DE NOVO CLASSIFICATION REQUEST FOR THE HEMANEXT ONE SYSTEM
DECISION SUMMARY

A. DEN Number

BR 220665

B. Purpose for Submission

Direct De Novo request for HEMANEXT ONE system

C. Device Trade Name

HEMANEXT ONE

D. Applicant

Hemanext Inc

E. Proprietary and Established Names

HEMANEXT ONE system

F. Regulatory Information

1. **Type of Device**

   FDA identifies this generic type of device as: **Container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions.** The container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions is a device intended for medical purposes that is used to process and store Red Blood Cell components and reduce oxygen levels in the storage environment.

2. **Regulation section:**

   21 CFR 864.9115

3. **Regulation name:**

   Container system for the processing and storage of Red Blood Cells under reduced oxygen conditions

4. **Classification:**

   Class II

5. **Product code:**

   QYC

6. **Panel**:
   Hematology and Pathology Devices

□ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Office's Signatory Authority**:**

Date of FDA Notice of Granting the Classification Request: September 15, 2023

G. Device Description:

The device (HEMANEXT ONE system) is a storage device intended to process and store CP2D/AS-3 Red Blood Cells, Leukocytes Reduced (LR RBC) under reduced oxygen and carbon dioxide conditions. Each system consists of:

- One Oxygen Reduction Bag (ORB): empty oxygen impermeable container for processing CP2D/AS-3 Red Blood Cells, Leukocytes Reduced (LR RBC)
- One Hemanext Storage Bag (HSB): empty oxygen impermeable container for storage of CP2D/AS-3 Red Blood Cells, Leukocytes Reduced, and O2/CO2 Reduced
- One Leukocytes Reduced, Red Blood Cell (LR RBC) blood line
- Three flow control blood line clamps

Device Technology Description

LR-RBCs in CP2D/AS-3 are incubated with agitation in the ORB which allows for the rapid diffusion of oxygen out of the blood through a sterile, oxygen-permeable membrane, and into iron-based oxygen sorbents. The processed LR RBCs are then transferred from the ORB to the HSB which preserves the anaerobic state of the LR RBCs for the duration of cold storage. The HSB is also a transfusion ready device.

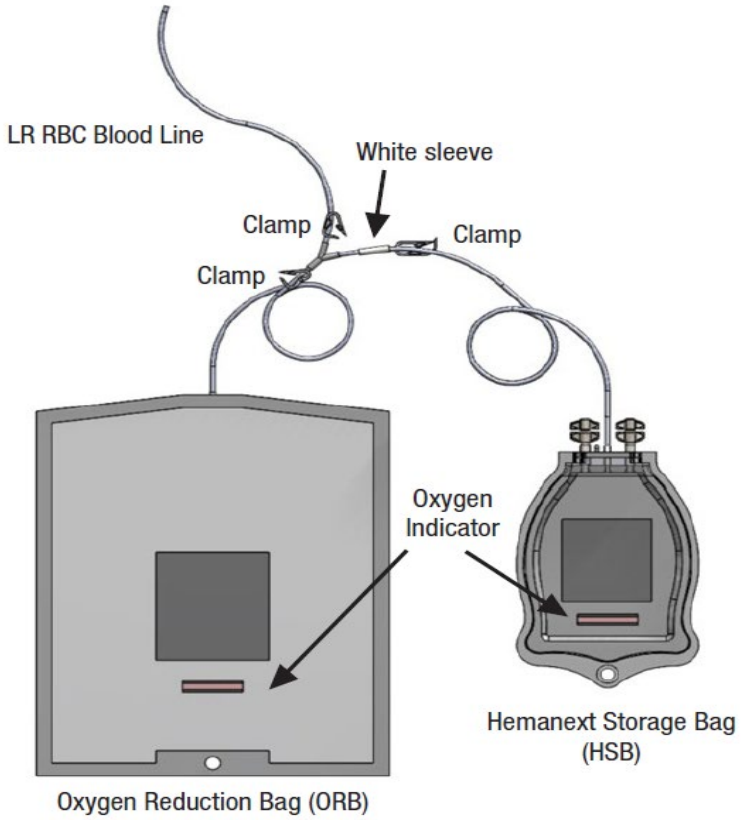

Figure 1: HEMANEXT ONE SYSTEM

Description of the Hemanext Process

A LR RBC unit is connected to the ORB using a sterile docking device. The sorbent quilt between the inner bag and the barrier bag creates an O_2 /CO_2 depleted environment. The HEMANEXT ONE One System is then placed on an agitator at room temperature (20-26°C) for 3 hours. During agitation the contents of the ORB are evenly distributed, creating a large thin layer of LR RBCs contacting the inner surface of the ORB inner bag.

The red blood cells in direct contact with the inner surface of the ORB release oxygen through the permeable membrane into the O_2/CO_2-starved environment between the inner bag and barrier bag of the ORB. Maintaining agitation ensures oxygen exchange between the red blood cells furthest from the walls of the bag and the relatively de-oxygenated solution closest to the bag surface. Oxygen near the bag surface is then transported across the membrane to the oxygen and carbon dioxide depleted environment outside of the ORB inner bag.

The O_2/CO_2 absorption rate is characteristic of the ORB material, exchange surface area, volume of RBCs and agitation. At the end of the 3-hour exposure time, the resulting LR RBCs are transferred to the HSB. The HSB utilizes the same principles as the ORB to maintain a low oxygen and carbon dioxide environment for cold storage of CP2D/AS-3 LR RBCs up to 42 days.

H. Indications for Use:

Blood container set used to process and store Red Blood Cells Leukocytes Reduced, O_2/CO_2 Reduced.

The HEMANEXT ONE system is intended to process and store CP2D/AS-3 Red Blood Cells, Leukocytes Reduced (LR RBC) that have been prepared within the standard 8-hour hold time. Processing of Red Blood Cells with the HEMANEXT ONE system must be initiated within 8 hours of collection and completed within 12 hours of collection. The Red Blood Cells must be processed at room temperature (20-26 °C). The HEMANEXT ONE system limits O_2 and CO_2 levels in the storage environment. Red Blood Cells Leukocytes Reduced, O_2/CO_2 Reduced may be stored for up to 42 days at 1-6 °C. The HEMANEXT ONE system is used for volumes no greater than 350 mL of LR RBC.

I. Labeling

The HEMANEXT ONE system labeling consists of the Instructions for Use which provides adequate instructions with respect to device setup and use, contraindications, warnings, and precautions.

Summary of Nonclinical/Bench Studies

I. Biocompatibility; Extractable and Leachables

A toxicological risk assessment for the HEMANEXT ONE system was based on data from Extractables and Leachables (E&L) studies and biocompatibility tests conducted according to the ISO 10993-1:2018 standards. Biocompatibility tests results indicated that the HEMANEXT ONE system is non-cytotoxic, non-sensitizing, non-irritating, non-toxic (in acute systemic toxicity and sub-chronic toxicity testing), non-pyrogenic, non-mutagenic and non-hemolytic. All components of the system were tested in their final, finished, and sterilized form.

II. Mechanical testing/integrity/sterility:

Testing included container closure integrity, sterility (sterilization and endotoxin testing) and physical tests for flexible containers (including package seal, port testing, thermal stability, resistance to pressure, transparency/coloration, resistance to dropping, particulate contamination, hanger test and identification/labeling).

III. Software:

Not applicable.

IV. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety:

Not applicable.

V. Usability Testing:

HEMANEXT ONE system human factors and usability studies consisted of a use related risk analysis (URRA) which included use failure mode and effects

analysis (uFMEA), training modules for blood center technicians and nurses and human factors validation testing.

VI. Performance Testing:

Evaluation of the HEMANEXT ONE system included studies to evaluate Red Blood Cell components processed and stored in the system. Studies included a) *in vitro* testing of the red blood cells for several parameters including hemolysis, 2,3, -DPG levels, ATP, P50, b) animal studies to demonstrate oxygen delivery, c) clinical studies (*in vivo* red blood cell recovery and survival).

A. In vitro studies

The in vitro studies showed that:

1. HEMANEXT ONE processed Red Blood Cell components at the end of storage (day 42) met the acceptance criteria for hemolysis (a one-sided 95% lower confidence limit that at least 95% of units have hemolysis at day 42 of < 1%).
2. HEMANEXT ONE processed Red Blood Cell components met the acceptance criteria for red blood cell recovery (a one-sided 95% lower confidence limit that at least 95% of units have a red blood cell recovery of > 85%).
3. HEMANEXT ONE lowers the oxygen saturation and partial pressure of carbon dioxide in the stored Red Blood Cell components consistent with the device labeling. HEMANEXT ONE processed Red Blood Cell components met deoxygenation limit acceptance criteria (<20% at 80% Confidence and 80% Reliability and < 30% for 100% Reliability).
4. Compared to control RBCs, HEMANEXT ONE processed Red Blood Cell components showed,
    i. Statistically higher 2,3-DPG levels at storage day 21.
    ii. Higher P50 at storage day 21.
    iii. Statistically higher morphology scores at storage day 21.
    iv. Similar ATP levels throughout storage.

    Generally, these parameters appeared similar to control RBC by the end of storage (day 42).

B. Animal studies

Animal testing was performed to demonstrate oxygen delivery in a rat hemorrhagic shock model.

Two animal studies were conducted to evaluate 1-week-old and 3-week-old anaerobically stored rat red blood cells compared to control red blood cells.

In the study of 1-week-old rat red blood cells, rats were hemorrhaged to 50% of blood volume, held in hypovolemia for 30 minutes, then resuscitated via exchange transfusion, with the infusion: withdrawal ratio

of 2:1.

1-week-old red blood cells were then transfused to recover mean arterial pressure (MAP) to 90% pre-hemorrhage MAP.

The study results of 1-week-old rat red blood cells demonstrated that the anaerobically- stored red blood cells were comparable to control rat red blood cells with regards to improving hemodynamics, cardiac function, volume required for resuscitation, and for organ hypoxia and organ inflammation. In no cases did resuscitation with anaerobic red blood cells indicate worse performance by any measure compared to conventionally stored red blood cells. Trends were observed of decreased resuscitation volumes, decreased lactate levels, accelerated glucogenesis and decreased tissue hypoxia in the anaerobic arm of the study.

In the study of 3-week-old rat red blood cells, rats were hemorrhaged to 50% of blood volume, held in hypovolemia for 30 minutes, and resuscitated to recover blood pressure to 90% pre-hemorrhage by transfusing 3-week-old red blood cells (anaerobically stored red blood cells or control red blood cells).

The study results demonstrated that anaerobically stored red blood cells compared to control red blood cells showed greater restoration of blood pressure and increased systemic vascular resistance (SVR), as well as decreased lactate levels, improved histologic markers of organ hypoxia, and improvement in serologic markers of organ damage.

Of note is the finding of significantly increased SVR in animals who received anaerobically stored red blood cells compared to 3-week-old control RBCs. Considering the improvement in lactate levels, organ hypoxia, and serologic markers of organ damage, it was concluded that this difference likely represents an appropriate physiologic response to effective transfusion where there is an increase in SVR to maintain perfusion (i.e., mean arterial pressure [MAP]) of critical organs (MAP = Cardiac output x SVR). Overall, the animal studies indicate that red blood cells stored under hypoxic conditions maintain their ability to deliver oxygen.

C. Clinical testing – in vivo evaluation of Red Blood Cell components processed with the HEMANEXT ONE system (red blood cell recovery and survival).

A clinical study was carried out to evaluate Red Blood Cell components processed with the HEMANEXT ONE system by conducting an RBC *in vivo* recovery and survival study. Healthy volunteer subjects received a small volume (15-30 mL) of autologous red blood cells processed with the device.

The results showed that HEMANEXT ONE processed red blood cells met FDA's criteria for *in vivo* red blood cell recovery (at least 75% with a

standard deviation of ≤ 9%, and the lower limit of a one-sided 95% confidence interval for the population proportion of successes is ≥ 70%). The HEMANEXT ONE processed red blood cells had statistically higher dual label *in vivo* recovery compared to control red blood cells [89.3±5.8% (hypoxic) versus 85.8±6.1% (control)] when a paired t-test was performed. The survival of HEMANEXT ONE processed red blood cells was similar to that of control red blood cells. While this study involved transfusion of a small volume of red blood cells, the reported adverse events did not raise safety concerns for Red Blood Cell components processed with the HEMANEXT ONE system.

Risks to Health:

The table below identifies the risks to health that may be associated with use of the HEMANEXT ONE system and the measures necessary to mitigate these risks.

Identified Risks to Health	**Mitigation Measures**
Toxicity that can result from contact of the component materials of the device with the red blood cells or patient's body	Biocompatibility evaluation
Toxicity of leached materials, or residual chemical sterilant, when in contact with red blood cells or transfused to patient	Extractables and leachables testing
Infection	Sterilization validation Endotoxin testing Container closure evaluation
Transfusion of poor-quality red blood cells because of inadequate storage conditions or device malfunction	Non-clinical and clinical studies Shelf-life testing Performance testing
Blood exposure because of device malfunction	Performance testing
Transfusion of poor-quality red blood cells due to processing of Red Blood Cells components collected from donors with hemoglobin S	Labeling

Special Controls:

In combination with the general controls of the FD&C Act, the Container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions is subject to the following special controls:

(1) The intended use of the device must specify:

(i) The Red Blood Cell components that can be processed and stored including acceptable anticoagulants and additive solutions.

(ii) The hold time after Red Blood Cell component collection.

(iii) The processing capacity (volume) of the device.

(iv) The storage temperature and dating period of processed Red Blood Cell components.

(2) Studies must demonstrate that the device is biocompatible and include detailed documentation of the biocompatibility evaluation.

(3) Performance testing and non-clinical studies must include a detailed study of leached materials extracted under conditions similar to clinical usage of the device, and a toxicologic risk assessment of those extracted or leached materials.

(4) Performance testing must support sterility of the device and include sterilization validation, endotoxin testing, and container closure integrity evaluation.

(5) Nonclinical and clinical studies must include evaluation of red blood cell quality throughout the duration of storage based on in vitro and in vivo studies, including hemolysis and red blood cell survival and recovery.

(6) Performance studies must include:

(i) Detailed documentation of functional and mechanical testing, including evaluation of oxygen and, if applicable, carbon dioxide levels during Red Blood Cell components storage.

(ii) Detailed documentation of device shelf-life testing demonstrating continued sterility, package integrity and functionality over the identified shelf life.

(7) The labeling must include:

(i) A contraindication against processing Red Blood Cell components collected from donors with hemoglobin S.

Benefit Risk Determination:

The benefits and risks of the device are based on the nonclinical bench and animal studies as well as clinical data submitted.

Evaluation of Red Blood Cell component storage containers typically includes the evaluation of *in vitro* and *in vivo* parameters of stored red blood cells. For this device, the sponsor also submitted animal studies and additional parameters to demonstrate that red blood cells processed and stored in the HEMANEXT ONE system are capable of oxygen delivery.

HEMANEXT ONE processed red blood cells met acceptance criteria for hemolysis and in vivo recovery. In vitro blood testing also showed that RBCs processed with the HEMANEXT ONE system had higher 2,3-DPG, P50 and morphology scores compared to conventionally stored RBCs at storage day 21. The overall results of these studies show the RBC components processed in the HEMANEXT ONE system are comparable to control Red Blood Cell components. Results of some of the parameters evaluated suggested improved oxygenation and overall red blood cell recovery. The observed benefits are clinically meaningful enough to outweigh the probable risks related to this device.

All probable risks from the HEMANEXT ONE system are characterized and mitigated through non-clinical and bench testing, including biocompatibility, extractables and leachables testing, sterilization and container closure evaluation, performance testing, and labeling. The probable risks identified are appropriately mitigated through special controls. These risks are acceptable and consistent with other blood processing systems. Overall, the clinical benefits of the HEMANEXT ONE system outweigh the probable risks.

Benefit Risk Conclusion:
In conclusion, given the available information above, for the following indication statement:

The HEMANEXT ONE system is intended to process and store CP2D/AS-3 Red Blood Cells, Leukocytes Reduced (LR RBC) that have been prepared within the standard 8-hour hold time. Processing of Red Blood Cells with the HEMANEXT ONE system must be initiated within 8 hours of collection and completed within 12 hours of collection. The Red Blood Cells must be processed at room temperature (20-26 °C). The HEMANEXT ONE system limits O_2 and CO_2 levels in the storage environment. Red Blood Cells Leukocytes Reduced, O_2/CO_2 Reduced may be stored for up to 42 days at 1-6 °C. The HEMANEXT ONE system is used for volumes no greater than 350 mL of LR RBC.

The probable benefits outweigh the probable risks for the HEMANEXT ONE system. The device provides benefits, and the risks can be mitigated using general controls and the identified special controls.

Conclusion:

The De Novo request for HEMANEXT ONE system is granted, and the device is classified under the following:

Identification: Container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions. The container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions is a device intended for medical purposes that is used to process and store Red Blood Cell components and reduce oxygen levels in the storage environment.

Product Code: QYC

Device Type: Container system for the processing and storage of Red Blood Cell components under reduced oxygen conditions

Class: II (Special Controls)

Regulation: 21 CFR 864.9115