasodilatation, although the exact mechanism is under debate (Croom et al., 1997; Linderoth et al., 1995).

Patient Selection

Spinal cord stimulation systems are relatively simple to implant, with many of the stimulation parameters under patient control. This has led to its use in a wide array of painful conditions without regard to the etiology or pathophysiology (De La Porte and Van de Kelft, 1993). Thus,

numerous reports have success rate of fewer than 25%. According to the European Group for the Study and Treatment of Pain, only 23% of the preliminary cases reported long-lasting pain relief using SCS (Krainick, 1984). The main reason for this low success has been the diverse group of pain conditions typically treated with SCS and the weak patient selection criteria that have been used. Only recently have more stringent selection criteria been followed. It is now recognized that the most appropriate patients for SCS are those with chronic, nonmalignant pain of neuropathic origin (Simpson, 1994). Another important selection criterion is psychological attitude. Patients are now routinely screened to eliminate those patients with major personality disorders, secondary gain issues, or drug abuse problems (Randolph, 1998; Gamsa, 1994; Burchiel, 1995).

Improved patient selection has increased the success rate of SCS. A recent report of the results of a series on failed back surgery syndrome and neuropathic pain of peripheral origin has shown good long-term outcome in 50-60% of cases treated (Turner, 1995; Burcheil, 1996). Kumar et al. report that SCS is an effective therapy for pain syndromes associated with peripheral neuropathy. However, they conclude that patients with postherpetic pain and intercostal neuralgia do not obtain long-term benefit with SCS. Numerous reports have shown success when using spinal cord stimulation to treat the pain from reflex sympathetic dystrophy (or complex regional pain syndrome I) (Kemler, 1999; Calvillo et al., 1998; Kumar et al., 1997). A recent report by Stanton-Hicks et al. included neuromodulation in the guidelines for therapy for complex regional pain syndromes (Stanton-Hicks et al., 1998). Spinal cord stimulation has also been found to be highly effective in treating the pain from angina and peripheral vascular disease (Eliasson, 1996; Kumar, 1997). A recent report suggests that the efficacy of spinal cord stimulation in the treatment of pain for angina is similar to that of coronary artery bypass surgery (Mannheimer, 1998). Patients with peripheral vascular disease have had success rates of 50-

80% for the relief of pain, with evidence of improved circulation (Kumar et al., 1997; Jivegard et al., 1995). With careful patient screening and improved technology, spinal cord stimulation may prove even more effective in the future.

SCS Systems

Two different SCS systems are routinely used, including those systems that use percutaneously placed electrode leads or those that require laminectomies to place the electrodes. The former involves the percutaneous insertion of electrodes into the epidural space. The lead from the electrodes may then be connected to an external generator, allowing a trial period of stimulation, or it may be connected subcutaneously to an implanted radio frequency (RF) controlled receiver or to a totally implanted pulse generator (IPG).

Paddle type leads require implantation into the epidural space via laminectomy. The leads are then connected subcutaneously to a radio-controlled receiver or an IPG. The RF-controlled receiver is activated by an external battery-powered transmitter, which operates through an antenna placed over the receiver. The IPG contains a battery, which supplies power to the electrodes.

Although the RF receiver is a class II device and the IPG is currently a class III device, the only difference between the two SCS devices is that the IPG has an internal power source while the RF receiver does not.

Surgical Procedure

To effectively treat pain, a spinal cord stimulation system must have the potential to target the anatomic areas where the patient feels pain. The target area must be provided with pain-relieving paresthesia at tolerable and patient adjustable intensity levels.

With the patient under local anesthesia, a small puncture is made in the skin with a paramedian approach at an angle of no more than 30-40 degrees. An epidural needle is inserted and confirmed as having entered into the epidural space. Using fluoroscopic guidance, a lead blank (a lead without any electrodes) is inserted through the needle into the dorsal epidural space, and is manipulated to establish an appropriate pathway. The lead is then introduced into the epidural space, either through the needle or through the use of a lead introducer. Proper lead placement is verified through intraoperative trial stimulation, in which paresthesia is experienced by the patient. Upon verification of proper lead placement, the lead is secured using a lead anchor and sutures.

The IPG / receiver is implanted by making a pocket incision at the desired location, and creating a subcutaneous pocket by blunt dissection to accommodate the receiver. A subcutaneous tunnel is made from the lead incision site to the IPG/receiver implantation site, using a tunneling tool, and the lead is tunneled to the IPG/receiver site. The lead is connected to the IPG/receiver, the IPG/receiver is placed in the subcutaneous pocket, and the incisions are closed.

Risks associated with Spinal Cord Stimulation

A list of the reported complications for **all** spinal cord stimulator devices by author is found on Table 1A and 1B. The first report listed, by Turner et al. summarizes the findings of 39 English and French language articles reporting on the use of SCS between the years 1966-June 1994. Fourteen of these articles were published before 1983 (Turner et al., 1995). The articles were chosen to include studies that provided at least 30 days of follow-up for the patients, and included data from patients with chronic low back and lower extremity pain following prior

surgery (Failed Back Surgery Syndrome). Most of the complications were minor consisting of electrode migration, lead wire complications or difficulty with the pulse generator.

The remaining summary of the available literature was obtained through a MEDLINE search using the key words "spinal cord stimulation" or "dorsal column stimulation" and "pain" for the years 1983 to present. This search yielded a total of 253 papers of which 31 English language papers were found to list complications irrespective of whether the power generator was implanted or external. Tables 1A and 1B includes lead migration, infection, epidural hemorage, seroma, hematoma, paralysis, cerebral spinal fluid (CSF) leak, over/under stimulation, intermittent stimulation, pain over the implant, allergic reaction, skin erosion, lead breakage, hardware malfunction, loose connection, other, biologic reaction specific to an IPG, and battery failure.

Five papers listed in the summary were also included in the Turner review. These include Meglio (1989), Probst (1990), Wester (1987), LeDoux (1993), and De La Porte (1993).

MDR report data for IPG devices was collected from the FDA website at http://www.fda.gov/cdrh/mdrfile.html, where records were sorted into the years 1984 through 1996. Data for each year was compressed into files, which were downloaded and put into a database (Table 2). Attempts to download information from 1991 were unsuccessful due to a minor glitch in the FDA's database for that particular year. The petitioner believes that the absence of the information for 1991 does not significantly impact the overall MDR data analysis in this petition. Each report was treated as an individual record in the database. Once in the database, searches could be performed for reports from a certain product, manufacturer, or date.

For incident reports occurring after 1996, a search engine at the FDA MAUDE site was used, http://www.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Multiple criteria could be used simultaneously for MAUDE searches, thus returning more applicable information.

A. Lead migration:

Lead migration is the most common risk associated with SCS and occurs when the lead moves out of its position. Lead migration results in a loss of proper paresthesia coverage and a subsequent reduction in pain relief. Turner et al. found that 16 of the 39 papers reviewed provided data regarding lead migration (Turner et al., 1995). They found that 24% of the patients in these 16 studies required either reoperation or reprogramming due to lead migration. Table 1A shows the results of 32 papers reporting complications. All but three of the papers reported lead migration as one of their complications. Analysis of this series gave a lead migration rate of 14.6%.

Andersen reported on the use of SCS for angina (Anderson, 1997). He found the most frequent complication that required reoperation was lead migration (23%). The incidence was statistically lower in patients with quadripolar leads (11%) than in patients with monopolar electrodes (45%, $p<0.003$). There was no difference in the frequency of migration of electrodes between the two types of electrodes. North et al. reported on the use of SCS in 62 chronic pain patients (North et al., 1991). They found that surgical revision was necessary in 23% of the cases with simple bipolar leads to obtain optimal paresthesia coverage. However, surgical revision was required in only 16% of those cases with "multi-channel" devices.

The introduction of multichannel leads has greatly reduced the need for reoperation as the result of lead migration. A report by North et al. found that programmable, multichannel systems have a significantly greater clinical reliability than single-channel systems (North et al., 1991). Alo et

al. reported that only 3.8% of their patients required revision of lead placement to improve capture, and the remaining 96.2% of the patients who lost paresthesia were able to regain it by reprogramming. He claimed this was the result of using the eight-electrode lead and complex programming (Alo et al., 1998).

Through analysis of the publicly available MDR data (n=408), there was only one occurrence in which lead migration led to an explantation. Other cases in which lead migration resulted in a loss of stimulation were remedied through reprogramming of the device. Both RF and IPG systems have reprogramming capabilities.

The special controls available for this risk include the following: the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, and FDA Guidance Documents for Design Control Guidance for Medical Devices. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include migration" as the special control for this risk.

B. Infection, epidural hemorrhage, seroma, hematoma and/or paralysis:

As with any surgical procedure the risk of infection is a possible adverse event. Although most infections that occur as result of a SCS implantation can be resolved either with antibiotics or with the removal of the SCS unit followed by antibiotics, life-threatening infections can occur. A report by Torrens et al. described one such case. This particular patient was found to have methicillin-resistant Staphylococcus aureus (MRSA) infection. Torrens suggests that the patient population typically identified for SCS systems have a higher risk of MRSA infection due to frequent and prolonged hospitalization for severe neuropathic pain and courses of antibiotics for

various infections. In addition, he points out that patients with diabetes mellitus have an increased susceptibility to infection. He suggests that screening for MRSA colonization would help in identifying patients at risk for infection (Torrens et al., 1997).

There has been one report of a bacterial infection located at the lead tip resulting in paralysis (Meglio et al., 1989). A myelographic block was found at the level of the electrode tip. An operation revealed a bacterial epidural and intradural abscess that was removed. The patient recovered well but not completely. Although, paralysis is a possible risk, only 1 case was found in the 2075 cases reviewed in Table 1. As with any surgical procedure involving implantation in the epidural space, paralysis is a possible adverse event regardless of whether the SCS system has an internally or externally powered device.

The average infection rate reported by Turner et al. was 5% from 20 papers. This is similar to the 4.5% infection rate reported in Table 1.

Meglio et al. reported three bacterial infections as the result of SCS, with two occurring at the electrode site and one at the subcutaneous pocket (Meglio et al. 1989).

Another complication that has been reported following the implantation of an SCS system is a hematoma. This was found to occur in only 5 cases out of 1984. Three cases of subcutaneous hematoma were reported by Meglio (Meglio et al., 1989). Subcutaneous hermatoma may occur regardless of whether the system is a RF or IPG device. All three patients were undergoing anticoagulation therapy. None of the papers summarized in Table 1 reported epidural hemmorage or seroma.

Of the 408 total MDR reports utilized, there were 14 events of infection (3.43%) and only one of seroma (0.25%) found. There were no reports of epidural hemorrhage, hematoma, or paralysis.

The special controls available for these risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, 510(k) Sterility Review Guidance, Sterilization validation standard- AAMI/ISO11135, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include infection, epidural hemorrhage, seroma, hematoma and/or paralysis" as the special control.

C. CSF leakage:

Cerebral spinal fluid (CSF) leaks occur following accidental dural puncture with either the epidural needle, guide wire (lead blank) or leads during the surgical procedure. A CSF leak can lead to a headache, which usually occurs in the early postoperative period and which characteristic features are those of a headache that may be frontal or occipital, relieved by recumbency, and accompanied by tinnitus, diplopia, neck pain and nausea. The cause of the headache is thought to be the result of decreased hydraulic support for intracranial structures (Brownridge, 1983). Small dural punctures usually heal spontaneously and the headache can be treated conservatively (Kumar, 1991). The injection of autologous blood into the patient's epidural space is commonly used to treat postdural postural headache if conservative measures are unsuccessful (DiGiovanni, 1970).

Of the 32 articles reviewed in Table 1 only 6 cases of CSF leaks were reported. This type of incident may occur regardless of whether the device is an IPG or RF system. Overall the incidence of CSF leaks is very small occurring in only 0.3% of the time.

There were no cases of CSF leakage found in the MDR search.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include CSF leakage", as the special control for this risk.

D. Undesirable changes in stimulation over time:

Changes in stimulation may occur over time. These changes can be the result of cellular changes in tissue around the electrodes or temporary changes in the electrode position. Reports of painful stimulation have been found in the literature as well as those cases of ineffective stimulation or loss of stimulation over time. The literature search summarized in Table 1A found eleven cases of either over or under stimulation. This type of incident may occur regardless of whether the device is an IPG or RF system. No cases of intermittent stimulation were observed.

Burchiel et al. reported seven cases of undesirable changes in stimulation over time. These included ineffective pain control with stimulation (n=5), change in stimulation pattern (n=1), and decreased stimulation (n=1) (Burchiel et al. 1996). Meglio et al. reported on two cases that complained of pinprick-like pain at the electrode site (Meglio et al. 1989). The last two cases that reported changes in stimulation were from a study by Mittal et al. They reported two cases of increased discomfort. In one of the patients the rate dial had been inadvertently increased, while in the second case the patient had repeatedly turned the system to full amplitude (Mittal et al. 1987).

A total of 106 of the available MDR cases involved changes in stimulation. This type of incident may occur regardless of whether the device is an IPG or RF system. These include 50 events of intermittent stimulation (12.25%), 33 of overstimulation (8.09%), and 23 shock (5.64%)

The special controls available for this risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety. See the attached Special Control Chart-Table 1C.

The petitioner proposes labeling special controls utilizing adverse events/warning/precautions in the labeling to state: "Adverse events include undesirable changes in stimulation", Warning: "Patients should not drive or use dangerous equipment during stimulation". Adverse Event: "Loss of stimulation" Precautions: "Systems maybe affected by or adversely affect cardiac pacemakers, cardioverter/defibrillators, external defibrillators, MRI, diathermy, ultrasonic equipment electrocautery, radiation therapy, theft detectors, security systems, and aircraft communication systems".

E. Pain at the sites over the implanted system components:

Whenever there is a disruption of body tissue temporary pain results. This temporary pain is due to the healing process. The usual location of the pain after a SCS implant is at the incision site. However, pain can also occur at the site of the implant. This type of pain usually subsides after 7 to 14 days. The actual tissue reaction resolves within 2 to 3 weeks. Occasionally, tenderness can occur over the receiver site or the connector at the spinous process, which does not resolve with time. In many cases this tenderness does not require removal of the unit. Pain over the implant was found to occur in 20 of the 1924 cases summarized in Table 1A. This type of

incident may occur regardless of whether the device is an IPG or RF system. Most of these cases did not require reoperation. When reoperation did occur, repositioning the receiver usually diminished the pain (Burchiel, 1996).

Burchiel et al. reported on four cases of pain or burning along the lead/pulse generator that did not require reoperation and two cases that required repositioning of the pulse generator (Burchiel et al. 1996). Le Doux and Langford reported on four cases of pain at the receiver site, which required reoperation (Le Doux and Langford, 1993). Barolat et al. found four cases of prolonged pain at the surgical sites (Barolat et al. 1989). Three cases, reported by Ohnmeiss et al., required a repositioning of the stimulator because the unit was originally implanted under the patients' beltlines (Ohnmeiss et al. 1996). Segal et al., Rossi and Rabar, and Wester each, reported on one case of discomfort over the receiver (Segal et al., 1998; Rossi and Rabar, 1994; Wester, 1987).

Pain at the implant site requiring explantation has occurred only 10 times (2.45%) of the 408 total cases in the MDR search.

The special controls available for this risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include possible pain at the implant site" as the special control.

F. Allergic or rejection response to implanted materials:

Although all the materials that come in contact with human tissue have been confirmed to be biocompatible there have been documented cases of allergic reactions. Allergic reactions occur

when there is an immune reaction to a foreign substance. When an allergic reaction does occur after the implantation of an SCS system, the implanted device must be removed. This type of risk is very rare. Table 1B shows 3 cases out of 1924 that reported an allergic reaction. All of these reactions occurred with the lead material, and required removal of the device (Meglio et al., 1989; Barolat et al., 1989).

There has been only one (0.25%) reported incident, out of 408 MDRs, involving an allergic reaction to an IPG system. This reaction was determined to be to the titanium case. Titanium has been well documented as a safe material for implant applications.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, Concensus Standard EN/ ISO 10993 – Biological Evaluation of Medical Devices – Part 1, and ASTM F67-95 Standard for Unalloyed Titanium. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include allergic response" as the special control.

G. Local skin erosion over the implanted receiver:

Diabetic peripheral neuropathy can result in pain of the extremities and has become an indication for the use of SCS. However, peripheral neuropathy can also result in skin problems, which can be exacerbated by an implant. When skin erosion can be attributed to the IPG or receiver they usually require removal. This type of incident may occur regardless of whether the device is an IPG or RF system. Skin erosion was found to occur in 3 of the 1924 cases examined. Ohnmeiss et al. described one patient with diabetic peripheral neuropathy who

required the removal of the unit due to local skin erosion, however, the skin problem resolved and a SCS unit was eventually replaced (Ohnmeiss et al., 1996). Rossi and Rabar described two cases of skin erosion at the receiver site, which resolved after debridement (Rossi and Rabar, 1994).

Two events involving skin erosion have been reported through MDR research, which is only 0.49% of the total MDRs.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include erosion" as the special control.

H. Device failure:

Device failure can be broken down into several subsets, including electrode breakage, hardware malfunction and loose connections. Device failures occurred in 144 of the 1924 cases (7.5%-see table 1B). Seventy-nine of these failures were the result of lead breakage and sixty-four were the result of hardware malfunctions and one was the result of a loose connection. These types of events may occur regardless of whether the device is an IPG or RF system.

Device failure was identified in 63 of the 408 MDRs. Loose connections (n=4), broken leads (n=15), and other hardware malfunctions (n=44) have occurred in 0.98%, 3.68% and 10.78% of the total MDRs respectively.

The special controls available for this risk include consensus standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety. See the attached Special Control Chart-Table 1C.

The petitioner proposes the consensus standard ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators and EN 45502-1 Active Implantable Medical Devices – General Requirements for Safety to be used as the special controls. See the attached Special Control Chart-Table 1C.

I. Other:

Various risks were found that did not fit into any of the above categories (12 out of 1984 cases). Two patients reported to have developed a psychosis as the result of an implant (Calvillo, 1998; Zdanowicz, 1999), which required the removal of the SCS system. There have also been reports of muscle spasm (N=1) and urinary hesitancy (N=1) (Burchiel et al., 1996).

Barolat et al. reported on one patient who had excessive positional changes in the stimulation threshold (Barolat et al., 1989). Paresthesiae were felt when lying in the supine position, but were greatly reduced when standing or sitting. Studies have found that the thresholds for stimulation are highest in the thoracic level (He et al. 1997). They have also found the largest usage range to be at this level. However, this range varies greatly between patients and between postures. A recent study by Cameron et al. studied the effects of posture of patient previously implanted with a percutaneous SCS lead (Cameron et al., 1998). In twenty patients the threshold for paresthesia was lowest when lying, while in three patients it was lowest when sitting. The mean range and standard error of stimulation required to achieve paresthesia at all three posture levels was found to be .51 $\pm$ .2 μC for leads in the cervical region (N=11) and 1.52 $\pm$ .2 μC for leads in the thoracic region (N=19).

There have been some recent reports of interference that occurs when a patient with an SCS system enters an electromagnetic field created by a security system. In one such case the patient experienced permanent neurological injuries due to the uncontrolled activation of the cervical SCS device (Eisenberg, 1997).

One patient reported by Mittal et al. suffered from a mild pulmonary embolism which occurred 10 days after the insertion of a permanent RF system (Mittal et al., 1987). This patient recovered with conservative therapy and the device was left in place.

There have been seven reported cases of aseptic meningitis associated with the implantation of an SCS system (Meglio et al. 1989; 1991; Cioni et al. 1995). All cases resolved without any permanent damage. Two of the cases resolved spontaneously, while the remaining five cases required the removal of the system. All reported cases of aseptic meningitis came from the same center.

Headache, asthenia, and dizziness occurred during stimulation in five patients. In two patients with spinal cord lesion, SCS increased muscle spasms. Muscle twitches due to radicular stimulation were described by three patients, and in one patient muscular contraction due to activation of the pyramidal tract was observed (Meglio et al., 1989)

The largest single category of MDRs were classified as other (n=144) due to a lack of reported information.

The special controls available for these risks include the labeling guidance Medical Device Labeling: Suggested Format and Content. See the attached Special Control Chart-Table 1C.

The petitioner proposes labeling special controls utilizing an adverse event warning/precaution statement in the labeling to state: Warning: "Other adverse events include headache, asthenia, and dizziness". Precaution: "Systems maybe affected by theft detectors or security systems".

Risks Associated with the Implanted Pulse Generator (IPG)

J. Battery Failure:

The battery of an IPG is located within the device, therefore when the battery is depleted replacement requires reoperation. When a battery requires replacement before the expected date (usually 2 to 3 years) it is considered a battery failure. Battery failure occurred in 28 of the 1538 cases or 1.8% of the time, although in 22 out of 28 cases the battery failure occurred after more than 3 years (see table 1B).

Nine studies reported on reoperation due to battery depletion. De La Porte and Van de Kelft and Fiume et al. each reported on eight cases of battery depletion (De La Porte and Van de Kelft, 1993; Fiume et al., 1995). Meglio et al. reported on four cases, Francavigilia et al. reported on two cases, that required reoperation due to battery depletion (Meglio et al., 1994; Francavigilia et al., 1994). The average follow-up period for all these studies was greater than the average expected battery life (approximately three years).

Meglio et al. reported on a case in which early battery depletion occurred, however, this patient required a very high current intensity to achieve paresthesia (Meglio et al., 1989). Burchiel et al. reported on two cases in which the battery depleted in less than one year, but no data regarding the usage were reported (Burchiel et al., 1996). Ohnmeiss et al. reported on one case that required battery replacement after 18 months probably due to continuous use of the system (Ohnmeiss et al., 1996). Segal et al. reported on a patient who kept the stimulator on 24 hours a

day and required battery replacement after only one year (Segal et al., 1998). Finally, Graziotti and Goucke reported a case study on a patient who used the device 24 hours per day and depleted the battery after one year (Graziotti and Goucke, 1993).

Battery failure was reported in 66 MDRs.

The special controls available for this risk include consensus standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety and labeling guidance Medical Device Labeling: Suggested Format and Content. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing a chart in the labeling that estimates the life of the battery under specific power consumption conditions be used as the special control.

(7) UNFAVORABLE REPRESENTATIVE DATA AND INFORMATION TO THE PETITIONER'S POSITION.

The literature review did not find any negative articles that would require a totally implanted spinal cord stimulator for pain relief device to remain in class III. The main difference between an implanted pulse generator device and an RF device is the internal battery. The limited battery life of an IPG requires that it is used in situations that require moderate to low power consumption, however, this limitation does not reduce the safety of the device.

(8) NEW INFORMATION UNDER SECTION 513(e), 514(b), OR 515(b) OF THE ACT

Not applicable

(9) NEW INFORMATION SOURCE DOCUMENTS

Not applicable

(10) FINANCIAL DISCLOSURE STATEMENT

Among the published literature studies identified in support of this petition, only 3 involved participation by individuals listed in tables 1A and 1B who had a financial relationship with the petitioner prior to publication. The relationships ranged from employment to compensation associated with performance of a clinical investigation and may have included either stock ownership or options for stock purchase.

All of these published literature studies were completed prior to the February 2, 1999 effective date of this regulation. There are no covered clinical studies ongoing as of February 2, 1999 which the petitioner relies on to establish device effectiveness or a significant contribution to the demonstration of safety in relation to this reclassification petition.

The petitioner does not intend to submit any clinical studies because of its reliance on the published literature. Therefore the petitioner believes that the provisions of 21 C.F.R. Part 54 relating to financial disclosure are not applicable.

SUMMARY

The petitioner believes that compliance with provisions of the FDCA applicable to class II devices, including the requirement for obtaining a premarket notification order from the FDA, is sufficient to provide reasonable assurance of the safety and effectiveness of totally implanted spinal cord stimulator devices for pain relief. This assurance is enhanced through the

requirement for compliance with special controls as demonstrated through the premarket notification process implemented through manufacturing compliance during commercial distribution, and confirmed by FDA surveillance activities.

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	A	B					C	D	
Author	Lead Migration	Infection	Epidural Hemorage	Seroma	Hematoma	Paralysis	CSF Leak	Over/under Stim	Intermittent Stim
Turner et at. 1995*	24%/16	5%/20							
Tesfaye et al. 1996	2/8	2/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
Ohnmeiss et al. 1996	4/40	1/40	0/40	0/40	0/40	0/40	0/40	0/40	0/40
Burchiel et al. 1996	3/70	3/70	0/70	0/70	0/70	0/70	1/219	7/70	0/70
Kumar et al. 1996	4/19	1/19	0/19	0/19	0/19	0/19	0/19	0/19	0/19
Calvillo et al. 1998	2/31	2/31	0/31	0/31	0/31	0/31	0/31	0/31	0/31
Kemler et al. 1999	7/18	2/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18
Kumar and Toth 1998	55/165	9/165	0/165	0/165	0/165	0/165	1/165	0/165	0/165
Fiume et al. 1995	6/36	5/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Alo et al. 1998	3/80	4/80	0/80	0/80	0/80	0/80	0/80	0/80	0/80
Segal et al. 1998	1/24	0/24	0/24	0/24	0/24	0/24	0/24	0/24	0/24
Kumar et al. 1998	64/189	10/235	0/189	0/189	1/189	0/189	0/189	0/189	0/189
Francaviglia et al. 1994	0/15	0/15	0/15	0/15	0/15	0/15	0/15	0/15	0/15
Meglio et al. 1994	1/21	3/21	0/21	0/21	0/21	0/21	1/21	0/21	0/21
Broggi et al. 1994	16/363	5/363	0/363	0/363	0/363	0/363	0/363	0/363	0/363
Rossi and Rabar 1994	4/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Robaina et al. 1989	2/11	1/11	0/11	0/11	0/11	0/11	0/11	0/11	0/11
Barolat et al. 1989	2/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18
Sanchez-Ledesma et 1989	1/36	1/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Westner 1987	0/30	2/30	0/30	0/30	0/30	0/30	0/30	0/30	0/30
Demirel et al. 1984	11/33	4/33	0/33	0/33	0/33	0/33	1/33	0/33	0/33
Meglio et al. 1989	3/64	3/109	0/109	0/109	3/109	1/200	2/109	2/64	0/64
North et al., 1993	0/298	15/298	0/298	0/298	0/298	0/298	0/298	0/298	0/298
Mittal et al., 1987	2/35	3/35	0/35	0/35	0/35	0/35	0/35	2/35	0/35
Racz et al., 1989	18/26	2/26	0/26	0/26	1/26	0/26	0/26	0/26	0/26
Graziotti and Goucke, 1993	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
LeDoux and Langord, 1993	10/23	0/23	0/23	0/23	0/23	0/23	0/23	0/23	0/23
Hasswnbusch et al., 1995	5/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26
Cioni et al., 1995	1/10	1/25	0/25	0/25	0/25	0/25	0/25	0/10	0/10
DeLa Porte and VandeKelft, 1993	8/64	5/64	0/64	0/64	0/64	0/64	0/64	0/64	0/64
Probst, 1990	20/92	5/92	0/92	0/92	0/92	0/92	0/92	0/92	0/92
Kumar et al., 1997	2/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12
Waisbrod, and Gerbershagen, 1985	5/16	1/16	0/16	0/16	0/16	0/16	0/16	0/16	0/16
Total	275/1924	91/2030	0/1984	0/1984	5/1984	1/2075	6/1984	11/1924	0/1924
%	14.2	4.48	0	0	.25	.05	.3	.6	0

Table 1A: This table shows the number of occurrences over the total number of implants for each of the studies cited. *This paper is a review of 39 articles the numbers in this row are the average percentages of each occurrence over the total number of studies.

Note: Citations cover both IPG and RF Systems

	E	F	G	H			I	K
Author	Pain over implant	Allergic Reaction	Skin Erosion	Lead Breakage	Hardware Malfunction	Loose Connection	Other	Battery Failure
Turner et al 1995.*				7%/15				2%/14
Tesfaye et al. 1996	0/8	0/8	0/8	0/8	0/8	0/8	0/8	N/A
Ohnmeiss et al. 1996	3/40	0/40	1/40	0/40	0/40	0/40	0/40	1/40
Burchiel et al. 1996	6/70	0/70	0/70	1/70	4/70	0/70	2/70	2/70
Kumar et al. 1996	0/19	0/19	0/19	2/19	2/19	0/19	0/19	0/19
Calvillo et al. 1998	0/31	0/31	0/31	0/31	0/31	0/31	1/31	0/31
Kemler et al. 1999	0/18	0/18	0/18	1/18	1/18	0/18	0/18	0/18
Kumar and Toth 1998	0/165	0/165	0/165	6/165	6/165	0/165	0/165	0/165
Fiume et al. 1995	0/36	0/36	0/36	3/36	0/36	0/36	0/36	8/36
Alo et al. 1998	0/80	0/80	0/80	0/80	0/80	0/80	0/80	N/A
Segal et al. 1998	1/24	0/24	0/24	1/24	0/24	0/24	0/24	1/24
Kumar et al. 1998	0/189	0/189	0/189	8/189	8/189	0/189	0/189	0/189
Francaviglia et al. 1994	0/15	0/15	0/15	0/15	0/15	0/15	0/15	2/15
Meglio et al. 1994	0/21	0/21	0/21	4/21	2/21	0/21	2/21	4/21
Broggi et al. 1994	0/363	0/363	0/363	6/363	0/363	0/363	0/363	0/363
Rossi and Rabar 1994	1/50	0/50	2/50	4/50	2/50	0/50	0/50	0/50
Robaina et al. 1989	0/11	0/11	0/11	0/11	0/11	0/11	0/11	0/11
Barolat et al. 1989	4/18	1/18	0/18	3/18	0/18	0/18	1/18	0/18
Sanchez-Ledesma et al. 1989	0/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Westner 1987	1/30	0/30	0/30	0/30	0/30	0/30	0/30	0/30
Demirel et al. 1984	0/33	0/33	0/33	0/33	3/33	0/33	0/33	0/33
Meglio et al. 1989	0/64	2/64	0/64	0/64	4/64	0/64	4/109	1/64
North et al., 1993	0/298	0/298	0/298	22/298	16/298	0/298	0/298	N/A
Mittal et al., 1987	0/35	0/35	0/35	4/35	0/35	0/35	1/35	0/35
Racz et al., 1989	0/26	0/26	0/26	6/26	3/26	0/26	0/26	0/26
Graziotti and Goucke, 1993	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1
LeDoux and Langford, 1993	4/23	0/23	0/23	0/23	4/23	1/23	0/23	0/23
Hasswnbusch et al., 1995	0/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26
Cioni et al., 1995	0/10	0/10	0/10	0/10	0/10	0/10	1/25	0/10
DeLa Porte and VandeKelft, 1993	0/64	0/64	0/64	6/64	0/64	0/64	0/64	8/64
Probst, 1990	0/92	0/92	0/92	0/92	7/92	0/92	0/92	0/92
Kumar et al., 1997	0/12	0/12	0/12	2/12	2/12	0/12	0/12	0/12
Waisbrod and Gerbershagen, 1985	0/16	0/16	0/16	0/16	0/16	0/16	0/16	0/16
Total	20/1924	3/1924	3/1924	79/1924	64/1924	1/1924	12/1984	28/1538
%	1.03	.15	.15	4.1	3.32	.05	.6	1.8

Table 1B: This table shows the number of occurrences over the total number of implants for each of the studies cited. *This paper is a review of 39 articles the numbers in this row are the average percentages of each occurrence over the total number of studies. **Note: Citations cover both IPG and RF Systems**

Totally Implanted Spinal Cord Stimulator for Pain Relief
Reclassification Petition
Summary of Literature Citing IPG's and RF Systems

Author	Receiver Type	Total # of Patients w/ permanent implants
Turner et at. 1995	Review paper	Review paper
Tesfaye et al. 1996	RF	8
Ohnmeiss et al. 1996	IPG	40
Burchiel et al. 1996	IPG	70
Kumar et al. 1996	Both	Doesn't specify(19)
Calvillo et al. 1998	doesn't specify	31
Kemler et al. 1999	IPG	18
Kumar and Toth 1998	Both	Doesn't specify(165)
Fiume et al. 1995	IPG	36
Alo et al. 1998	RF	80
Segal et al. 1998	IPG	24
Kumar et al. 1998	Both	(doesn't specify)189
Francaviglia et al. 1994	IPG	15
Meglio et al. 1994	Both	12 RF & 9 IPGs
Broggi et al. 1994	Both	23 RF&260 IPG
Rossi and Rabar 1994	RF	50
Robaina et al. 1989	Both	Doesn't specify(11)
Barolat et al. 1989	Both	Doesn't specify(14)
Sanchez-Ledesma et 1989	Both	Doesn't specify(36)
Westner 1987	IPG	30
Demirel et al. 1984	RF	33
Meglio et al. 1989	Both	34 RF&30 IPG
North et al., 1993	RF	298
Mittal et al., 1987	RF	31

Totally Implanted Spinal Cord Stimulator for Pain Relief

Reclassification Petition

Summary of Literature Citing IPG's and RF Systems

Author	Receiver Type	Total # of Patients w/ permanent implants
Racz et al., 1989	IPG	26
Graziotti and Goucke, 1993	IPG	1
LeDoux and Langord, 1993	Doesn't specify	23
Hasswnbusch et al., 1995	IPG	26
Cioni et al., 1995	IPG	9
DeLa Porte and VandeKelft, 1993	RF/IPG/Cordis (IPG)	42 RF,18 IPG & 4 Cordis
Probst, 1990	IPG	92
Kumar et al., 1997	IPG	39
Waisbrod, and Gerbershagen, 1985	RF	16

Totally Implanted Spinal Cord Stimulator for Pain Relief
Reclassification Petition
Summary of Literature Citing IPG's and RF Systems

Receiver Type	Totals
RF	627
IPG	743
Cordis IPG	4
Doesn't Specify	488
Total Permanent Implants	1862

IPG SPECIAL CONTROLS FOR IDENTIFIED RISK
TABLE 1C

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
A) LEAD MIGRATION	• **Identify lead migration as possible adverse event** • Directions to secure lead with anchors in Physician's Manual	• EN 1441 Medical Device Risk Analysis	• Design Control Guidance for Medical Device Manufacturers • Medical Device Labeling Suggested Format and Content
B) INFECTION	• **Identify infection as possible adverse event**	• Sterilization validation per AAMI/ISO 11135 • Sterilization validation per EN 556 • Sterile labeled medical devices EN 556 • EN 45501-1 subset has EN 861-1 " Packaging materials and systems for Medical Devices which are to be sterilized " • EN 1441 Medical Device Risk Analysis	• 510(k) Sterility Review Guidance • Medical Device Labeling Suggested Format and Content
B) EPIDURAL HEMORRHAGE	• **Identify epidural hemorrhage as possible adverse event** • Directions for needle insertion in Physician Manual	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
B) SEROMA	• **Identify seroma as possible adverse event**	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
B) HEMATOMA	• **Identify Hematoma as possible adverse event** • Directions for implantation technique in Physician Manual	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content

NOTE : RECOMMENDED SPECIAL CONTROLS IN **BOLD** PRINT

IPG SPECIAL CONTROLS FOR IDENTIFIED RISK
TABLE 1C

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
B) PARALYSIS	• **Identify paralysis as possible adverse event** • Directions for needle insertion in Physician Manual • Directions for implantation in Physician Manual • Patient size selection guidance in Physicians manual • Identify infection as possible adverse event	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
C) CSF LEAKAGE	• **Identify CSF leakage as possible adverse event** • Directions for implantation and insertion technique in Physician Manual	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
D) UNDESIRABLE CHANGES IN STIMULATION • Intermittent Stimulation • Over Stimulation • Shock	• **Identify undesirable changes in stimulation as possible adverse event** • **Warning regarding Anti-Theft Devices** • Cautions regarding effects of postural changes	• EN/IEC-60601 series • EN 1441 Medical Device Risk Analysis • **EN 45502-1 Active Implantable Medical Device -General Requirements for Safety, Marking ...** • **ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators**	• FDA letter to industry "Important Information on Anti-Theft and Metal Dectector Systems....Spinalcord Stimulators", Sept 28, 1998 • Guidance for Content of Premarket Submissions for Software Contained in Medical Devices • General Principals of Software Validation
E) PAIN AT THE IMPLANT SITE	• **Identify implant site pain as possible adverse event** • Directions for needle insertion in Physician Manual	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content

NOTE : RECOMMENDED SPECIAL CONTROLS IN **BOLD** PRINT

IPG SPECIAL CONTROLS FOR IDENTIFIED RISK
TABLE 1C

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
F) ALLERGIC OR REJECTION RESPONSE TO IMPLANTED MATERIALS	• **Identify immune response as possible adverse event**	• EN ISO 10993-1Biological Evaluation of Medical Devices - Part 1 • EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
G) LOCAL SKIN EROSION	• **Identify skin erosion response as possible adverse event** • Directions for implantation in Physician Manual • Patient size selection guidance in Physician manual	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content
H) DEVICE FAILURE • Lead Breakage • Hardware Malfunction • Loose Connection		• **ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators** • **EN 45502-1 Active Implantable Medical Device -General Requirements for Safety, Marking ...**	• Design Control Guidance for Medical Devices • Guidance for Content of Premarket Submissions for Software Contained in Medical Devices • General Principals of Software Validation
I) OTHER • **Psychosis**	• **Recommend patients have Psycological Screening prior to implant in Physician Manual** • Contraindications: Patients are contraindicated for internalization if they are clearly unsuccessful during screening procedure, or if they are unable to properly operate the system		
J) BATTERY FAILURE	• **Disclose expected battery life in patient & Physician Manuals**	• EN 1441 Medical Device Risk Analysis	• Medical Device Labeling Suggested Format and Content • Design Control Guidance for Medical Devices

NOTE : RECOMMENDED SPECIAL CONTROLS IN **BOLD** PRINT

TABLE 2

MDR REPORTS

Event Category	Total Set Count	Total Set %	Last 5 ¼ Count	Last 5 ¼ %	1998 Count	1998 %
A) Lead Migration	1	0.25%	1	0.51%	0	0.00%
B) Infection	14	3.43%	14	7.07%	3	12.50%
Epidural Hemorrhage	0	0.00%	0	0.00%	0	0.00%
Seroma	1	0.25%	1	0.51%	1	4.17%
Hematoma	0	0.00%	0	0.00%	0	0.00%
Paralysis	0	0.00%	0	0.00%	0	0.00%
C) CSF Leak	0	0.00%	0	0.00%	0	0.00%
D) Intermittent Stimulation	50	12.25%	21	10.61%	0	0.00%
Over Stimulation	33	8.09%	18	9.09%	4	16.67%
Shock	23	5.64%	18	9.09%	0	0.00%
E) Pain at Implant Site	10	2.45%	6	3.03%	0	0.00%
F) Allergic Reaction	1	0.25%	1	0.51%	1	4.17%
G) Skin Erosion	2	0.49%	2	1.01%	2	8.33%
H) Lead Breakage	15	3.68%	11	5.56%	1	4.17%
Hardware Malfunction	44	10.78%	16	8.08%	1	4.17%
Loose Connection	4	0.98%	1	0.51%	0	0.00%
I) Other	144	35.29%	80	40.40%	11	45.83%
J) Battery Failure	66	16.18%	8	4.04%	0	0.00%
Total	**408**	**100.00%**	**198**	**100.00%**	**24**	**100.00%**

Table 2: This table shows the number of incidents reported as MDR's during the period from 1984 to March 22, 1999, with the exception of 1991.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE — FOOD AND DRUG ADMINISTRATION

SUPPLEMENTAL DATA SHEET

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 1, 2000
(See OMB Statement on Page 2)

1. GENERIC TYPE OF DEVICE
STIMULATOR, SPINAL CORD, TOTALLY IMPLANTED FOR PAIN RELIEF

2. ADVISORY PANEL
NEUROLOGICAL DEVICES PANEL

3. IS DEVICE AN IMPLANT ?
[XX] Yes [ ] No

4. INDICATIONS FOR USE PRESCRIBED, RECOMMENDED, OR SUGGESTED IN THE DEVICE'S LABELING THAT WERE CONSIDERED BY THE ADVISORY
TOTALLY IMPLANTED SPINAL CORD STIMULATORS FOR PAIN RELIEF ARE INDICATED FOR THE TREATMENT OF CHRONIC INTRACTABLE PAIN OF THE TRUNK AND LIMBS

5. IDENTIFICATION OF ANY RISKS TO HEALTH PRESENTED BY DEVICE

General LEAD MIGRATION, INFECTION, EPIDURAL HEMORRHAGE, SEROMA, HEMATOMA, PARALYSIS, CSF LEAKAGE, UNDESIRABLE CHANGES IN STIMULATION, PAIN AT RECEIVER SITE, ALLERGIC RESPONSE, SKIN EROSION, DEVICE FAILURE, BATTERY FAILURE

Specific Hazards to Health	Characteristics or Features of Device Associated with Hazard
a. INFECTION	a. SURGICAL TECHNIQUE/CARE
b. LEAD MIGRATION	b. INADEQUATE LEAD ANCHORING
c. SEROMA AT IPG SITE	c. SURGICAL TECHNIQUE
d. OTHERS	d. SURGICAL TECHNIQUE

6. RECOMMENDED ADVISORY PANEL CLASSIFICATION AND PRIORITY

Classification CLASS II Priority (Class II or III Only)

7. IF DEVICE IS AN IMPLANT, OR IS LIFE-SUSTAINING OR LIFE-SUPPORTING AND HAS BEEN CLASSIFIED IN A CATEGORY OTHER THAN CLASS III, EXPLAIN FULLY, THE REASONS FOR THE LOWER CLASSIFICATION WITH SUPPORTING DOCUMENTATION AND DATA

RF SYSTEMS WITH EXTERNAL POWER SOURCES ARE CLASS II. THESE SYSTEMS ARE DEFINED IN 882.5880 OF THE CFR.

8. SUMMARY OF INFORMATION, INCLUDING CLINICAL EXPERIENCE OR JUDGMENT, UPON WHICH CLASSIFICATION RECOMMENDATION IS BASED

1. OVER 10 YEARS OF CLINICAL USE DEMONSTRATING THE DEVICE IS SAFE AND EFFECTIVE
2. SPECIAL CONTROLS AND GENERAL CONTROLS ARE AVAILABLE TO REASONABLY ASSURE THE DEVICE'S SAFETY AND EFFECTIVENESS
3. RISK ASSOCIATED WITH TOTALLY IMPLANTED DEVICE ARE SIMILAR TO STIMULATORS USED FOR THE SAME INDICATION WHICH ARE CLASS II

9. IDENTIFICATION OF ANY NEEDED RESTRICTIONS ON THE USE OF THE DEVICE

ATTACHMENT 1D

10. IF DEVICE IS IN CLASS I, RECOMMEND WHETHER FDA SHOULD EXEMPT IT FROM

Justification / Comments

☐ a. Registration / Device Listing

☐ b. Premarket Notification

☐ c. Records and Reports

☐ d. Good Manufacturing Practice

11. EXISTING STANDARDS APPLICABLE TO THE DEVICE, DEVICE SUBASSEMBLIES *(Components)* OR DEVICE MATERIALS *(Parts and Accessories)*

- ANSI/AMMI NS14-1995 STANDARD "IMPLANTABLE SPINAL CORD STIMULATORS"
- EN 45502-1 ACTIVE IMPLANTABLE MEDICAL DEVICE-GENERAL REQUIREMENTS FOR SAFETY, MARKING ...
- SEE SPECIAL CONTROLS CHART FOR ADDITIONAL STANDARDS

12. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Health and Industry Programs (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer, Paperwork Reduction Project (0910-0138)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

(Please DO NOT RETURN this form to this address.)

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE — FOOD AND DRUG ADMINISTRATION

GENERAL DEVICE CLASSIFICATION QUESTIONNAIRE

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 1, 2000
(See OMB Statement on Page 2)

PANEL MEMBER / PETITIONER	DATE
ADVANCED NEUROMODULATION SYSTEMS, INC.	5/20/99

GENERIC TYPE OF DEVICE	CLASSIFICATION RECOMMENDATION
STIMULATOR, SPINAL-CORD, TOTALLY IMPLANTED FOR PAIN RELIEF	CLASS II

1. IS THE DEVICE LIFE-SUSTAINING OR LIFE-SUPPORTING ?	☐ YES	☒ NO	Go to Item 2.
2. IS THE DEVICE FOR A USE WHICH IS OF SUBSTANTIAL IMPORTANCE IN PREVENTING IMPAIRMENT OF HUMAN HEALTH ?	☐ YES	☒ NO	Go to Item 3.
3. DOES THE DEVICE PRESENT A POTENTIAL UNREASONABLE RISK OF ILLNESS OR INJURY ?	☐ YES	☒ NO	Go to Item 4.
4. DID YOU ANSWER "YES" TO ANY OF THE ABOVE 3 QUESTIONS ?	☐ YES	☒ NO	If "Yes," go to Item 7. If "No," go to Item 5.
5. IS THERE SUFFICIENT INFORMATION TO DETERMINE THAT GENERAL CONTROLS ARE SUFFICIENT TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	☐ YES	☒ NO	If "Yes," Classify in Class I. If "No," go to Item 6.
6. IS THERE SUFFICIENT INFORMATION TO ESTABLISH *SPECIAL CONTROLS* TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	☒ YES	☐ NO	If "Yes," go to Item 7. If "No," Classify in Class I.
7. IS THERE SUFFICIENT INFORMATION TO ESTABLISH *SPECIAL CONTROLS* TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ? IF YES, CHECK THE SPECIAL CONTROL(S) NEEDED TO PROVIDE SUCH REASONABLE ASSURANCE. FOR CLASS II. ☒ Postmarket Surveillance ☒ Performance Standard(s) ☐ Patient Registries ☐ Device Tracking ☒ Testing Guidelines ☒ Other (specify) LABELING	☒ YES	☐ NO	If "Yes," Classify in Class II. If "No," Classify in Class III
8. IF A REGULATORY PERFORMANCE STANDARD IS NEEDED TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF A CLASS II OR III DEVICE, IDENTIFY THE PRIORITY FOR ESTABLISHING SUCH A STANDARD. ☒ Low Priority ☐ Medium Priority ☐ High Priority ☐ Not Applicable			
9. FOR A DEVICE RECOMMENDED FOR RECLASSIFICATION INTO CLASS II, SHOULD THE RECOMMENDED REGULATORY PERFORMANCE STANDARD BE IN PLACE BEFORE THE RECLASSIFICATION TAKES EFFECT ?	☐ YES ☒ NOT Applicable	☐ NO	
10. FOR A DEVICE RECOMMENDED FOR CLASSIFICATION / RECLASSIFICATION INTO CLASS III, IDENTIFY THE PRIORITY FOR REQUIRING PREMARKET APPROVAL APPLICATION (PMA) SUBMISSIONS. ☐ Low Priority ☐ Medium Priority ☐ High Priority ☐ Not Applicable			

ATTACHMENT 1E

1a. CAN THERE OTHERWISE BE REASONABLE ASSURANCE OF ITS SAFETY AND EFFECTIVENESS WITHOUT RESTRICTIONS ON ITS SALE, DISTRIBUTION OR USE, BECAUSE OF ANY POTENTIALITY FOR HARMFUL EFFECT OR THE COLLATERAL MEASURES NECESSARY FOR THE DEVICE'S USE ?	☐ YES ☒ NO	If "Yes," go to Item 12. If "No.", go to Item 11b.
1b. IDENTIFY THE NEEDED RESTRICTION(S) *(If Item 11a. was checked "NO.")* ☐ Only upon the written or oral authorization of a practitioner licensed by law to administer or use the device ☐ Use only by persons with specific training or experience in its use ☐ Use only in certain facilities ☒ Other (Specify) PRESCRIPTION DEVICE LABELING REQUIREMENT		

12. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Health and Industry Programs (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

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"Active implantable medical devices -- Part 1: General requirements for safety, marking and information to be provided by the manufacturer," EUROPEAN STANDARD, CENELEC EN 45502-1, August 1997

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"NS14, Implantable Spinal Cord Stimulators," American National Standard, ANSI/AAMI NS14--1995 (Revision of ANSI/AAMI NS14--1984), Association for the Advancement of Medical Instrumentation, 1997

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