DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

July 7, 2016

Medtronic Sofamor Danek USA, Incorporated
Ms. Kristi Frisch
Senior Regulatory Affairs Specialist
1800 Pyramid Place
Memphis, Tennessee 38132

Re: P090029/S003
PRESTIGE LP™ Cervical Disc
Filed: June 3, 2015
Amended: July 20, July 27, and August 10, 2015; February 12 and April 4, 2016
Procode: MJO

Dear Ms. Frisch:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the PRESTIGE LP™ Cervical Disc to expand the indication for use to include use at two contiguous levels and to add a 5mm device height for use at either one or two contiguous levels. This device is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following discectomy at one level or two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to abnormality localized to the level of the disc space and at least one of the following conditions confirmed by imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. The PRESTIGE LP™ Cervical Disc is implanted using an anterior approach. Patients should have failed at least 6 weeks of non-operative treatment or have had the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management prior to implantation of the PRESTIGE LP™ Cervical Disc. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following data as part of the Annual Report:

1. Results from *The PRESTIGE LP™ Cervical Disc Post-Market Device Failure Study and Complaint Analysis* that will be conducted for the 10 years following approval of this PMA supplement. *The PRESTIGE LP™ Cervical Disc Post-Market Device Failure Study and Complaint Analysis* is a 10 year study designed to fully characterize adverse events, complaints, and the long-term modes and causes of failure when the PRESTIGE LP™ Cervical Disc is used in the intended patient population under general conditions of use in the United States and in the rest of the world, as well as to identify new safety concerns that were not observed in the clinical study. This study will include the following elements:

    a. Adverse event and complaint analysis for 10 years following approval of this PMA supplement through which you will collect, analyze, and submit to FDA data regarding all adverse events including subsequent surgeries, heterotopic ossification, device malfunction, and other serious device-related complications. Information will be collected passively through complaints, MDRs, and literature reviews.

    b. An analysis of all available explanted PRESTIGE LP™ Cervical Discs for 10 years following approval of this PMA supplement (including, but not limited to,

those retrieved from subjects in the Office of Device Evaluation (ODE)-Lead PMA Post-Approval Study (*10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels*) as outlined below, those retrieved from subjects in the Office of Surveillance and Biometrics (OSB)-Lead PMA Post-Approval Study (*PRESTIGE LP™ 2-Level Metal Concentrations*) as outlined below, and those retrieved from commercial use of the PRESTIGE LP™ Cervical Disc (including in patients treated at one level, two contiguous levels, or off-label at more than two levels).

Surgeon training on the use of the PRESTIGE LP™ Cervical Disc will include detailed training on the requirements of this *Post-Market Device Failure Study and Complaint Analysis*. Also, as part of the active collection of surgeon feedback, you will regularly interact with the surgeon users of the device to gather data on the number of PRESTIGE LP™ Cervical Discs implanted as well as subsequently explanted and to encourage participation in this *Post-Market Device Failure Study and Complaint Analysis*. In cases where a PRESTIGE LP™ Cervical Disc is explanted but not submitted for analysis as part of the *Post-Market Device Failure Study and Complaint Analysis*, you will be responsible for documenting the reason as part of the Annual Report.

For each known device removal since the prior Annual Report, you will report the following information or explain why certain information is not available: a detailed clinical narrative, a copy of the operative report from the original PRESTIGE LP™ Cervical Disc implantation surgery, copies of operative reports from all subsequent surgeries including the removal surgery, copies of any available histologic analyses of the host response to the device and any particulate debris conducted by an independent laboratory (or the hospital where the device was removed if the surgeon did not send the sample to the independent laboratory) for explants in the United States, copies of any available metal ion data analysis conducted by an independent laboratory for the ODE-Lead and OSB-Lead PMA Post-Approval Studies outlined below, and any available explant analysis including a detailed explant analysis conducted by an independent laboratory (for explants in the United States) per the *Plan For The Retrieval And Analysis Of Explanted PRESTIGE LP™ Artificial Cervical Disc Device Used In The PRESTIGE LP™ Cervical Disc (Two-Level) Post-Approval Study* (Version A, provided by email 06/16/2016) reviewed and approved by FDA.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Separate PAS Progress Reports must be submitted for each study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. You will submit a final report within 3 months of the last subject visit. Two (2) copies of each report, identified as an "ODE-Lead PMA Post-Approval Study Report" or an "OSB-Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted.

1. ODE-Lead PMA Post-Approval Study – *10 Year Extended Follow-up of IDE Subjects*

Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study will be conducted per the protocol dated January 2015 and approved by FDA on March 5, 2015 (Version G) and the Statistical Analysis Plan dated June 2016 (Version 2.0).

The *10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels* is a 10-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the PRESTIGE LP™ Cervical Disc used for reconstruction of the disc at two contiguous levels from C3-C7 in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain or myelopathy due to abnormality localized to the level of the disc space as compared to 2-level Anterior Cervical Discectomy and Fusion (ACDF). This PAS will follow the 397 subjects treated in the pivotal investigational device exemption (IDE) study (209 2-level PRESTIGE LP™ subjects and 188 2-level ACDF control subjects) annually through 10 years post-operative.

At each periodic (±3 months) visit, you will collect the following data: Neck Disability Index (NDI), Neck and Arm Pain Questionnaire, health status questionnaire (SF-36), neurological status, gait assessment and foraminal compression test, subject satisfaction, subject perceived effect, physician perception of results, medication use and postoperative treatment for pain management, work status, radiographic information, and all adverse events regardless of cause including all subsequent surgical interventions. Radiographic information collected will include: range of motion (ROM) on flexion/extension films (angulation and translation as well as the correlation of range of motion with clinical outcomes), functional spinal unit (FSU) height, implant condition (including evaluation of implant migration), radiolucency, heterotopic ossification (including grade, progression over time and correlation with subject characteristics and post-operative clinical outcomes). You will also collect clinical and radiographic data on adjacent level degeneration including both surgical and non-surgical adjacent level treatment as well as adjacent level diagnoses and adjacent level range of motion.

You will analyze all PRESTIGE LP™ Cervical Discs that are explanted as part of this Post-Approval Study per the Plan for the Retrieval and Analysis of Explanted PRESTIGE LP™ Artificial Cervical Disc Devices reviewed and approved by FDA and will present the results in the relevant section of each PMA Annual Report, as outlined above.

The primary objective of this PAS is to evaluate Overall Success (Protocol Definition) at 120 months, which is defined consistent with the IDE study as:

a. Improvement (reduction) of at least 15 points in the NDI score at 120 months compared to pre-operative baseline;

b. Maintenance or improvement in neurological status at 120 months compared to pre-operative baseline as measured based on motor function, sensory function,

and reflexes;

c. No serious adverse event classified as implant associated, or implant/surgical procedure associated by the independent Clinical Adjudication Committee (CAC); and

d. No additional surgical procedure classified as a "failure."

In addition, consistent with the IDE study, because the additional surgical procedure component of Overall Success (Protocol Definition) did not consider all subsequent surgeries at the index level as failures, you have also agreed to conduct the following additional analysis referred to as Overall Success (Alternate Analysis) in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures.

Overall Success (Protocol Definition) and Overall Success (Alternate Analysis) rates in the 2-level PRESTIGE LP™ Cervical Disc group and the 2-level ACDF control group will be compared and assessed for non-inferiority based on a ten percent non-inferiority margin. Subjects who were non-recoverable non-responders prior to 24 months will carry forward as failures for each subsequent annual visit. Numerous sensitivity analyses as specified in the protocol and statistical analysis plan will be done to assess the robustness of the study conclusions. As outlined in the study protocol, you will conduct all of the same analyses as were included in the FDA Summary of Safety and Effectiveness Data.

FDA will expect at least 85% follow-up at the 10-year timepoint to provide sufficient data to evaluate longer-term safety and effectiveness. You will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. You will submit a final study report within 6 months of the last subject visit.

2. OSB-Lead PMA Post-Approval Study – *PRESTIGE LP 2-Level Metal Concentrations*: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. This study will be conducted per protocol dated June 22, 2016 (Version A, provided by email).

   The *PRESTIGE LP™ 2-Level Metal Concentrations* study is a prospective, one-arm cohort study of thirty (30) new subjects who will be enrolled and treated with the PRESTIGE LP™ Cervical Disc at 2 contiguous levels from C3–C7 in accordance with the approved indications for use. The 30 newly enrolled patients will be followed for 24 months post-operative to assess the metal concentrations (titanium, vanadium, and aluminum) present in blood serum after implantation with the PRESTIGE LP™ Cervical Disc at two contiguous levels.

   You will collect the following data at baseline, 6 weeks, 3 months, 6 months, 12 months, and 24 months: blood samples for serum metal concentration testing (titanium, vanadium, aluminum), Neck Disability Index (NDI), Neck and Arm Pain Questionnaire,

neurological status, medication use, work status, and all adverse events regardless of cause including all subsequent surgical interventions.

Metal concentration data will be collected, stored, tested and analyzed in accordance with the methodology employed for the *1-Level PRESTIGE LP™ Metal Ion* study protocol (P090029/S002/A005). You will evaluate the change in metal concentrations at each study time-point.

You will also analyze all PRESTIGE LP™ Cervical Discs that are explanted as part of this Post-Approval Study per the *Plan For The Retrieval And Analysis Of Explanted PRESTIGE LP™ Artificial Cervical Disc Device Used In The PRESTIGE LP™ Cervical Disc (Two-Level) Post-Approval Study* reviewed and approved by FDA and will present the results in the relevant section of each PMA Annual Report, as outlined above.

You will evaluate Overall Success at 24 months which is defined consistent with the IDE study as:

a. NDI score improvement of at least 15 points from baseline;

b. Maintenance or improvement in neurological status (as measured based on motor function, sensory function, and reflexes);

c. No serious adverse event classified as implant associated or implant/surgical procedure associated by the independent Clinical Adjudication Committee (CAC);

d. No additional surgical procedures classified as a “failure.”

In addition, consistent with the IDE study, because the additional surgical procedure component of Overall Success (Protocol Definition) did not consider all subsequent surgeries at the index level as failures, you will also conduct an additional analysis referred to as Overall Success (Alternate Analysis) in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures.

As outlined in the study protocol, you will summarize and analyze the data as follows:

a. The metal concentrations of titanium, aluminum, and vanadium in blood serum at all study time-points will be summarized descriptively using mean, standard deviation, median, minimum and maximum.

b. Changes in metal concentrations of titanium, aluminum, and vanadium at all study time-points as compared to pre-operative concentrations will be assessed using a paired t-test for normally distributed data or a Wilcoxon signed rank test for not normally distributed data.

c. Secondary measurements, including time-course data on the rate of overall

success and the rates of NDI and neurological success (as defined in the study protocol) will be summarized in frequency tables.

d. Changes in NDI score, neck pain score and arm pain score at all study time-points as compared to pre-operative will be assessed using a paired t-test for normally distributed data or a Wilcoxon signed rank test for not normally distributed data.

e. Correlation analyses will be conducted as outlined in the study protocol to assess possible trends between metal concentrations and clinical variables (including overall success, neurological success, NDI outcomes, and neck and arm pain outcomes).

FDA will expect at least 90% (n=27) follow-up at the 2-year time-point to provide sufficient data to evaluate possible changes in the metal concentrations.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes complete protocols for the *PRESTIGE LP™ Cervical Disc Post-Market Device Failure Study and Complaint Analysis* as well as the two (2) post-approval studies (*10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels* and *PRESTIGE LP™ 2-Level Metal Concentrations*) described above. Your PMA supplements should be clearly labeled as an "ODE Lead" or "OSB Lead" PMA Post-Approval Study Protocol as noted above and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all final labeling. Final

labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in six copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any minor clarification questions concerning the contents of the letter, please contact Ms. Melissa Hall at 301-796-6947 or melissa.hall@fda.hhs.gov.

Sincerely yours,

Vincent J. Devlin -S

for

Mark N. Melkerson
Division Director
Division of Orthopedic Devices
Office of Device Evaluation
Center for Devices and Radiological Health