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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition; Enhancing Special Controls for Non-Implanted Nerve Stimulators for Functional Abdominal Pain Relief

Dear Sir or Madam:

On behalf of Innovative Health Solutions, Inc. ("IHS"), we hereby submit this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs refrain from making a determination of certain subject devices' substantial equivalence to the IB-Stim (21 C.F.R. § 876.5340, Product Code QHH) without preclinical studies and at least one clinical trial establishing non-inferiority of the subject device to the IB-Stim in head-to-head evaluations.

A. Action Requested

On June 7, 2019, FDA issued a classification order for non-implanted nerve stimulators for functional abdominal pain relief based on its review of a *de novo* submission for the IB-Stim percutaneous electrical nerve field stimulator (PENFS) device. While we applaud FDA's commitment to reducing regulatory burdens through use of the *de novo* process, and paving the way for improved patient access to new, beneficial devices, we are concerned that the special controls promulgated for the classification are inadequate to assure the performance of any proposed device within this classification that is not essentially identical to the IB-Stim (the only current predicate) in terms of product design, labeling, and indications for use. Many of these concerns parallel those that were provided in our still pending April 10, 2018 citizen petition regarding substance use disorder devices that FDA has yet to address, but some are particular concerns related to pediatric patients.

As you know, the IB-Stim is a PENFS system intended to be used in patients 11-18 years of age with functional abdominal pain associated with irritable bowel syndrome (IBS). The IB-Stim is intended to be used for 120 hours per week up to 3 consecutive weeks, through application to branches of Cranial Nerves V, VII, IX and X, and the occipital nerves identified by transillumination, as an aid in the reduction of pain when combined with other therapies for IBS. The IB-Stim is specially programed to deliver a signal of fixed frequency, amplitude, and duration over the 120 hours of use.

Even seemingly minor differences in indication or design from the IB-Stim may have an adverse effect on pediatric patients. For example, there are devices that are currently marketed for electro-acupuncture which encourage providers to adjust stimulation frequencies, and durations of stimulation. Where those adjustments might be appropriate for acupuncture, to claim substantial equivalence to the IB-Stim, the frequency and stimulation of a candidate device must be fixed. This is especially important given the CNS developmental stage and neuroplasticity of children: the IB-Stim has been shown to be safe and effective through a thorough FDA review, whereas the same cannot be said for other products. FDA's announced special controls are insufficient to assess such risks to children, so these devices should not be cleared as substantially equivalent to the IB-Stim.

Therefore, based on these concerns and available research, we request that FDA require preclinical studies demonstrating similar efficacy in an animal model of IBS and at least one head-to-head clinical study demonstrating non-inferiority to the IB-Stim in U.S. pediatric patients who are diagnosed with IBS if the candidate device differs from the IB-Stim with regard to: (a) the specific parameters of stimulation including frequencies and waveform, (b) the targeted cranial nerves to which the device is applied, (c) specific grounding of the device, (d) the novel pin/array design employed by the device, (e) the field effect/signal resulting from the device (including both geometry, signal strength, and operating time), and (f) use of transillumination to identify and target specific neurovascular bundles and branches.

B. Statement of Grounds

On June 7, 2019, the FDA granted *de novo* marketing authorization to the IB-Stim, the first and currently, the only, device within the functional abdominal pain relief classification (21 C.F.R. § 876.5340). In its *de novo* submission, IHS established the performance of the IB-Stim though a randomized, sham controlled trial in patients ages 11-18 years old with functional abdominal pain. The efficacy and safety of the device has also been further corroborated since the clearance through clinical use in many of the top children's hospitals in the country.

Although the IB-Stim is currently the sole device within its classification, we expect various other products to emerge as proposed solutions to ease abdominal pain associated with irritable bowel syndrome, particularly since the condition is very prevalent and can negatively impact quality of life and functioning. It is important for FDA to provide an efficient pathway to market for such devices. However, it is also critical that the performance of such devices be adequately validated before reaching patients; in particular, where substantial equivalence to the IB-Stim is being claimed, it is critical that the subject device have adequate supporting data. The special controls at 21 C.F.R. § 876.5340 may be appropriate for what are essentially copies of the IB-Stim. However, deviations in terms of key design features or indication (method of use) would require additional support, as discussed below.

1. FDA's Substantial Equivalence Standard

A 510(k) premarket notification submission must demonstrate that a device is "substantially equivalent" to a legally marketed device (a "predicate" device).[1] Specifically, section 513(i) of the federal Food, Drug, and Cosmetic Act states:

> (A) For purposes of determinations of substantial equivalence…the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device:
>
> (i) has the same technological characteristics as the predicate device, or
> (ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data. . . that demonstrate that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

2. Key Features of the IB-Stim Established by Preclinical and Clinical Data

As noted above, the IB-Stim is a percutaneous electrical nerve field stimulator system intended to be used in patients 11-18 years of age with functional abdominal pain associated with IBS. The IB-Stim is intended to be used for 120 hours (5 days) per week for up to 3 consecutive weeks, through application to branches of Cranial Nerves V, VII, IX and X, and the occipital nerves identified by transillumination, as an aid in the reduction of pain when combined with other therapies for IBS. The device is unique in its indication and design that couples device grounding, a unique neuromodulation electrical signal, the patented array design, and a resulting unique fractal design of signal pattern generated by the pin/array design. The IB-Stim has a 4-pin needle array for grounding that is more stable and delivers a more consistent signal throughout the course of the 5 days. This unique signal generated cannot be duplicated by single pin "point" stimulation as is used with many "electro-acupuncture" devices.

When properly implanted utilizing transillumination, the patented method of application which FDA authorized through the *de novo* review determination, the IB-Stim produces neuromodulation through auricular nerves and produces a unique field with the added safety and minimal invasiveness of percutaneous implantation. The overall effect is an efficacious, non-surgical, percutaneous electrical nerve field stimulation.

Based on research to date, we believe the effectiveness of the device is related to the combination of (a) the specific parameters of stimulation including frequencies and waveform, (b) the targeted cranial nerves to which the device is applied, (c) specific grounding of the device, (d) the novel pin/array design employed by the device, (e) the field effect/signal resulting from the device (including both geometry, signal strength, and operating time), and (f) use of transillumination to identify and target specific neurovascular bundles and branches. It is

[1] 21 C.F.R. § 807.92(a)(3).

particularly critical that the performance of any proposed device to target functional abdominal pain in children that deviates from the IB-Stim with respect to any of these key features be validated through preclinical and clinical testing equivalent to that employed by IHS for the IB-Stim. This section describes these six key features of the IB-Stim in further detail and summarizes the suite of testing conducted by IHS to support the performance of the device.

a. Parameters of Stimulation

The IB-Stim device delivers 3.2V in a rectangular wave pulse and is programmed to cycle between 1 and 10 Hz every two seconds. The polarity cycles between electrodes in order to prevent nerve saturation and allow for prolonged, continuous stimulation. Our studies have demonstrated that these parameters of stimulation are not perceived as painful or noxious by humans or animals. Further, these stimulation parameters were noted to have a dampening effect on neurons of the central nucleus of the amygdala with a 65% decrease in the spontaneous firing in an animal model of IBS. The role of the amygdala in the pathophysiology of IBS in humans has been well described. The safety of the device was established with a maximum of 5 days of stimulation per week in children.

Several currently marketed devices, which were designed for electro-acupuncture, deliver very different electrical currents and require precise placement of needles in specific ‘‘acupoints” by a trained expert or with the use of bioimpedance. Many are designed to allow for adjustable programming, which might be appropriate for electro-acupuncture, but is inconsistent with the fixed treatment frequencies used in the IB-Stim. There is no evidence that using frequencies and pulse waves that differ from those used in the IB-Stim would produce stimulation substantially equivalent to the efficacy and safety of that produced by the IB-Stim. Further, special consideration must be given to how differences may impact the developing brain or create complications locally, at the site of stimulation.

Clearing a device which has very different features of stimulation for the same indication as IB-Stim would suggest that variations in these parameters don’t matter, but there is no evidence to support such a conclusion (unless FDA were to require preclinical and clinical testing as part of the clearance process).

b. Application of the IB-Stim to Target Cranial Nerves

The percutaneous, titanium needles on the IB-Stim are placed on the ventral and dorsal region of the ear, away from neurovascular bundles to create a field effect in the auricle and not on specific acupoints. Unlike other non-IHS auricular devices, the theory behind IB-Stim is not based upon an acupuncture technique such as points, reflex, chi, etc., but rather PENFS, precise targeting of the anatomical location of cranial nerves and/or neurovascular bundles, and energy transfer based upon accepted laws of energy transfer in human tissue. PENFS is an accepted procedure for affecting targeted nerves to alter pain processing at the level of the CNS. FDA has classified the IB-Stim as a non-implanted nerve stimulator for functional abdominal pain relief. FDA further recognized that it is a device that stimulates the nerves remotely from the source of the pain. The transfer of energy with respect to the IB-Stim is based upon neuroanatomy, blood vessel anatomy, proximity of the electrodes to the actual affected nerves being targeted, and verification of electrode proximity.

Cranial nerves V, VII, IX, and X are anatomically located in predictable areas of the ear

which can access the central nervous system. Peripheral branches of the lesser and greater occipital nerves are also present and communicate directly to cervical spinal cord neurons. There are distinct areas of the auricle on both the dorsal and ventral aspects which carry a predominance/ concentration of the cranial and occipital neurovascular bundles, as well as arterial branches of the superior temporal and posterior auricular arteries. These physical entities are selectively targeted for percutaneously implanting the electrode arrays and are not related to acupuncture points. Any device that requires identification of acupuncture points (acupoints) through knowledge of acupuncture or by using bioimpedance would, by definition, fall into the category of electro-acupuncture and not be equivalent to IB-Stim.

c. Grounding on the Ear

The IB-Stim is unique in the way the grounding of the device is accomplished. In the area of auricular stimulators, the IB-Stim is the only device that uses a patented 4-pin microneedle array to ground the device on the ear itself. This is essential to produce the electrical pattern which creates the peri-auricular field effect. 4-pin grounding is more stable and delivers a consistent signal across 5 days. Grounding the device by any other means, such as the skin away from the ear and/or without the array, cannot produce the field effect that is critical to stimulating all cranial nerve branches and modulating amygdala and spinal cord neurons, as shown in the IB-Stim preclinical study.

d. Fractal Design of the IB-Stim Arrays

The IB-Stim electrode arrays were designed to decrease sympathetic stimulation of targeted neuro-vascular bundles while creating less shear stress on the vascular walls. One of the wire leads is a single/4-pin ground electrode attached to the ear. The other three electrodes consist of individual pin arrays. All pins are 2.1 mm in length to assure when the transillumination-guided percutaneous implantation technique is precisely followed, the electrical neuro-modulating signal is within the accepted 1.5-2 mm range of the neurovascular bundles, assuring proper energy transfer in accordance with Ohm's and Coulomb's laws. The functioning surface area of the pins is over 5.15 sq. mm, creating a substantial electrode/tissue interface.

In addition, the patented draft of the pins/arrays is designed to help reduce tissue displacement. The draft design also allows the signal to interface with the neurovascular bundles which, co-joined with the pin length, allows for maximum neurovascular interfacing, reducing vascular impedance and resulting signal scatter. The resulting reduction in tissue "resistance" not only increases efficacy, but helps with reduction of discomfort for the patient. The patented array design is also essential for proper transfer of energy. These elements are critical for the electrical signals to reach the CNS structures effectively and for prolonged periods of time, which translates to clinical efficacy. The IB-Stim has not only been proven to reduce visceral pain in animals through a reduction in limbic and spinal neurons, but also safe and effective in a clinical trial involving children with functional abdominal pain. The same level of safety and efficacy cannot be inferred by the use of any device that simply uses needles and electrical stimulation of the ear. To do so would be misleading to clinicians, children, and their families.

e. Field Effect

The design of the microneedle array is such that it utilizes the maximum amount of surface area to deliver a current to create a field effect during the stimulation cycle. The grade 5

implantable titanium conducts the current in human tissue very efficiently. Using the array combined with the grounding on the ear directs all the current to travel though the entire ear in a 3-dimensional field. No other device currently on the market can produce this field effect. The combination of the initial electrical signal, specific frequencies, signal shape, signal timing and length, designed grounding, delivered through the unique physical design of the arrays, needles, and the resulting energy patterns creates a field effect that cannot be duplicated without the precise combination which is unique to the IB-Stim. Further, the operating time of up to 120 hours, with only a very brief rest period, is not seen in other devices which are currently marketed for the purposes of electro-acupuncture. More importantly, for these reasons, efficacy of other devices cannot be inferred and would require the proper studies.

f. Transillumination

To properly verify and isolate the neurovascular anatomy for targeted electrode implantation and effective energy transfer, transillumination must be utilized. The optic tip of the transillumination device must be placed on the dorsal or ventral aspect of the ear at a 90-degree angle so the concentrated light passes through the tissue. Since the light passes through the tissue and the auricular tissue density differs from the neurovascular bundles, there is a visible outline of the neurovascular bundles.

Due to tissue resistance, the electrodes must be percutaneously implanted within 2 mm of the cranial nerve and vascular tissues to assure proper energy transfer based on Ohm's and Coulomb's laws. Implantation of a needle directly into an arterial branch will result in bleeding and pain. Implantation farther away than 2 mm will not allow for proper energy transfer. Therefore, anatomical precision is essential, and this can only be achieved through use of transillumination. Placing needles arbitrarily without transillumination or relying on bioimpedance alone could limit the efficacy of stimulation. More importantly, it could potentially lead to adverse outcomes such as bleeding, pain or increased risk of infections locally, at the site of electrode implantation.

3. <u>Nature and Scope of Data Necessary to Support Clearance of a Device for Functional Abdominal Pain Associated with Irritable Bowel Syndrome</u>

Our understandings of the IB-Stim effects are the result of animal and human investigations that were necessary to demonstrate the clinical efficacy of the design and the effects of the device on the central nervous system, which are described below.

a. Demonstrated Reduction in Visceral and Somatic Hyperalgesia in an Animal Model Using Active Neurostimulation Compared to Sham

Using a well-established method of assessing visceral pain (EMG from abdominal musculature and balloon colorectal distension) in animals, the effect of the IB-Stim device was compared to an inactive (sham) device. Awake, male, Sprague-Dawley rats developed visceral and somatic hyperalgesia following intracolonic TNBS (a well-established model of irritable

bowel syndrome). The study demonstrated that post-inflammatory visceral and somatic hyperalgesia can be prevented and reversed using neurostimulation with the IB-Stim device.[2]

b. Demonstrated Specific Action of Neurostimulation in Reducing Firing of Spinal Neurons by More than 40% Using Electrophysiological, Extracellular, Single Unit Recordings

A group of animals underwent electrophysiology recordings to assess the effect of the IB-Stim device on spinal lumbo-sacral neurons. Surgical preparations for recordings have been previously described.[3] After the appropriate surgical preparation and laminectomy under anesthesia, the background and evoked activity of one neuron in each animal was recorded from the dorsal horn of the lumbo-sacral spinal cord. Results showed that the IB-Stim device decreased baseline firing and response to somatic stimulation of spinal neurons by approximately 47%, which likely contributes to the attenuation of functional abdominal pain seen in the clinical studies.[4]

c. Demonstrated Specific Action of Neurostimulation in Reducing Firing of Neurons in the Central Nucleus of the Amygdala by Greater than 50% Using Electrophysiological, Extracellular, Single Unit Recordings

A group of animals underwent electrophysiology recordings to assess the modulation of amygdala neurons with the IB-Stim device. After the appropriate surgical preparation, the background and evoked activity of one neuron in each animal was recorded from the right central nucleus of the amygdala. Results showed that the IB-Stim device decreased baseline firing and response to somatic stimulation of amygdala neurons by greater than 50%, which likely accounts for the improvement in global symptoms and functional pain in children with IBS.

d. Demonstrated Superiority of Active Stimulation Over Placebo in At Least a 30% Decrease in Weekly Worst Pain in Children with IBS

Pediatric patients (11-18 years old) with functional abdominal pain associated with irritable bowel syndrome based on Rome III criteria were included in the study. The primary outcome was the number of patients with greater than 30% reduction in worst abdominal pain severity after 3 weeks of therapy with IB-Stim. 59% of patients receiving active therapy with IB-Stim compared to 26% of patients receiving the sham device showed ≥ 30% reduction in worst abdominal pain from baseline to 3 weeks of therapy (p=0.024). The number needed to treat (NNT), or the number of patients that need to be treated for 1 subject to get the desired outcome of 30% improvement in worst pain severity with IB-Stim therapy was 3.

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[2] Babygirija, R, et al. Percutaneous electrical nerve field stimulation modulates central pain pathways and attenuates post-inflammatory central pain pathways and attenuates post-inflammatory visceral and somatic hyperalgesia in rats. Neuroscience. 2017;356:11-21 (Attachment A).

[3] Miranda, A, et al. Neonatal nociceptive somatic stimulation differentially modifies the activity of spinal neurons in rats and results in altered somatic and visceral sensation. The Journal of Physiology. 2006;572:775-787 (Attachment B).

[4] Babygirija, *supra* note 2.

e. Demonstrated Superiority of Active Stimulation Over Placebo in Improving Global Symptoms in Children with IBS

In a study of pediatric patients (11-18 years old) with irritable bowel syndrome based on Rome III criteria, global symptom improvement was measured with the symptom response scale (SRS), a validated pediatric questionnaire. The active IB-Stim group reported global symptom improvement after 3 weeks, while there was no change in the sham group ($p=0.003$). At the end of both 2 and 3 weeks of therapy using a SRS threshold of ≥ 2, 78% of IB-Stim group compared to 39% of the sham group ($p=0.0089$), and 82% of the IB-Stim group compared to 26% of the sham group ($p \leq 0.001$), reported overall symptom improvement, respectively. Using a higher cut-off score of ≥ 3, 67% of subjects receiving IB-Stim therapy compared to 22% of the sham group reported overall improvement after 3 weeks ($p=0.002$).

f. In a Randomized, Sham Controlled Trial, Demonstrated Superiority Over Placebo in Worst Pain and Functional Disability in Children with Functional Abdominal Pain Disorders

In a randomized, sham-controlled trial, 115 adolescents (11–18 years old) who met Rome III criteria for FAPDs were enrolled. Overall, 29 (60%) of 48 patients in the active treatment group had a reduction in worst pain of 30% or more from baseline to 3 weeks of treatment compared with ten (22%) of 45 patients in the sham group ($p=0{\cdot}00031$). Using the validated functional disability index (FDI) as a measure of disability, the treatment group improved by approximately 36% compared to 0% in the sham group ($p=0.01$).

g. Demonstrated Modulation of Vagal Nerve with Active Neurostimulation Compared to Sham Using Heart Rate Variability as an Indirect Measure of Vagal Tone

Subjects (11-18 years old) with functional abdominal pain disorders (FAPDs) were randomized to active vs. sham IB-Stim therapy for 5 days per week x 4 consecutive weeks. Subjects underwent heart rate variability (HRV) testing before and 8-12 weeks after the last week of therapy. Three-minute HRV recordings were performed in supine, sitting, and standing positions. HRV data was analyzed using Kubios software and the root mean square of successive differences (RMSSD) and high frequency (HF) domain were used. The RMSSD standing parameter showed significant improvement in RMSSD from pre to post time points ($p<0.00001$). In contrast, the sham group did not show any increase in standing RMSSD from pre to post treatment. The HF power similarly increased significantly from pre to post in the treatment group ($p=0.001$) while there was no improvement in the sham group ($p=0.711$). The LF power also improved in the treatment group ($p=0.009$) and did not improve in the sham group ($p=0.845$). Overall, IB-Stim and not sham therapy, modulated several indices of HRV which correlates with increased vagal tone in adolescents with FAPDs. The results also indicated that the effects are sustained up to two months following neurostimulation therapy.[5]

[5] Data on file.

The data from these studies confirm that the product has been validated in preclinical and clinical studies to be safe and effective. Establishing this has been a priority since the targeted population involves children. Future devices that claim to be equivalent to the IB-Stim must be put through the same scientific rigor to ensure their efficacy and safety in vulnerable subjects.

4. Advancing the Public Health Through Assessment of Follow-on Products

Reduction of functional abdominal pain in children can have significant social and economic implications. As detailed above, preclinical and clinical testing has revealed significant information about how specific features of the IB-Stim contribute to the device's performance in this regard, and ultimately improve pain, global symptoms, and functioning in children. To assure that products claiming substantial equivalence to the IB-Stim provide the same beneficial effects for patients, it will be incumbent on a 510(k) sponsor to demonstrate that any differences between the subject device and the IB-Stim would not result in inferior performance or in harm to vulnerable subjects.

It is well established that the IB-Stim can aid in reducing functional pain and promoting global wellbeing in children. However, based on the available science at this time, whether, and how significantly, changes in key attributes would affect performance generally cannot be determined without a deep dive into intricate details that involve parameters of stimulation, engineering, and method of placement, which are paramount to ensure efficacy and safety in children. Therefore, in the absence of less burdensome testing options, changes would need to be validated through preclinical testing and a clinical study comparing the subject device to the IB-Stim to establish non-inferiority with an appropriate patient population of IBS-diagnosed pediatric patients. Given the potential variability in standards of care for IBS, as well as patient environment, we would recommend any such testing be done in the United States.

C. Environmental Impact

An environmental impact analysis is not required for the requested action. Accordingly, we claim a categorical exclusion pursuant to 21 C.F.R. § 25.34.

D. Economic Impact

We will supply an economic impact analysis if the Commissioner determines that such an analysis is required for this request.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to petitioners which are unfavorable to the petition.

Sincerely,

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