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

November 3, 2015

Cerapedics, Incorporated
Mr. Roger N. White
Clinical and Regulatory Affairs
11025 Dover Street Suite 1600
Westminster, Colorado 80021

Re: P140019
i-FACTOR™ Peptide Enhanced Bone Graft
Filed: August 27, 2014
Amended: February 13, May 20, and June 9, 2015
Procode: NOX

Dear Mr. White:

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 i-FACTOR™ Peptide Enhanced Bone Graft. This combination product is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic 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, after failure of at least 6 weeks of conservative treatment. i-FACTOR™ Peptide Enhanced Bone Graft P-15 Putty must be used inside an allograft bone ring and with supplemental anterior plate fixation. 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 3 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 (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 the following product stability requirements with the reports submitted separately from the annual reporting requirement:

1. Conduct bioactivity stability test for the first 3 production batches of i-FACTOR™ Peptide Enhanced Bone Graft product manufactured and packaged according to the commercialized manufacturing process. The stability study should be performed at the long term controlled storage condition of 25°C/60%RH with test frequency of 0, 6, 12 months for the 1st year, every 6 months for the 2nd year and annually thereafter through the shelf life. The stability data report should be submitted as a "Report – Other" due at the same time as the annual report, but submitted separately from the annual report.

2. Place a minimum one commercial batch of the finished product into long-term stability testing at 25°C/60% RH through the shelf life on an annual basis if manufactured.

3. Withdraw from the market, any batches that fail to meet the approved specifications for the putty product during long-term stability evaluations.

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. Two (2) copies of each report, identified

as an "ODE 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.

ODE Lead PMA Post-Approval Study – i-FACTOR™ Peptide Enhanced Bone Graft Continuation Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The i-FACTOR™ Peptide Enhanced Bone Graft Continuation Study is a continuation of the collection of data from subjects who were enrolled in the clinical study used to support approval of the PMA. The purpose of the study is to collect longer-term data describing the safety and effectiveness of the identified product. The clinical and radiographic endpoints identified in the original protocol (included in Attachment IV-4.6 of the original PMA submission) will continue to be collected annually until each subject has had a total of six years' worth of data collected.

It is expected that 220 total subjects will be enrolled in the study. A conservative estimate of expected number of subjects at 6 years follow-up is 170 subjects (*i.e.* loss of 10 subjects per year due to withdrawals, death and other causes). Further, a follow-up rate of up to 70% is expected at all follow-ups. Thus, data from a total of 154 subjects are expected to be available at year 3 and from 120 subjects at year 6.

The working study hypothesis is that i-FACTOR™ Peptide Enhanced Bone Graft will be non-inferior to autologous bone. This working hypothesis will be tested by a non-inferiority approach as follows. In order to be a success, non-inferiority structured H0 for each primary efficacy endpoint has to be rejected. Three independent hypotheses will be tested, for each of the primary endpoints using the same non-inferiority margins as in the main study. The hypotheses will be tested with one-sided and two-sided 95% C.I. For the fusion and neurological success primary endpoints, the exact binomial confidence interval will be created. For the change in NDI primary endpoint, the confidence intervals for the differences in mean change between the groups adjusting for baseline NDI value will be created. If the confidence interval does not include non-inferiority margin, the H0 will be rejected. An evaluation for the need to adjust the analysis for possible differences between the groups will be included.

Statistical power:

- It is estimated that the fusion rate will be between 98% and 100% at all follow-ups based on the main study results. At 3 years, the study will have 99% power and at 6 years it will have 98% power to reject non-inferiority H0 with non-inferiority margin of 10%.

- The study will have 97% power at 3 years and 93% power at 6 years to reject H0 for the change in NDI outcome under the standard deviation assumption of 19 (based on the main study) and a non-inferiority margin of 11.

- The study will have 95% power at 3 years and 90% power at 6 years to reject non-inferiority H0 for neurological success outcome under the assumption of a neurological success rate of 93% as observed in the main study and a non- inferiority margin of 15%.

The rate of adverse events will be compared between the i-FACTOR™ Peptide Enhanced Bone Graft and the control arm using the Fisher exact test and superiority approach, in the same way as in the original IDE study. Failure to reject H0 or, rejection of H0 in favor of i-FACTOR™ Peptide Enhanced Bone Graft group will meet safety success. The rate of subsequent surgical interventions at the index level will also be compared.

The data from this study will be submitted as part of the annual report and will include the following data collected annually for each subject:

1. a description of any surgical interventions, which will include reoperations, removals, revisions, and supplemental fixations;

2. a radiographic assessment of fusion using the same criteria employed in the original IDE study;

3. an assessment of neurological outcomes;

4. an assessment of pain and function using the same criteria employed in the original IDE study (*i.e.*, change in NDI and change in neck and arm VAS for pain); and

5. other primary and secondary endpoints not specified in items 1-3 above, as specified in the IDE study protocol addendum.

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 a complete protocol of your post-approval study described above. Your PMA supplement should be clearly labeled as an "ODE Lead" 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 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 Aric Kaiser at 301-796-6425 or aric.kaiser@fda.hhs.gov.

Sincerely yours,

Mark N. Melkerson -S

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