DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

DEC 16 2011

Ms. Mary Beth Kepler
VP Regulatory Affairs and Quality Assurance
Berlin Heart, Inc.
200 Valleywood, Suite A500
The Woodlands, TX 77380

Re: H100004
HUD Number: 2000-0064
Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD)
Filed: June 22, 2010
Amended: July 22, 2010; August 27, 2010; October 18, 2010; December 29, 2010; January 5, 2011; January 27, 2011; March 1, 2011; March 2, 2011; March 17, 2011; March 28, 2011
Product Code: DSQ

Dear Ms. Kepler:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD). This device is indicated for the following:

EXCOR is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR.

CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device upon receipt of this letter.

In addition to the conditions outlined above, you must conduct a post-approval study (PAS) to evaluate whether safety and outcomes of the device use in the commercial setting are comparable to the safety and outcomes of the device use in the IDE study.

The primary safety objective for the EXCOR PAS is to assess the safety and demonstrate that the serious adverse event (SAE) rate in subjects implanted with the EXCOR in the registry is not greater than the rate experienced in the IDE study. The primary safety endpoint is the SAE rate

which will be calculated as the total number of SAEs divided by the sum of days all subjects are supported on the EXCOR device.

The primary effectiveness objective for the EXCOR PAS is to assess the outcome following implantation of the EXCOR for transplant eligible children in need of mechanical circulatory support. Outcome is defined as transplant, recovery, or death.

Secondary objectives for the EXCOR PAS are to evaluate device malfunctions and examine pumps replaced for suspected thrombus. As agreed upon, an assessment of a learning curve is to be included as an additional secondary endpoint.

The study will be an "all-comers" prospective registry of patients implanted with the EXCOR who are transplant eligible children in need of mechanical circulatory support and who consent to be enrolled into the study. Accounting for a 25% attrition rate due to death and patients lost to follow-up, a sufficient number of subjects must be enrolled to ensure you will have a total of 39 subjects with at least 58 days of follow-up.

Baseline data will be collected within 48 hours prior to the implant date for inclusion to the study. Clinical data as recorded in hospital records will be collected at the time of pre-implant, baseline, implant, planned follow-ups (3 weeks, 6 weeks, 3 months, 6 months and every 3 months thereafter while on device support and up to transplant/recovery), and "unscheduled" follow-ups (e.g. device testing or replacement, evaluation of symptoms). Assessments will be made to determine if any adverse events occurred during the entire duration of device support. Following explant of the device, a follow-up will occur at hospital discharge, 12 months and 24 months post explant.

Upon your receipt of this letter, you must submit an HDE supplement that includes a complete protocol of your post-approval study, for FDA review and formal approval. Your HDE supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the HDE number above to facilitate processing.

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 an HDE Supplement.

FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "HDE Post-Approval Study Report" and bearing the applicable HDE 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 HDE Order"
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

The Pediatric Medical Device Safety and Improvement Act of 2007 allows HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). This device is indicated for use in pediatric patients and, based on the information provided in your HDE application, the ADN for this device is determined to be 1000. As stated in section 520(m)(8) of the Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted. You must immediately notify the agency by submitting an HDE report whenever the number of devices shipped or sold in a year exceeds the ADN. For additional information on the ADN, please see the "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm.

FDA wishes to remind you that failure to comply with any postapproval requirement constitutes a ground for withdrawal of the HDE. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE 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 requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling 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.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

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

If you have any questions concerning this approval order, please contact Shreya Mehta at (301) 796-0750.

Sincerely yours,

Martha C. Foreman MD PhD for

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

Enclosure

## CONDITIONS OF APPROVAL FOR AN HDE

### I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment (if submitted prior to HDE approval) or supplement (if submitted after HDE approval) to the HDE. The amendment/supplement should be submitted to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

### II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

### III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the

replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

## IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

## V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

### A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be

included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

DEC 29 2011

**Medical Device Tracking Order**

Ms. Mary Beth Kepler
VP Regulatory Affairs and Quality Assurance
Berlin Heart, Inc.
200 Valleywood, Suite A500
The Woodlands, TX 77380

Re: H100004
HUD Number: 2000-0064
Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD)

Dear Ms. Kepler:

You are notified by this letter of your obligation to adopt a method of tracking for the device referenced above, as authorized by section 519(g) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C.§ 360i(g). The implementation of section 519(g) of the Act requires the Food and Drug Administration (FDA) to issue an order to manufacturers when FDA determines that a person who manufactures and distributes a device meets the relevant statutory requirements and tracking is required to protect the public health. This order is effective immediately.

Section 519(g) of the Act, states that FDA, "may by order require a manufacturer to adopt a method of tracking a class II or class III device—

(A) the failure of which would be reasonably likely to have serious adverse health consequences; or

(B) which is—

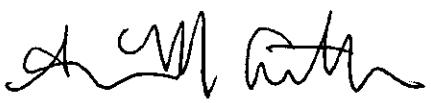
(i) intended to be implanted in the human body for more than one year, or

(ii) a life sustaining or life supporting device used outside a device user facility."

As you know, the corresponding medical device tracking regulations, found in Title 21 Code of Federal Regulations (CFR) Part 821, are intended to ensure that tracked devices can be traced from the device manufacturing facility to the person by whom the device is intended to be used when patient notification (under section 518(a) of the Act) or device recall (under section 518(e) of the Act) actions are ordered by the agency. The device tracking requirements for exemptions and variances, system and content requirements of tracking, the obligations of persons other than device manufacturers, records and inspection requirements, confidentiality, and record retention requirements, which were published in the Federal Register on August 16, 1993, remain in effect.
(21 CFR sections 821.2, 821.25, 821.30, 821.50, 821.55 and 821.60, copy enclosed)

This order to adopt a tracking method does not change your obligations concerning other existing FDA regulations affecting your device. FDA published in the Federal Register on February 28, 2002, an amendment to the final rule to revise the scope of the regulation and add certain patient confidentiality requirements and non-substantive changes to remove outdated references and simplify terminology. (67 FR 6943) If you need specific guidance, please contact Ann Ferriter, in the Office of Compliance, FDA Center for Devices and Radiological Health at (301) 796-5686. Other general information on your responsibilities under the Act, or more specific information, such as non-binding guidance on medical device tracking (copy enclosed), may be obtained from the Division of Small Manufacturers, International, and Consumer Assistance at its toll-free number (800) 638-2041, or at the internet address www.fda.gov/cdrh.

Sincerely yours,



Steven Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosures

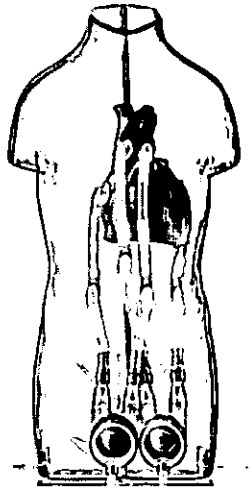
cc: WO66 rm. 1644 DGarcia
WO66 rm. 2678 BYoung
HFR-SW140
R/D:BYoung:12/29 /2011
Berlin Heart, Inc. (1)

| Office | Surname | Date | Office | Surname | Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

U.S. FOOD AND DRUG ADMINISTRATION

# New Humanitarian Device Approval

**Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD) – H100004**



*FDA approved this device under the Humanitarian Device Exemption (HDE) Program. See the links below to the Summary of Safety and Probable Benefit (SSPB) and other sites for more complete information on this product, its indications for use, and basis for FDA's approval.*

**Product Name: EXCOR® Pediatric Ventricular Assist Device (VAD)**
**PMA Applicant: Berlin Heart, GmbH**
**Address:** 200 Valleywood Suite A500, The Woodlands, TX 77382
**Approval Date:** December 16, 2011
**Approval Letter:** A link to web for the approval letter

**What is it?** The EXCOR® Pediatric VAD is a blood pump that vibrates rhythmically and is designed to assist patients who cannot pump enough blood with their own natural heart. The device can be used in patients who cannot effectively pump blood with their left and/or right ventricle The VAD device consists of one or two air-driven blood pumps (depending on single-ventricle or double-ventricle support), small tubes inserted into the body that are used to connect the blood pumps to the atrium or ventricle and to the great arteries, and the IKUS driving unit. The IKUS provides air pulses that drive the rhythm of the pumps and also has computer controls to be used by hospital staff.

**How does it work?** The EXCOR® Pediatric VAD does not entirely replace the natural function of the heart. Instead, it works along with the patient's own heart to pump blood. In a healthy heart, the left ventricle pumps blood rich with oxygen (oxygenated) to the vital organs and the right ventricle pumps non-oxygenated blood to the lungs to obtain oxygen. In a heart weakened by heart failure, the left and/or right ventricles are not strong enough to pump blood sufficiently. The EXCOR® Pediatric VAD helps the heart by supporting the weak ventricles.

The blood pump interior is divided into an air chamber and a blood chamber by a flexible membrane. Air pressure provided by the IKUS driving unit causes the membrane inside the pump to inflate and deflate. The air pulse moves the membrane, thus allowing blood to enter and exit the device. Valves are located at the blood pump connection branches to ensure one-way directional blood flow. The pulse rate and pump pressures can all be monitored and adjusted on the IKUS driving unit by hospital staff.

**When is it used?** The EXCOR® Pediatric VAD is used when the natural heart is unable to maintain normal blood flows and/or pressure or if it cannot adequately provide oxygenated blood to the vital organs. It is intended to provide support to the heart while these pediatric patients await a heart transplant.

**What will it accomplish?** The Berlin Heart EXCOR® Pediatric VAD U.S. clinical trial demonstrated that approximately 65% EXCOR® Pediatric VAD patients survived to cardiac transplantation or were successfully weaned from the device (since their hearts recovered). Of the 65% of patients, greater than 70% were transplanted or weaned with either no neurologic events or a good neurologic outcome.

**When should it not be used?** The device should not be implanted in patients with implanted artificial aortic valves due to an increased risk of blood clots. Additionally, patients who cannot tolerate medicines that stop blood from clotting should not be implanted with the EXCOR® Pediatric VAD.

**Additional information**: Summary of Safety and Probable Benefit and labeling are available at: [redacted]

**Other Resources:**

- FDA News Release
- NIH - MedlinePlus - Heart Failure