

# **IMPLANTED SPINAL CORD STIMULATORS FOR PAIN RELIEF**

**Illustrating the FDA's Dangerously Lax Oversight of High-Risk Implantable Medical Devices**

Michael A. Carome, M.D.  
Health Research Group

June 10, 2020



## ACKNOWLEDGMENTS

This report was written by Michael A. Carome, M.D., Director of Public Citizen’s Health Research Group, and edited by Sidney M. Wolfe, M.D., Founder and Senior Adviser of Public Citizen’s Health Research Group. Throughout the drafting and editing of the report, Public Citizen’s Health Research Group consulted with and received input from Victor Krauthamer, Ph.D., the former Director of the Division of Biomedical Physics, Center for Devices and Radiological Health, Food and Drug Administration (FDA). Dr. Krauthamer retired from the U.S. Public Health Service in 2017 after a 30-year career at the FDA; he discloses that he is a paid part-time consultant for two foreign-based medical device companies that are seeking FDA approval to market their products. The report was copyedited by Fiona Lynn, Managing Editor of Public Citizen’s Health Research Group.

## ABOUT PUBLIC CITIZEN

Public Citizen is a national nonprofit organization with more than 500,000 members and supporters. We represent consumer interests through lobbying, litigation, administrative advocacy, research, and public education on a broad range of issues including consumer rights in the marketplace, drug and medical device safety, financial regulation, worker safety, safe and affordable healthcare, campaign finance reform and government ethics, fair trade, climate change, and corporate and government accountability.

### Contact Public Citizen

Main Office  
1600 20th Street NW  
Washington, D.C. 20009

Capitol Hill  
215 Pennsylvania Ave SE  
Washington, D.C. 20003

Texas Office  
309 E 11th Street, Suite 2  
Austin, Texas 78701

Phone: 202-588-1000

Phone: 202-546-4996

Phone: 512 477-1155

For more information, please visit [www.citizen.org](http://www.citizen.org).

© 2020 Public Citizen

# TABLE OF CONTENTS

Executive Summary .....	4
I. Introduction.....	8
II. Classification of Implanted Spinal Cord Stimulators for Pain Relief: Dangerously Inconsistent Application of the Statutory Medical Device Classification Scheme.....	10
<i>A. Inconsistent Classification of Preamendment Implanted Spinal Cord Stimulators: Pain Relief Versus Bladder Evacuation .....</i>	<i>11</i>
<i>B. Inconsistent Classification of Preamendment Implanted Spinal Cord Stimulators With External Transmitters for Pain Relief Versus Totally Implanted Spinal Cord Stimulators for Pain Relief.....</i>	<i>12</i>
III. 510(k) Premarket Clearances of Class II Implanted Spinal Cord Stimulators for Pain Relief	13
IV. Inadequate Safety and Effectiveness Data and FDA Review for Original PMAs for Totally Implanted Spinal Cord Stimulators for Pain Relief: Approval Based on Poorly Designed Clinical Trials or Inadequate Scientific Medical Literature Surveys .....	14
V. PMA Supplement Process for Class III Spinal Cord Stimulators for Pain Relief: Misused and Lacking Transparency .....	26
VI. The Opioid Overdose Epidemic: An Obvious Factor Driving the Accelerated Rate of PMA Supplement Approvals for Spinal Cord Stimulators for Pain Relief.....	34
VII. Adverse Events Caused by Implanted Spinal Cord Stimulators for Pain Relief: Evidence of Substantial Harm .....	36
<i>A. Published Reports of Adverse Events .....</i>	<i>36</i>
<i>B. Adverse Event Reports Filed in the FDA’s MAUDE Database.....</i>	<i>38</i>
VIII. Recalls of Implanted Spinal Cord Stimulators for Pain Relief .....	47
IX. Conclusions and Recommendations .....	49
Appendix - Device Events Search Terms for Table 5.....	53

## Executive Summary

For years, numerous commentators and patient safety advocates, including Public Citizen, have criticized the Food and Drug Administration's (FDA's) dangerously lax regulatory oversight of medical devices. The goals of this report, which was prompted by concerns about the safety of implanted spinal cord stimulators for pain relief that were raised in a 2018 Associated Press investigation by Weiss and Mohr,<sup>1</sup> were to better understand the history of the FDA's regulatory oversight of these devices, identify the deficiencies in this oversight that endangered patients, and recommend necessary changes to address those deficiencies.

Under the Medical Device Amendments of 1976, medical devices are categorized by the FDA into three classes: I, II, or III. These classifications generally are based on the level of risk the devices pose and the controls necessary to provide reasonable assurance of their safety and effectiveness. In general, Class I medical devices pose the least risk and Class III medical devices pose the greatest risk. Class II devices in most cases require a 510(k) premarket notification submission and are cleared for marketing based upon a determination that the device is substantially equivalent to a legally marketed device not subject to a premarket approval application (PMA) — known as a predicate device. Class III devices generally require FDA approval of PMAs prior to marketing and, usually, submission of clinical data on use of the device in humans to provide reasonable assurance that the device is safe and effective.

The FDA has arbitrarily divided implanted spinal cord stimulators for pain relief into Class II (product code GZB) and Class III (product code LGW) based, respectively, on whether the devices have an external transmitter and power source or are totally implanted. Our analysis of the regulatory history regarding the classification of spinal cord stimulators with external transmitters, which were marketed prior to 1976, found that there was no public health justification for classifying such spinal cord stimulators as Class II when indicated for pain relief and as Class III when indicated for bladder evacuation given that both types of devices had similar risk profiles. Likewise, we found no sound public health rationale for maintaining the classification of the preamendment implanted spinal cord stimulators with external transmitters for pain relief as lower-risk Class II while at the same time classifying the totally implanted spinal cord stimulators for pain relief, which were first marketed after 1976, as Class III given their overlapping risk profiles.

From 1978 to 2019, the FDA cleared 137 510(k) premarket notification submissions for implanted spinal cord stimulators with external transmitters for pain relief. Of note,

---

<sup>1</sup> Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others. *Associated Press*. November 26, 2018. <https://www.apnews.com/86ba45b0a4ad443fad1214622d13e6cb>. Accessed April 7, 2020.

many of these submissions were for components of these devices, most commonly stimulator leads, or for modifications to previously cleared devices.

From 1981 to 2019, the FDA approved six original PMAs for totally implanted spinal cord stimulators for pain relief. A review of the clinical data used to support the approval of these PMAs revealed that at least one of the first two PMAs for these devices was approved by the FDA based on a seriously flawed clinical study of the actual device for which approval was being sought. More troubling, for three of the subsequent four original PMAs for totally implanted spinal cord stimulators (and for one of the two approved indications for the fourth subsequent original PMA), despite having concluded that special controls used for Class II devices “cannot substitute for actual clinical trials designed to demonstrate the safety and effectiveness of these devices,” the FDA based its approval on clinical data derived only from published scientific medical literature for *other* spinal cord stimulator systems, not, as would reasonably be expected, prospective clinical trials that tested the safety and effectiveness of the actual devices for which approval was being sought. Moreover, a review of the studies included in the cited published scientific medical literature revealed significant flaws and limitations. FDA approval documents for these original PMAs indicate that the agency essentially treated the newer totally implanted spinal cord stimulators for pain relief as Class II devices and allowed them to be marketed based on the type of “substantial equivalence” determination that should only be made under the 510(k) premarket notification process, rather than on any clinical studies designed to evaluate the safety and effectiveness of the actual devices themselves that typically occur for Class III devices. As a result, the FDA subverted the PMA process intended for such permanently implanted high-risk devices.

After a PMA is approved, the applicant generally must submit a PMA supplement for review and approval by the FDA before making any change affecting the safety or effectiveness of the device. From 1980 to 2019, the FDA approved 945 of 1,008 submitted PMA supplements for the six PMAs for Class III totally implanted spinal cord stimulators for pain relief, which represented an approval rate of 94% by the end of 2019. Since 2000, the rate of these PMA supplement approvals has steadily increased. In the most recent three-year period included in our analysis (2017-2019), the PMA supplement approval rate was approximately 1.5 per week, whereas prior to 2001 the approval rate averaged less than 3 per year, which represents a 28-fold increase in the rate of approvals.

A search of the FDA’s PMA database revealed that numerous new models of totally implanted spinal cord stimulators for pain relief have been approved via PMA supplements. Other PMA supplements were for changes to the design of stimulator leads, pulse generators, batteries, software, and other device components; labeling changes, including new indications for use; and modifications to manufacturing facilities and manufacturing procedures, among other things. The scope of device changes being

approved under PMA supplements is troubling in two respects. First, the FDA's review process for PMA supplements appears to be even less rigorous than the deficient review process for original PMAs. Second, in contrast to the approval of original PMAs, there is lack of transparency regarding the full nature of the changes proposed in PMA supplements and the FDA's review and assessment of those changes.

Published literature reviews and an analysis of data from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database reveal that implanted spinal cord stimulators for pain relief can cause substantial harm. Overall complication rates for such stimulators documented in literature reviews were 30% to 40%. Common complications include lead migration, lead fracture, implant-related pain, infection, hematomas, seromas, and cerebrospinal fluid leakage. One rare but particularly troubling adverse event is chronic scar tissue formation around epidural leads, which can lead to spinal compression and myelopathy with various forms of paresis and sensory loss.

A search of the MAUDE database for the period of 2004 to 2019 revealed a total of 40,457 medical device adverse event reports (MDRs) (including 38,545 reports of injuries and 174 reports of death) for the Class II spinal cord stimulators with external transmitters for pain relief (product code GZB) and 179,917 reports (including 118,272 reports of injury and 757 reports of death) for the totally implanted spinal cord stimulators for pain relief (product code LGW). The most common types of adverse events described in the MDRs for both types of implanted spinal cord stimulators combined included infection, lead migration, heating, falls, lead fracture, inappropriate electrical shocks or shocking sensations, and headaches.

Finally, for the Class II implanted spinal cord stimulators with external transmitters for pain relief (product code GZB), there have been a total of five recalls from 2004 to 2019. For the Class III totally implanted spinal cord stimulators for pain relief (product code LGW), there have been 44 device recalls from 2004 to 2019. Notably, there were no Class 1 recalls (a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death) for either class of implanted spinal cord stimulators. Given the large number of serious adverse events associated with the use of implanted spinal cord stimulators, the relatively small number of recalls and the lack of any Class 1 recalls is troubling and suggests dangerously inadequate postmarket surveillance of these devices.

In conclusion, our report illustrates that the FDA's regulatory oversight of implanted spinal cord stimulators for pain relief has had serious, wide-ranging deficiencies since the enactment of the Medical Device Amendments of 1976 and is emblematic of what's wrong with the agency's oversight of medical devices and the serious harm to patients that can result.

We offer a series of recommendations to better ensure the safety and effectiveness of implanted spinal cord stimulators for pain relief and to ensure that similar problems are addressed for other high-risk, permanently implanted devices.

## I. Introduction

For years, numerous commentators and patient safety advocates, including Public Citizen, have criticized the Food and Drug Administration's (FDA's) lax regulatory oversight of medical devices.<sup>2,3,4,5,6,7,8</sup>

This report was prompted by concerns about the safety of implanted spinal cord stimulators for pain relief that were raised in a 2018 Associated Press investigation by Weiss and Mohr.<sup>9</sup> The goals of the report were to better understand the history of the FDA's regulatory oversight of these devices, identify the deficiencies in this oversight that endangered patients, and recommend necessary changes to address those deficiencies.

In their investigation of the FDA's Center for Devices and Radiological Health Manufacturer and User Facility Device Experience (MAUDE) database, Weiss and Mohr found that from 2008 to 2017, the FDA had received 78,172 device injury reports associated with use of spinal cord stimulators. Spinal cord stimulators thus accounted for the third highest number of such reports submitted to the FDA from 2008 to 2017, for any type of medical device, ranking behind only hip prostheses (103,104 reports) and insulin pumps with sensors (94,826 reports). The number of injury reports for spinal cord stimulators stood out among all 4,000 device types tracked by MAUDE.

The number of spinal cord stimulators that are implanted each year is uncertain because manufacturers closely guard these numbers. In 2007, the estimated number in the U.S. was 27,484 based on data from Medicare and the Agency for Healthcare Research and

---

<sup>2</sup> Garber AM. Modernizing device regulation. *N Engl J Med*. 2010;362(13):1161-1163.

<sup>3</sup> Hines JZ, Lurie P, Yu E, Wolfe S. Left to their own devices: breakdown in the United States medical device premarket review. *PLoS Med*. 2010;7(7):e1000280.

<sup>4</sup> Public Citizen. *Substantially Unsafe: Medical Devices Pose Great Threat to Patients; Safeguards Must be Strengthened, Not Weakened*. February 2012. <https://www.citizen.org/wp-content/uploads/substantially-unsafe-medical-device-report.pdf>. Accessed April 7, 2020.

<sup>5</sup> Rome BN, Kramer DB, Kesselheim AS. Approval of high-risk medical devices in the US: Implications for clinical cardiology. *Curr Cardiol Rep*. 2014;16(6):489.

<sup>6</sup> Zuckerman D, Brown P, Das A. Lack of publicly available scientific evidence on the safety and effectiveness of implanted medical devices. *JAMA Intern Med*. 2014;174(11):1781-1787.

<sup>7</sup> Zheng SY, Dhruva SS, Redberg RF. Characteristics of clinical studies used for US Food and Drug Administration approval of high-risk medical device supplements. *JAMA*. 2017;318(7):619-625.

<sup>8</sup> Redberg RF, Dhruva SS. Moving from substantial equivalence to substantial improvement for 510(k) devices. *JAMA*. 2019;322(10):927-928.

<sup>9</sup> Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others. *Associated Press*. November 26, 2018. <https://www.apnews.com/86ba45b0a4ad443fad1214622d13e6cb>. Accessed April 7, 2020.



Quality,<sup>10</sup> and in 2016, it was estimated to be 34,000 worldwide.<sup>11</sup> Weiss and Mohr projected that approximately 60,000 spinal cord stimulators are implanted annually in the U.S.<sup>12</sup> Of note, for medical devices approved under a premarket approval application (PMA) since August 1, 2009, PMA annual reports submitted to the FDA must include data about the number of devices shipped or sold during the reporting period. FDA guidance also recommends that for devices that are implanted, data regarding the number of devices actually implanted should be provided in the PMA annual reports if they are available.<sup>13</sup> However, PMA annual reports are not available on the FDA website. Moreover, data on aggregate sales or implant numbers (which would not disclose sales by individual companies) have not been released by the FDA. The lack of transparency regarding the number of patients implanted with spinal cord stimulators is one of the major factors impeding the ability to estimate the incidence rate of serious adverse events associated with the use of these devices.

The mechanism of the purported pain relief induced by electrical stimulation of the spinal cord is unknown.<sup>14</sup> Several theories have been proposed, each of which postulates that the devices block transmission of pain signals by nerve fibers in the spinal cord to the parts of the brain involved in pain perception.<sup>15</sup> The theories, though plausible, remain unproven. In practice, electrode placement and electrical stimulation dosing for spinal cord stimulators are done empirically.

---

<sup>10</sup> Prager J. Estimates of annual spinal cord stimulator implant rises in the United States. *Neuromodulation*. 2010;13(1):68-69.

<sup>11</sup> International Neuromodulation Society. Spinal cord stimulation's role in managing chronic disease symptoms. November 14, 2016. <https://www.neuromodulation.com/spinal-cord-stimulation>. Accessed April 7, 2020.

<sup>12</sup> Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others. *Associated Press*. November 26, 2018. <https://www.apnews.com/86ba45b0a4ad443fad1214622d13e6cb>. Accessed April 7, 2020.

<sup>13</sup> Food and Drug Administration. Annual reports for approved premarket approval applications: Guidance for industry and Food and Drug Administration staff. December 16, 2019. <https://www.fda.gov/media/73391/download>. Accessed April 7, 2020. Approval orders for the two original PMA approved after 2009 (P130022 and P130028) and the single available PMA supplement approval order (P030017/S275), which are discussed later in this report, specified the requirement to provide in annual reports the number of devices sold or distributed during the reporting period. Approval orders were accessed from

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on April 12, 2020.

<sup>14</sup> Jensen MP, Brownstone RM. Mechanisms of spinal cord stimulation for the treatment of pain: Still in the dark after 50 years. *Eur J Pain*. 2019;23(4):652-659.

<sup>15</sup> Sdrulla AD, Guan Y, Raja SN. Spinal cord stimulation: Clinical efficacy and potential mechanisms. *Pain Pract*. 2018; 18(8):1048-1067.

## II. Classification of Implanted Spinal Cord Stimulators for Pain Relief: Dangerously Inconsistent Application of the Statutory Medical Device Classification Scheme

Under the Medical Device Amendments of 1976, medical devices are categorized by the FDA into three classes: I, II, or III. These classifications generally are based on the level of risk the devices pose and the controls necessary to provide reasonable assurance of their safety and effectiveness. In general, Class I medical devices pose the least risk and Class III medical devices pose the greatest risk.

Class II devices require a 510(k) premarket notification submission (unless the device is exempt from the 510(k) requirements) and are cleared for marketing based upon a determination that the device is substantially equivalent to a legally marketed device not subject to a PMA — known as a predicate device.<sup>16</sup> In general, clinical data on use of the device in humans is not required for Class II devices, nor is a review of the scientific medical literature or a discussion of adverse events associated with use of the predicate device or other similar devices. The FDA instead relies on a combination of general and special controls to provide a reasonable assurance of safety and effectiveness. The agency does require submission of individual medical device adverse event reports for Class II devices once they are cleared for marketing.

In general, Class III devices require FDA approval of PMAs prior to marketing and, usually, submission of clinical data on use of the device in humans to provide a reasonable assurance that the new device is safe and effective. FDA regulations at 21 C.F.R. § 860.7 regarding medical device classification procedures stipulate that “the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.” The FDA is permitted to accept a wide range of clinical data in support of PMAs, including evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.<sup>17</sup> Often, the quality of such clinical data is very poor and does not constitute “valid scientific evidence.” Thus, the FDA should — but too often does not — require prospective, well-controlled clinical trials to provide such evidence to support PMA approvals. The FDA also requires submission of

---

<sup>16</sup> Food and Drug Administration. Premarket notification 510(k). September 27, 2018.

<https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k>. Accessed April 7, 2020.

<sup>17</sup> Food and Drug Administration. PMA clinical studies. <https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies>. Accessed April 7, 2020.

individual medical device adverse event reports for Class III devices once they are approved.

The FDA has divided implanted spinal cord stimulators for pain relief into two classes, Class II and Class III, based on whether the devices have an external transmitter and power source or are totally implanted.<sup>18</sup>

*A. Inconsistent Classification of Preamendment Implanted Spinal Cord Stimulators: Pain Relief Versus Bladder Evacuation*

Implanted spinal cord stimulators with external transmitters and power sources for pain relief were legally marketed before the Medical Device Amendments of 1976. In 1978, the FDA's Neurological Devices Advisory Panel recommended that these devices be classified as Class II devices (relying on performance standards to provide a reasonable assurance of safety and effectiveness), even though severe adverse events clearly caused by these devices had been reported, including spinal cord compression, subarachnoid bleeding, paralysis, and infection.<sup>19,20</sup> In 1979, the FDA issued a final rule at 21 C.F.R. § 882.5880 classifying implanted spinal cord stimulators with external transmitters for pain relief as Class II and assigning to them product code GZB.<sup>21</sup>

In contrast, in 1978, the Neurological Devices Advisory Panel recommended classifying a subset of essentially the same implanted spinal cord stimulator devices as Class III (requiring premarket approval) when they were indicated for bladder evacuation.<sup>22</sup> A 1978 notice of proposed rulemaking regarding the classification of these devices noted that the "Commissioner believes that the device presents a potential unreasonable risk of illness or injury, because of the possibility of neural damage."<sup>23</sup> In 1979, the FDA issued

---

<sup>18</sup> Food and Drug Administration. Product classification.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/classification.cfm>. Accessed April 7, 2020. The database was searched for the term "spinal cord stimulator."

<sup>19</sup> Food and Drug Administration. Proposed rule: Medical devices; classification of implanted spinal cord stimulators for pain relief. November 28, 1978. 43 FR 55725-55726.

<https://www.regulations.gov/document?D=FDA-1978-N-0628-0001>. Accessed April 7, 2020.

<sup>20</sup> Food and Drug Administration. Product classification: Stimulator, spinal-cord, implanted (pain relief). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/classification.cfm?id=3734>. Accessed April 7, 2020.

<sup>21</sup> Food and Drug Administration. Final rule: Neurological devices; classification of implanted spinal cord stimulators for pain relief. September 4, 1979. 44 FR 51774-51775.

<https://www.govinfo.gov/content/pkg/FR-1979-09-04/pdf/FR-1979-09-04.pdf>. Accessed April 7, 2020.

<sup>22</sup> Food and Drug Administration. Proposed rule: Medical devices; classification of implanted spinal cord stimulators for bladder evacuation. November 28, 1978. 43 FR 55721-55722.

<https://www.regulations.gov/document?D=FDA-1978-N-0360-0001>. Accessed April 7, 2020.

<sup>23</sup> *Ibid.*

a final rule at 21 C.F.R. § 882.5850 classifying just those implanted spinal cord stimulators with external transmitters that are indicated for bladder evacuation as Class III.<sup>24</sup>

Given the FDA's reasonable concern about the possibility of neural damage with the spinal cord stimulators for bladder evacuation and the fact that spinal cord stimulators for pain relief were also known to cause similar neurological damage at the time of their initial classification, there was no public health justification for the different classifications of these two types of preamendment spinal cord stimulators.

*B. Inconsistent Classification of Preamendment Implanted Spinal Cord Stimulators With External Transmitters for Pain Relief Versus Totally Implanted Spinal Cord Stimulators for Pain Relief*

The first totally implanted spinal cord stimulators, including batteries, for pain relief were developed after the 1976 Medical Device Amendments were enacted. The FDA then determined that these devices did not qualify for the Class II designation and therefore classified them as Class III and reviewed them under the PMA process, although the FDA has not yet promulgated a regulation formalizing this classification. These devices were assigned product code LGW.<sup>25</sup> Most spinal cord stimulators for pain relief marketed in the U.S. are totally implanted Class III devices.

These newer types of implants differed from the preamendment implanted spinal cord stimulators in that all components of the device, including the batteries for stimulus power, were implanted, rather than having external transmitters with the power source. The implanted power source is the only major feature that distinguishes these Class III devices (product code LGW) from the Class II devices (product code GZB). Again, given that the major risks of these two categories of stimulators significantly overlap, there is no sound public health rationale for maintaining the classification of the preamendment implanted spinal cord stimulators with external transmitters for pain relief as lower-risk Class II devices.

---

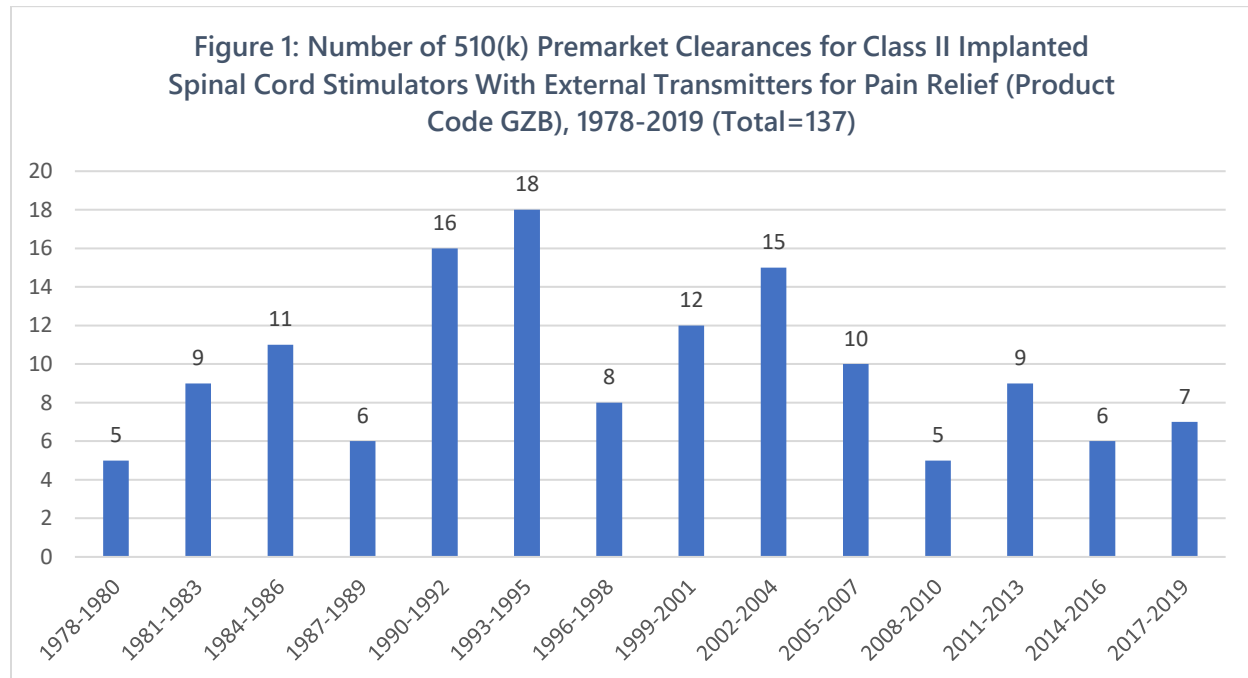
<sup>24</sup> Food and Drug Administration. Final rule: Neurological devices; classification of implanted spinal cord stimulators for bladder evacuation. September 4, 1979. 44 FR 51773.

<https://www.govinfo.gov/content/pkg/FR-1979-09-04/pdf/FR-1979-09-04.pdf>. Accessed April 7, 2020.

<sup>25</sup> Food and Drug Administration. Product classification: Stimulator, spinal-cord, totally implanted for pain relief. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/classification.cfm?id=3888>. Accessed April 7, 2020.

### III. 510(k) Premarket Clearances of Class II Implanted Spinal Cord Stimulators for Pain Relief

From 1978 to 2019, the FDA cleared 137 510(k) premarket notification submissions for implanted spinal cord stimulators with external transmitters for pain relief (product code GZB).<sup>26</sup> Figure 1 shows the number of such clearances by three-year intervals. Of note, many of these submissions were for components of these devices, most commonly stimulator leads, or for modifications to previously cleared devices.



Source: Search of the FDA's 510(k) premarket notification database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnmn.cfm> on February 11, 2020, using the search term "GZB" in the "Product Code" field.

<sup>26</sup> Note that a search of the FDA's 510(k) premarket notification database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnmn.cfm> on February 11, 2020, using the search term "GZB" in the "Product Code" field yielded 138 product clearances. One of these clearances was for Antigenz Chlamydia (decision date 3/11/1991) and was excluded from our analysis.

#### IV. Inadequate Safety and Effectiveness Data and FDA Review for Original PMAs for Totally Implanted Spinal Cord Stimulators for Pain Relief: Approval Based on Poorly Designed Clinical Trials or Inadequate Scientific Medical Literature Surveys

Table 1 lists the six original PMAs for totally implanted spinal cord stimulators (product code LGW) for pain relief approved by the FDA following enactment of the 1976 Medical Device Amendments. The table identifies the companies that held the PMAs for these devices, the model names, the types of clinical study data provided to support the original PMAs, and the number of PMA supplements subsequently approved as of December 31, 2019.

The first two totally implanted spinal cord stimulators for pain relief approved by the FDA were the Cordis Programmable Neural Stimulator Model 900a (Cordis 900a device; PMA number P800040; approved in 1981 and withdrawn in 2016)<sup>27</sup> and the Medtronic Itrrel Totally Implantable Spinal Cord Stimulation System (Medtronic Itrrel device; PMA number P840001; approved in 1984).<sup>28</sup>

The Summary of Safety and Effectiveness Data (SSED) for the original PMA for the Cordis 900a device could not be located on either the FDA's online PMA database or the regulations.gov website (searched April 7, 2020). Therefore, the clinical study data that was used to establish the safety and effectiveness of the device were not available to the authors of this report.

---

<sup>27</sup> Food and Drug Administration. Premarket approval database: PMA number P800040, Cordis Programmable Neurostimulator Models 900A.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P800040>. Accessed April 7, 2020.

<sup>28</sup> Food and Drug Administration. Premarket approval database: PMA number P840001, of Medtronic Itrrel Totally Implantable Spinal Cord Stimulation System.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P840001>. Accessed April 7, 2020.

Table 1: PMA Applications for Totally Implanted Spinal Cord Stimulators for Pain Relief (Product Code LGW), 1980-2019

Original PMA Number	PMA Holder(s)	Model Name(s)	Approval Date for the Original PMA	Clinical Study Data Supporting the Original PMA Approval	Number of Approved PMA Supplements Through 2019
<b>P800040</b>	Cordis	Cordis Programmable Neural Stimulator 900a	4/14/1981	Not available	9
<b>P840001</b>	Medtronic	Original PMA: Itrel Totally Implantable Spinal Cord Stimulation System  Subsequent PMA supplements: Itrel 2 Spinal Cord Stimulation System, Itrel 3 Spinal Cord Stimulation System, Itrel 4 Neurostimulation System, Synergy Spinal Cord Stimulation System, Synergy Plus+ Neurostimulation System, Synergy Compact+ Neurostimulation System, RestoreSensor Neurostimulator, RestoreUltra Neurostimulation System, RestorePrime Neurostimulation System, RestoreAdvanced Neurostimulation System, Restore Prime Advanced Neurostimulation System, Surescan MRI Neurostimulation System	11/30/1984	Open label, single-group, uncontrolled trial	432
<b>P010032</b>	Advanced Neuromodulation Systems (original PMA)  St. Jude Medical (2005)  Abbott Medical (2017)	Original PMA: Genesis Neurostimulation IPG System  Subsequent PMA supplements: Genesis G4 Neurostimulation System, Genesis RC Neurostimulation System, Eon Neurostimulation System, Eon Mini IPG Neurostimulation System, Eon C Neurostimulation System, Protégé Neurostimulation System, Proclaim Neurostimulation System, Proclaim Elite Neurostimulation System, Infinity Neurostimulation System, Prodigy MRI Neurostimulation System	11/21/2001	Literature review	143
<b>P030017</b>	Advanced Bionics Corporation (original PMA)	Original PMA: Precision Spinal Cord Stimulation System	4/27/2004	Literature review	308

	Boston Scientific (2004)	Subsequent PMA supplements: Precision Spectra Spinal Cord Stimulation System, Precision Novi Spinal Cord Stimulation System, Precision Montage MRI Spinal Cord Stimulation System, Spectra WaveWriter Spinal Cord Stimulation System			
<b>P130022</b>	Nevro Corporation	Senza Spinal Cord Stimulation System	5/8/2015	Prospective, randomized, controlled, unblinded, non-inferiority trial for assessing stimulation with 10 kHz output for intractable pain without paresthesia  Literature review for assessing stimulation with outputs between 2 and 1,200 Hz for intractable pain with paresthesia	25
<b>P130028</b>	Algostim (original PMA)  Nuvector Corporation (2016)	Algovita Spinal Cord Stimulation System	11/20/2015	Literature review	28

Abbreviations: Hz, hertz; IPG, Implantable Pulse Generator; kHz, kilohertz; MRI, magnetic resonance imaging; PMA, premarket approval application; SCS, spinal cord stimulation.  
Source: Search of the FDA's PMA database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on February 11, 2020, using the search term "LGW" in the "Product Code" field. Additional separate searches were performed using the search terms "P800040," "P840001," "P010032," "P030017," "P130022," and "P130028" in the "PMA Number" field.



The SSED for the original PMA for the Medtronic Irel device described a poorly designed, non-randomized, single-group prospective clinical trial that enrolled 80 subjects with intractable pain of the trunk or limbs.<sup>29</sup> Three subjects did not have a pulse generator implanted and were excluded from the effectiveness assessment. At the time the PMA was submitted to the FDA, effectiveness data was available for only 42 of the 80 subjects, with a mean follow-up time postimplant of only 2.9 months. Thirty-one (74%) of these 42 subjects reported 50-100% pain relief at follow-up. However, the lack of a control group, small subject number, and short-term follow-up made it impossible to adequately assess the safety and effectiveness of the device, particularly given that the device is intended to treat chronic pain. Nevertheless, the FDA approved the PMA.

In 1999, prior to submitting the third original PMA for a totally implanted spinal cord stimulator for pain relief (see Table 1), Advanced Neuromodulation Systems petitioned the FDA to reclassify totally implanted spinal cord stimulators intended for treatment of chronic intractable pain of the trunk or limbs from Class III into Class II.<sup>30</sup> The FDA subsequently referred the petition to the agency's Neurological Devices Panel of the Medical Devices Advisory Committee (the Panel). In September 1999, the Panel recommended that the devices be reclassified.<sup>31</sup> This recommendation was made over the objections of Medtronic, which wanted these devices to remain in Class III<sup>32</sup> and at the time dominated the market for totally implanted spinal cord stimulators intended for treatment of pain. The Panel identified the following as potential special controls to reasonably assure the safety and effectiveness of the devices: FDA guidance documents, voluntary consensus standards, postmarket surveillance, patient registries, device tracking, biennial manufacturing site inspections, and submission of annual reports on device failures.

---

<sup>29</sup> Food and Drug Administration. Summary of safety and effectiveness data, Medtronic's Irel Spinal Cord Stimulation System, P840001. November 30, 1984. <https://www.regulations.gov/document?D=FDA-1984-M-0018-0001>. Accessed April 7, 2020.

<sup>30</sup> Food and Drug Administration. Notice: Neurological devices; reclassification of the totally implanted spinal cord stimulator; denial of petition. April 30, 2001. 66 FR 21401-21403. <https://www.govinfo.gov/content/pkg/FR-2001-04-30/pdf/01-10619.pdf>. Accessed April 7, 2020.

<sup>31</sup> Food and Drug Administration. Neurological Devices Advisory Panel Meeting summaries. <http://web.archive.org/web/20060926074919/http://www.fda.gov/cdrh/ndp.html#91699>. Accessed on April 7, 2020. See the summary for the September 16-17, 1999 panel meeting.

<sup>32</sup> Food and Drug Administration. Transcript for the Neurological Devices Panel's September 16-17, 1999, meeting, part 4. <http://web.archive.org/web/20030329212759/http://www.fda.gov/OHRMS/DOCKETS/ac/99/transcpt/3545t2c.pdf>. Accessed April 7, 2020. PDF pages 1-8.

In September 2000, the FDA requested public comment on the Panel's recommendation<sup>33</sup> and on draft guidance on special controls for totally implanted spinal cord stimulators for pain relief.<sup>34</sup> At that time, the FDA stated that the special controls identified in the draft guidance document were sufficient to control the identified risks to health associated with these devices.<sup>35</sup> Remarkably, the FDA disagreed with the Panel's conclusion that consensus standards, postmarket surveillance, manufacturing inspections, device tracking, and patient registries were necessary special controls for these device.

But in April 2001, the FDA unexpectedly reversed its preliminary determination and decided to keep totally implanted spinal cord stimulators for pain relief in Class III.<sup>36</sup> In explaining its final decision, the agency stated that, despite its original position to the contrary, it had subsequently concluded that Class II special controls *were not* adequate to address the risks associated with these devices. In particular, the FDA noted the following:

The most serious risk to health presented by the device is the risk of device failure. Device failure is frequently the result of improper device design. Device failure always requires reoperation with all of the attendant risks of secondary surgery. Many of the comments suggested that general controls and special controls could not adequately control the risk of device failure...

Specifically, FDA determined that special controls, such as **bench and animal testing, cannot substitute for actual clinical trials designed to demonstrate the safety and effectiveness of these devices.** [Emphasis added]

Nevertheless, shortly after this decision, the FDA disregarded its own final determination and began approving original PMAs for new totally implanted spinal cord stimulators for pain relief based only on clinical data derived from published scientific medical

---

<sup>33</sup> Food and Drug Administration. Notice of panel recommendation: Neurological devices; reclassification of the totally implanted spinal cord stimulator. September 6, 2000. 65 FR 54053-54056.

<https://www.govinfo.gov/content/pkg/FR-2000-09-06/pdf/00-22618.pdf>. Accessed April 7, 2020.

<sup>34</sup> Food and Drug Administration. Notice: Draft guidance for industry; special control guidance for premarket notifications for totally implanted spinal cord stimulators for pain relief. September 6, 2000. 65 FR 54058-54059. <https://www.govinfo.gov/content/pkg/FR-2000-09-06/pdf/00-22619.pdf>. Accessed April 7, 2020.

<sup>35</sup> Food and Drug Administration. Notice of panel recommendation: Neurological devices; reclassification of the totally implanted spinal cord stimulator. September 6, 2000. 65 FR 54053-54056.

<https://www.govinfo.gov/content/pkg/FR-2000-09-06/pdf/00-22618.pdf>. Accessed April 7, 2020.

<sup>36</sup> Food and Drug Administration. Notice: Neurological devices; reclassification of the totally implanted spinal cord stimulator; denial of petition. April 30, 2001. 66 FR 21401-21403.

<https://www.govinfo.gov/content/pkg/FR-2001-04-30/pdf/01-10619.pdf>. Accessed April 7, 2020.

literature for *other* spinal cord stimulator systems, not, as would reasonably be expected, prospective clinical trials that tested the safety and effectiveness of the actual devices for which approval was being sought (see Table 1).

The first such approval occurred in November 2001 when the FDA approved the PMA for the Genesis Neurostimulation Implantable Pulse Generator (IPG) System (PMA number P010032) that was submitted by Advanced Neuromodulation Systems.<sup>37,38</sup> According to the FDA's SSED for this PMA, the only clinical study data provided to support the application was a review of 16 previously published clinical studies of *other* implanted spinal cord stimulators, three of which the agency somehow relied upon to assess the effectiveness of the Genesis Neurostimulation IPG System and all of which the agency relied upon to assess its safety.<sup>39</sup>

In addition to not providing any clinical data about the Genesis Neurostimulation IPG System, the three studies on other devices used to support effectiveness were small (involving a total of 93 patients who received permanently implanted spinal cord stimulators<sup>40</sup>), uncontrolled, open-label, and single-site, with one being a retrospective case series.<sup>41,42,43</sup> All three studies examined one or more models of the Medtronic Itriel Totally Implantable Spinal Cord Stimulation System and various permanently implanted leads. The other thirteen studies, which were included in the safety assessment, all had flaws and limitations similar to those of the three studies used to assess effectiveness and,

---

<sup>37</sup> Food and Drug Administration. Approval letter for PMA application P010032. November 21, 2001.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P010032A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P010032A.pdf). Accessed April 7, 2020.

<sup>38</sup> Advanced Neuromodulation Systems was acquired in 2005 by St. Jude Medical (see: FDANews. St. Jude cleared to acquire ANS. November 4, 2005. <https://www.fdanews.com/articles/82190-st-jude-cleared-to-acquire-ans>. Accessed April 7, 2020.), which subsequently was acquired in 2017 by Abbott (see: Abbott. Abbott completes the acquisition of St. Jude Medical. January 4, 2017.

<https://abbott.mediaroom.com/2017-01-04-Abbott-Completes-the-Acquisition-of-St-Jude-Medical>.

Accessed April 7, 2020.)

<sup>39</sup> Food and Drug Administration. Summary of safety and effectiveness data, Advanced Neuromodulation Systems' Genesis Neurostimulation (IPG) System, P010032. Approval date November 21, 2001. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P010032B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P010032B.pdf). Accessed April 7, 2020.

<sup>40</sup> *Ibid.* Note that the FDA's SSED stated that the effectiveness "studies included a total of 116 patients [who] were implanted with [a spinal cord stimulation] system," but not all these patients underwent permanent implantation of a system.

<sup>41</sup> Hassenbusch S, Stanton-Hicks M, Covington EC. Spinal cord stimulation versus spinal infusion for low back and leg pain. *Acta Neurochir Suppl.* 1995;64:109-115.

<sup>42</sup> Ohnmeiss DD, Rashbaum RF, Bogdanffy GM. Prospective outcome evaluation of spinal cord stimulation in patients with intractable leg pain. *Spine (Phila Pa 1976).* 1996;21(11):1344-1350.

<sup>43</sup> Villavicencio AT, Leveque JC, Rubin L, et al. Laminectomy versus percutaneous electrode placement for spinal cord stimulation. *Neurosurgery.* 2000;46(2):399-40.

in some cases, did not even specify the actual devices being studied<sup>44,45</sup> or included some patients who received spinal cord stimulators with external transmitters.<sup>46,47,48,49</sup>

As the FDA is well aware, such open-label, uncontrolled studies are unable to assess the magnitude of the placebo response, regression to the mean (a phenomenon in statistics in which a random variable is extreme on the first measurement but closer to the mean or average on the second measurement), or the effects of changes in medications or other treatments to alleviate pain or in the natural course of the pain disorder.<sup>50</sup> The obvious inadequacies of the data from this literature review of studies evaluating other spinal cord stimulators for pain relief precluded any meaningful assessment of the safety and effectiveness of the Genesis Neurostimulation IPG System for pain relief.

In explaining its 2001 decision to approve the PMA for the Genesis Neurostimulation IPG System, the FDA stated the following:

Although the [petition from Advanced Neuromodulation Systems] to reclassify this device type from class III (premarket approval) to class II (special controls) was subsequently denied by the Agency, much of the data and information submitted in this PMA had been carefully evaluated by FDA during the review of the reclassification petition. In fact, on September 17, 1999, FDA consulted with the Neurological Devices Panel (the Panel) during which time the Panel reviewed many of the nonclinical studies, as well as the clinical literature, that [Advanced Neuromodulation Systems] included in PMA number P010032 as evidence of their device's safety and effectiveness. While FDA disagreed with the Panel's recommendation that the device be reclassified from class III to class II, FDA acknowledged that considerable valid scientific evidence existed in the public

---

<sup>44</sup> Devulder J, De Laat M, Van Bastelaere M, Rolly G. Spinal cord stimulation: a valuable treatment for chronic failed back surgery patients. *J Pain Symptom Manage.* 1997;13(5):296-301.

<sup>45</sup> Kavar B, Rosenfeld JV, Hutchinson A. The efficacy of spinal cord stimulation for chronic pain. *J Clin Neurosci.* 2000;7(5):409-413.

<sup>46</sup> Meglio M, Cioni B, Rossi GF. Spinal cord stimulation in the management of chronic pain (A 9 year experience). *J Neurosurg.* 1989;70(4):519-524.

<sup>47</sup> Simpson BA. Spinal cord stimulation in 60 cases of intractable pain. *J Neurol Neurosurg Psychiatry.* 1991;54(3):196-199.

<sup>48</sup> Spieglemann R, Friedman WA. Spinal cord stimulation: A contemporary series. *Neurosurgery.* 1991;28(1):65-71.

<sup>49</sup> Meglio M, Cioni B, Visocchi M, et al. Spinal cord stimulation in low back and leg pain. *Stereotact Funct Neurosurg.* 1994;62(1-4):263-266.

<sup>50</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED). Nevro Corporation's Senza Spinal Cord Stimulator System, P130022. Approval date May 8, 2015.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130022B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022B.pdf). Accessed April 7, 2020.

domain that the applicant could use to streamline the PMA process and support approval of a PMA.

Upon completion of the evaluation of the information submitted in this PMA, FDA has concluded that the Genesis Neurostimulation (IPG) System is **sufficiently similar to the [spinal cord stimulation] systems reported in literature in regard to intended use, targeted patient population, technology, device design, and electrical output characteristics, that the literature can provide a basis upon which the performance of the Genesis Neurostimulation (IPG) System can be judged.** [Emphasis added] FDA has also concluded that the available published clinical studies constitute valid scientific evidence for the purposes of determining safety and effectiveness.<sup>51</sup>

The FDA subsequently approved two additional original PMAs — one for Advanced Bionics Corporation's<sup>52</sup> Precision Spinal Cord Stimulation System (PMA number P030017) in 2004<sup>53</sup> and the other for Algostim's<sup>54</sup> Algovita Spinal Cord Stimulation System (PMA number P130028) in 2015<sup>55</sup> — for which the primary clinical data used to assess the safety and effectiveness of the devices were also reviews of published studies of other spinal cord stimulator systems.<sup>56,57</sup> The literature review for Advanced Bionics Corporation's PMA cited 11 published clinical studies, seven of which had been cited in the literature review for the PMA for the Genesis Neurostimulation IPG System. The three studies the FDA relied upon to assess the effectiveness of Advanced Bionics Corporation's Precision Spinal Cord Stimulation System were the same flawed studies

---

<sup>51</sup> Food and Drug Administration. Summary of safety and effectiveness data, Advanced Neuromodulation Systems' Genesis Neurostimulation (IPG) System, P010032. Approval date November 21, 2001. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P010032B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P010032B.pdf). Accessed April 7, 2020.

<sup>52</sup> Advanced Bionics Corporation was acquired by Boston Scientific in 2004 (see: Boston Scientific. Boston Scientific announces acquisition of Advanced Bionics Corporation. June 1, 2004. <http://news.bostonscientific.com/news-releases?item=58598>. Accessed April 7, 2020.)

<sup>53</sup> Food and Drug Administration. Approval letter for PMA application P030017. April 27, 2004. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/P030017A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017A.pdf). Accessed April 7, 2020.

<sup>54</sup> Algostim, a subsidiary of Greatbatch, Inc., was spun-off in 2016 and became Nuvectra Corporation (see: Nuvectra. Investor relations: Corporate profile. <http://investors.nuvectramed.com/investor-relations>. Accessed April 7, 2020.)

<sup>55</sup> Food and Drug Administration. Approval letter for PMA P130028. November 20, 2015. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130028a.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028a.pdf). Accessed April 7, 2020.

<sup>56</sup> Food and Drug Administration. Summary of safety and effectiveness data. Advanced Bionics Corporation's Precision Spinal Cord Stimulator System, P030017. Approval date April 27, 2004. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/P030017B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017B.pdf). Accessed April 7, 2020.

<sup>57</sup> Food and Drug Administration. Summary of safety and effectiveness data. Algostim's Altovita Spinal Cord Stimulation (SCS) System, P130028. Approval date November 12, 2015. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130028B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028B.pdf). Accessed April 7, 2020.

the agency used to assess the effectiveness of the Genesis Neurostimulation IPG System.<sup>58,59,60</sup> The SSED for the Precision Spinal Cord Stimulation System did describe data from actual clinical experience with the device in 26 subjects who had a successful trial stimulation period, underwent permanent implantation of the system, and were followed for periods ranging from two weeks to six months.<sup>61</sup> However, the FDA did not base its decision on this clearly insufficient clinical experience with the actual device; instead, the FDA offered the following clinical assessment and justification for approval:

**The determination of the safety and effectiveness of the PRECISION™ System was based on available published clinical studies for similar implanted spinal cord stimulation systems.** FDA has concluded that these available published clinical studies constitute valid scientific evidence for the purposes of determining safety and effectiveness. Upon completion of the evaluation of the information submitted in this PMA, FDA has concluded that the PRECISION™ System is **sufficiently similar to the [spinal cord stimulation] systems reported in literature in regard to intended use, targeted patient population, technology, device design, and electrical output characteristics.**<sup>62</sup> [Emphasis added]

The literature review for Algostim's PMA cited 23 studies of varying but generally poor quality for other spinal cord stimulators, five of which were used to assess effectiveness (two of these were randomized controlled trials) and all of which were used to assess safety.<sup>63</sup> The FDA also assessed reports submitted to the agency's MAUDE database for fully implantable spinal cord stimulation systems that were deemed to be similar to the Algovita Spinal Cord Stimulation System. As with its approvals of Advanced Neuromodulation Systems' Genesis Neurostimulation IPG System and Advanced Bionics Corporation's Precision Spinal Cord Stimulation System, the FDA again offered an unacceptable justification for approving the Algovita Spinal Cord Stimulation System:

---

<sup>58</sup> Hassenbusch S, Stanton-Hicks M, Covington EC. Spinal cord stimulation versus spinal infusion for low back and leg pain. *Acta Neurochir Suppl.* 1995;64:109-115.

<sup>59</sup> Ohnmeiss DD, Rashbaum RF, Bogdanffy GM. Prospective outcome evaluation of spinal cord stimulation in patients with intractable leg pain. *Spine (Phila Pa 1976).* 1996;21(11):1344-1350.

<sup>60</sup> Villavicencio AT, Leveque JC, Rubin L, et al. Laminectomy versus percutaneous electrode placement for spinal cord stimulation. *Neurosurgery.* 2000;46(2):399-40.

<sup>61</sup> Food and Drug Administration. Summary of safety and effectiveness data. Advanced Bionics Corporation's Precision Spinal Cord Stimulator System, P030017. Approval date April 27, 2004.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/P030017B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017B.pdf). Accessed April 7, 2020.

<sup>62</sup> *Ibid.*

<sup>63</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED). Algostim's Algovita Spinal Cord Stimulation (SCS) System, P130028. FDA Notice of Approval date November 13, 2015.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130028B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028B.pdf). Accessed April 7, 2020.

The results from the clinical evaluation support reasonable assurance of the safety and efficacy of the Algovita [Spinal Cord Stimulation] System, as well [as] its long-term performance, when used in a manner consistent with its labeling and intended use. **The evidence supporting the safety and effectiveness of the Algovita [Spinal Cord Stimulation] System is based on a foundation of 30 years of clinical research and experience as documented in the literature with fully implantable [spinal cord stimulation] systems and the similarities of the Algovita system to market-released implantable [spinal cord stimulation] systems.**<sup>64</sup> [Emphasis added]

The FDA essentially treated the Genesis Neurostimulation IPG System, Precision Spinal Cord Stimulation System, and Algovita Spinal Cord Stimulation System as Class II devices and allowed them to be marketed based on the type of “substantial equivalence” determination that would be made under the 510(k) premarket notification process, rather than on prospective clinical trials designed to evaluate the safety and effectiveness of the actual devices themselves that would typically occur for Class III devices. As a result, the FDA subverted the PMA process intended for such permanently implanted high-risk devices.

Notably, Advanced Neuromodulation Systems later successfully defended itself against a patient injury lawsuit related to its spinal cord stimulator based on a federal preemption defense — the notion that FDA approval of the PMA for the device overrides state-law claims based on defective design or inadequate product labeling.<sup>65</sup>

The Institute of Medicine (IOM; now the National Academy of Medicine) in its 2011 report, *Medical Devices and the Public’s Health: The FDA’s 510(k) Clearance Process at 35 Years*, concluded that the legal standard used by the FDA for clearance of Class II medical devices under the 510(k) process — “substantial equivalence” to a predicate device already on the market — failed to ensure that devices are safe and effective and needed to be replaced.<sup>66</sup> The IOM likely would have been appalled to learn that the FDA, in violation of the 1976 Medical Device amendments for the approval of Class III devices, had extended use of the substantial equivalence standard for Class II devices to the PMA process.

Additionally, as Public Citizen documented in its 2016 report, *A Risky Shortcut: Proposal to Permit the FDA to Rely on Journal Articles to Approve High-Risk Medical Devices is*

---

<sup>64</sup> *Ibid.*

<sup>65</sup> Supreme Court of Mississippi. *Sanders v. Advanced Neuromodulation Systems*. No. 2009-CA-00594-SCT. April 30, 2010. <https://courts.ms.gov/images/Opinions/CO64676.pdf>. Accessed on April 7, 2020.

<sup>66</sup> Institute of Medicine. *Medical Devices and the Public’s Health: The FDA 510(k) Clearance Process at 35 Years*. 2011. Washington, DC: The National Academies Press.

*Misguided*, basing high-risk medical device approvals on information from published scientific medical literature is fraught with pitfalls.<sup>67</sup> Many peer-reviewed scientific articles often contain errors, omissions, misrepresentations or fraudulent information. Conflicts of interest between authors of peer-reviewed journal articles and device manufacturers may increase the likelihood of such problems occurring.

Since 2001, the only totally implanted spinal cord stimulator for pain relief for which the approval of an original PMA was not based solely or primarily on clinical data derived from literature reviews, was the approval of Nevro Corporation's Senza Spinal Cord Stimulation System (PMA number P130022) in May 2015.<sup>68</sup> The clinical data for assessing the safety and effectiveness of this device for treating intractable back pain of the trunk or limbs *without paresthesia* using a stimulation output of 10 kilohertz (kHz) came from a single prospective, randomized, controlled, unblinded, noninferiority clinical trial.<sup>69</sup> However, the clinical assessment of the safety and effectiveness of the device for treatment of pain *with paresthesia* using stimulation outputs between 2 hertz (Hz) and 1.2 kHz was based on a literature review of five small, open-label, uncontrolled trials of other spinal cord stimulators, each of which had been cited in the literature reviews for one of more of the prior original PMAs.<sup>70</sup>

The noninferiority trial compared high-frequency (10 kHz) stimulation using the Senza Spinal Cord Stimulation System with traditional low-frequency stimulation (2 Hz to 1.2 kHz) (90 subjects) with a legally marketed permanently implanted spinal cord stimulator from a single manufacturer that was not identified in the SSED (71 subjects).<sup>71</sup> The primary endpoint was a composite endpoint that was flawed because it combined an effectiveness parameter with a safety parameter; specifically, the percentage of patients who responded to the therapy for back pain and did not have stimulation-related neurological deficits.<sup>72</sup> Seventy-five percent of the test group subjects and 38% of the control subjects met this ill-defined primary endpoint, a difference which met the

---

<sup>67</sup> Public Citizen. A Risky Shortcut: Proposal to Permit the FDA to Rely on Journal Articles to Approve High-Risk Medical Devices is Misguided. February 9, 2016.

<https://www.citizen.org/sites/default/files/risky-shortcut-FDA-medical-device-report-2016.pdf>. Accessed April 7, 2020.

<sup>68</sup> Food and Drug Administration. Food and Drug Administration. Approval letter for PMA application P130022. May 8, 2015. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130022A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022A.pdf). Accessed April 7, 2020.

<sup>69</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED). Nevro Corporation's Senza Spinal Cord Stimulator System, P130022. Approval date May 8, 2015.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130022B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022B.pdf). Accessed April 7, 2020.

<sup>70</sup> *Ibid.*

<sup>71</sup> *Ibid.*

<sup>72</sup> *Ibid.*



noninferiority margin.<sup>73</sup> However, as the FDA acknowledged, the lack of blinding may have resulted in investigator and subject bias, which may have accounted for the lower response rates seen in the control group than those reported in the literature.<sup>74</sup>

---

<sup>73</sup> *Ibid.*

<sup>74</sup> *Ibid.*

## V. PMA Supplement Process for Class III Spinal Cord Stimulators for Pain Relief: Misused and Lacking Transparency

After a PMA is approved, the applicant in general must submit a PMA supplement for review and approval by the FDA before making any change affecting the safety or effectiveness of the device.<sup>75</sup> Such changes include, but are not limited to, new indications for use of the device; labeling changes; use of a different facility or establishment to manufacture, process, or package the device; changes in sterilization procedures; changes in packaging; changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device; and extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not yet been approved by FDA.

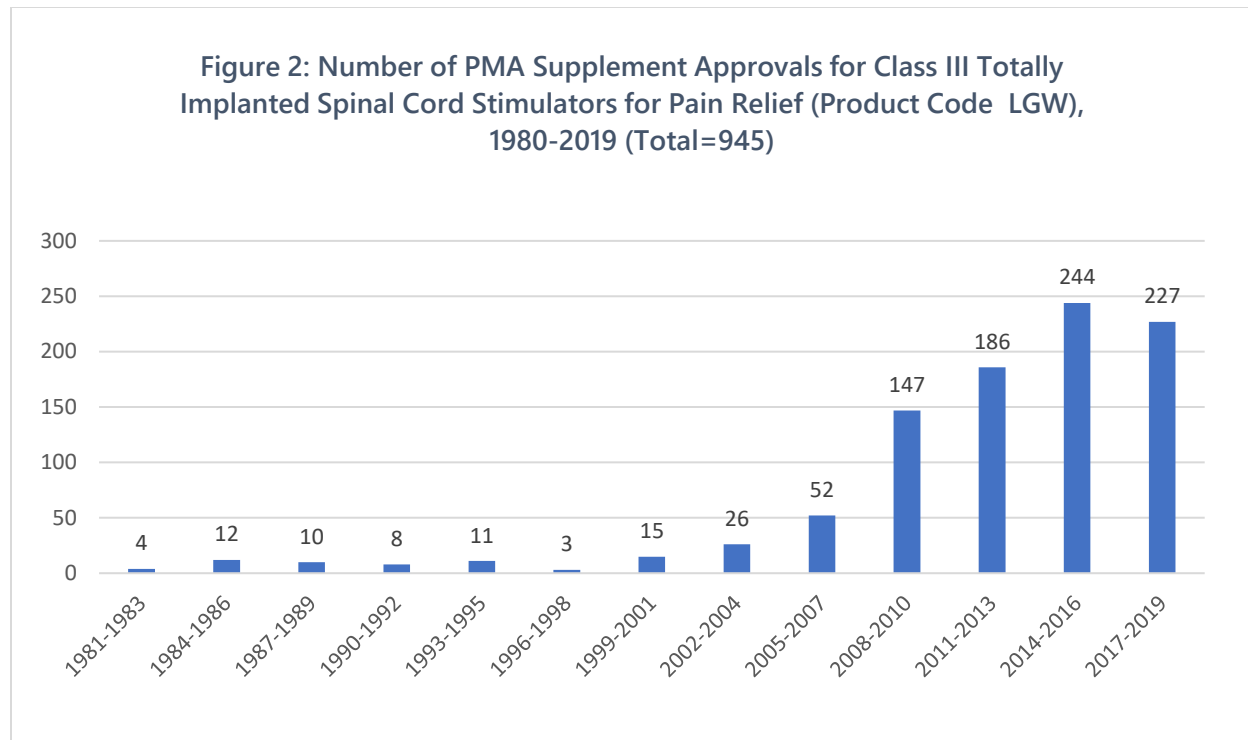
From 1980 to 2019, the FDA approved, 945 of 1,008 submitted PMA supplements for the six PMAs for Class III totally implanted spinal cord stimulators for pain relief (product code LGW) listed in Table 1. This represented an approval rate of 94% by the end of 2019.<sup>76</sup> The actual PMA supplement approval rate is slightly higher because some supplements the FDA received prior to the end of 2019 have since been or will be approved in 2020 or later. Figure 2 shows the number of such approvals by three-year intervals. Since 2000, the rate of these PMA supplement approvals has steadily increased. In the most recent three-year period included in our analysis (2017-2019), the PMA supplement approval rate was approximately 1.5 per week, whereas prior to 2001 the approval rate averaged less than three per year, which represents a 28-fold increase in the rate of approvals.

---

<sup>75</sup> 21 C.F.R. § 814.39.

<sup>76</sup> Food and Drug Administration. Premarket approval (PMA) database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. Searched on February 11, 2020, using the search terms "P800040," "P840001," "P010032," "P030017," "P130022," and "P130028" in the "PMA Number" field. The most recently submitted supplements that were approved prior to the end of 2018 were P800040/S09, P840001/S416, P010032/S145, P030017/S321, P130022/S018, P130028/S022. The following nine supplements submitted before the end of 2018 were subsequently approved in 2019: P840001-S418, S417, S419, S406, S384, and S405; P010032-S146 and S147; and P130022-S019.



Source: Search of the FDA's PMA database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on February 11, 2020, using the search term "LGW" in the "Product Code" field. Additional separate searches were performed using the search terms "P800040," "P840001," "P010032," "P030017," "P130022," and "P130028" in the "PMA Number" field.

A search of the FDA's PMA database<sup>77</sup> reveals that numerous new models of totally implanted spinal cord stimulators for pain relief have been approved via PMA supplements.<sup>78</sup> Other PMA supplements were for changes to the design of stimulator leads, pulse generators, batteries, software, and other device components; labeling changes, including new indications for use; and modifications to manufacturing facilities and manufacturing procedures, among other things.

The scope of device changes being approved under PMA supplements is troubling in two respects. First, the FDA's review process for PMA supplements appears to be even less rigorous than the deficient review process for original PMAs.<sup>79</sup> Second, in contrast to the approval of original PMAs, there is a lack of transparency regarding the full nature of the

<sup>77</sup> Food and Drug Administration. Premarket approval (PMA) database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. Searched on February 11, 2020, using the search term "LGW" in the "Product Code" field.

<sup>78</sup> As another example, PMA supplements were used to approve numerous new models of cardiac implantable electronic devices — including pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices — as safe and effective without requiring new clinical data. See: Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012. *JAMA*. 2014;311(4):385-391.

<sup>79</sup> *Ibid.*

changes proposed in PMA supplements and the FDA's review and assessment of those changes. In particular, the FDA in general does not make publicly available on its website either SSEDs or summary review memos for approved PMA supplements, except for a small fraction of PMA summary review memos for 180-day design changes for approved PMA devices.<sup>80</sup> Of the 876 supplements for totally implanted Class III spinal cord stimulators for pain relief that were approved by the FDA from 1980 to 2018, we found only one SSED<sup>81</sup>, no PMA annual reports (which also describe device changes),<sup>82</sup> and no summary review memos on the agency's website. As a result, the features of the new models of totally implanted spinal cord stimulators for pain relief approved under the PMA supplement process and the evidence supporting their safety and effectiveness contained in the PMA supplements cannot be discerned from the information posted on the FDA's website.

Some of the most significant changes to device design and labeling for FDA-approved totally implanted Class III spinal cord stimulators for pain relief under the PMAs now held by Medtronic Neuromodulation, Abbott Medical, and Boston Scientific are listed in Tables 2 to 4. The changes include multiple new models of totally implanted spinal cord stimulators, pulse generators, and electrode leads, as well as new indications for use. The manufacturers of these devices tout improvements that include new electrodes, pulse generators, placements, stimulation waveforms, stimulation algorithms, electrode combinations, sub-perception of stimulation, numbers of electrode contacts, magnetic resonance imaging compatibility and safety, and adaptive stimulation.<sup>83,84,85</sup>

---

<sup>80</sup> Food and Drug Administration. Premarket approval (PMA) Summary Review Memos for 180-day design changes. December 19, 2017.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pmamemos.cfm>. Accessed February 11, 2020.

<sup>81</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED), Boston Scientific Neuromodulation Corporation's Precision and Spectra WaveWriter Spinal Cord Stimulation Systems, P030017/S275. Approval date August 11, 2017.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/P030017S275B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017S275B.pdf). Accessed April 7, 2020.

<sup>82</sup> Food and Drug Administration. Guidance for industry and Food and Drug Administration staff: Annual reports for approved premarket approval applications. February 10, 2014.

<https://www.fda.gov/media/73391/download>. Accessed April 7, 2020.

<sup>83</sup> Medtronic. Spinal cord stimulation system, healthcare professionals. <https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/spinal-cord-stimulation-systems.html>. Accessed April 7, 2020.

<sup>84</sup> Abbott. Spinal column stimulation. <https://www.neuromodulation.abbott/us/en/hcp/products/spinal-column-stimulation-for-chronic-pain.html>. Accessed April 7, 2020.

<sup>85</sup> Boston Scientific. Spinal cord stimulator systems. <http://www.bostonscientific.com/content/gwc/en-US/products/spinal-cord-stimulator-systems.html>. Accessed April 7, 2020.

**Table 2: Examples of Major Changes to Medtronic’s Spinal Cord Stimulator Systems Made Only Through PMA Supplements to PMA P840001 Since the Original PMA Approval on November 30, 1984**

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S025	7/9/1992	Design change	Itrel II models 7495,7496,7441,7441NC
S037	8/29/1995	Design change	Approval of Itrel III SCS for treatment of chronic intractable pain of trunk and/or limbs
S042	11/19/1999	Design change	Approval for the Dual Chamber Itrel Synergy Neurostimulation System and Model 7459 MemoryMod Software for use with the existing Itrel III Spinal Cord Stimulation System
S045	6/13/2000	Design change	Approval for expanded indications for models 7421 Itrel, 7424 Itrel II, 7425 Itrel III, and model 7427 Synergy devices. These devices are indicated "as [a]n aid in the management of chronic intractable pain of the trunk and limbs, including chronic and intractable unilateral or bilateral pain associated with the following: failed back syndrome or low back syndrome or failed back, radicular pain syndrome or radiculopathies resulting in pain secondary to failed back..."
S047 S052	2/21/2001 8/03/2001	Labeling change - new indications	Approval for expanded indications for use of the 7421 Itrel, 7424 Itrel II, 7425 Itrel III, and 7427 Synergy spinal cord stimulation systems. These devices are now indicated "as an aid in the management of chronic intractable pain of the trunk or limbs, including unilateral or bilateral pain associated with the following: failed back syndrome or low back syndrome..., radicular pain syndrome or radiculopathies resulting in pain secondary to failed back syndrome or herniated disc, post-laminectomy pain, multiple back operations, unsuccessful disc surgery, degenerative disc disease/herniated disc pain refractory to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, complex regional pain syndrome...reflex sympathetic dystrophy...or causalgia."
S058	12/14/2001	Design change	Approval of model 7427v Synergy Versitrel dual channel implantable pulse generator
S064	09/26/2002	Design change	Approval of Pisces Z Quad leads

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S073	6/16/2004	Design change	Approval for new permanently implanted surgical lead (model 3999 hinged 2 x 4 lead)
S074	4/8/2005	Design change	Approval for the Restore rechargeable neurostimulation system
S077	4/15/2005	Design change	Approval for the Synergy Plus+ (model 7479) and Synergy Compact+ (model 7479b) neurostimulation systems
S089	3/17/2006	Design change	Approval for the model 37701 RestorePrime implantable neurostimulator
S092	7/7/2006	Design change	Approval of RestoreAdvanced and PrimeAdvanced neurostimulation systems
S097	1/8/2008	Design change	Approval of RestoreUltra rechargeable implantable neurostimulation system
S185	11/3/2011	Design change	Approval of RestoreSensor rechargeable implantable neurostimulation system
S211	5/30/2012	Design change	Approval of Itrel 4 neurostimulators, models 37703 and 37704
S219	3/20/2013	Labeling change	Approval of SureScan MRI implantable neurostimulation system (note that this appears to have been a design change as well given the approval of a new model)
S344	7/11/2017	Design change	Approval for their new Implantable Neurostimulation System for SCS called Intellis
S425	6/12/2019	Design change	Approval for modifying the Restore Clinician Programmer and changing the name to Restore Clinician Programmer, Model A71100.

Abbreviations: MRI, magnetic resonance imaging; PMA, premarket approval application; SCS, spinal cord stimulation.

Source: Search of the FDA's PMA database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on February 11, 2020, using the search term "P840001" in the "PMA Number" field.

**Table 3: Examples of Major Changes to Abbott Medical's Spinal Cord Stimulator Systems Made Through PMA Supplements to PMA P010032 Since the Original PMA Approval on November 21, 2001**

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S002	7/16/2002	Design change	Approval of Genesis XP and Genesis Dual XP neurostimulation systems
S006	12/23/2002	Design change	Approval of Genesis G4 neurostimulation system (model 3604)
S009	1/20/2004	Design change	Approval for the use of the Axxess percutaneous lead, models 4143, 4146, 4153, and 4156
S012	11/9/2004	Design change	Approval for the Genesis RC neurostimulation system, model 3708, and Genesis RC Dual (IPG) neurostimulation system, model 3744

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S014	3/4/2005	Design change	Approval for the Eon neurostimulation system, model 3716
S016	5/5/2005	Design change	Approval for the Genesis dual 4-channel implantable pulse generator, model 3643
S020	6/11/2007	Design change	Approval for the use of the Tripole 8, Tripole 8C, Tripole 16C, and Exclaim 8 Lamitrode series leads, models 3208, 3210, 3214, and 3224
S021	12/10/2007	Design change	Approval of ANS Eon C (IPG) neurostimulation system
S023	3/28/2008	Design change	Approval for the Eon Mini IPG neurostimulation system, model 3788
S048	4/10/2012	Design change	Approval for modifications to electrode design of S-series Lamitrode lead, models 3243, 3246, 3283, 3286, 3266, and 3268
S085	4/22/2015	Design change	Approval for the Protégé MRI IPG model 3771 and updated labeling that will allow patients to undergo MRI scans
S096	11/2/2015	Design change	Approval of Proclaim neurostimulation system
S125	7/21/2017	Design change	Enabling the Burst stimulation feature (marketed as BurstDR stimulation) for Proclaim IPGs with Medtronic headers
S135	12/9/2017	Design change	Approval for enabling the BurstDR stimulation feature on the already-implanted Eon family devices
S147	3/26/2019	Design change	Approval for design changes including increasing the thickness of the polyimide substrate and decreasing the thickness of the polyimide coverfilm on the Flex Printed Circuit Board (PCB) on the Spinal Cord Stimulation External Pulse Generator (SCS EPG) header, model 3032

Abbreviations: IPG, implantable pulse generator; MRI, magnetic resonance imaging; PMA, premarket approval application.

Source: Search of the FDA's PMA database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on February 11, 2020, using the search term "P010032" in the "PMA Number" field.

**Table 4: Examples of Major Changes to Boston Scientific's Spinal Cord Stimulator Systems Made Through PMA Supplements to PMA P030017 Since the Original PMA Approval on April 27, 2004**

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S002	10/1/2004	Design change	Approval for the model SC-1110 implanted pulse generator (IPG) and the model SC-5210 remote control and updates to the clinician programmer
S008	8/18/2005	Design change	Approval for Artisan 2 x 8 paddle lead, model SC-8116-XX

Supplement Number	Approval Date	Reason for Supplement	Description From Title or Approval Statement and Other Notable Information
S015	11/17/2006	Design change	Approval for the implanted pulse generator IPG 2.2
S119	10/21/2011	Design change	Approval for the Infinion 1x16 percutaneous lead and 2x8 splitter
S134	12/21/2012	Design change	Approval for the Precision Spectra SCS System
S275	8/11/2017	Labeling change	Approval for expanding indications to Complex Regional Pain Syndrome Types I and II and the following associated conditions and etiologies: radicular pain syndrome, radiculopathies resulting in pain secondary to failed back syndrome or herniated disc, epidural fibrosis, degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions), arachnoiditis, and multiple back surgeries
S297	12/21/2017	Labeling change	Approval for labeling changes associated with the demonstrated safety and effectiveness of subperception therapy

Abbreviations: MRI, magnetic resonance imaging; PMA, premarket approval application; SCS, spinal cord stimulation.

Source: Search of the FDA's PMA database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> on February 11, 2020, using the search term "030017" in the "PMA Number" field.

The only supplement for which an SSED was posted on the FDA website was one that substantially expanded the indications for the Boston Scientific Precision (five separate models) and Spectra Wavewriter Spinal Cord Stimulation Systems (P030017/S275, approved August 11, 2017).<sup>86</sup> The approved indication for Boston Scientific's totally implanted spinal cord stimulators under the original PMA for the first Precision Spinal Cord Stimulation System was as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain. PMA supplement P030017/S275 expanded the indications for several Boston Scientific models of spinal cord stimulators to complex regional pain syndrome, Types I and II, and the following associated conditions and etiologies: radicular pain syndrome, radiculopathies resulting in pain secondary to failed back syndrome or herniated disc, epidural fibrosis, degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions), arachnoiditis, and multiple back surgeries.

<sup>86</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED), Boston Scientific Neuromodulation Corporation's Precision and Spectra Wavewriter Spinal Cord Stimulation Systems. P030017/S275. Approval date August 11, 2017.

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/P030017S275B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017S275B.pdf). Accessed April 7, 2020.



Importantly, the clinical data to support the safety and effectiveness of using the six Boston Scientific spinal cord stimulators for these new indications once again was derived from a literature review of published studies, most of which assessed the safety and effectiveness of other such devices and all of which had serious design flaws, such as a lack of a control group.<sup>87</sup> For example, the literature review for the effectiveness assessment cited 22 papers reporting data from 19 studies that were published from 1982 to 2013. Eleven were uncontrolled retrospective case series, five were uncontrolled prospective studies, and three were small randomized controlled trials that enrolled a total of 214 subjects, 105 of whom were randomly assigned to receive a spinal cord stimulator. Only two small uncontrolled studies assessed the effectiveness of an Advanced Bionics/Boston Scientific totally implanted spinal cord stimulator. One prospective study conducted prior to the approval of Advanced Bionics' original PMA involved 49 subjects who were implanted with Advanced Bionics' original Precision Spinal Cord Stimulation System,<sup>88</sup> and one retrospective study involved 10 subjects, only some of whom received a Boston Scientific spinal cord stimulator.<sup>89</sup> Such low-quality clinical evidence was insufficient for assessing the safety and effectiveness of the six Boston Scientific totally implanted spinal cord stimulation systems for the proposed expanded indications for use.

For the two most recently approved totally implanted Class III spinal cord stimulators for pain relief manufactured by Nevro Corporation and Nuvectra Corporation (no tables shown), the number of PMA supplements to date is small, and the only major design or labeling change made appears to be for Nevro Corporation's Senza Spinal Cord Stimulation System (PMA P130022), for which the FDA approved supplement S019 for conditional magnetic resonance labeling for the pulse generator.<sup>90</sup>

---

<sup>87</sup> *Ibid.*

<sup>88</sup> Oakley JC, Krames ES, Prager JP, et al. A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study. *Neuromodulation* 2007;10:262-278.

<sup>89</sup> Verdolin MH, Stedje-Larsen ET, Hickey AH. Ten consecutive cases of complex regional pain syndrome of less than 12 months duration in active duty United States military personnel treated with spinal cord stimulation. *Anesth Analg.* 2007;104(6):1557-1560.

<sup>90</sup> Food and Drug Administration. Premarket approval (PMA) database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm>. Searched on February 14, 2020, using the search terms "P13022" and "P130028" in the "PMA Number" field.

## VI. The Opioid Overdose Epidemic: An Obvious Factor Driving the Accelerated Rate of PMA Supplement Approvals for Spinal Cord Stimulators for Pain Relief

An important factor that is certainly contributing to the accelerated rate of FDA approvals of PMA supplements for totally implanted spinal cord stimulators for pain relief is the ongoing opioid overdose epidemic<sup>91,92</sup> and the increasing push for the development and use of non-opioid treatments for pain. The proportion of adults reporting painful health conditions went from 34.2% in 2001-2002 to 41.0% in 2013-2014, whereas the use of strong opioids specifically for pain management among adults with severe pain-related interference associated with their painful conditions more than doubled from 11.5% in 2001-2002 to 24.3% in 2013/2014.<sup>93</sup> According to the Centers for Disease Control and Prevention, from 1999 to 2018, nearly 450,000 people died from an overdose involving any opioid, including prescription and illicit opioids.<sup>94</sup>

In the midst of the opioid crisis, medical device companies and medical centers that implant spinal cord stimulators increasingly have been marketing spinal cord stimulation as an alternative to opioids for chronic pain (for example, see the promotional materials from Abbott<sup>95</sup> and Medtronic<sup>96</sup>). In addition, in 2018, the FDA announced an initiative to spur the development of medical devices to target pain, addiction, and opioid diversion.<sup>97</sup> The announcement boasted that “In the past few years, the FDA has cleared, granted, or approved more than 200 devices related to the treatment or management of pain, including 10 with new or novel technologies, such as brain and spinal cord stimulators that can relieve pain and reduce the need to administer opioid drugs to patients suffering

---

<sup>91</sup> Manchikanti L, Helm S 2nd, Fellows B, *et al.* Opioid epidemic in the United States. *Pain Physician*. 2012;15(3 Suppl):ES9-38.

<sup>92</sup> Nahin RL, Sayer B, Stussman BJ, Feinberg TM. Eighteen-year trends in the prevalence of, and health care use for, noncancer pain in the United States: Data from the Medical Expenditure Panel Survey. *J Pain*. 2019;20(7):796-809.

<sup>93</sup> *Ibid.*

<sup>94</sup> Centers for Disease Control and Prevention. Opioid overdose: Understanding the epidemic. March 19, 2020. <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Accessed April 7, 2020.

<sup>95</sup> Abbott. For chronic pain, a non-opioid alternative. <https://www.lifetothefullest.abbott/en/articles/for-chronic-pain--a-non-opioid-alternative.html>. Accessed on April 7, 2020.

<sup>96</sup> Medtronic. A non-opioid option for chronic pain. <https://www.medtronic.com/us-en/about/news/pain-patient-story.html>. Accessed April 7, 2020.

<sup>97</sup> Food and Drug Administration. FDA news release: As part of efforts to combat opioid crisis, FDA launches innovation challenge to spur development of medical devices – including digital health and diagnostics – that target pain, addiction and diversion. May 30, 2018. <https://www.fda.gov/news-events/press-announcements/part-efforts-combat-opioid-crisis-fda-launches-innovation-challenge-spur-development-medical-devices>. Accessed April 7, 2020.

from either acute or chronic pain.” Importantly, no evidence was provided that spinal cord stimulators reduce the use of opioids.

It is noteworthy that lax standards for FDA approval of opioids helped to fuel the opioid overdose epidemic.<sup>98</sup> But the FDA’s lax oversight and speedier approvals of implanted spinal cord stimulators for pain relief may be creating a separate public health problem in which these devices are being used widely without sufficient evidence of benefit while exposing patients to increased risk of serious injury, as discussed below.

---

<sup>98</sup> Wolfe SM, Brown RE. Requesting an Immediate Moratorium on the Approval of New Drug Applications for New Opioids or New Opioid Formulations. Citizen Petition. Public Citizen March 21, 2019. <https://www.citizen.org/wp-content/uploads/2474.pdf>. Accessed April 7, 2020.

## VII. Adverse Events Caused by Implanted Spinal Cord Stimulators for Pain Relief: Evidence of Substantial Harm

### *A. Published Reports of Adverse Events*

The frequency of adverse events caused by implanted spinal cord stimulators for pain relief has been described in published literature reviews that analyzed data from multiple clinical studies.<sup>99,100,101,102</sup> Eldabe et al. (2016) reviewed studies, including several prior systematic reviews, published up to December 2014 that reported complications associated with the use of implanted spinal cord stimulators.<sup>103</sup> They found an overall complication rate of 30% to 40%. They reported lead migration as the most common complication of spinal cord stimulation ranging from 2 to 27% across 10 published studies. The largest study included in Eldabe et al's review was a 2004 review by Cameron<sup>104</sup> that included adverse event data from 51 studies with an overall population of 2,972 patients, which documented a lead migration rate of 13%. Other common complications reported by Eldabe et al were lead fracture rates (rate range of 0 to 10%; 9% in the 2004 Cameron review), implant-related pain (rate range of 1 to 12%; 1% in the 2004 Cameron review), and infection (rate range 3% to 10%; 3% in the 2004 Cameron review).<sup>105,106</sup>

As previously noted, original PMAs for totally implanted spinal cord stimulators for pain relief routinely relied on literature reviews to provide clinical data to support the safety and effectiveness of the devices. The literature review for Algostim's PMA for the Algovita Spinal Cord Stimulation System (P130028) — the most recent original PMA for a totally implanted spinal cord stimulator for pain relief approved by the FDA — showed

---

<sup>99</sup> Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg.* 2004;100(3 Suppl Spine):254–267.

<sup>100</sup> Compton AK, Shah B, Hayek SM. Spinal cord stimulation: a review. *Curr Pain Headache Rep.* 2012;16(1):35-42.

<sup>101</sup> Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg.* 2014;82(6):1359-1368.

<sup>102</sup> Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature. *Pain Med.* 2016;17(2):325-336.

<sup>103</sup> *Ibid.*

<sup>104</sup> Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg (Spine 3).* 2004;100:254–267.

<sup>105</sup> Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature. *Pain Med.* 2016;17(2):325-336.

<sup>106</sup> Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review.

*J Neurosurg.* 2004;100(3 Suppl Spine):254–267.

an overall surgical revision<sup>107</sup> rate of 26%; an overall rate of surgical explantation (removal of the implanted spinal cord stimulation system) without system replacement of 5%; and an overall rate of explantation with eventual replacement with a new system of 5%.<sup>108</sup> The most common reason for revision surgery was lead migration (41% of procedures), and the most common reason for surgical explantation with or without system replacement was infection (75% and 63% of procedures, respectively).

Other common adverse events caused by implanted spinal cord stimulators for pain relief that have been reported in literature reviews include pain at the pulse generator implantation site (reported rates of 0.9% to 12%), subcutaneous hematoma and seroma (reported rates up to 9%), electrode fracture (reported rates 3% to 9%), and cerebrospinal fluid leakage (reported rates of 0.3% to 7%).<sup>109</sup> Infrequent-to-rare serious complications include unexplained temporary paralysis (reported rate of 1.8%), nerve root or spinal cord injury, spinal epidural hematoma (reported rate of 0.2%), chronic spinal cord compression, skin erosion, and allergic reactions.

One rare but particularly troubling adverse event is chronic scar tissue formation around epidural leads, which can cause spinal compression and myelopathy with various forms of paresis and sensory loss. These events develop over time in correctly implanted epidural leads. Scranton et al (2014) described a case of spastic quadriparesis (arms and legs being involved) caused by cervical spinal cord compression due to fibrosis and granuloma around spinal cord stimulator leads in a 41-year-old woman.<sup>110</sup> Device effectiveness was lost at four months after stimulator implantation, and symptoms of cord compression began five months later. Similarly, Dimar et al (2016) reported cervical spinal cord compression caused by silicone granuloma formation 10 years after implantation of a spinal cord stimulator in a 61-year-old man.<sup>111</sup> Here the silicone insulation of a lead degraded and triggered formation of a foreign body granuloma and fibrous tissue mass, compressing the spinal cord, which resulted in progressive paresthesia, numbness, and weakness of the patient's upper extremities. Multiple other

---

<sup>107</sup> *Revision* was defined as "any surgical procedure required that did not involve complete explant of the system for adverse events such as lead failure/fracture, battery replacement, or [implantable pulse generator] change-out."

<sup>108</sup> Food and Drug Administration. Summary of safety and effectiveness data (SSED). Algostim's Algovita Spinal Cord Stimulation (SCS) System, P130028. FDA Notice of Approval date November 13, 2015. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130028B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028B.pdf). Accessed April 7, 2020.

<sup>109</sup> Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg*. 2014 Dec;82(6):1359-1368.

<sup>110</sup> Scranton RA, Skaribas IM, Simpson RK. Spinal stimulator peri-electrode masses: case report. *J Neurosurg Spine*. 2015;22(1):70-74.

<sup>111</sup> Dimar JR, Endriga DT, Carreon LY. Osteolysis and cervical cord compression secondary to silicone granuloma around a dorsal spinal cord stimulator: A case report. *J Neurol Surg Rep*. 2016;77(2):e67-72.

cases of spinal cord compression have been reported in the literature and were reviewed by Tamimi et al (2017).<sup>112</sup>

### *B. Adverse Event Reports Filed in the FDA's MAUDE Database*

Under FDA regulations at 21 C.F.R. Part 803, device manufacturers, importers, and user facilities have the following mandatory reporting obligations:

- Manufacturers are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury or when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
- Importers are required to report to the FDA when they learn that one of their devices may have caused or contributed to a death or serious injury and are required to report to the manufacturer if their imported devices have malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
- Device user facilities (hospitals, ambulatory surgical facilities, nursing homes, outpatient diagnostic facilities, and outpatient treatment facilities, which are not physicians' offices) must report a suspected medical-device-related death to both the FDA and the manufacturer and must report a medical-device-related serious injury to the manufacturer (or to the FDA if the medical device manufacturer is unknown).<sup>113</sup>

User facilities are not required to report device malfunctions but can voluntarily advise the FDA of such product problems using the voluntary MedWatch program.<sup>114</sup>

The FDA maintains the MAUDE database, which contains mandatory reports of medical device adverse events and failures filed by device manufacturers (since August 1996) and by user facilities (since 1991).<sup>115</sup> The database also includes voluntary reports filed after June 1993.

---

<sup>112</sup> Al Tamimi M, Aoun SG, Gluf W. Spinal cord compression secondary to epidural fibrosis associated with percutaneously placed spinal cord stimulation electrodes: Case report and review of the literature. *World Neurosurg.* 2017;104:1051.e1-1051.e5.

<sup>113</sup> Food and Drug Administration. Medical device reporting (MDR): How to report medical device problems. July 8, 2019. <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>. Accessed April 7, 2020.

<sup>114</sup> *Ibid.*

<sup>115</sup> *Ibid.*

The FDA MAUDE database was searched for medical device adverse event reports (MDRs) regarding injuries, malfunctions, deaths, and other events associated with implanted spinal cord stimulators for pain relief using the online cloud-based software service provided by Device Events (York, PA).<sup>116</sup> The Device Events software service extracts, consolidates, and provides clear and comprehensive metrics and reports for the millions of MDRs and reports of recalls that have been filed with the FDA.<sup>117</sup> The Device Events software service provides a much more user-friendly platform for searching the MAUDE database than the MAUDE search tools available on the FDA's website, which allow for limited search terms when using the "Advanced Search" webpage, return a maximum of only 500 reports for any search, and access MDRs for only the past 10 years.<sup>118,119</sup>

Figures 3 and 4 show the total number of MDRs received by the FDA each year from 2004 to 2019 for Class II implanted spinal cord stimulators with external transmitters for pain relief (FDA product code GZB) and for Class III totally implanted spinal cord stimulators for pain relief (product code LGW), respectively, that were identified from the MAUDE database through the Device Events software service search engine.<sup>120</sup>

For the period from 2004 to 2019, there were a total of 40,457 such reports for the GZB devices and 179,917 reports for LGW devices. There were notable year-to-year fluctuations in the number of these reports received by the FDA annually for the GZB devices from 2013 to 2019 (Figure 3). For the LGW devices, there was a marked year-to-year decrease in the number of reports received by FDA from 2013 to 2014, followed by a gradual increase in the number of reports in subsequent years, reaching a maximum of nearly 30,000 in 2019 (Figure 4). The year-to-year changes in the number of reports

---

<sup>116</sup> Device Events. Homepage. <https://www.deviceevents.com/>. Accessed April 7, 2020.

<sup>117</sup> Device Events. About Us. <https://www.deviceevents.com/about-us/>. Accessed April 7, 2020.

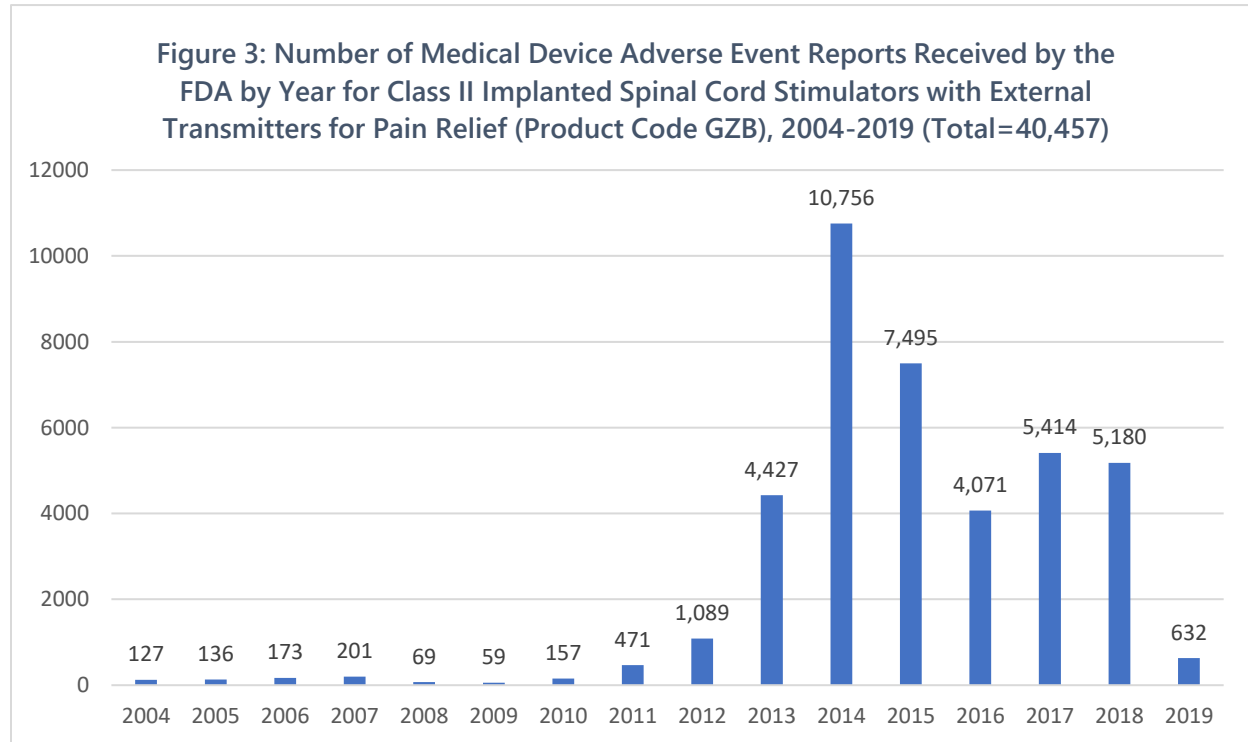
<sup>118</sup> Food and Drug Administration. MAUDE – Manufacturer and Use Facility Device Experience. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/TextSearch.cfm>. Accessed April 7, 2020.

This "Simple Search" webpage allows for text searches for medical device adverse event reports, but such text searches cannot be used for periods less than 1 year and will return a maximum of 500 results for any search.

<sup>119</sup> Food and Drug Administration. MAUDE – Manufacturer and Use Facility Device Experience. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Search.cfm>. Accessed April 7, 2020. This "Advanced Search" webpage permits searches for medical device adverse event reports for specified date ranges. Advanced Search is limited by FDA-defined search words that do not include terms related to specific patient harms (e.g., infection).

<sup>120</sup> Separate searches were performed using the Device Events software service search engine at <https://www.deviceevents.com/> with the search term "product-code:GZB" or "product-code:LGW" in the primary search field and an "FDA Received Date" from "2004-01-01." The following MDR "Report Types" were included: injury, malfunction, death, other, and blank. Reports of recalls were excluded from the analysis.

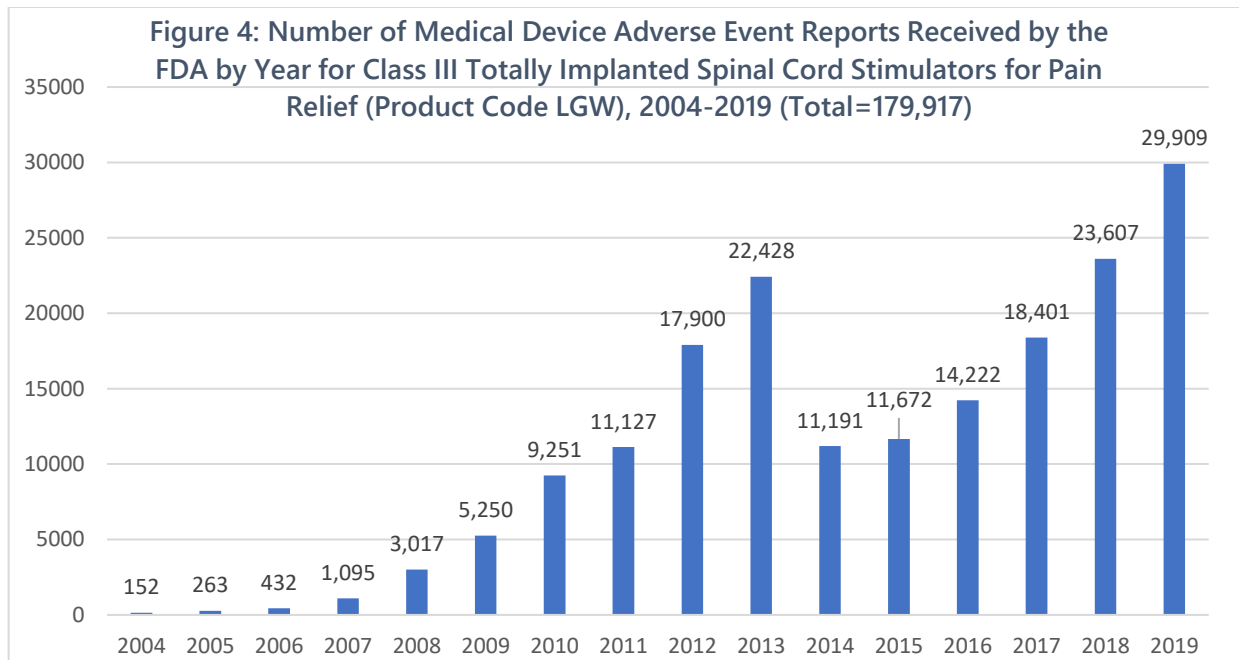
received by the FDA for the LGW devices from 2013 to 2019 were predominantly driven by year-to-year changes in the number of reports submitted by one company, Abbott Medical.<sup>121</sup>



Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term “product-code:GZB” in the primary search field. The following MDR “Report Types” were included: injury, malfunction, death, other, and blank. Two reports of recalls from the specified time period were excluded from the analysis.

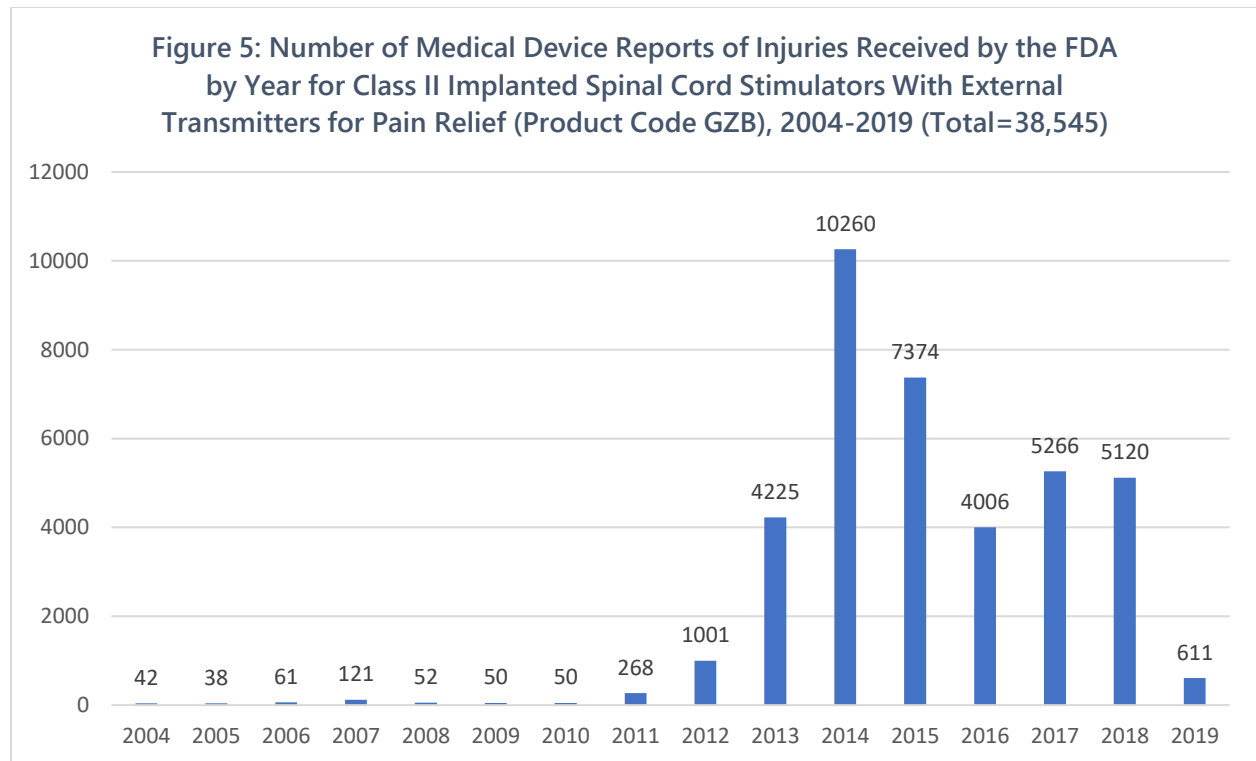
<sup>121</sup> Separate searches were performed by manufacturer for the three companies with the most numbers of reports (Abbott, Boston Scientific, and Medtronic) using the Device Events software service search engine at <https://www.deviceevents.com/> with the search for “product-code:LGW AND [company name]” in the search field on April 17, 2020. The results showed that the most marked year-to-year changes in the number of reports received by FDA after 2013 was for Abbott Medical for which the number of reports by year was as follows: 2013-12,664; 2014-322; 2015-0; 2016-1,975; 2017-4,582; 2018-8,012; 2019-14,967. Reports for Boston Scientific were: 2013-2,488; 2014-2,665; 2015-2,937; 2016-3,140; 2017-3,932; 2018-4,112; 2019-6,314. Reports for Medtronic were: 2013-7,235; 2014-8,189; 2015-8,679; 2016-5,802; 2017-6,312; 2018-8,195; 2019-6,452.



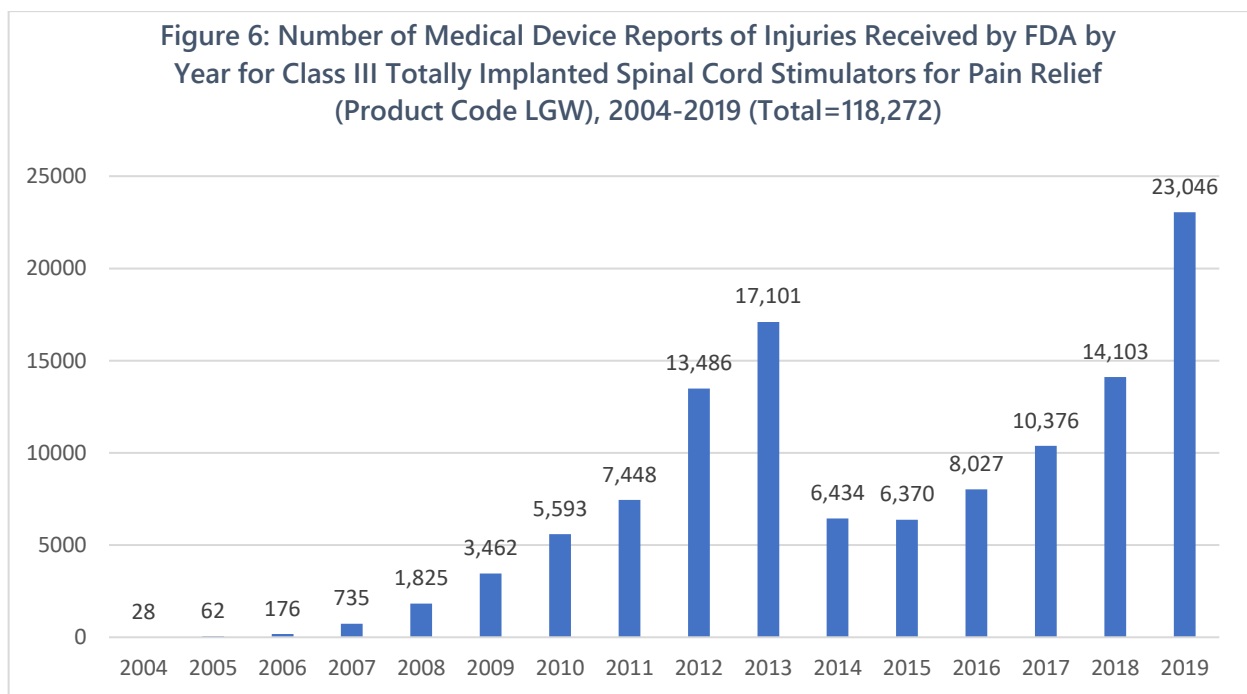


Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term "product-code:LGW" in the primary search field. The following MDR "Report Types" were included: injury, malfunction, death, other, and blank. Twenty-four reports of recalls from the specified time period were excluded from the analysis.

Figures 5 and 6 show the number of MDRs for injuries that were received by the FDA each year from 2004 to 2019 for Class II implanted spinal cord stimulators with external transmitters for pain relief (FDA product code GZB) and for Class III totally implanted spinal cord stimulators for pain relief (product code LGW), respectively. For that period, there were a total of 38,545 injury reports for GZB devices and 118,272 injury reports for the LGW devices, which represented 95% and 66%, respectively, of all MDRs submitted to the FDA for these devices.



Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term "product-code:GZB" in the primary search field. The following MDR "Report Types" were included: injury.



Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term "product-code:LGW" in the primary search field. The following MDR "Report Types" were included: injury.

Table 5 shows the search results for the number of specific types of injuries and other adverse events described in MDRs for Class II implanted spinal cord stimulators with external transmitters for pain relief (FDA product code GZB) and for Class III totally implanted spinal cord stimulators for pain relief (product code LGW) for the 16-year period 2004-2019 based on text searches of MDRs on the Device Events software service. The search terms used to search the text of the reports are presented in the Appendix and were selected based upon adverse events identified in the SSEDs for the Class III totally implanted spinal cord stimulators for pain relief and the published reports cited in section VII.A. above.

We acknowledge that using simple text searches of the MDRs to quantify the number of reports for specific types of injuries and adverse events has a number of pitfalls. Some reports will be incorrectly included in the search results, and others will be incorrectly excluded. In addition, some cases resulted in the submission of more than one report. Nevertheless, the searches of the MDRs provide an approximation of the relative frequency of the various types of injuries and adverse events associated with the use of implanted spinal cord stimulators for pain relief that were described in MDRs submitted to the FDA.

Importantly, one often cannot ascertain, based on a review of the MDR narratives, whether implantation and use of the device directly caused or contributed to the reported adverse event. However, a review of the narratives in the MDRs revealed that many of the reported serious adverse events were caused by the implantation or use of the device.

The most common types of adverse events described in the MDRs for both types of implanted spinal cord stimulators combined included infection, lead migration, heating, falls, lead fracture, inappropriate electrical shocks or shocking sensations, and headaches. The large number of reported falls associated with implanted spinal cord stimulators for pain relief raises the concern that use of the implants increases the risk of falls, which could result in traumatic injuries. Such questions regarding falls (or other adverse events) could be answered by well-controlled studies, which have not been done for these devices.

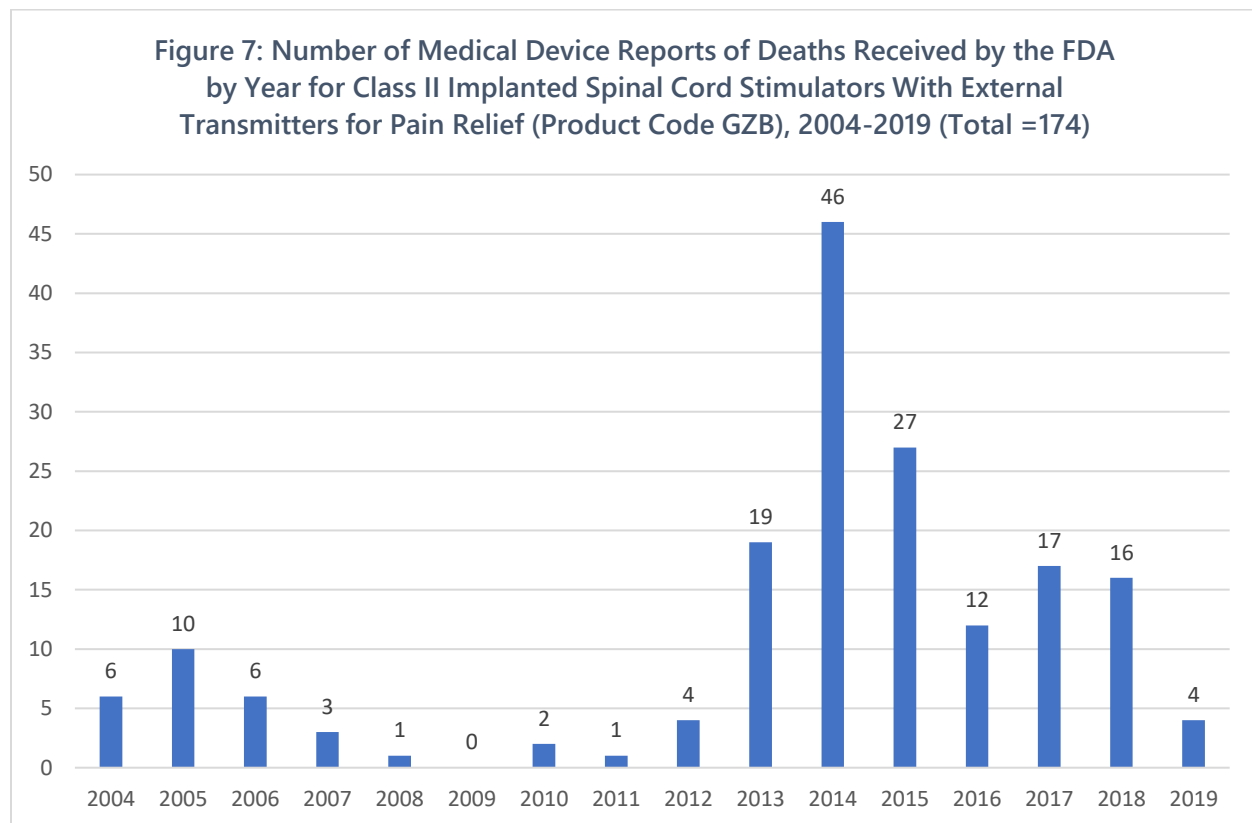
**Table 5: Number of Specific Types of Injuries and Other Adverse Events Noted in MAUDE Reports for Class II Implanted Spinal Cord Stimulators With External Transmitters for Pain Relief (FDA Product Code GZB) and for Class III Totally Implanted Spinal Cord Stimulators for Pain Relief (Product Code LGW), 2004-2019**

Specific Injury/Adverse Event	Product Code GZB Devices	Product Code LGW Devices	Total
<b>All reports</b>	40,457	179,917	220,374
<b>All injury reports</b>	38,545	118,272	156,817
<b>Revision surgery</b>	1,103	23,311	24,414
<b>Infection</b>	3,746	15,709	19,455
<b>Falls</b>	2,146	14,016	16,162
<b>Lead migration</b>	2,813	9,299	12,112
<b>Heating</b>	2,008	7,463	9,471
<b>Inappropriate shock/shocking sensations</b>	631	8,765	9,396
<b>Lead fracture</b>	1,174	4,226	5,400
<b>Headache</b>	666	2,037	2,703
<b>Hematoma</b>	294	1,183	1,477
<b>Weakness</b>	314	942	1,256
<b>Cerebral spinal fluid leak</b>	453	470	923
<b>Nausea</b>	112	490	602
<b>Dural puncture</b>	157	407	564
<b>Paralysis</b>	60	405	465
<b>Bladder problems</b>	45	407	452
<b>Seroma</b>	43	339	382
<b>Spinal cord compression</b>	45	314	359
<b>Bowel problems</b>	52	298	350
<b>Sensory loss or deficit</b>	40	118	158
<b>Suicidal behavior or thoughts</b>	9	91	100
<b>Fibrosis</b>	9	63	72
<b>Granuloma</b>	11	52	63
<b>Hemorrhage</b>	10	44	54
<b>Cauda equina</b>	1	19	20
<b>Ataxia</b>	2	6	8

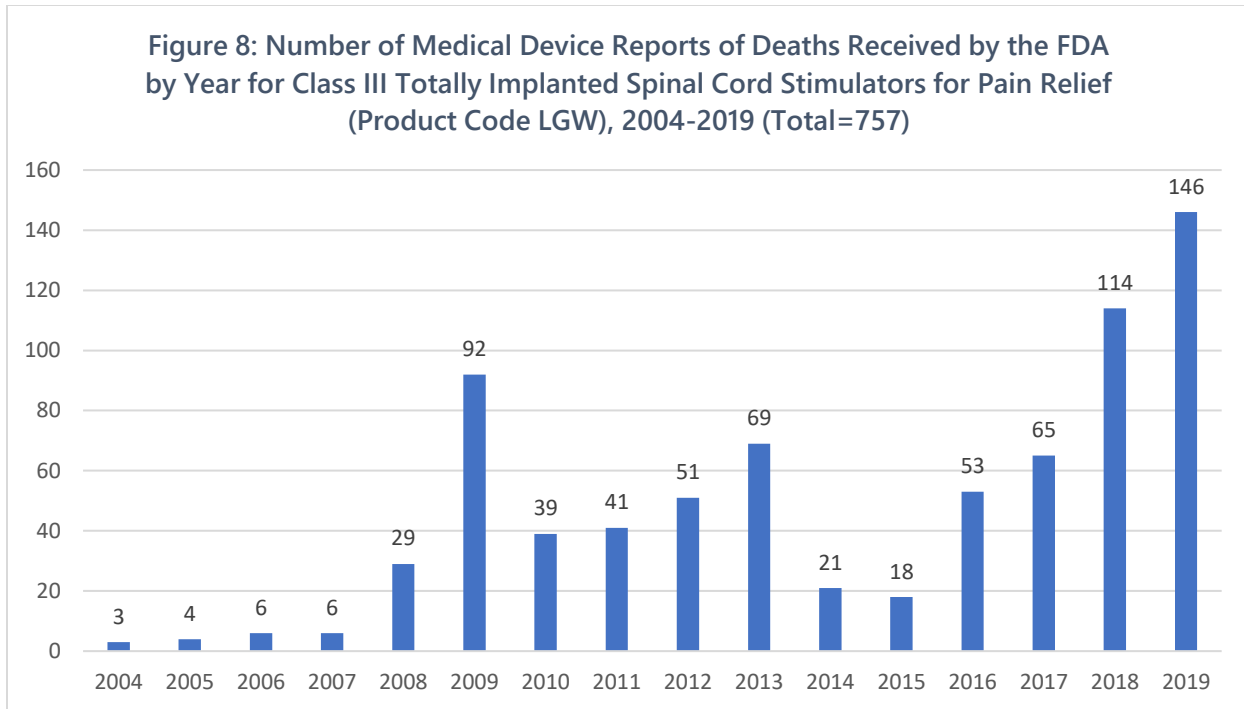
Source: Searches of the Device Events software service search engine at <https://www.deviceevents.com/> on February 12, 2020, using the search queries listed in the Appendix.

Finally, figures 7 and 8 show the number of MDRs involving deaths that were received by the FDA each year from 2004 to 2019 for Class II implanted spinal cord stimulators with external transmitters for pain relief (product code GZB) and for Class III totally implanted spinal cord stimulators for pain relief (product code LGW), respectively. For that period, there were a total of 174 such reports for GZB devices and 757 reports for the

LGW devices. The proportion of all identified MDRs for the Class II and Class III implanted spinal cord stimulators combined that involved a patient death was 0.42%. Of note, it is often not clear based on the report narratives whether the use or implantation of the device was coincidental to the death or contributed to the death. However, for a minority of the MDRs reporting patient deaths, a review of the narrative descriptions indicated that the patients died during the implantation procedure from cardiac arrest, complications related to anesthesia, or other unspecified circumstances. For a few reports, the patient died following surgery to address complications related to the devices.



Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term “product-code:GZB” in the primary search field. The following MDR “Report Types” were included: death.



Source: Search of the Device Events software service search engine at <https://www.deviceevents.com/> on February 11, 2020, using the search term “product-code:LGW” in the primary search field. The following MDR “Report Types” were included: death.

## VIII. Recalls of Implanted Spinal Cord Stimulators for Pain Relief

For the Class II implanted spinal cord stimulators with external transmitters for pain relief (product code GZB), there have been a total of five recalls from 2004 to 2019, with one each in 2006, 2008, and 2010, and two in 2014.<sup>122</sup> Four recalls were designated as Class 2 (a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote<sup>123</sup>), and one was designated as Class 3 (a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences<sup>124</sup>). Four recalls were for lead kits or lead anchors and were initiated because of incorrect information in the directions for use or package labeling. One recall was for a limited number of units of a single model of a neurostimulator and was initiated because of a minor software issue that caused an error in the indicated level of battery recharge. No adverse events were noted as being among the reasons for these recalls.

For the Class III totally implanted spinal cord stimulators for pain relief (product code LGW), there have been 44 device recalls from 2004 to 2019.<sup>125</sup> Figure 9 shows the number of these recalls by three-year intervals. Thirty-nine recalls were designated as Class 2, and five were designated as Class 3. The recalls were initiated to address a wide range of problems, including in some cases malfunctions related to the spinal cord stimulator systems, pulse generators, leads, software/programmers, and charging systems. In several cases, the reasons for initiating the recall involved adverse events, including reports of burn injuries during charging of a device; patient complaints of warmth or heating at the implantable pulse generator site during charging; and loss of the ability to recharge the device battery due to a faulty weld, which necessitated surgery to remove the device.

---

<sup>122</sup> Food and Drug Administration. Medical device recalls database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm>. Searched on February 12, 2020, using the search term “GZB” in the “Product Code” field was performed. The assigned year was based on the date the recall notice was posted on the FDA’s website.

<sup>123</sup> Food and Drug Administration. Recalls, corrections and removals (devices).

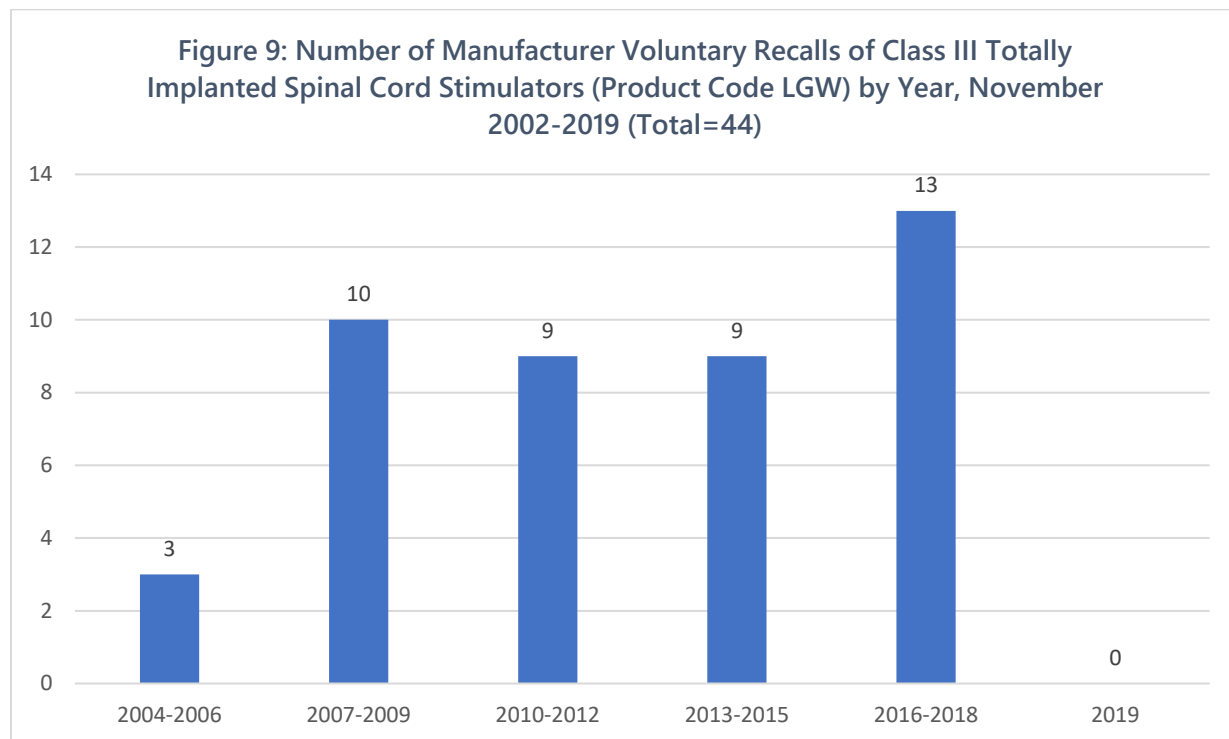
<https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices>. Accessed April 7, 2020.

<sup>124</sup> *Ibid.*

<sup>125</sup> Food and Drug Administration. Medical device recalls database.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm>. Searched on February 12, 2020, using the search term “LGW” in the “Product Code” field. Note that the search yielded one report for neurostimulators used for deep brain stimulation (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=122449>). This report was excluded from our analysis.

Notably, there were no Class 1 recalls (a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death<sup>126</sup>) for either the Class II implanted spinal cord stimulators with external transmitters for pain relief or the Class III totally implanted spinal cord stimulators for pain relief.



Source: Search of the FDA's medical device recalls database at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm> on February 12, 2020, using the search term "LGW" in the "Product Code" field. The assigned year was based on the date the recall notice was posted on the FDA's website.

<sup>126</sup> *Ibid.*



## IX. Conclusions and Recommendations

This report illustrates that the FDA's regulatory oversight of implanted spinal cord stimulators for pain relief has had serious, wide-ranging deficiencies since the enactment of the Medical Device Amendments of 1976 and is emblematic of what's wrong with the agency's oversight of medical devices and the serious harm to patients that can result.

The FDA's initial misstep was classifying preamendment implanted spinal cord stimulators with external transmitters for pain relief (product code GBZ) as Class II, thus permitting these devices to be marketed under the 510(k) premarket notification process based on a determination of substantial equivalence to an already marketed predicate device without any clinical data demonstrating that the devices were safe and effective. This decision cannot be reconciled with the agency's contradictory decisions to classify nearly identical stimulators for bladder evacuation, as well as totally implanted spinal cords stimulators for pain relief, as Class III devices, despite the fact all three device types share similar mechanisms of action and risk profiles.

With respect to the totally implanted spinal cord stimulators for pain relief (product code LGW) that were classified as Class III, at least one of the first two PMAs for these devices was approved by the FDA based on a seriously flawed clinical study. Then, starting in 2001, despite having concluded that "special controls, such as bench and animal testing, cannot substitute for actual clinical trials designed to demonstrate the safety and effectiveness of these devices," the FDA dangerously subverted the PMA process by approving a series of PMAs for these devices for which the only clinical data provided was literature reviews of poorly designed studies of *other* devices. FDA approval documents indicate that the agency essentially assessed these devices as if they were in Class II and allowed them to be marketed based on the type of "substantial equivalence" determination that would be made under the 510(k) premarket notification process, rather than on any clinical studies designed to evaluate the safety and effectiveness of the actual devices themselves that would typically occur for Class III devices.

Finally, the FDA has inexcusably misused the secretive PMA supplement process to approve multiple entirely new models of totally implanted spinal cord stimulators for pain relief, as well as major design changes and new indications for previously approved models. Documents describing the full nature of the changes, the evidence to support the changes, and the FDA's rationale for approval, with one exception out of several hundred, have not been made publicly available on the agency's website.

Against the backdrop of the FDA's dangerously lax premarket oversight of spinal cord stimulators for pain relief are a remarkable number of reports of injuries (more than 156,000 from 2004 to 2019) and deaths (931 from 2004 to 2019) associated with use of these

devices. Most of these reports were received by the FDA over the past decade, a period when the range of indications for spinal cord stimulators for pain relief expanded and the marketing of these devices as an alternative to opioids surged.

Moreover, postmarket surveillance by the FDA also appears to be deficient. In particular, given the large number of serious adverse events associated with the use of implanted spinal cord stimulators for pain relief, the relatively small number of recalls and the lack of any Class 1 recalls is troubling and suggests inadequate postmarket surveillance by the agency.

Taken together, the observations summarized in this report demonstrate that there is not a reasonable assurance that implanted spinal cord stimulators for pain relief with product codes GBZ or LGW are safe and effective for their FDA-cleared or FDA-approved uses.

To better ensure the safety and effectiveness of implanted spinal cord stimulators for pain relief, we recommend that the FDA take the following actions:

- (1) Initiate the regulatory actions needed to reclassify and more tightly regulate implanted spinal cord stimulators with external transmitters for pain relief (product code GZB) from Class II to Class III and require PMA submission for all such devices currently on the market.
- (2) Publicly provide a reliable list of adverse events and the number of their occurrences for each implanted spinal cord stimulator model and lead kit.
- (3) Reassess the safety of all implanted spinal cord stimulators for pain relief and determine whether any of them should be removed from the market.
- (4) Require original PMA submissions for all new models of these devices rather than allowing use of the supplemental PMA process for such approvals.
- (5) Require appropriately designed, prospective, randomized, controlled clinical trials for any future PMA submissions for implanted spinal cord stimulators for pain relief. Such trials need to provide the mandated reasonable assurance of safety and effectiveness and information for labeling to define appropriate patient selection, predict long-term safety and effectiveness, predict adverse event rates, predict interactions with other medical procedures and imaging, and provide the necessary information for practitioner training.

The problems described in this report for implanted spinal cord stimulators for pain relief undoubtedly extend to many other high-risk, permanently implanted medical devices. Therefore, we further recommend that the FDA take the following additional actions:

- (1) Make available summary review memoranda for all PMA supplements for all Class III medical devices and provide SSEDs for any approved PMA supplement for which the device is modified in ways that could alter its safety or effectiveness.
- (2) Perform and publish a comprehensive analysis and assessment of adverse events from all approved PMAs and PMA supplements (currently not available to the public), PMA annual reports (not available to the public), and the MAUDE database.
- (3) Initiate a retrospective review program within the recently reorganized CDRH to evaluate previous regulatory decisions that are inconsistent between different product codes, may be causing harm to the public, and may violate the requirements of the Medical Device Amendments of 1976.
- (4) Make the online MAUDE database more user friendly. This should include allowing text searches that can return more than 500 reports for a single year or any other specified time period.
- (5) Compile and make publicly available a list of all other Class III devices for which PMA approval was granted based on literature reviews of studies assessing devices other than the one for which PMA approval was sought, rather than well-designed prospective clinical trials of the actual devices for which PMA approval was sought.
- (6) To provide an essential context for understanding numbers of medical device adverse event reports submitted to the FDA for each type of medical device, take the following steps:
  - (a) Make available to the public the PMA annual report information (required for approvals since August 1, 2009) that reveals the number of devices shipped or sold, as well as the number of devices actually implanted, if available. If such data are considered to be trade secrets or confidential commercial information, make available data on aggregate sales and implantation numbers by device product code, which would not disclose sales data by individual companies.

- (b) Require that each permanent implantation of a medical device be reported by device user facilities to a publicly accessible database maintained by the FDA. If the FDA believes it lacks the legal authority to implement such a requirement, the agency should seek legislation from Congress granting such authority.

Finally, Congress needs to conduct long-overdue oversight hearings and draft legislation to strengthen the FDA's oversight of medical devices and implement the above recommendations. As a first priority, Congress should immediately pass legislation to override the Supreme Court's 2008 decision in *Riegel v. Medtronic*, which held that the existing law preempts the right of patients to bring damages claims against medical device manufacturers for injuries caused by high-risk medical devices marketed pursuant to a PMA. The *Riegel* decision ended a period of more than 30 years in which federal and state laws had worked hand in hand to strengthen device safety. The multiple dangerous weaknesses in the FDA's regulatory oversight of medical devices make the preemption decision in *Riegel* a dangerous outcome for patients.

## Appendix - Device Events Search Terms for Table 5

### Revision surgery

product-code:GZB AND (revision) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (revision) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

### Infection

product-code:GZB AND (infection OR infected) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (infection OR infected) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

### Falls

product-code:GZB AND (fall) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (fall) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

### Lead migration

product-code:GZB AND (lead AND migration) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (lead AND migration) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

### Heating

product-code:GZB AND (heating OR hot) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (heating OR hot) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

### Inappropriate shock/shocking sensation

product-code:GZB AND (shock) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (shock) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Lead fracture product-code:GZB AND (lead AND fracture) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (lead AND fracture) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Headache product-code:GZB AND (headache) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (headache) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Hematoma product-code:GZB AND (hematoma) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (hematoma) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Weakness product-code:GZB AND (weakness) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (weakness) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Cerebral spinal fluid leak

product-code:GZB AND (“csf leak” OR “cerebral spinal fluid leak” OR “cerebrospinal fluid leak”) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (“csf leak” OR “cerebral spinal fluid leak” OR “cerebrospinal fluid leak”) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Nausea product-code:GZB AND (nausea) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (nausea) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Dural Puncture

product-code:GZB AND (puncture AND [dura OR dural]) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (puncture AND [dura OR dural]) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Paralysis

product-code:GZB AND (paralysis OR hemiplegia OR paraplegia OR quadriplegia) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (paralysis OR hemiplegia OR paraplegia OR quadriplegia OR paresis) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Bladder problems

product-code:GZB AND (bladder NOT gall) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (bladder NOT gall) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Seroma

product-code:GZB AND (seroma) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (seroma) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Spinal cord compression

product-code:GZB AND (cord compression OR compression of the spinal cord OR compression on the spinal cord) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND ("cord compression" OR "compression of the spinal cord" OR "compression on the spinal cord") date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

## Bowel problems

product-code:GZB AND (bowel) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (bowel) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Sensory loss or deficit

product-code:GZB AND (sensory) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (sensory) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Suicide behavior or thoughts

product-code:GZB AND (suicide OR suicidal) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (suicide OR suicidal) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Fibrosis

product-code:GZB AND (fibrosis) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (fibrosis) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Granuloma

product-code:GZB AND (granuloma) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (hemorrhage) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Hemorrhage

product-code:GZB AND (hemorrhage) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (hemorrhage) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

#### Cauda equina

product-code:GZB AND (cauda OR equina) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31



product-code:LGW AND (cauda OR equina) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

Ataxia

product-code:GZB AND (ataxia) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31

product-code:LGW AND (ataxia) date-received-start GT 2004-01-01 date-received-end LT 2019-12-31



[www.citizen.org](http://www.citizen.org)

© 2020 Public Citizen.