December 9, 2021

OrganOx Limited
% Monica Montanez
Principal Product Development Strategist
NAMSA
400 Highway 169 South, Suite 500
Minneapolis, Minnesota 55426

Re: P200035
Trade/Device Name: OrganOx *metra*® System
Product Code: QQK
Filed: July 17, 2020
Amended: July 30, 2020, September 10, 2021

Dear Monica Montanez:

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 OrganOx *metra*® System. This device has the following Indications for Use:

> The OrganOx *metra*® is a transportable device intended to be used to sustain donor livers destined for transplantation in a functioning state for a total preservation time of up to 12 hours.
>
> The OrganOx *metra*® device is suitable for liver grafts from donors after brain death (DBD), or liver grafts from donors after circulatory death (DCD) ≤40 years old, with ≤20 mins of functional warm ischemic time (time from donor systolic blood pressure <50 mmHg), and macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

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. 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 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 12 months for the disposable set and 3 years for the sodium taurocholate. 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 the 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. 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 PMA 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 post-approval requirements.

1. **Post-Approval Inspection Requirement:** Due to the ongoing COVID-19 pandemic, the Agency has been unable to conduct pre-approval inspections of the sites involved in the manufacture of the OrganOx *metra*® device. In lieu of pre-approval inspections, the Agency has requested and considered additional information that would help it understand the adequacy of your Quality systems and how they contribute to your device's safety. The Agency has determined that there is sufficient Good Manufacturing Practices (GMP) information to support approval of your PMA at this time. However, approval is contingent upon the following condition:

   The following four manufacturing sites: OrganOx Ltd. (FEI: 3011560054), Rimer Alco (FEI: 3011600206), Raumedic AG (FEI: 3006946348), and Hugo Technology Ltd. (FEI: 3013775218), should be readily available for an inspection with no other hindering factors once ORA resources are available to conduct an inspection. If upon inspection by FDA, the sites are deemed as not in compliance with the requisite FDA Current Good Manufacturing Practices (CGMPs) as outlined in 21 CFR 820, FDA has the authority to withdraw the approval of the PMA in accordance with 21 CFR 814.82(c).

Be advised that failure to comply with any post-approval requirement constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(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.

1. **OrganOx *metra*® WP01 Long-Term Follow-Up PAS (Protocol Version 1, dated November 2021)**

The WP01 Long-Term Follow-Up PAS is an observational study designed to evaluate the long-term outcomes of patients from the WP01 trial. The outcomes of the 136 patients randomized into the normothermic machine perfusion (NMP) cohort, and 129 of the 130 patients randomized into the static cold storage (SCS) cohort will be monitored through 36 months post-transplant using data as reported in the United Network of Organ Sharing (UNOS) database.

This study has two primary objectives: the first is to assess graft and subject survival in the identified subjects. Graft and subject survival rates will be evaluated using 24-month and 36-month survival data. The second primary objective is to assess evidence of biliary complications in identified subjects. This objective will be evaluated using biochemical (bilirubin) and clinical (cause of graft failure and subject death) outcomes. All objectives will be evaluated using data as reported in the UNOS database.

This study has two secondary objectives: The first is to report post-transplant malignancy in identified subjects. This objective will be evaluated using post-transplant malignancy information. The second secondary endpoint is to report viral detection in identified subjects.

You must meet the following timelines for the WP01 Long-Term Follow-Up PAS:

- Submit an annual report by February 28 of each year, beginning on February 28, 2022
- Submit an interim report by August 31, 2022 and August 31, 2023
- Complete 36-month follow-up on all PAS participants by February 28, 2023
- Submit a Final Report by May 31, 2023

2. OrganOx *metra*® WP02 Continued Access Protocol Long-Term Follow-Up PAS (Protocol Version 1, dated November 2021)

The WP02 CAP Long-Term Follow-Up PAS is an observational study designed to evaluate the long-term outcomes of patients from the WP02 trial. The outcomes of the 105 patients transplanted with NMP-perfused donor livers will be monitored through 36 months post-transplant using data as reported in the UNOS database.

This study has two primary objectives: the first is to assess graft and subject survival in the identified subjects. Graft and subject survival rates will be evaluated using 24-month and 36-month survival data. The second primary objective is to assess evidence of biliary complications in identified subjects. This objective will be evaluated using biochemical (bilirubin) and clinical (cause of graft failure and subject death) outcomes. All objectives will be evaluated using data as reported in the UNOS database.

This study has two secondary objectives: The first is to report post-transplant malignancy in identified subjects. This objective will be evaluated using post-transplant malignancy information. The second secondary endpoint is to report viral detection in identified subjects.

You must meet the following timelines for the WP02 Continued Access Protocol Long-Term Follow-Up PAS:

- Submit an annual report by June 30 of each year, beginning on June 30, 2023
- Submit an interim report by December 31, 2023 and December 31, 2024
- Complete 36-month follow-up on all PAS participants by June 30, 2025
- Submit a Final Report by September 30, 2025

3. OrganOx *metra*® New Enrollment PAS (Protocol Version 1, dated November 2021)

The OrganOx *metra*® New Enrollment PAS is a multi-center, single-arm, unblinded post-approval study designed to compare recipients of PAS NMP livers versus IDE SCS livers with respect to adverse biliary-related events. Recruitment will take place at a minimum of 10 sites which are UNOS member liver transplant centers.

The New Enrollment PAS study will include 210 transplanted livers from deceased DBD and DCD donors with a minimum of 40 transplanted livers from DCD donors. Enrolled subjects will be followed for 12 months post-transplant.

The primary objective is to compare the effect of NMP to SCS in the prevention of adverse biliary-related events as measured by biliary complications at 3 months, 6 months, and 12 months post-transplant.

There are two secondary objectives. The first is to assess graft survival rates at 3 months, 6 months, and 12 months post-transplant. The second secondary objective is to assess subject survival rates at 3 months, 6 months, and 12 months post-transplant.

In addition to the above data, the following preservation parameters will be collected for all study livers: degree of steatosis at time of retrieval, quality of *in-situ* perfusion, perfusion parameters for NMP livers, perfusate ALT and AST (for NMP livers), lactate levels (for NMP livers), perfusion solution used for *in-situ* and back-bench perfusion, perfusion solution used for organ transport (SCS organs only), and glucose levels.

The following inpatient/discharge assessment data will be evaluated: length of stay in ICU, total length of hospital stay, primary-non function via evaluation of irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation, biliary complications, biliary interventions, graft and subject survival, and device-related adverse events.

A modified intent-to-treat (mITT) analysis will be performed for all outcomes as the primary analysis. The New Enrollment NMP cohort in the mITT population will be compared against the as-treated IDE control population (SCS) for the primary outcome. The primary outcome—the difference in biliary complication rates—will be analyzed using propensity score stratification to adjust for potential differences in risk factors. Propensity modeling will be performed based on the baseline characteristics of sex, donor age, recipient age, donor type, and recipient MELD score.

Subgroup analyses will be performed for donor type (DCD versus DBD), by donor risk index (DRI), and by duration of machine preservation in the NMP arm of the study.

In the event of missing data, the extent and types of missing data for key study variables will be assessed as part of sensitivity analyses and reported upon. Withdrawals from the study after transplantation will be documented and a summary of withdrawals will be performed. For all study endpoints, data will be summarized for those recipients with available data.

From the time of study protocol approval, you must meet the following timelines for the New Enrollment PAS:

a. The first subject is enrolled within 6 months
b. 20% of subjects are enrolled within 12 months
c. 50% of subjects are enrolled within 18 months
d. 100% of subjects are enrolled within 24 months
e. The submission of final study report is due 3 months from study completion (i.e., last subject, last follow-up date)

In addition, you must submit separate periodic reports on the progress of the New Enrollment PAS as follows:

- PAS Progress Reports every six months until subject enrollment has been completed, and annually thereafter.

- If any enrollment milestones are not met, you must begin submitting quarterly enrollment 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 a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA 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 PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

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 accordance with 21 CFR 814.46(a)(3)-(4).

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 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" (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). 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. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). 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 effectiveness of the PMA 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" https://www.fda.gov/media/81431/download.

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.

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 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 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 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 PMA 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 Jade Noble, PhD at 240-402-5077 or Jade.Noble@fda.hhs.gov.

Sincerely,

Glenn B. Bell -S

Glenn B. Bell, Ph.D.
Director
DHT3A: Division of Renal,
Gastrointestinal, Obesity
and Transplant Devices
OHT3: Office of GastroRenal, ObGyn,
General Hospital and Urology Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health