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

June 11, 2015

Aesculap Implant Systems, LLC
Ms. Lisa M. Boyle
Regulatory Affairs Manager
3773 Corporate Parkway
Center Valley, Pennsylvania 18034

Re: P120024
activL® Artificial Disc
Filed: December 18, 2012
Amended: September 12, 2013, September 18, 2013, March 5, 2014, October 23, 2014, and November 19, 2014
Procode: MJO

Dear Ms. Boyle:

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) for the activL® Artificial Disc. This device is indicated for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature patients with symptomatic degenerative disc disease (DDD) with no more than Grade I spondylolisthesis at the involved level. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, physical examination, and radiographic studies. The activL® Artificial Disc is implanted using an anterior retroperitoneal approach. Patients receiving the activL® Artificial Disc should have failed at least six months of nonoperative treatment prior to implantation of the device. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device 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.

Expiration dating for this device has been established and approved at five years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year 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 an Explant Analysis Retrieval Study that will be conducted for the 10 years following PMA approval and will include an analysis of all explanted activL® Artificial Discs (including, but not limited to, those retrieved from subjects in the Office of Device Evaluation (ODE) Lead PMA Post-Approval Study (Post-Approval Clinical Study) as well as patients in the Office of Surveillance and Biometrics (OSB) Lead PMA Post-Approval Study (Enhanced Safety Surveillance Study)) as outlined below. The annual results from the Explant Analysis Retrieval Study will include the following information for each known subject who has undergone device removal since the prior Annual Report: a detailed clinical narrative, a copy of the operative report from the original activL® Artificial Disc implantation surgery, copies of operative reports from all subsequent surgeries including the removal surgery, copies of any pathology reports, and a detailed explant analysis per the Aesculap activL® Retrieval Protocol included in the approved Post-Approval Study and Enhanced Surveillance Study protocols.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Two (2) copies of each report, identified as an "ODE Lead PMA Post-Approval Study Report" or "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 to the address below.

1. ODE Lead PMA Post-Approval Study – Post-Approval Clinical Study to Evaluate the Safety and Effectiveness of the Aesculap activL® Artificial Disc in the Treatment of Degenerative Disc Disease: 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 as per the protocol dated May 26, 2015, Version 9.0.

   The Post-Approval Clinical Study to Evaluate the Safety and Effectiveness of the Aesculap activL® Artificial Disc in the Treatment of Degenerative Disc Disease is a 7-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the activL® Artificial Disc as compared to the alternative lumbar total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference) by following the 376 subjects from the pivotal investigational device exemption (IDE) study (218 randomized activL subjects, 46 non-randomized activL subjects, 106 randomized control subjects, and 6 non-randomized control subjects) annually through 7 years. At each annual (±60 days) visit, the applicant will collect the following data: Oswestry Disability Index (ODI), back and right/left leg pain Visual Analog Scale (VAS), health status survey (SF-36), subject satisfaction, neurological status, radiographic information, medication usage and postoperative treatment for pain management, work status, and all adverse events regardless of cause including all subsequent surgical interventions (SSIs). 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), disc height, local segmental lordosis, radiolucency, device condition, device migration, device subsidence, osteophyte formation, and heterotopic ossification (including grade, stability over time, and correlation with subject characteristics and postoperative clinical outcomes). The applicant will also collect clinical and radiographic data on adjacent level degeneration/disease including both surgical and non-surgical adjacent level treatments as well as adjacent level diagnoses, adjacent level range of motion, and radiographic changes at adjacent levels. The applicant will also analyze all activL® Artificial Discs that are explanted as part of this Post-Approval Study according to the Aesculap activL® Retrieval Protocol and will present the results in the relevant section of each PMA Annual Report, as outlined above.

The primary objective of the PAS is to evaluate individual subject success, which is defined as:

- Improvement of at least 15 points in the ODI score at 7 years compared to baseline;
- Maintenance or improvement in neurological status at 7 years compared to baseline as measured by motor and sensory evaluations with a decrease of one grade in either evaluation considered a failure;
- Maintenance or improvement in motion at the index level (7 year ROM minus preoperative ROM ≥ 0 with $\pm 2°$ measurement error applied) and avoidance of fusion as defined in the protocol;
- No device failures requiring revision, reoperation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events as adjudicated by the Clinical Events Committee (CEC).

In addition, because the ROM success component of the primary endpoint was such a notable driver of the difference in individual subject success rates when comparing the two treatment groups in the IDE study, the applicant has also agreed to conduct the following additional analysis of individual subject success without the ROM success component:

- Improvement of at least 15 points in the ODI score at 7 years compared to baseline;
- Maintenance or improvement in neurological status at 7 years compared to baseline as measured by motor and sensory evaluations with a decrease of one grade in either evaluation considered a failure;
- No device failures requiring revision, reoperation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events as adjudicated by the Clinical Events Committee (CEC).

Individual subject success rates in the randomized activL and randomized control groups will be compared and assessed for non-inferiority based on a ten percent non-inferiority margin for both definitions of individual subject success. 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 will also be done to assess the robustness of the study conclusions.

FDA will expect at least 85% follow-up at the 7-year time point to provide sufficient data to evaluate safety and effectiveness.

The applicant will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. A final report will be submitted within 6 months of the last subject visit.

2. OSB Lead PMA Post-Approval Study – Enhanced Safety Surveillance Study of the Aesculap activL® Artificial Disc: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. This study will be conducted as per the protocol dated May 20, 2015, Version 1.0.

   The Enhanced Safety Surveillance Study (ESS) of the Aesculap activL® Artificial Disc is a 10-year study to fully characterize adverse events and complaints when the device 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 trial.

   The study is an unmasked, uncontrolled surveillance study of all patients treated with the activL® Artificial Disc for the 10 years following PMA approval. The applicant will collect, analyze, and submit all adverse event data including subsequent surgeries, heterotopic ossification, device malfunction, device removal, and other device issues. Data will be collected through annual surgeon surveys, reporting of adverse events, complaints and Medical Device Reports (MDRs), explant analysis, and literature review.

   As part of the active collection of surgeon feedback, the applicant will utilize annual surgeon surveys to collect data related to heterotopic ossification, device malfunction, subsequent surgery at the index level including device removal, and other serious potentially device-related complications. All of the surgeons who have been trained on the use of the activL® Artificial Disc worldwide will be surveyed annually, and the number of surveys issued and received will be reported. If a survey response includes any information related to an adverse event, the applicant will collect additional data as specifically outlined in the ESS protocol and report that data to FDA. The endpoints of the study include information related to patient outcomes, subsequent surgical interventions (SSIs), pain management procedures, device ease of use and satisfaction, device malfunction, and any other serious device-related adverse events.

   The applicant will also analyze all activL® Artificial Discs that are explanted as part of this Enhanced Safety Surveillance Study according to the Aesculap activL® Retrieval Protocol and will present the results in the relevant section of each PMA Annual Report as outlined above.

The applicant will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. A final report will be submitted within 3 months of study completion.

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).

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 approved labeling in final printed form. Final printed 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 printed labeling is identical to the labeling approved in draft form. If the final printed 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 6 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 questions concerning this approval order, please contact Constance P. Soves at (301) 796-6951 or Constance.Soves@fda.hhs.gov.

Sincerely yours,

Mark N. Melkerson -S

Mark N. Melkerson
Director
Division of Orthopedic Devices
Office of Device Evaluation
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