

**DE NOVO CLASSIFICATION REQUEST FOR  
IB-STIM**

**REGULATORY INFORMATION**

FDA identifies this generic type of device as:

**Non-implanted nerve stimulator for functional abdominal pain relief.** A non-implanted nerve stimulator for functional abdominal pain relief is a device that stimulates nerves remotely from the source of pain with the intent to relieve functional abdominal pain. This generic type of device does not include devices designed to relieve pelvic pain.

**NEW REGULATION NUMBER:** 21 CFR 876.5340

**CLASSIFICATION:** Class II

**PRODUCT CODE:** QHH

**BACKGROUND**

**DEVICE NAME:** IB-Stim

**SUBMISSION NUMBER:** DEN180057

**DATE DE NOVO RECEIVED:** October 25, 2018

**CONTACT:** Innovative Health Solutions (IHS), Inc.  
829 South Adams St.  
Versailles, IN 47042

**INDICATIONS FOR USE**

The IB-Stim is indicated as follows:

The IB-Stim is a percutaneous electrical nerve field stimulator (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.

**LIMITATIONS**

For prescription use only.

The device is contraindicated for use by patients with cardiac pacemakers, hemophilia, and psoriasis vulgaris.

The device should only be applied to healthy, clean, intact skin.

The device therapy is limited to 120 hours, after which the device should be disposed.

The appliance is splash-proof but not watertight. When showering, the device must not be allowed to come into direct contact with water.

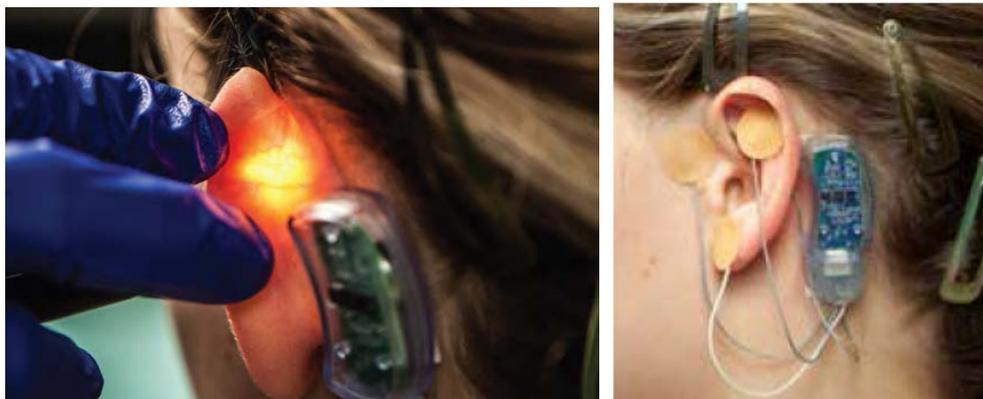
Treatment protocols are for 3 consecutive weeks, and not to exceed 4 weeks

**PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.**

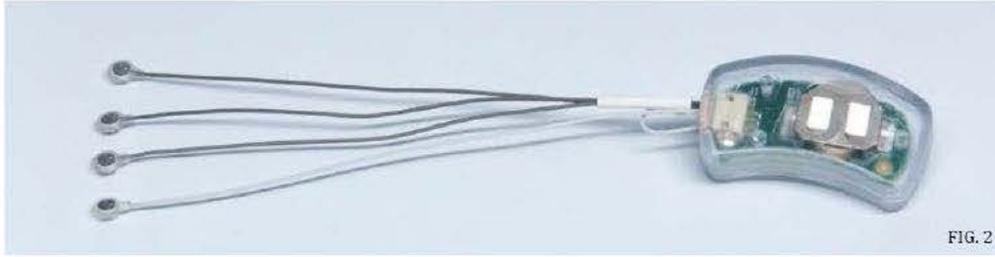
### **DEVICE DESCRIPTION**

The IB-Stim is a device that delivers electrical stimulation through percutaneous electrodes to areas usually innervated by branches of occipital nerves and cranial nerves V, VII, IX and X that are located by transillumination. The device consists of (1) a percutaneous electrical nerve field stimulator (PENFS), (2) a multi-pin wire harness percutaneous electrode array, and (3) a pen light for use in the transillumination technique that aids in positioning of the percutaneous electrodes (Figure 1).

The wire harness percutaneous electrode array consists of 4 leads. The 1-1-1-4 configuration consists of three single-needle leads, and one 4-needle array (Figure 2).



**Figure 1: (Left) Visualization of neurovasculature of the ear using transillumination technique. (Right) Representative image of the placement of the IB-Stim device.**



**Figure 2: PENFS System**

The stimulator is placed behind the ear and the percutaneous electrodes are positioned utilizing the transillumination function of the device (Figure 1). The transillumination technique assists in the visualization of the vasculature of the ear to aid in the placement of the percutaneous electrodes near the nerve branches in the ear. The system specifications are listed in Table 1.

**Table 1: System Specifications**

Device Technology Description	
General Device Characteristics	IB-Stim
Power supply	1 x 3V battery (Type CR1220 Li)
Output	Max 3.2V @ 1k $\Omega$ -10k $\Omega$
Total duration of treatment	5 x 24hr
Weight including battery	5g
Dimensions	36mm x 16mm x 7mm

The following components are part of a convenience kit sold with the IB-Stim:

1. Tweezers
2. Transilluminator (pen light)
3. Alcohol swab
4. Surgical marker
5. Adhesive bandages
6. Foam adhesive
7. Multi-pin wire harness percutaneous electrode array

The IB-Stim is similar to the NSS-2 BRIDGE device previously granted in DEN170018 for a different intended use. It is also like the Electronic Auricular Device (EAD) electroacupuncture device cleared in K140530, which is the precursor device to both the NSS-2 BRIDGE and IB-Stim device. The IB-Stim duty cycle is identical to the duty cycle cleared in the Electronic Auricular Device (EAD) electroacupuncture device (K140530).

**SUMMARY OF NONCLINICAL/BENCH STUDIES**

This De Novo request refers to the nonclinical bench testing, biocompatibility, electrical safety, electromagnetic compatibility, shelf life, sterility, and software testing provided in DEN170018 for the NSS-2 BRIDGE device. The DEN170018 used a significant amount of nonclinical testing submitted for the EAD device in K140530.

The sections below summarize testing used from DEN170018 and K140530 to support the safety and effectiveness of this device for its intended use. The technological changes detailed above do not change any results of the prior non-clinical testing. Additional information on these changes and why they do not adversely impact the safety of the device are discussed below.

**BIOCOMPATIBILITY/MATERIALS**

Table 2, below, summarizes the patient-contacting materials for the IB-Stim device and references the source of any biocompatibility evaluations.

**Table 2: List of Patient-Contacting Materials**

<b>Patient Contacting Device Component</b>	<b>Nature of Tissue Contact</b>	<b>Duration of Tissue Contact</b>
Tweezers	No skin contact	No skin contact
Transilluminator pen light	Behind ear	Less than 1 minute  Materials used in the pen light are identical to the materials used in in the granted NSS-2 BRIDGE (DEN170018).
Kitted Bag containing Fixation Plasters	Over needle arrays on front surface of ear	Up to 120 hours  Materials used for the fixation plasters are identical to the materials used in in the granted NSS-2 BRIDGE (DEN170018) and cleared EAD.
Surgical Marker	On front surface of ear	Up to 120 hours  Materials used for the surgical marker are identical to the materials used in in the granted NSS-2 BRIDGE (DEN170018).
Multi-pin wire harness percutaneous electrode array	Implanted percutaneously on front surface of ear	Up to 120 hours  Materials used in the needle arrays are identical to the materials used in the granted NSS-2 BRIDGE (DEN170018).
Foam Adhesives	Behind ear	Up to 120 hours

		Foam adhesive material is identical to the materials used in in the granted NSS-2 BRIDGE (DEN170018).
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The tweezers, transilluminator (pen light), alcohol swab, and surgical marker are Class I, 510(k)-exempt products packaged as part of the convenience kit.

The fixation plasters and foam adhesive were tested for cytotoxicity, sensitization, and irritation in K140530 per FDA Blue Book Memorandum #G95-1 “Use of International Standard ISO-10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,’” May 1, 1995, and International Standard ISO 10993-1 “Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process,” as recognized by FDA. All results demonstrated acceptable performance.

The multi-pin percutaneous electrode array for the IB-Stim is identical to the needle array granted in DEN170018.

**STERILITY AND SHELF LIFE**

Sterilization validation was conducted on the wire harness percutaneous electrode arrays using the VDMA25 method according to ISO 11137-2:2007 “Sterilization of health care products -- Radiation -- Part 2: Establishing the sterilization dose.” The device achieved a sterility assurance level of 10<sup>-6</sup> with (b) (4) kGy. The device fulfilled the requirements of sterility according to ISO 11737-2:2009 “Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.”

The master packaging for the device is comprised of three parts:

1. The main tray is a vacuum formed single piece of plastic approximately 12 inches in length and 8 inches wide. The depth of the packaging is ¾ of an inch. There are five vacuum formed compartments that house the internal components in a secure fashion.
2. The cover for the packaging is clear sheet of film that is heat-sealed to ensure proper closure and protection of vital components.
3. The sterile sub-pack that houses the wire harness and needle array assembly. It is a 4 ½ x 1-inch vacuum formed enclosure consisting of a top and bottom that is then vacuum sealed inside a plastic medical grade bag.

The performance and stability of the device’s packaging system during sterilization, distribution and labeled shelf life of (b) (4) were validated in accordance with ISO 11607-1:2009, using accelerated-aged device samples. Accelerated aging of the device was performed according to ASTM F1980-07:2011. Validation was based on packaging material qualification, according to

ISO 11607-1:2009, and the machine qualifications of the sealing processes, according to ISO 11607-2:2006.

### **ELECTROMAGNETIC COMPATIBILITY & ELECTRICAL SAFETY**

Electrical safety and EMC information is identical to the NSS-2 BRIDGE device granted in DEN170018. In DEN170018, the electrical safety and EMC information was leveraged from information previously provided for the EAD device cleared under K140530 because there were no changes to the electrical components of the device. The only change associated with electrical safety is an alteration to the duty cycle of the IB-Stim to be consistent with the original duty cycle of the EAD device (K140530).

The device conformed to the following electromagnetic compatibility, electrical, mechanical, and thermal safety standards:

- IEC 60601-1 - Medical Electrical Equipment; Part 1: General Requirements for Basic Safety and Essential Performance.
- IEC 60601-1-2 - Medical Electrical Equipment; Part 1-2: General Requirements for Safety – Section 2: Collateral Standard: Electromagnetic Compatibility - Requirements and Tests.
- IEC 60601-2-10 - Medical Electrical Equipment; Part 2-10: Particular Requirements for the Safety of Nerve and Muscle Stimulators.

### **SOFTWARE**

Software verification and validation testing were conducted, and documentation was provided in K140530 as recommended in FDA's Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005. The software for this device was considered a "Minor" level of concern.

### **PERFORMANCE TESTING - BENCH**

The electrical bench testing is identical to the NSS-2 BRIDGE device granted in DEN170018. In DEN170018, this electrical bench testing was leveraged from information previously provided for the EAD device cleared under K140530. The following tests were performed under a 1k $\Omega$  resistance to validate that the electrical performance met the specifications of the device:

- Verification of the temporal characteristics and amplitude of the pulse train through the leads and percutaneous electrodes
- Verification of the pulse train duty cycle
- Verification that the device does not exceed the maximum operating time of 120 hours

## **SUMMARY OF CLINICAL INFORMATION**

### **Trial Design**

A 115-patient, double blind, randomized, sham-controlled trial<sup>1</sup> enrolled adolescents 11 to 18 years of age who had abdominal pain-related functional gastrointestinal disorders. During the trial, patients could continue stable doses of medication if there were no dose changes during the four weeks of treatment and two weeks prior to enrolling in the trial. Patients reported any concurrent medication use at each weekly visit.

Patients were provided with an IB-Stim or sham device after baseline measurements and returned to the clinic for a replacement at the end of Weeks 1, 2, and 3 at which time data were recorded. Patients were asked to return to the clinic within 8-12 weeks for long-term follow-up data collection. This follow-up data was ultimately not considered in FDA's decision.

### **Outcome measures**

The study collected the following patient-reported outcome measures at the end of Weeks 1, 2, 3 and at follow-up:

- Rating of usual, or average, pain experienced in the past week scored from 0 for no pain to 10 for worst pain;
- Rating of worst pain experienced in the past week scored from 0 for no pain and 10 for worst pain;
- Composite pain frequency-severity-duration (PFSD) score. The PFSD composite score is derived by multiplying the number of days of pain (0-7), the ratings of usual pain (0-10) and worst pain (0-10) over the past week, and then dividing the product by 10 with the highest possible score of 70; and
- Symptom response scale (SRS) score. Symptoms are recorded as better, worse, or no change based on a 15-point scale across individual domains for both improvement and deterioration of overall symptoms (-7 to -1= worse; 0 = no change; +1 to +7 = better).

Primary outcomes included change from baseline to end of third week in worst abdominal pain and composite PFSD scores.

Secondary outcomes included: 1) the global symptom improvement based on a minimum of +2 in the SRS score and 2)  $\geq 30\%$  improvement (defined and analyzed post hoc) in worst and usual abdominal pain at Week 3.

### **Results**

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<sup>1</sup> Kovacic K, Hainsworth K, Sood M, Chelimsky G, Unteutsch R, Nugent M, Simpson P, Miranda A. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. *Lancet Gastroenterol Hepatol.* 2017;2:727-737 ([https://www.thelancet.com/journals/langas/article/PIIS2468-1253\(17\)30253-4/fulltext](https://www.thelancet.com/journals/langas/article/PIIS2468-1253(17)30253-4/fulltext))

The trial enrolled and randomized 60 subjects to receive active treatment and 55 to receive sham treatment for a total of 115 subjects. During the study, 11 subjects either discontinued their participation in the trial or were excluded from the trial. Three patients discontinued in the active treatment group: two patients were excluded as they were diagnosed during the trial with either peptic ulcer or eosinophilic oesophagitis (both are exclusion criteria for the study) and one patient discontinued because they found the device too uncomfortable to continue. Eight patients discontinued from the sham group: three discontinued participation due to a needle phobia or anxiety, two discontinued for aesthetic reasons, one discontinued as they found the device uncomfortable, one discontinued due to an adhesive allergy, and one was excluded as they were diagnosed with eosinophilic oesophagitis (an exclusion criterion for the study). A total of 104 subject completed the trial. The investigator's final analysis was not a true intent-to-treat analysis because it used only the data from the 104 patients who completed the trial (57/60 patients in the active group and 47/55 patients in the sham group).

The primary condition studied was irritable bowel syndrome (IBS) with 28/57 patients in the active group and 23/47 in the sham group. The remaining 29/57 and 24/47 patients in the active and sham groups, respectively, had other functional abdominal pain conditions (e.g., functional dyspepsia, abdominal migraine).

Of the patients who completed the trial, a majority of these patients (N=78) had not previously responded to one or more medications commonly used to treat chronic abdominal pain, whereas 26 patients were treatment naïve.

A blinding assessment was included in the trial after Week 3 for all patients. One half of sham-treated patients believed they were receiving sham treatment compared to one fifth of IB-Stim-treated patients. No blinding assessment analysis was provided for the IBS subgroup.

A pre-specified repeated measures analysis demonstrates a statistically significant difference between groups in all prespecified primary and secondary outcome measures. However, the different etiologies of the patient conditions raises concerns about pooling data from different populations. In this evaluation, the small number of patients with other functional abdominal pain disorders (i.e., functional dyspepsia, abdominal migraine, and functional abdominal pain) and the lack of a prespecified subgroup analysis demonstrating statistical or clinical effectiveness in each studied etiology would not support a general "functional abdominal pain" indication. Therefore, a post hoc sub-group analysis for each of the various disorders studied was analyzed. The study was not sufficiently powered to investigate differences in the subcategories of functional abdominal pain, functional dyspepsia or abdominal migraine. However, the irritable bowel syndrome (IBS) sub-group had a sufficient number of subjects for this analysis and is summarized below.

### **Post-hoc irritable bowel syndrome (IBS) subgroup analysis requested by FDA**

FDA requested this post-hoc analysis to assist in understanding whether the results for patients in the IBS sub-group, who comprised of the majority of the participating subjects in the trial, were consistent with the results reported for the overall cohort studied.

A total of 51 subjects met Rome III criteria for IBS. They represent 44% (51/115) of the 115 randomized subjects. Of the 51 subjects with IBS, 50 completed the study and were included in the subgroup analysis (one subject with IBS discontinued participation during the trial, described above). Of these 50 subjects, 23 received the sham device and 27 received the active IB-Stim device. Both groups were comparable in age, gender, BMI, ethnicity, negative diagnostic workup as well as baseline pain (PFSD) and functional disability inventory (FDI) scores (see Table 3). One patient reported taking Tramadol during the study (total of 3 doses). No other medication use during the trial was reported.

The majority of IBS patients in the IB-Stim group (70%; 19/27) and the sham group (87%; 20/23) had not responded to one or more medications commonly used to treat chronic abdominal pain, whereas 30% (8/27) and 13% (3/23) were treatment naïve.

Group Characteristics	n	IB-Stim (n=27)	n	Sham (n=23)	p-value
<b>Demographics</b>					
Age (years) median (IQR)	27	15.3 (13.8,16.7)	23	15.6 (14.2,17.2)	(b) (4)
BMI, median (IQR)	27	22.4 (20.0,29.2)	23	23.4 (20.9,26.1)	
Female	27	24 (89%)	23	21 (91%)	
Race					
Caucasian	27	22 (82%)	23	21 (91%)	
African American	27	5 (19%)	23	2 (9%)	
<b>Diagnostic workup</b>					
Normal Screening Labs	27	27 (100%)	23	23 (100%)	(b) (4)
Normal Abdominal Imaging	19	19 (100%)	16	16 (100%)	
Normal Endoscopy +/- Colonoscopy	19	19 (100%)	14	14 (100%)	

**Table 3: IBS Group Comparison Data**

Assessment in worst pain and PFSD composite score were recorded weekly and compared to sham (weeks 1, 2 and 3). The analysis of change in worst pain and change in composite PFSD scores from baseline included a mixed model using compound symmetry as the covariate structure. Time (week) was a random effect. A Tukey-Kramer adjustment was used to adjust for multiple comparisons. The models were run for outcomes in worst pain and PFSD scores, and SRS.

The repeated measures analysis demonstrated group differences in worst pain from baseline to Week 1 and 3 in the IB-Stim group compared to the sham group. Similarly, there was a greater improvement in the composite pain score from baseline to weeks 1, 2 and 3 in the IB-Stim group compared to the sham group. In both worst pain and composite pain scores, the most significant effects were seen at Week 3.

Between group differences in composite pain scores noted after 3 weeks showed that the IB-Stim group had a lower PFSD composite pain score (median 7.5, interquartile range [IQR] 3.6-14.4) compared to the sham group (median 14.4, IQR 4.5-39.2). Similar findings were seen in worst abdominal pain scores: IB-Stim group had a lower worst pain score (median 5.0, IQR 4.0-7.0) compared to the sham group (median 7.0, IQR 5.0-9.0).

Fifty-nine percent (59%; 16/27) of patients receiving the active IB-Stim compared to 26% (6/23) of patients receiving sham showed greater than 30% reduction in worst abdominal pain from baseline to 3 weeks of therapy. Similarly, 52% (14/27) of the IB-Stim group compared to 30% (7/23) of the sham group had greater than 30% reduction in usual abdominal pain after 3 weeks of therapy.

### *Global Symptoms*

The active IB-Stim treatment group reported global symptom improvement after 3 weeks while there was no change in the sham group: median SRS score of 3 (IQR: 2-4) in IB-Stim group versus a median of 0 (IQR: 0-2) in the sham group. At the end of 3 weeks of therapy, 81% (22/27) of the IB-Stim group compared to 26% (6/23) of the sham group reported overall symptom improvement with an SRS score of 2 or more. Similar findings were noted after 2 weeks of therapy where 78% (21/27) of the IB-Stim group compared to 39% (9/23) of the sham group had an SRS score of 2 or more.

### *Safety analysis*

No serious adverse events were recorded in any subject during IB-Stim study. Ten patients reported the following adverse events:

- Ear discomfort (n=6)
- Adhesive allergy (n=3)
- Syncope (n=1)

In addition to the adverse events reported in this study, percutaneous therapies generally have risks of bleeding or infection at the puncture site, skin irritation or pain at the site of application. Additional information about the safety of percutaneous electrical nerve field stimulators (PENFS) is discussed below.

### **LABELING**

Labeling for the IB-Stim resembles labeling previously provided for the NSS-2 BRIDGE and EAD device (DEN170018 and K140530, respectively). The IB-Stim Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The labeling includes the following contraindications:

- *Use of cardiac pacemakers because no clinical data is available;*
- *Hemophilia; and*
- *Psoriasis vulgaris.*

The labeling also clarifies that *an intact skin surface is essential for the use of IB-Stim stimulator*. A summary of the clinical data used to support the proposed intended use is provided including a description of the risks and adverse events associated with normal use of the IB-Stim. The labeling provides adequate instructions for use to inform the health care provider in the correct placement and safe use of the IB-Stim including information on the shelf life and technical parameters of the device. Specific instructions for the practical use of the IB-Stim as an aid to IBS therapies was provided:

*Patients should be encouraged to make lifestyle modification during treatment. Long-term treatment options with psychological or pharmacological interventions should also be discussed with patient prior to, or at the time of initiating therapy with IB-Stim.*

The labeling satisfies the requirements of 21 CFR § 801.109.

**RISKS TO HEALTH**

The table below identifies the risks to health that may be associated with use of a non-implanted nerve stimulator for functional abdominal pain relief and the measures necessary to mitigate these risks:

**Table 4 – Identified Risks to Health and Mitigation Measures**

<b>Identified Risks to Health</b>	<b>Mitigation Measures</b>
Adverse tissue reaction	Biocompatibility evaluation Labeling
Electrical, mechanical, or thermal hazards leading to user discomfort or injury	Electromagnetic compatibility testing Electrical, mechanical, and thermal safety testing Non-clinical performance testing Software verification, validation and hazard analysis Labeling
Infection	Sterility testing Shelf life testing Labeling

**SPECIAL CONTROLS**

In combination with the general controls of the FD&C Act, the non-implanted nerve stimulator for functional abdominal pain relief is subject to the following special controls:

- (1) The patient-contacting components of the device must be demonstrated to be biocompatible.
- (2) Electromagnetic compatibility and electrical, mechanical, and thermal safety testing must be performed.
- (3) Electrical performance testing of the device and electrodes must be conducted to validate the specified electrical output and duration of stimulation of the device.
- (4) Software verification, validation, and hazard analysis must be performed.
- (5) Sterility testing of the percutaneous components of the device must be performed.

(6) Shelf life testing must be performed to demonstrate continued sterility, package integrity, and device functionality over the labeled shelf life.

(7) Labeling must include the following:

- (i) A detailed summary of the device technical parameters;
- (ii) A warning stating that the device is only for use on clean, intact skin;
- (iii) Instructions for use, including placement of the device on the patient; and
- (iv) A shelf life.

### **BENEFIT-RISK DETERMINATION**

The risks of the device are based on data collected in a clinical study described above.

Overall, risks from device use appear to be low. There were no serious adverse events recorded for any subject during the clinical study. There were ten patient reported adverse events of ear discomfort (n=6), adhesive allergy (n=3), and syncope (n=1). These are reported to be typical for this device type.

Although not specifically reported in the study described above, percutaneous therapies generally have risks of bleeding or infection at the puncture site, and skin irritation or pain at the site of application.

The probable benefits of the device are based on data collected in the clinical study as described above.

The overall cohort of the clinical study demonstrate statistically significant results for all prespecified primary and secondary endpoints. However, an indication for use statement can only be supported by the patient population adequately represented in the study, which is reflected only in the IBS subgroup which included 44% (51/115) of patients randomized.

The IBS subgroup analysis shows a decrease in usual pain and worst pain. This reduction was seen in more patients in the active treatment group than those in the sham group. This was also reflected in the responder rates for patients with at least 30% reduction in worst pain and usual pain, as described above. These results demonstrate that there is a clinically meaningful benefit for use of the device in the IBS subpopulation.

This clinically meaningful benefit of reduction in pain for adolescents with IBS treated with this device and other therapies.

The benefits outweigh the probable risks associated with this device, as described above.

### **PATIENT PERSPECTIVES**

This submission did not include specific information on patient perspectives for this device.

## **BENEFIT/RISK CONCLUSION**

In conclusion, given the available information above, for the following indication statement:

The IB-Stim is a percutaneous electrical nerve field stimulator (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 device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

## **CONCLUSION**

The De Novo request for the IB-Stim is granted and the device is classified as follows:

Product Code: QHH

Device Type: Non-implanted nerve stimulator for functional abdominal pain relief

Regulation Number: 21 CFR 876.5340

Class: II