



December 1, 2020

HDL Therapeutics, Inc.
% Janice Hogan
Partner
Hogan Lovells, US LLP
1735 Market Street, Suite 2300
Philadelphia, PA 19103

Re: H190001

HUD Number: 14-0331

Trade/Device Name: Plasma Delipidation System (PDS-2™ System)

Product Code: QNB

Filed: March 13, 2019

Amended: February 12, 2019, March 13, 2019, April 8, 2019, July 15, 2019, November 20, 2019,
January 28, 2020, June 18, 2020

Dear Janice Hogan:

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 Plasma Delipidation System (PDS-2™ System). This device is indicated to reduce coronary artery atheroma in adult patients with homozygous familial hypercholesterolemia (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for HoFH, including the latest medications and other device therapies approved by the FDA. We are pleased to inform you that the HDE is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> identifies combination product submissions.

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 probable benefit 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 four (4) years for the PDS-2 disposable kit.

Continued approval of the HDE is contingent upon the submission of periodic reports, required under 21 CFR 814.126, at intervals of one year (unless otherwise specified) from the date of approval of the original HDE. This report, identified as "Annual Report" and bearing the applicable HDE 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 814.126.

In accordance with 21 CFR 814.124, an HDE holder is responsible for ensuring that a humanitarian use device (HUD) under an approved HDE is administered only in facilities having institutional review board (IRB) oversight. In addition, approval by an IRB or an appropriate local committee is required before the HUD can be used at a facility, with the exception of emergency use. An HDE holder is also required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRBs as well as any other information requested by a reviewing IRB or FDA (21 CFR 814.126(b)(2)).

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below.

You must obtain approval of your PAS protocols within 60 days from the date of this order and prior to enrollment in the PAS. Within 30 days of your receipt of this letter, you must submit HDE supplements that include complete protocols of your post-approval studies described below. Your HDE supplements should be clearly labeled as an "HDE Post-Approval Study Protocol" as noted below and submitted to the address below. Please reference the HDE number above to facilitate processing. If there are multiple protocols being finalized after HDE approval, please submit each protocol as a separate HDE supplement.

1. The HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-FHII) PAS is a prospective, multicenter, open-label new enrollment clinical investigation to provide ongoing safety and probable benefit assessment of the Plasma Delipidation System PDS-2, to reduce coronary artery atheroma in adult patients with homozygous familial hypercholesterolemia (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for HoFH, including the latest medications and other device therapies approved by the FDA. The PAS will address the following questions:
 - What are the probable benefits of serial infusions of autologous selectively delipidated HDL/pre β -enriched plasma on coronary artery atheroma volume with the use of the HDL Therapeutics PDS-2 System?
 - Does the HDL Therapeutics PDS-2 System decrease the incidence of major adverse cardiovascular events (MACE)?
 - What is the safety profile of the HDL Therapeutics PDS-2 System, including the rate and severity of adverse events and changes in blood laboratory values?

A total of 30 consented HoFH patients, aged 21 years or older, will be enrolled consecutively at up to 40 sites in the United States and will receive 7 weekly infusions of autologous selectively delipidated HDL/pre β enriched plasma following use of the PDS-2 System. Follow up clinical data will be collected at 2 weeks \pm 7 days, 3 months, 6 months, 9 months, and 12 months after infusion 7.

The primary safety endpoints are as follows: 1) The rates of serious adverse events (SAEs), and device-related and procedure-related adverse events from the start of infusion visit 1 through visit 7, and 1 week following infusion 7. The evaluated adverse events include, but are not limited to, hypotension, n-Butanol solvent toxicity, hypoglycemia, and hypocalcemia. 2) Laboratory values, specifically complete blood count parameters, comprehensive metabolic parameters and lipid profile parameters before and after serial infusions of autologous selectively delipidated HDL/pre β enriched plasma following use of the HDL Therapeutics PDS-2 System as compared to baseline values. The primary probable benefit endpoint will be coronary atheroma volume, as assessed by coronary computed tomography angiography (CCTA), at 2 weeks \pm 7 days and 6 months \pm 14 days after infusion visit 7 compared to baseline.

The secondary safety endpoints include the rates of SAEs, and device-related and procedure-related adverse events at 3 months, 6 months, 9 months, and 12 months after infusion visit 7. Other secondary endpoints include the rates of major adverse cardiac events (MACE) including cardiac death, myocardial infarction, ischemic stroke, and coronary artery revascularization at 3 months, 6 months, and 12 months after infusion visit 7.

From the time of study protocol approval, you must meet the following timelines for the HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-FHII) PAS:

- First subject enrolled within 6 months
 - 20% of subjects enrolled within 12 months
 - 50% of subjects enrolled within 18 months
 - 100% of subjects enrolled within 24 months
 - Submission of Final study report: 3 months from study completion (i.e., last subject, last follow-up date)
2. The HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study is a single arm prospective post-market human factors study to demonstrate that the system can be used by the certified operators, who are HDL employees, under both simulated and actual use conditions without producing patterns of use errors or issues that could result in a negative clinical impact to patients or harm to users or patients. The PAS will address the following question:
- Are the training and certification materials sufficient to ensure HDL employees are able to set up the device, prepare the solvents, and operate the device as indicated to generate a safe and effective delipidated plasma?

In this study, operators will be trained and certified according to the Employee Training Standard Operating Procedure (SOP-025-01). The study will be conducted with five certified operators (100% of device users). These certified operators will also be HDL employees. Operators will be observed

during simulated use testing conducted in a laboratory environment and during the operators' first actual use case at a clinical site to ensure they can complete the required tasks.

In both simulated use and actual use cases, to evaluate each operator, an observer will document the operator's performance on critical tasks. The required critical tasks for the PDS-2 will be dependent on the results from HDL's use-related risk analysis, and include but are not limited to the following tasks:

- Loading disposables and consumables,
- Preparation of the delipidation solvent mixture,
- Preparation of the solvent transfer set, and
- Transferring the delipidation solvent mixture to the solvent in-bag.

Study moderators will interview each participant to determine the root cause of any close calls, use difficulties, or use errors that are observed. An interim human factors validation report summarizing the observations and results after testing with two operators will be provided to FDA to ensure the data collected in the human factors study is adequate. A final human factors validation report summarizing the observations and results following completion of the study will be produced. The final human factors report for the PDS-2 System will be considered adequate if the human factors validation (summative) study evaluation yields results that:

1. Demonstrate that the device can be used by representative intended users under simulated and actual use conditions, without producing patterns of failures that could result in a negative clinical impact to patients or harm to users or patients;
2. Demonstrate that the device design, representative training and labeling are effective in mitigating all use-related risks to an acceptable level;
3. Demonstrate that no new use-related hazards or hazardous scenarios have emerged, and evidence supports that benefits outweigh the residual use-related risks; and
4. Demonstrate that operators are able to prepare the solvent mixture correctly, including verification of the mixture.

The PAS will not be considered complete until the above results are met in the final human factors report.

From the time of study protocol approval, you must meet the following timelines for the HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study:

- Submission of an Interim study report on the first two operators within 3 months
- Study completion (with all operators) within 6 months
- Submission of Final study report: 30 days from study completion

In addition, you must submit separate periodic reports on the progress of the HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-FHII) PAS and the HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study as follows:

- PAS Progress Reports every six months until subject enrollment has been completed, and annually thereafter.
- If any of the above milestones are not met, you must begin submitting quarterly status reports (i.e., every 3 months), in addition to your periodic (6-months) PAS Progress Reports, until FDA notifies you otherwise.

Each PAS report should be submitted to the address below identified as an "HDE Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable HDE reference number.

Be advised that failure to comply with any post-approval requirement, including the initiation, enrollment, and completion requirements outlined above, constitutes grounds for FDA withdrawal of approval of the HDE in accordance with 21 CFR 814.118(a) and 21 CFR 814.126.

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 HDE in accordance with 21 CFR 814.118(a)(6)-(7).

Be advised that protocol information, interim and final results will be published on the Post Approval Study Webpage https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

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 an HDE Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (<https://www.fda.gov/media/71327/download>).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (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). For more information on these requirements, please see the UDI website, <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system>.

Before making any change affecting the safety or probable benefit of the HDE device, you must submit an HDE supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.108 and 814.39 except a request for a new indication for use of a humanitarian use device (HUD). A request for a new indication for use for a HUD shall comply with the requirements set forth in 21 CFR 814.110 which includes obtaining a new designation of HUD status for the new indication for use and submission of 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.

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 for devices or post-marketing safety reporting (21 CFR 4, Subpart B) for combination products, 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 <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems> and on combination product post-marketing safety reporting is available at (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>).

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the post-marketing safety reporting requirements (21 CFR 4, Subpart B) for combination products, 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 <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls>.

This device may not be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device. See section 520(m)(3) of the Federal Food, Drug, and Cosmetic Act.

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 HDE by making available, among other information, a summary of the safety and probably benefit data upon which the approval is based. The information can be found on the FDA CDRH Internet Home Page located at

<https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals>. 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 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 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 HDE. 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 HDE submission with a copy 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, 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 Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Jessica K. Nguyen, Ph.D. at (301) 796-6277 or Jessica.Nguyen@fda.hhs.gov.

Sincerely,

Charles Viviano -S
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Charles Viviano, M.D., Ph.D.
Acting Director
OHT3: Office of GastroRenal, ObGyn,
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