July 29, 2024

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Re: Citizen Petitions – Docket Numbers: FDA-2018-P-1469
FDA-2019-P-5048

Dear Mr. Boiani:

This letter responds to your petition dated and received by the Food and Drug Administration (FDA, we, or the Agency) on April 10, 2018 (Petition-1)[1] submitted on behalf of Innovative Health Solutions, Inc. (IHS) concerning its NSS-2 BRIDGE device, specifically the special controls for Percutaneous Nerve Stimulator for Substance Abuse Disorders established in the Agency's November 15, 2017 De Novo order (DEN170018)[2] granting marketing authorization of the device (codified at 21 CFR 882.5896).

This letter also responds to your similar petition dated and received by FDA on October 29, 2019 (Petition-2)[3] submitted on behalf of the same entity, IHS, concerning its IB-Stim device. Specifically, this petition concerns the special controls for Nonimplanted Nerve Stimulator for Functional Abdominal Pain Relief Devices, established in the Agency's August 9, 2019, De Novo order (DEN180057)[4] granting marketing authorization of the device (codified in 21 CFR 876.5340).

FDA issued an interim response to Petition-1 on October 18, 2018, by email,[5] and an interim response to Petition-2 on April 27, 2020, also transmitted by email.[6]

[1] See https://www.regulations.gov (search for document FDA-2018-P-1469-0001).
[2] Available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170018.pdf.
[3] See https://www.regulations.gov (search for document FDA-2019-P-5048-0001).
[4] Available at https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180057.pdf.
[5] See https://www.regulations.gov (search for document FDA-2018-P-1469-0006).
[6] See https://www.regulations.gov (search for document FDA-2019-P-5048-0005).

A. Actions Requested

1. Petition-1

In Petition-1, you request FDA to "refrain from making a determination of certain subject devices' substantial equivalence to the NSS-2 BRIDGE (21 CFR 882.5896) without preclinical studies *and* at least one clinical trial establishing non-inferiority of the subject device to the NSS-2 BRIDGE in head-to-head evaluations."[7] Petition-1 argues that if any new device is claiming the NSS-2 BRIDGE as the predicate device without being identical to it in certain respects, the proposed new device could present unmitigated risks.[8]

Specifically, Petition-1 requests that the Agency require information in the form of "head-to-head preclinical (animal model) studies and at least one head-to-head clinical study demonstrating [device performance] non-inferiority to the NSS-2 BRIDGE" whenever the subject device "differs from the NSS-2 BRIDGE with regard to: (a) the indicated nerves to which the device is applied, (b) the grounding of the device, (c) the novel pin/array design employed by the device, (d) the field effect/signal resulting from the device (including both geometry, signal strength, and operating time), and (e) use of transillumination to identify specific neurovascular bundles and branches to which the product is applied."[9]

By implication, Petition-1 argues that the special controls codified in § 882.5896 are "inadequate to assure the [safe and effective] performance of any proposed device within this classification" unless: (i) the new proposed device claiming substantial equivalence to the NSS-2 BRIDGE in the 510(k) review process conforms identically to the design, labeling, and indications for use of the NSS-2 BRIDGE, and (ii) if not identical, unless the new device demonstrates non-inferior performance in animal model and clinical studies.[10]

In accordance with 21 CFR 10.30(e), FDA denies Petition-1 for the reasons discussed below.

2. Petition-2

In Petition-2, you request FDA to "refrain from making a determination of certain subject devices' substantial equivalence to the IB-Stim (21 CFR 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." [11] Petition-2 argues that, if the new device is claiming the IB-Stim as the predicate device without being identical to it in these respects, the proposed new device would present unmitigated risks.[12]

Specifically, Petition-2 requests that the Agency require information in the form of "preclinical studies demonstrating similar efficacy in an animal model [for the treatment] of IBS [irritable

[7] Petition-1, at 1.
[8] Petition-1, at 8.
[9] Petition-1, at 2.
[10] Petition-1, at 1.
[11] Petition-2, at 1.
[12] Petition-2, at 9.

bowel syndrome] and at least one head-to-head clinical study demonstrating [device performance] non-inferiority to the IB-Stim in U.S. pediatric patients who are diagnosed with IBS" whenever the subject 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."[13]

By implication, Petition-2 argues that the special controls codified in § 876.5340 are "inadequate to assure the [safe and effective] performance of any proposed device within this classification" unless: (i) the new proposed device claiming substantial equivalence to the IB-Stim in the 510(k) review process conforms identically to the design, labeling, and indications for use of the IB-Stim, and (ii) if not identical, unless the new device demonstrates non-inferior performance in animal model and clinical studies.[14]

In accordance with 21 CFR 10.30(e), FDA denies Petition-2 for the reasons discussed below.

B. Legal and Regulatory Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act)[15] establishes a comprehensive system for the regulation of medical devices intended for human use with three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness.[16] The three categories of devices are class I (general controls), class II (special controls and general controls), and class III (premarket approval and general controls).[17]

FDA refers to devices that were not in commercial distribution before May 28, 1976, as "postamendments devices."[18] These devices are classified automatically by statute into class III without FDA rulemaking and regardless of the risks they may pose.[19] These devices remain in class III and require premarket approval, unless FDA reclassifies the device into class I or class II. This can occur on FDA's own initiative or in response to a petition from a manufacturer or importer.[20] FDA can also issue an order finding the device to be substantially equivalent (SE) to a predicate device that does not require premarket approval.[21] Alternatively the De Novo classification process provides a pathway for low and moderate risk postamendments devices to

[13] Petition-2, at 2.
[14] Petition-2, at 1.
[15] As amended and codified at 21 U.S.C. 301 *et seq*.
[16] Section 513, 21 U.S.C. 360c.
[17] Section 513(a)(1).
[18] See 21 CFR 860.134; see also 83 FR 64,443, at 64,446 (Dec 17, 2018) (amending 21 CFR part 860 and discussing the classification and reclassification processes for postamendments devices).
[19] Section 513(f)(1), 21 U.S.C. 360c(f)(1).
[20] Section 513(f)(3), 21 U.S.C. 360c(f)(3).
[21] See Section 513(i), 21 U.S.C. 360c(i). The Agency determines whether new devices are SE to predicate devices by means of the premarket notification procedures set forth in Section 510(k), 21 U.S.C. 360(k), and 21 CFR part 807 ("the 510(k) review process").

obtain marketing authorization as class I or class II devices, rather than remaining automatically designated as a class III device requiring premarket approval.[22] The De Novo classification process is intended to provide an efficient path to marketing authorization that ensures the most appropriate classification of postamendments devices consistent with the protection of the public health and the statutory scheme for device regulation.[23] In the De Novo classification process, the review standard balances probable benefits and probable risks of using the device.[24] In general, FDA will grant a De Novo classification request if the device meets the statutory criteria[25] for a classification into class I or II and if none of the reasons for denial in 21 CFR 860.260(c) are met.

In the De Novo classification process, we classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use.[26] In determining the safety and effectiveness of a device for purposes of classification and for the establishment of special controls, FDA considers the following, among other relevant factors: (1) the persons for whose use the device is represented or intended; (2) the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) the reliability of the device.[27]

Once a device is classified under the De Novo process, it may serve as a predicate for a new postamendments device that goes through the 510(k) review process to establish its substantial equivalence. Section 513(i)(1)(A) defines "substantial equivalence" to mean that a device has the same intended use as the predicate device and that FDA, by order, has found (i) that the device has the same technological characteristics as the predicate device, or (ii) if the device has different technological characteristics, that the clinical or scientific data, if deemed necessary by FDA, demonstrates that the device is as safe and effective as a legally marketed device and the device does not raise different questions of safety and effectiveness than the predicate device. [28]

When FDA requests information to demonstrate that devices with differing technological characteristics are SE, FDA "shall only request information that is *necessary* to making substantial equivalence determinations" (emphasis added) and "shall consider the least

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[22] Section 513(f)(2), 21 U.S.C. 360c(f)(2), and 21 CFR 860.200 *et seq*.

[23] See 86 FR 54,826 (Oct 5, 2021) (establishing in 21 CFR part 860, subpart 200 the procedures for De Novo reclassification and discussing the intent of the De Novo process).

[24] For more information about FDA's thinking on this topic see FDA's guidance, see "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," available at https://www.fda.gov/media/99769/download.

[25] Section 513(a)(1), 21 U.S.C. 360c(a)(1).

[26] Section 513(a)(1)(B), 21 U.S.C. 360c(a)(1)(B).

[27] 21 CFR 860.7(b).

[28] 21 U.S.C. 360c(i)(1)(A).

burdensome means of demonstrating substantial equivalence…."[29] The term "necessary" in this context means the Agency must consider "the *minimum* required information that would support a determination of substantial equivalence" (emphasis added).[30]

In the 510(k) review process, FDA's data requests typically follow a stepwise analytical process to ensure the minimum required information is requested that is necessary for making substantial equivalence determinations.[31] First, FDA considers descriptive information about the technological characteristics, such as the materials, design, and specifications, of the new device.[32] When this information is not sufficient to support a substantial equivalence determination, FDA then considers whether non-clinical bench performance testing or analytical studies using clinical samples would be sufficient. Non-clinical animal and/or biocompatibility studies are typically requested in the 510(k) review process when other forms of non-clinical bench performance testing are not sufficient to support a substantial equivalence determination.

When analytical or non-clinical bench performance testing data and animal and/or biocompatibility studies are insufficient, or available scientific methods are not acceptable, e.g., the scientific methods are deemed unacceptable because they are not clinically validated or are not supported by a valid scientific rationale, FDA may request clinical performance data to support a substantial equivalence determination. In general, requests for clinical data constitute a minority of the submissions considered during the 510(k) review process. Regardless, FDA may request such data on a case-by-case basis when necessary to support a substantial equivalence determination for a new device.

C. Factual Background

1. De Novo Classification Decisions

a. DEN170018

In the DEN170018 granting order, FDA granted marketing authorization for the NSS-2 BRIDGE in response to IHS's De Novo classification request. That grant reflects an FDA determination under section 513(f)(2) of the FD&C Act[33] that the NSS-2 BRIDGE can be classified as a Class II device for use "as an aid to reduce the symptoms of opioid withdrawal, through application to branches of Cranial Nerves V, VII, IX, and X, and occipital nerves identified by transillumination" and subject to general controls and to the special controls for this device type (product code PZR) specified in the DEN170018 order.

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[29] Section 513(i)(1)(D)(i), 21 U.S.C. 360c(i)(1)(D)(i)). For more information about FDA's thinking on this topic see FDA's guidance, see "The Least Burdensome Provisions: Concept and Principles; Guidance for Industry and FDA Staff" (February 2019) (Least-Burdensome Principles Guidance), available at https://www.fda.gov/media/73188/download.

[30] Section 513(i)(1)(D)(ii), 21 U.S.C. 360c(i)(1)(D)(ii).

[31] For more information about FDA's thinking on this topic see FDA guidance entitled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] and Guidance for Industry and FDA Staff" (July 2014) (510(k) Guidance), at 18-26, available at https://www.fda.gov/media/82395/download.

[32] See 21 CFR 807.87(f) and (g).

[33] 21 U.S.C. 360c(f)(2).

In the DEN170018 granting order, FDA determined that special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device. In the final order classifying the device and by issuing classification regulation § 882.5896 for the device type (the PZR Final Order),[34] FDA codified the special controls that are required for all new devices of the device type identified in the new classification regulation.

b. DEN180057

In the DEN180057 granting order, FDA granted marketing authorization for the IB-Stim in response to IHS's De Novo classification request. That grant reflects an FDA determination under section 513(f)(2) of the FD&C Act[35] that the IB-Stim could be classified as a Class II device "intended to be used in patients 11-18 years of age with functional abdominal pain associated with irritable bowel syndrome (IBS)… through [device] application to branches of Cranial Nerves V, VII, IX, and X, and occipital nerves identified by transillumination, as an aid in the reduction of pain when combined with other therapies for IBS" and subject to general controls and to the special controls for this device type (product code QHH) specified in the DEN180057 order.

In the DEN180057 granting order, FDA determined that special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device. In the final order classifying the device type and by issuing classification regulation § 876.5340 for the device type (the QHH Final Order),[36] FDA codified the special controls that are required for all new devices of the device type identified in the new classification regulation.

2. Special Controls

In the PZR Final Order and in the QHH Final Order, we identified the same risks to health for these two device types: adverse tissue reaction; electrical, mechanical, or thermal hazards leading to user discomfort or injury; and infection. In addition to general controls, we determined that the following special controls, as identically listed in § 882.5896(b) and in § 876.5340(b), are required to mitigate the identified risks to health:

(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.

[34] 83 FR 5033 (Feb 5, 2018).
[35] 21 U.S.C. 360c(f)(2).
[36] 86 FR 71,142 (Dec 15, 2021).

(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 specified 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.

Special control (1) mitigates the risk of adverse tissue reaction from the device. Special controls (2), (3), and (4) mitigate user risks to health due to electrical, mechanical, and thermal hazards. Special controls (5) and (6) mitigate infection risk. Finally, special control (7) mitigates all the identified risks to health.

Any device of the same type is required to comply with the codified special controls to gain marketing clearance through the 510(k) review process, whether or not the proposed device is claiming one of IHS's devices as a predicate.

The special controls set forth in §§ 882.5896 and 876.5430, respectively, do not preclude FDA in the 510(k) review process from requesting performance testing for a particular device that the Agency deems necessary to make a substantial equivalence decision, even if device performance data was not explicitly required as a special control in § 882.5896 or in § 876.5430.[37]

D. Discussion and Response to the Requested Actions

As outlined above, the DEN170018 and DEN180057 granting orders identified the relevant risks of the subject devices and set forth the special controls, codified in §§ 882.5896 and 876.5340, for the device types and any future devices claiming substantial equivalence within those types. The special control requested in the Petitions—i.e., to demonstrate non-inferior performance in preclinical studies and at least one clinical trial—was not required at the time the De Novo granting orders were issued, and FDA declines to do so in response to these Petitions outside the context of specific facts in a future submission that claims the NSS-2 BRIDGE or the IB-Stim as a predicate and warrants a request for this type of information to establish substantial equivalence.

[37] While the 510(k) manufacturer should determine whether there are applicable special controls for the device type in the classification regulation, the performance data that FDA may request to support substantial equivalence depends upon the device type and the differences that affect safety and effectiveness between the new device and the predicate device. See 510(k) Guidance, pp. 6 and 22 n.31.

At the time of each of the DEN170018 and DEN180057 granting orders, FDA determined that the special controls listed in the granting orders were necessary to provide reasonable assurance of safety and effectiveness for devices of those types.

As part of the De Novo process in establishing the special controls for a particular device type, FDA considers the risks posed by the device and addresses the mitigations for such risks.[38] Ultimately, FDA establishes controls that are necessary to provide reasonable assurance of the safety and effectiveness of the device type. It is not necessarily the case that the evidence provided to support a De Novo granting order would be established as a special control in the classification regulation for the device type or, in the 510(k) review process, that such evidence would be required of a particular device subject to the classification regulation, including a proposed device claiming the grantee device as its predicate. Even if a particular special control is not established at the time of De Novo grant, the Agency has discretion to determine for a new device of this device type with different technological characteristics whether there are other types of additional information or data, beyond what is required under the codified special controls, that may be needed in the 510(k) review process to make a substantial equivalence determination consistent with applicable law, regulations, and established policy.[39]

Adhering to the statutory provisions for establishing special controls, as well as implementing regulations, and consistent with existing guidance documents and procedures for the De Novo process and the least-burdensome principles of the FD&C Act, FDA has reviewed, and will continue to review, each premarket notification that claims the NSS-2 BRIDGE or the IB-Stim as a predicate device to evaluate the relative safety and effectiveness of the new device.[40] Different technological characteristics of the new device compared to the claimed predicate will be considered individually and holistically for their potential impact on safety and effectiveness. Consistent with this approach, we decline to amend the special controls or otherwise adopt a policy that categorically requires "head-to-head" animal model studies and/or a clinical study to demonstrate effectiveness, as applicable in every instance to all premarket notification submissions or by adding a special control requiring such testing data for all proposed new devices of the device type. On the other hand, neither our least-burdensome principles, the 510(k) review process, nor this response to Petition-1 and Petition-2 precludes FDA from requesting such information on a case by case basis in the 510(k) review process *when the*

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[38] Under our least burdensome principles, the minimum performance data necessary to demonstrate substantial equivalence for the device type can change over time based on new information the Agency receives. Least-Burdensome Principles Guidance, at 19. See also 510(k) Guidance, at 25, available at https://www.fda.gov/media/82395/download.

[39] Section 513(i)(1)(A)(ii)(I) specifies that when the new device and the claimed predicate have different technological characteristics, the required information includes "appropriate clinical or scientific data *if deemed necessary by* [FDA]." (italics added).

[40] On May 2, 2018, the Agency determined in the 510(k) review process that another device claiming the NSS-2 BRIDGE device as a predicate is SE to it and may be marketed (K173861). The FDA 510(k) notification clearance data for the K173861 decision is available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K173861. On December 29, 2020, the Agency determined in the 510(k) review process that another device claiming the IB-Stim device as a predicate is SE to the IB-Stim and may be marketed (K202940). The FDA 510(k) notification clearance data for the K202940 decision is available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K202940.

Agency deems it necessary to make a substantial equivalence decision even if such information is not codified as a special control.

Accordingly, to the extent that the Agency action requested in the Petition-1 or Petition-2 is to categorically require animal model or clinical testing for every future proposed device claiming the NSS-2 BRIDGE or the IB-Stim as a predicate, such request is denied as it is contrary to the law, our regulations, and FDA's guidance for establishing special controls in the context of a De Novo proceeding, as well as inconsistent with the application of least burdensome principles in substantial equivalence determinations. As explained above, our decision on these Petitions does not preclude the Agency from requesting animal model or clinical testing when necessary to determine whether a proposed new device of these types is SE and provides a reasonable assurance of safety and effectiveness.

E. Conclusion

In accordance with 21 CFR 10.30(e), FDA denies Petition-1 and Petition-2 for the reasons discussed above.

If you have any questions about this response, please contact John Maiers in our Office of Policy at (301) 796-0343.

Sincerely,

Ellen J. Flannery -S

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