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Dorsal root ganglion stimulation approval by the Food and Drug Administration: advice on evolving the process

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1. Introduction

In February 2016, the US FDA approved dorsal root ganglion (DRG) spinal stimulation in the United States for the treatment of chronic nerve pain associated with complex regional pain syndrome (CRPS) and/or peripheral causalgia in the groin and lower limb. This decade-long process gives patients access to this life-changing therapy and serves as a predicate for the process of approval for patient-centric innovation.

2. The DRG story

The responsibility for introduction of meaningful, safe therapies to patients with historically few options is one that is not to be taken lightly. Unfortunately, the process of approval has been criticized, with an increasing bureaucratic process that leads to delays in device approval compared to governing bodies in the European Union (EU) and Australia [1]. Not only is overregulation a concern, but also underregulation, as accusations of rushing to approve opioid formulations have surfaced [2], with a potential increasing contribution to the opioid overuse and abuse epidemic [3].

Sensitivity surrounding pain care therapy approval, with a keen eye on efficacy and safety, is crucial. Device-related FDA approvals have been performed largely by the acquisition of level 1 data, regarded as the most robust and scientifically valid evidence available [4–6]. Understandably, it is the foremost position of the FDA to approve products that have proven efficacy and safety and to protect the public while allowing access to the best care possible and innovation. In a decision that will very likely help many patients, the FDA recently approved DRG spinal stimulation. This represents a major advancement of the therapy, and we hope the FDA will continue to evaluate future alterations to the approval process to improve access and maintain excellence.

The use of spinal cord stimulation (SCS) involves electrical delivery by an implanted device to the dorsal columns of the spinal cord and has been in the public domain for almost 50 years [7]. A decade ago, an interest developed in targeting the DRG to improve stimulation specificity and accuracy [8]. In the past, physicians had attempted multiple strategies to treat the DRG, including excision and radio-frequency [8]. Stimulation of these structures by placing a conventional lead at the foramen has been attempted, but this resulted in stimulation of the spinal cord and nerve root and, due to the shape and size of the lead, with very little activation of the primary nerve cell bodies of the DRG and little desired effect [9–12]. Importantly, the pathologic changes that occur during the development of neuropathic pain create a reduced membrane-firing threshold for the injured cells [13], creating an opportunity for selective neuromodulation. Innate to the DRG, researchers identified that the T-junction serves as a filter for propagation of action potentials to the dorsal horn of the spinal cord [14]. DRG stimulation appears to augment this low-pass filter effect, limiting the generation of action potentials to the dorsal horn, manifesting as a reduction in pain [15]. These observations led researchers to develop a novel device that has a stimulating lead, markedly different from a conventional SCS lead, with a much smaller diameter, increased flexibility, and reduced contact size and spacing. In order to reach the target, the lead is deployed by a contralateral, interlaminarily placed introducer system composed of a curved sheath and stylleted lead system, with ultimate placement along the superior dorsal position near the DRG. The system can be powered externally during a trial or internally by an internal pulse generator for permanent cases.

The first-in-human work was performed on this novel method of spinal stimulation as a proof of concept by Deer in 2008 in three patients. This experience helped mold the next phase of engineering, modifying the system, and recharacterize the epidural entry and placement philosophy. Once a reproducible device was available, a pilot study was conducted in the spring of 2009 that demonstrated a statistically significant pain improvement in an acute window of 72 h [16]. At this time, due to restrictions in the United States, the next phase of research was moved to the EU and Australia in 2010. This multicenter study showed a very good ability to specifically target a damaged nerve area and do so with minimal energy requirements. This study led to approval in both the EU and Australia in 2011 [17]. Since that time, this therapy has become a preferred method of treatment in many countries for...
CRPS; causalgia; peripheral neuropathy; post-thoracotomy syndrome; and many other nerve injuries of the trunk, upper limbs, and lower limbs. Despite this approval and use in over 2000 patients worldwide, use in the United States was prohibited due to the need for regulatory approval. In 2013, the ACCURATE study (A Safety and Effectiveness Trial of Spinal Cord Stimulation of the Dorsal Root Ganglion for Chronic Lower Limb Pain) was launched in a multicenter, comparative, prospective, controlled efficacy trial with DRG stimulation compared to a commercially available SCS device for the treatment of CRPS type I and type II and peripheral causalgia from nerve damage of the groin, lower limb, or foot [18]. This was an investigational device exemption study designed to obtain FDA approval for use in the United States.

The results of the ACCURATE study were presented at the International Neuromodulation Society Meeting in Montreal, Canada, in 2015. The results described that the DRG stimulation device to be both non-inferior and superior to the conventional SCS device for the primary end point (>50% pain relief in the affected extremity both during the trial and at 3 months, along with no stimulation-induced neurologic deficits) and many secondary and tertiary end points. The device safety was also found to be equal to that of conventional SCS. These results were submitted to the FDA for consideration of approval for labeled use in the United States in September of 2015. After careful consideration of these pivotal results, demonstrating clear superiority, and ongoing discussion, the FDA approved the device in February 2016. We believe this represents an important point in the pathway of innovative device to first concepts, to human trials, to the development of an FDA-recommended trial development for ultimate approval.

In the next phase of this therapy, we are excited to develop data and study that will likely ultimately lead to approval for labeled use of this device for trunk and upper limb pain. We are also very enthusiastic to see the FDA clear a paddle version of the DRG lead to accommodate spine surgeons to implant the lead in those with difficult anatomy or in need of a revision. The use of new waveforms and frequencies in the DRG lead may also further improve outcomes.

The FDA has a large task and responsibility. They are charged with keeping the citizens of the United States safe, while simultaneously permitting access to life-altering therapies. Would we have preferred an earlier approval similar to the EU and Australia? Certainly, we would like to have earlier access, but there are trade-offs. The collaboration of the study sponsor with the FDA led to the approval of the device safety was also found to be equal to that of conventional SCS. These results were submitted to the FDA for consideration of approval for labeled use in the United States in September of 2015. After careful consideration of these pivotal results, demonstrating clear superiority, and ongoing discussion, the FDA approved the device in February 2016. We believe this represents an important point in the pathway of innovative device to first concepts, to human trials, to the development of an FDA-recommended trial development for ultimate approval.

The world of technology and innovation in medicine has become a global community of sharing and collaboration. Going forward we would recommend the FDA allow studies to be done concurrently in the US and in countries recognized for scientific credibility. This would allow for a strong commitment to safety and earlier access for those who suffer from nerve pain. The role of domestic and global societies committed to science and research could play a critical role in organizing and credentialing study centers in the future.

Key issues
- Dorsal Root Ganglion Spinal Stimulation has level one evidence supporting both efficacy and safety.
- The FDA approval process resulted in the creation of this high level study and without the need for approval this type of scientific merit would not be likely to be accomplished by any device manufacturer.
- Researchers in Europe and Australia were able to complete a less vigorous study and achieve approval in those continents years before United States approval.
- We recommend going forward the FDA allow collaborative research between US doctors and those in the EU and Australia to achieve patient access to major therapy advances at an earlier time.
- We feel the DRG approval process, level one evidence, and careful scrutiny is otherwise an excellent model for approving devices in the United States.

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Declaration of interest
TR Deer: consultant for St. Jude Medical, Bioness, Axonics, Nevro, Medtronic, and Flowonix. Former equity holder in Spinal Modulation. JE Pope: consultant for St. Jude Medical, Nevro, Medtronic, Flowonix, Suture Concepts and Jazz Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

• This presentation describes the largest randomized controlled trial for the treatment of CRPS.
• This paper reviews the landscape of spinal cord simulation and offers recommendations on appropriate use.


