DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-002

February 4, 2023

Jeffrey G. Thomas
On behalf of Marteen Moore
Thomas Law Company
201 Wilshire Blvd, Suite A22
Santa Monica, CA 90401

Re: Citizen Petition - Docket Number FDA-2013-P-0944

Dear Mr. Thomas:

This letter responds to the above referenced citizen petition that you submitted to the Food and Drug Administration (FDA). The petition makes several requests pertaining to FDA's regulatory oversight of DuraSeal® Spinal Sealant ("the product"), which was approved for marketing via the premarket approval (PMA) process (see P080013 and associated amendments[1]). This device is indicated for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure. Your petition requests that the Commissioner of Food and Drugs:

1) "Enforc[e] post-approval conditions of the PMA" by ordering the Sponsor to complete enrollment in its post-approval study of infection rates under 21 CFR 814.82.
2) Investigate risks disclosed in "serious adverse effects [during the clinical trial] that were not discussed in the PMA" and to require revisions to the product labeling and/or package inserts as appropriate to the findings of the Agency. Specifically, you request FDA:
    a. Investigate the product labeling related to the contraindication for use in revision surgeries and require a stronger ("black box") warning against use of the product in revision surgeries;
    b. Require the Sponsor to clarify the precaution in the product's labeling "against use of the product with another non-autologous sealant or assistive agent" and to include such clarification in a "stronger ("black box") warning;"
    c. Require the Sponsor to provide a warning "against application of the product in the gutters of the spine and/or confined bony spaces enclosing nerves adjacent to the spine;" and
    d. Per the Neurological Device Panel's ("the Panel") recommendation, require "a warning to the surgeon to be as diligent as possible to close the durotomy using traditional methods."
3) Investigate your allegation of false advertising that you claim, "misrepresents a safety feature of the product concerning [its] blue dye."

[1] Information on FDA's original premarket approval of this product can be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P080013.

4) Investigate the "sponsor's compliance with its duties to report serious adverse effects" to FDA.
5) Disclose the "identities and contact information" of (adverse event) reporters; and
6) Grant a hearing under section 515(g)(1) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") concerning "denied disclosure of the sponsor's complaint files and serious adverse effects reports for the product by both the sponsor and the agency."

Additionally, your petition further recommends "temporary suspension of the PMA" pursuant to 21 CFR 814.47 for "violation(s) of the Federal Food Drug and Cosmetic Act."

FDA has reviewed the arguments in support of the requests you have made in your petition and has reviewed the administrative record for P080013 along with medical device adverse event reports (MDRs) submitted for the product since its approval. One of your requests is denied as moot and the remaining requests in your petition are denied. We address each of your specific requests in turn, below.

(1) Enrollment in the Post-Approval Study

Your petition requests that FDA order the Sponsor to complete enrollment in its post-approval study of infection rates pursuant to 21 CFR 814.82. As a condition of approval for P080013, the Sponsor was required to conduct a post-approval study (PAS) designed to estimate the rates of post-operative cerebrospinal fluid (CSF) leak, deep surgical site infection (SSI), and neurological serious adverse events (SAEs) at 90 days.[2] Your request to order the Sponsor to complete enrollment in its post-approval study is denied as moot because the study was completed and a final report was submitted to FDA on October 31, 2016.[3]

With respect to the study's primary endpoint to estimate the rates of post-operative CSF leak, the product was found to be non-inferior to the control. Specifically, of the 886 study subjects on whom data were available, 58 (6.6%) subjects (DuraSeal® Exact Spine Sealant: 30 [6.6%]; Control arm: 28 [6.5%]) experienced a CSF leak within 90 days after the spine surgical procedure. The difference estimate and its 95% Confidence Interval (%) between treatment arms was reported as -0.9 (- 3.7, 2.0) from an unstratified analysis and as -0.5 (-3.4, 2.3) from a stratified analysis by propensity score quintile. Additionally, there was no statistically significant difference in distribution of subjects with deep SSI between the treatment groups or in the proportion of subjects with any adverse event between the DuraSeal® Exact Spine Sealant and the control arms.[4]

Notably, the PAS resulted in a labeling change recommendation regarding the rate of SSIs. Originally, the label stated that "the incidence of post-operative SSIs was also comparable between the two groups (6.9% and 7.1% of subjects in the DuraSeal Spine Sealant and Control groups, respectively, p=1.00)." Based on the PAS results, the recommended labeling

[2] See P080013 Approval Order at https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080013A.pdf
[3] FDA, Post-Approval Studies (PAS) Database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=407006&c_id=308
[4] PAS Database.

change would read, "there was no statistically significant difference in distribution of subjects with deep Surgical Site Infection (SSI) between the treatment groups."[5]

(2) Require Revisions to the Product Labeling and/or Package Inserts

Your petition requests that FDA investigate risks disclosed in serious adverse events that took place during the clinical trial that you allege were not discussed in the PMA. Accordingly, you request several revisions to the product labeling and/or package inserts as appropriate to the findings of the Agency.

As required by the FD&C Act and its implementing regulations, device labeling must provide adequate information for use under which practitioners can use the device safely and for the purpose for which it is intended.[6] At times, to be used safely and effectively, device labeling includes contraindications, warnings, and/or precautions. Contraindications in device labeling describe situations in which the device should not be used because the risk of use clearly outweighs any possible benefit and where hazards are known and not theoretical possibilities. An appropriate warning should be included if there is reasonable evidence of an association of a serious hazard with the use of the device. Precautions include information regarding any special care to be exercised by the practitioner and/or patient for the safe and effective use of the device.[7]

In your petition, you request the following with respect to the labeling of the DuraSeal® Spinal Sealant:

a. Investigate the product labeling related to the contraindication for use in revision surgeries and require a stronger ("black box") warning against use of the product in revision surgeries

FDA believes that accurate labeling and effective communication of that labeling are important to help ensure that patients are aware of the risks associated with a particular device. A device shall be deemed misbranded if, among other things: its labeling is false or misleading in any particular, including whether the labeling fails to reveal a material fact; its labeling does not contain adequate warnings; or any information required to be in the labeling is not prominently placed with such conspicuousness and in such terms to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.[8]

---

[5] PAS Database (emphasis added). The current language can be found at https://www.integralife.com/file/general/1608309944.pdf and reads, "Analysis of key safety endpoints showed that there was no statistically significant difference in the proportion of subjects with deep surgical site infections between DuraSeal Exact Spine Sealant and Control arms (1.6% versus 2.1%; p=0.6160)."

[6] See 21 CFR 801.5. Prescription devices also carry their own unique requirements for labeling. See 21 CFR 801.109.

[7] See Device Labeling Guidance #G91-1 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm).

[8] See sections 502(a), 201(n), 502(c), and 502(f)(2) of the FD&C Act. Additionally, other authorities allow FDA to set restrictions on the use of devices in certain circumstances. See Section 520(e) of the FD&C Act.

Under the FD&C Act, FDA regulates dural sealants as Class III devices subject to premarket approval.[9] During the premarket approval process, FDA determines whether the device's premarket approval application (PMA) demonstrates "reasonable assurance of safety and effectiveness" by weighing any probable benefit to health from use of the device against any probable risk of injury or illness and by considering the persons for whose use the device is represented or intended and the conditions of use for the device prescribed, recommended, or suggested in the device's labeling.[10] In light of the relevant FDA authorities, and based on our review of the MDR reports and the PAS results relevant to revision surgery risks, the Agency's current position is that the labeling of the subject device is not misbranded and therefore does not require additional risk information or warnings regarding the subject device's approved indications for use. Separately, and on this same set of evidence, it is also the Agency's current position that a boxed warning to convey the risks associated with the use in revision surgeries of DuraSeal® Spinal Sealant is not necessary to provide a reasonable assurance of safety and effectiveness of the subject device.

First, our analysis of the MDRs submitted to FDA between January 1st, 2013, and April 21st, 2022, identified only two MDRs that reported patient injury from DuraSeal swelling after use in a revision procedure. One of the MDRs was associated with a published journal article from 2012.[11] The second MDR was submitted to FDA in 2017 and reported patient injury after an unapproved off label use of the device. Neither of these incidents present evidence of a risk associated with the use of the subject device under its approved conditions for use. Accordingly, FDA believes that the current DuraSeal® labeling does not fail to reveal a material fact, contain adequate warnings, or otherwise provide required information such that the subject device would be misbranded. Additionally, the current DuraSeal® labeling is sufficient to provide a reasonable assurance of the safety and effectiveness of the subject device, and that additional warnings, including a boxed warning, are not necessary.

Second, the PAS results included a discussion of risks of use in revision surgery. As set forth in the "Clinical Experience" section of the original product labeling,[12] revision surgeries were a pre-operative exclusion criterion during the study and, as such, the initial approval study did not specifically collect clinical data on use in revision surgeries. However, the PAS results show that there was no significant risk of post-operative CSF leak, deep SSI, or neurological SAEs at 90 days with the DuraSeal® Spinal Sealant compared to the control group in which the DuraSeal® Spinal Sealant was not used.

Accordingly, the MDR analysis and PAS results fail to suggest risks associated with the subject device under its approved conditions for use that would merit the imposition of new

---

[9] See Section 513(a)(1)(C) of the FD&C Act, 21 U.S.C. 360c(a)(1)(C), and 21 CFR 860.7.

[10] Section 513(a)(2)(C) of the FD&C Act and 21 CFR 860.7(d). To aid in this process, PMA sponsors submit valid scientific evidence, including one or more clinical investigations where appropriate, which FDA reviews. See our guidance document entitled "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.

[11] THE JOURNAL OF CLINICAL ORTHOPAEDICS AND RELATED RESEARCH (2012) 470:1640-1645, A Publication of The Association of Bone and Joint Surgeons. An Article Titled Cauda Equina Syndrome After a Tlif Resulting From Postoperative Expansion of a Hydrogel Dural Sealant.

[12] See http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080013c.pdf.

information or warnings on the subject device's labeling. As noted above, the MDR analysis did not identify any new or unknown patient problems, and in part reflected issues related to an unapproved off label use of the subject device. The PAS results showed no significant risk of post-operative CSF leak, deep SSI, or neurological SAEs at 90 days with the DuraSeal® Spinal Sealant compared to the control group in which the DuraSeal® Spinal Sealant was not used. Based on this evidence, FDA has determined that additional information, such as a black box warning, is not needed on the labeling of the subject device to avoid being misbranded pursuant to sections 502(a), 201(n), 502(c), or 502(f)(2) of the FD&C Act. On the same evidence, FDA also believes that the company's current labeling effectively communicates the risks associated with the subject device and reflects sufficient information that reasonably assures the safety and effectiveness of the subject device when used as directed. Therefore, your request is denied.

b. Require DuraSeal's® Sponsor to clarify the precaution in the product's labeling against use of the product with another non-autologous sealant or assistive agent and to include such clarification in a stronger ("black box") warning

Your petition requests clarification of the precaution in the labeling against use of the product with another non-autologous sealant or assistive agent. Based on our understanding of your request, we believe you are requesting a labeling change to connect this precaution with a warning against applying excess product due to the danger of runoff in the confined bony spaces and gutters of the spine. The product labeling includes both a warning "Do not use the DuraSeal® Spine Sealant as a hemostatic agent" and a precaution "Do not use in combination with other sealants or hemostatic agents." The safety and effectiveness of the product as a hemostatic agent was not studied in the clinical trial. Due to the lack of valid scientific evidence of safety or effectiveness of the product as a hemostatic agent and the potential for the product to interfere with the function of other sealants and hemostatic agents if used in conjunction, a warning against use as a hemostatic agent and a precaution against use in combination with other hemostatic agents or sealants have already been appropriately included in the labeling. In addition, as we discuss below, a contraindication for use of the product itself in confined bony spaces is already included in the labeling.

FDA believes the potential risks presented by use of the DuraSeal® Spinal Sealant with other non-autologous sealants or assistive agents is adequately addressed through the existing precautions in the labeling. Specifically, the labeling currents warns against use of DuraSeal® Spinal Sealant in "[p]rocedures involving non-autologous duraplasty." Therefore, your request for a specific "black box" warning for use with other non-autologous sealants or assistive agents is denied.

c. Require a warning against application of the device in the gutters of the spine and/or confined bony spaces enclosing nerves adjacent to the spine

Your petition requests a warning against application of the device in the gutters of the spine and/or confined bony spaces enclosing nerves adjacent to the spine. Because of case reports of neurologic injury caused by the product in conjunction with hemostatic agents in confined

anatomical locations, the product labeling already includes a contraindication against use of the product in confined bony spaces (which is inclusive of the gutters of the spine). Specifically, the labeling originally stated, "Do not apply the DuraSeal hydrogel to confined bony structures where nerves are present since neural compression may result due to hydrogel swelling. The hydrogel may swell up to 50% of its size in any dimension."[13] We believe the existing contraindication adequately addresses the issue and no additional labeling changes are required. Therefore, your request is denied.

d. Require a warning to close the durotomy using traditional methods

Your petition requests that FDA require a warning to the surgeon to be as diligent as possible to close the durotomy using traditional methods as recommended by the Neurological Device Panel ("the Panel"). The product is currently indicated as an *adjunct* to sutured dural repair, and this use is supported by the premarket clinical study. FDA is not aware of existing information to support that the product is not safe and effective as indicated, and FDA is not aware of any evidence that the inclusion of such a warning is needed to use the device safely.[14] Therefore, your request is denied.

(3) Blue Dye

Your petition requests that FDA investigate what you allege is false advertising and misrepresentation by the Sponsor. You assert the Sponsor represented in materials presented with the PMA that the product's dye retains its blue color for fourteen days after surgery as a safety feature of the product. You claim that the blue dye is a "diagnostic tool which assists the surgeon who must re-operate on the patient to determine whether the product was effective to seal the dura mater, and to prevent a leak of CSF."[15] You claim that, "[i]t also assists the surgeon to determine whether the product malfunctioned because it was applied to the wrong body part or whether another agent or sealant used after surgery interacted with it in a harmful manner."[16] You then cite more recent promotional literature allegedly published by the Sponsor which states that the blue dye of the product fades instantly upon application and the blue color is not retained after application. You use this as evidence that the Sponsor has "eliminated an important safety feature of the product which was prominently disclosed and discussed in the PMA."[17] Further, you claim that the sponsor misrepresented to FDA that the blue dye in the product retains its blue color for fourteen days after the surgery as a tool

---

[13] DuraSeal® Spinal Sealant Labeling, https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080013C.pdf. The current labeling states, "Do not apply the DuraSeal hydrogel to confined bony structures where nerves and spinal cord are present since neural compression may result due to hydrogel swelling. The hydrogel may swell up to 12% of its size in any dimension." *See* https://www.integralife.com/file/general/1608309944.pdf.

[14] Also, please note that while FDA carefully considers all input received from the Panel, the Panel's purpose is to provide advice and recommendations to the Agency. However, the Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by the Panel. See 21 CFR 14.5.

[15] Citizen Petition Regarding the Conditions of the Pre-Marketing Approval of the DuraSeal® Spinal Sealant, Docket Number FDA-2013-P-0944 (hereinafter "Petition"), 13.

[16] Petition at 13.

[17] Petition at 13.

for diagnosis.

Requests for FDA to initiate investigations of information that suggests a firm has submitted false information to the FDA with their PMA and related regulatory activity are outside the scope of our citizen petition regulations.[18] Nonetheless, FDA has carefully reviewed the record pertaining to the approval of this PMA submission and has not found any claim that the blue dye was intended as a safety feature. Rather, the record indicates that the purpose of the dye was as a visual aid for the clinician when applying the sealant to the surgical site. During premarket review of this product, FDA did not consider the blue dye's function as a visual aid for a clinician to be a safety feature, nor was the blue color relied upon by the Sponsor in its PMA materials to specifically mitigate any specific identified product risks. FDA's review of the dye was limited to its chemical safety, biocompatibility profile, and residence time in the body. FDA has investigated this matter and finds no basis to conclude that the Sponsor ever represented or promoted the blue dye as a safety feature. Similarly, FDA finds no basis to conclude that the Sponsor falsely advertised or misrepresented its product. For these reasons, your request is denied.

(4) Compliance with Adverse Event Reporting Requirements

You request that FDA investigate the Sponsor's compliance with its duties to report serious adverse effects to FDA. FDA's citizen petition regulations include requests "to issue, amend, or revoke a regulation;" "issue, amend, or revoke an order;" and a request "to take or refrain from taking any other form of administrative action."[19]As noted above, requests for FDA to initiate investigations and related regulatory activity are outside the scope of our citizen petition regulations and therefore this request is denied.[20]

(5) Disclosure of Adverse Event Reporter's Identities and Contact Information

You requested the identities and contact information of those who submitted the adverse events reports that were provided to you in response to your Freedom of Information Act (FOIA) request and included in Exhibit E of your petition.

Under 21 CFR 10.25, citizen petitions are a venue for individuals to request that FDA issue, amend, or revoke a rule/order, or that the Agency take or refrain from taking an administrative action.[21] This petition does not constitute such a request and is, therefore, denied and improper for FDA consideration through the Agency's citizen petition regulations.

---

[18] See 21 CFR 10.30(k) ("This section does not apply to the referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence, or to requests, suggestions, and recommendations made informally in routine correspondence received by FDA.")
[19] 21 CFR 10.30(b)(3).
[20] 21 CFR 10.30(k).
[21] Definition in 21 CFR 10.3 for administrative action: Administrative action includes every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral.

The appropriate mechanism for requesting such records is through FDA's FOIA process. FDA's FOIA request procedures can be found at 21 CFR 20.40. If you submitted a FOIA request and were denied records, you should have received a letter from the Agency giving the reasons for denial and explaining that an appeal may be made to the Department of Health and Human Services.[22] However, because your original FOIA request was filed in 2012 and it appears that no appeal was made within the required time period following FDA's initial determination, you should file a new FOIA request that asks for the records in unredacted form.

If you choose to submit a new FOIA request, please be aware that the identities of adverse event reporters will likely continue to be redacted. While FDA has an obligation to make certain publicly releasable information available in response to a FOIA request, including an obligation to release user facility adverse event reports when requested, certain information in the reports could be considered confidential and redacted from user facility reports prior to disclosure. FDA makes these redactions in accordance with statutory and regulatory provisions described below.

a. Reports required by law

Where the report involves a death or serious injury, section 519(b)(2) of the FD&C Act prohibits FDA from releasing the identity of the user facility except in connection with an action to enforce the user facility's reporting obligations or in a communication to the manufacturer of the device that is the subject of the report. Similarly, FDA regulations also prohibit the release of this information except to employees of the Department of Health and Human Services, to the Department of Justice, or to the duly authorized committees and subcommittees of Congress.[23] While 21 CFR 803.9(b)(2) provides that FDA will disclose to a patient who requests a report all the information concerning that patient in the report, this disclosure does not include the identity of the user facility reporter or personal privacy information of persons other than the requesting patient.[24]

b. Reports submitted voluntarily

Where the event is not required by law to be reported, and thus is reported voluntarily, FDA does not disclose information which would disclose the identity of the voluntary reporter, including the user facility and any individuals making the report on behalf of a user facility.[25] A patient involved in an adverse event will receive a copy of the report of that event upon request, but the identities of the individual voluntary reporters will not be included unless they consent to this disclosure, or unless there is a court order in the course of medical malpractice litigation involving both parties.[26] If both the voluntary reporter and the person identified in an adverse event consent in writing, their identities may also be disclosed to

[22] See 21 CFR 20.49 and 45 CFR 5.61.
[23] See also 21 CFR. 803.9(c).
[24] Also, please be aware that, with limited exceptions, section 519(b)(3) of the FD&C Act provides that adverse event reports made by device user facilities are inadmissible in civil actions involving private parties.
[25] 21 CFR 20.63(f); 21 CFR 20.111(c)(3)(ii)(*c*) and (iii); 21 CFR 803.9(b)(3).
[26] 21 CFR 20.63(f)(1).

third parties.[27] However, FDA may not be required to solicit consent for disclosure from either the voluntary reporter or the person identified in a voluntary report.[28]

(6) Request for a Public Hearing

In your petition, you request a hearing under section 515(g)(1) of the FD&C Act because the petitioner was "denied disclosure of the sponsor's complaint files and serious adverse effects reports for the product by both the sponsor and the agency."[29] Please note that while you may request a hearing under section 515(g)(1) through the submission of a citizen petition under 21 CFR 10.30, a hearing under section 515(g)(1) is held to review an order approving or denying approval of a PMA or an order withdrawing approval of an application. To the extent that you are requesting to use this process to compel the disclosure of FDA records, a hearing under section 515(g)(1) is not an appropriate mechanism. Such information is appropriately requested via the Agency's FOIA process. FDA's FOIA request procedures can be found at 21 CFR 20.40, as described above. Because a hearing under section 515(g)(1) is not the appropriate mechanism to request Agency records or to appeal a denial of such request, FDA is denying this request for a hearing.

(7) Suspension of PMA

In your petition, you request temporary suspension of the product's PMA approval for "violation(s) of the Federal Food Drug & Cosmetic Act ('Act')."[30] Section 515(e)(3) of the FD&C Act and 21 CFR 814.47 provides FDA with the authority to order the temporary suspension of approval of a PMA if FDA determines that there is reasonable probability that continued distribution of a device would cause "serious adverse health consequences or death." Here, the results from the PAS support that this device has a reasonable assurance of safety and effectiveness for its intended use. Moreover, FDA has not made such a determination in this case that the subject device poses a reasonable probability that continued distribution would cause serious adverse health consequences or death. Accordingly, FDA is denying your request to temporarily suspend the DuraSeal® Spinal Sealant PMA.

Conclusion

FDA has reviewed your petition along with other relevant data and information available to the Agency. For the reasons discussed above, one of your requests is denied as moot and the remaining requests in your petition are denied.

---

[27] 21 CFR 20.63(f)(1)(i).
[28] *Id.*
[29] Petition at 3.
[30] Petition at 2.

If you have any questions, please contact Rachael Hunt by e-mail at Rachael.Hunt@fda.hhs.gov.

Sincerely,

Ellen J. Flannery -S

Digitally signed by Ellen J. Flannery -S
Date: 2023.02.04 17:37:28 -05'00'

Ellen J. Flannery, J.D.
Deputy Center Director for Policy
Director, Office of Policy
Center for Devices and Radiological Health