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

Theodore Heise, Ph.D.
Vice President, Regulatory Scientific Affairs
Cook Incorporated
750 Daniels Way
P.O. Box 489
Bloomington, IN 47402-0489

NOV 14 2012

Re: P100022
Zilver PTX Drug-Eluting Peripheral Stent (6 - 8 mm diameter; 20 - 80 mm length)
Filed: June 4, 2010
Amended: March 11, 2011; June 15, 2011; July 5, 2011; July 16, 2012
Procode: NIU

Dear Dr. Heise:

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 Zilver PTX Drug-Eluting Peripheral Stent. This device is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameters from 4 mm to 9 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient. 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 six months.

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.

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 a future report, as indicated below:

1. Within 12 months of PMA approval, you should submit a non-clinical post-approval report discussing the results of particulate testing conducted on manufactured lots. If this information indicates that tightening the particulate specification is appropriate, you should submit a PMA supplement requesting such a change.

In addition to the Annual Report requirements, you must conduct two post-approval studies to: (1) follow up newly enrolled US patients through one year post-implantation and (2) follow the newly enrolled US patients, the premarket cohort, the Japan post-approval study (PAS) cohort, and the global single-arm study through five years post-implantation, and provide the following data in post-approval study reports (PAS). Two (2) copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. *New US Enrollment:* The study will be a prospective, single-arm, multi-center study of newly enrolled subjects implanted with a Zilver PTX stent. A total of 200 *de novo* subjects will be enrolled from a minimum of 10 investigational sites across the United States.

   The primary endpoint is the incidence of target lesion revascularization (TLR) at one year post-procedure. The primary endpoint will be compared to a performance goal of 83.1%, with the study having greater than 80% power to test the primary endpoint.

2. *Zilver PTX Stent PAS*: The study will be a prospective, single-arm, multi-center study of all subjects from the *New US Enrollment* study (detailed above), the Zilver PTX subjects from the pivotal study, the Japanese post-approval study, and if needed additional subjects from the global single-arm pre-market study if needed. A total of 900 subjects will be enrolled and a minimum of 50% will be from the US.

   The objective of this study is to evaluate longer-term stent integrity and any other emerging safety signals. The endpoints are (1) target lesion revascularization (TLR) and stent thrombosis assessed annually through five years post-procedure and (2) stent integrity assessed by X-ray at one, three, and five years post-procedure.

The incidence of TLR and stent thrombosis will be assessed annually through five years post-implantation in the entire cohort of 900 subjects. This will be reported descriptively for each follow-up interval using 95% confidence intervals.

Stent integrity, defined as no fractures visible on x-ray imaging, will be assessed in a subset of 600 subjects (all new US enrollment subjects, all Zilver PTX subjects from the pivotal study, and the remainder consisting of the earliest sequentially enrolled subjects in the Japanese post-approval study). The study will evaluate the five-year stent fracture rate and it is designed to detect a difference of at least 2% change in the rate with 95% confidence and 80% power.

In addition, patency will be assessed annually through five years post-procedure in all new US enrollment subjects and all Zilver PTX subjects from the Pivotal Study, and any remainder consisting of the earliest sequentially enrolled subjects in the Japanese post-approval study. This will be reported descriptively for each follow-up interval using 95% confidence intervals.

Please be advised that the results from these studies 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.

FDA would like to remind you that you are required to submit PAS Progress Reports for each of the studies every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Reports. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. 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

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.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes complete protocols of your post-approval studies. Your PMA supplements should be clearly labeled as a "Post-Approval Study Protocol" 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. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.h

tm).

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 Mail Center – WO66-G609
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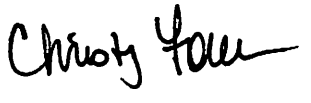
If you have any questions concerning this approval order, please contact Allison Kumar at (301) 796-6369.

Sincerely yours,



Christy Foreman
Office Director
Office of Device Evaluation
Center for Devices and Radiological Health