Hemanext®

HEMANEXT ONE Red Blood Cell Processing System

Neil Beckman – Hemanext Technical Director

Hemanext Introduction

***Mission**: Hemanext is committing its resources to the continuing effort of the transfusion medicine community to **save lives and improve patient outcomes**. Our distinctive focus is on innovations in systems enabling blood collection, processing, storage and transfusion that will promote radical improvement in the quality, safety, efficacy and cost of transfusion therapies*

- **Started in 2008**
- **~35 Employees**
- **Office in Lexington, MA. Manufacturing Facility in Avon, MA**
- **Raised ~$50M from the NIH and private investors**
- **Management team includes senior life sciences executives**

Scientific Advisors

Hemanext®

- **Paul M. Ness, MD**
  - Johns Hopkins University School of Medicine.
- **Larry Dumont, MBA, PhD**
  - Blood Systems Research Institute.
- **Jose Cancelas, MD, PhD**
  - Hoxworth Blood Center at University of Cincinnati
- **Steven Spitalnik, MD**
  - Columbia University
- **Christopher Silliman, MD, PhD**
  - Bonfils Blood Center Research Department
- **Ralph Vassallo, MD, FACP**
  - Blood Systems, Inc., Scottsdale, AZ.
- **Philip C. Spinella, MD**
  - Washington University School of Medicine
- **Angelo D'Alessandro, PhD**
  - University of Colorado
- **Biree Andemariam, MD**
  - UConn Health

LD RBC

Oxygen Reduction Bag (ORB)

Hemanext Storage Bag (HSB)

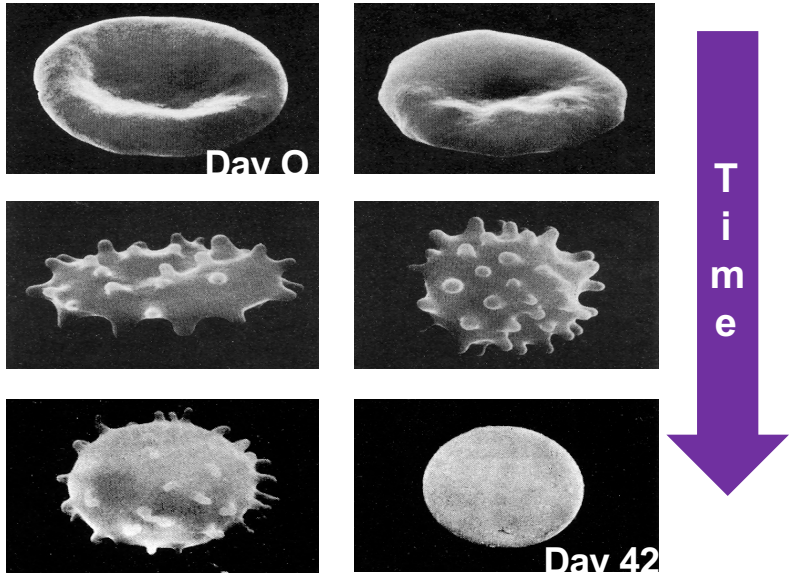
The Hemanext® One Blood Processing and Storage System

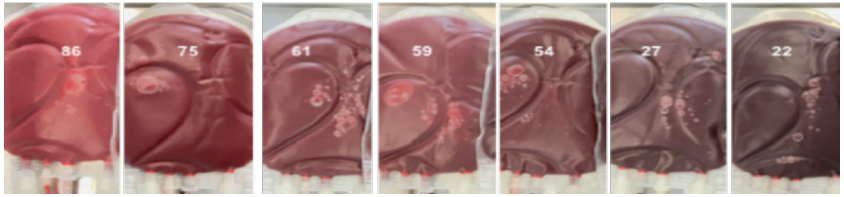
The Role of $\%SO_2$ in Red Cell Quality

Hemanext®

Patient adverse events are associated with degradation in storage

+ RBCs degrade across the 5/6 week permitted storage period
+ Degradation varies by donor
+ Degradation is $\%SO_2$ dose dependent
+ Oxygen leaches through PVC container
+ Storage degradation increases risk in vulnerable patients especially after large volumes of blood
  - Sickle cell disease
  - Thalassemia
  - Trauma or other massive bleeding etiologies
+ **Red cell degradation is O_2 dose dependent**

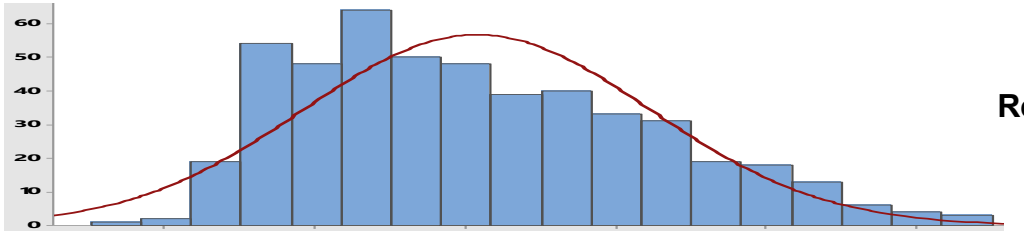


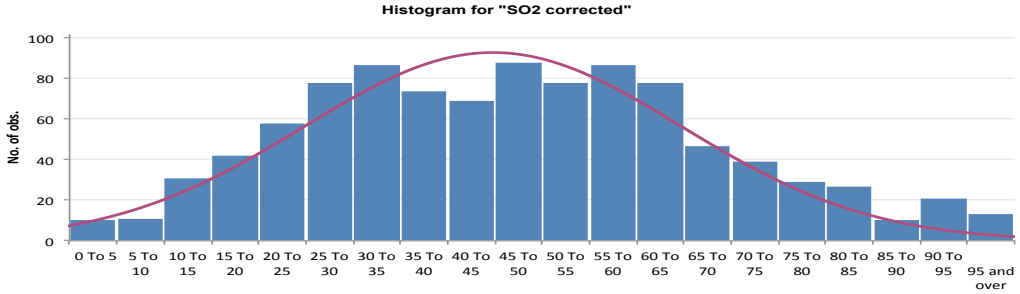


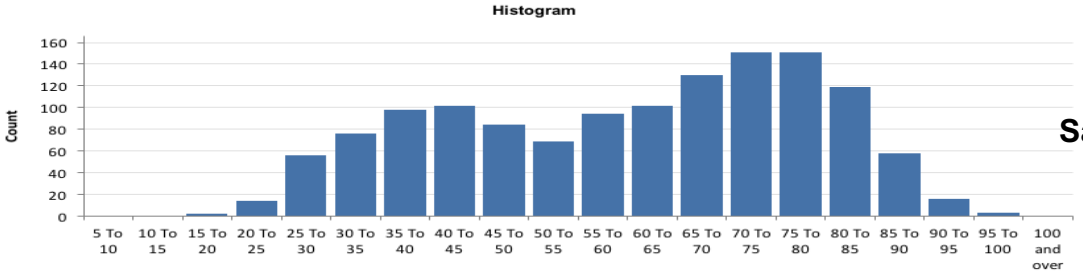
Wang et al, Transfusion. 2012 Jun; 52(6): 1537-2995
Reisz et al, Blood 2016 128:32-42

Wide Variation in Saturated Oxygen Levels at time of Storage

Research and Blood Center %SO_2 distributions Day 0



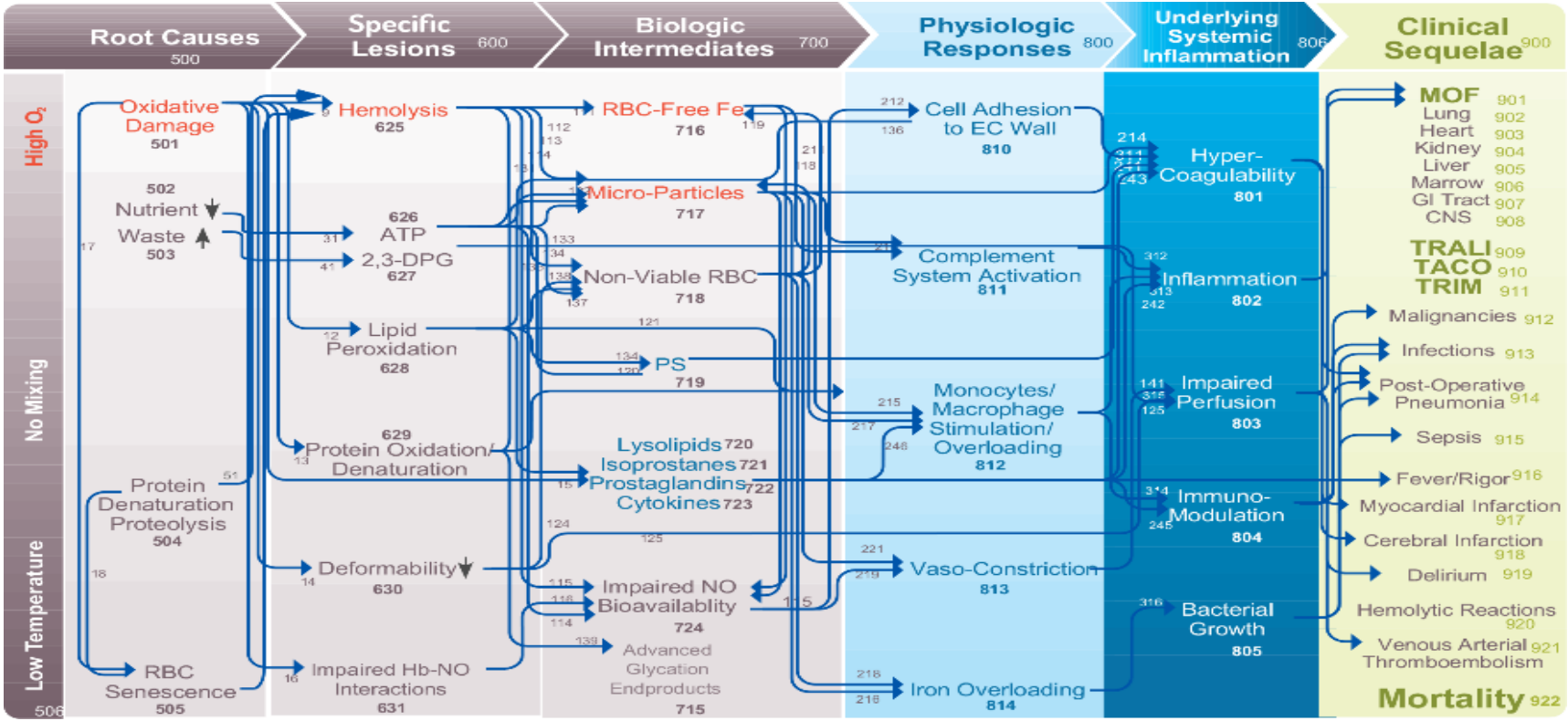




	N	Mean	SD
Research units[1]	492	45.9%	17.5%
RIBC units[2]	977	47.0%	21.0%
Sanquin units[3]	1325	59.7%	18.2%

[1] Yoshida et al, Blood Transfusion, 15(2), 172-181
[2] Nemkov et al., Haematologica, 103(2), 361-372
[3] De Korte, et al., Vox Sanguinis (2018) 113 (Suppl.1), 5-347

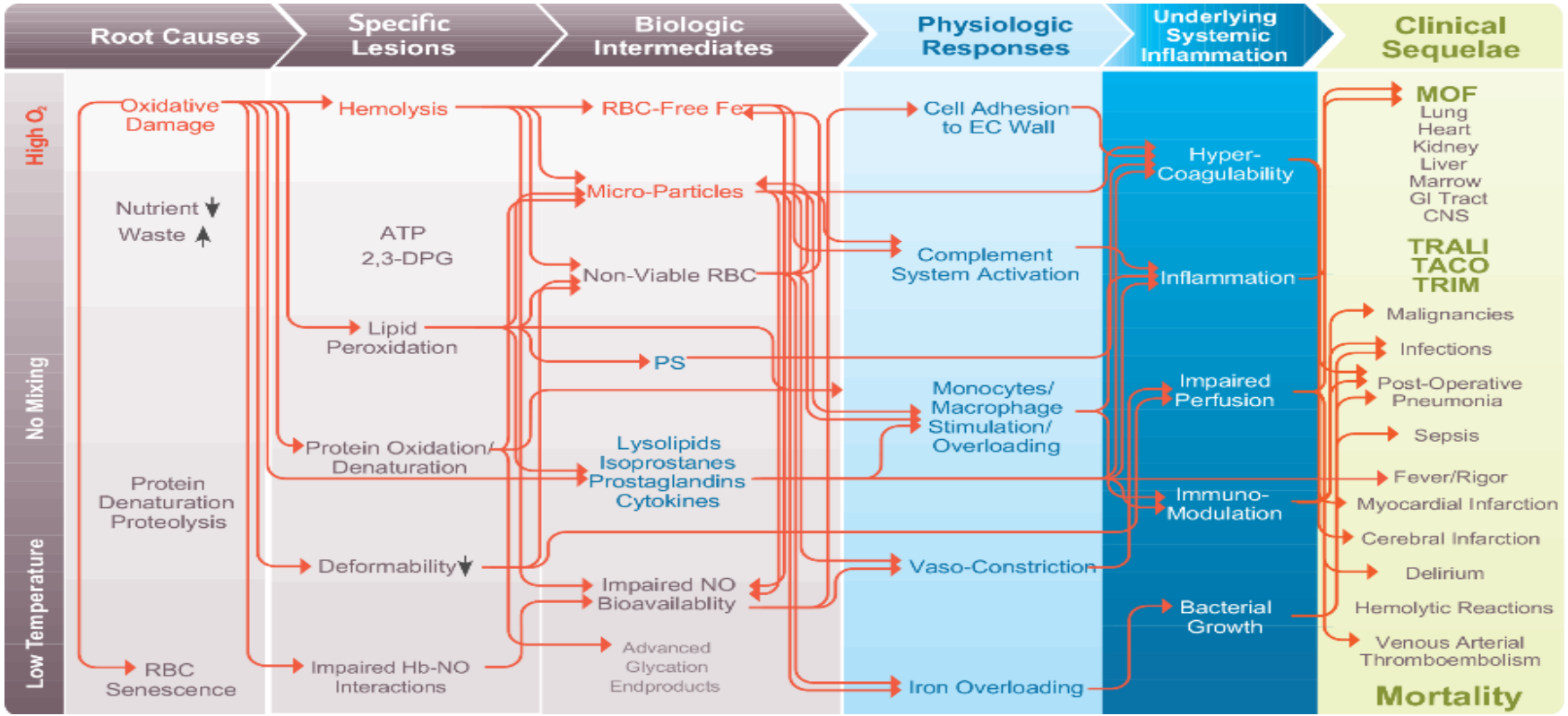
RBC Storage Lesion: Causes and Consequences



Tatsuro Yoshida, Michel Prudent, Angelo D'Alessandro. Red blood cell storage lesion: causes and potential clinical consequences. Blood Transfus 2019; 17: 27-52

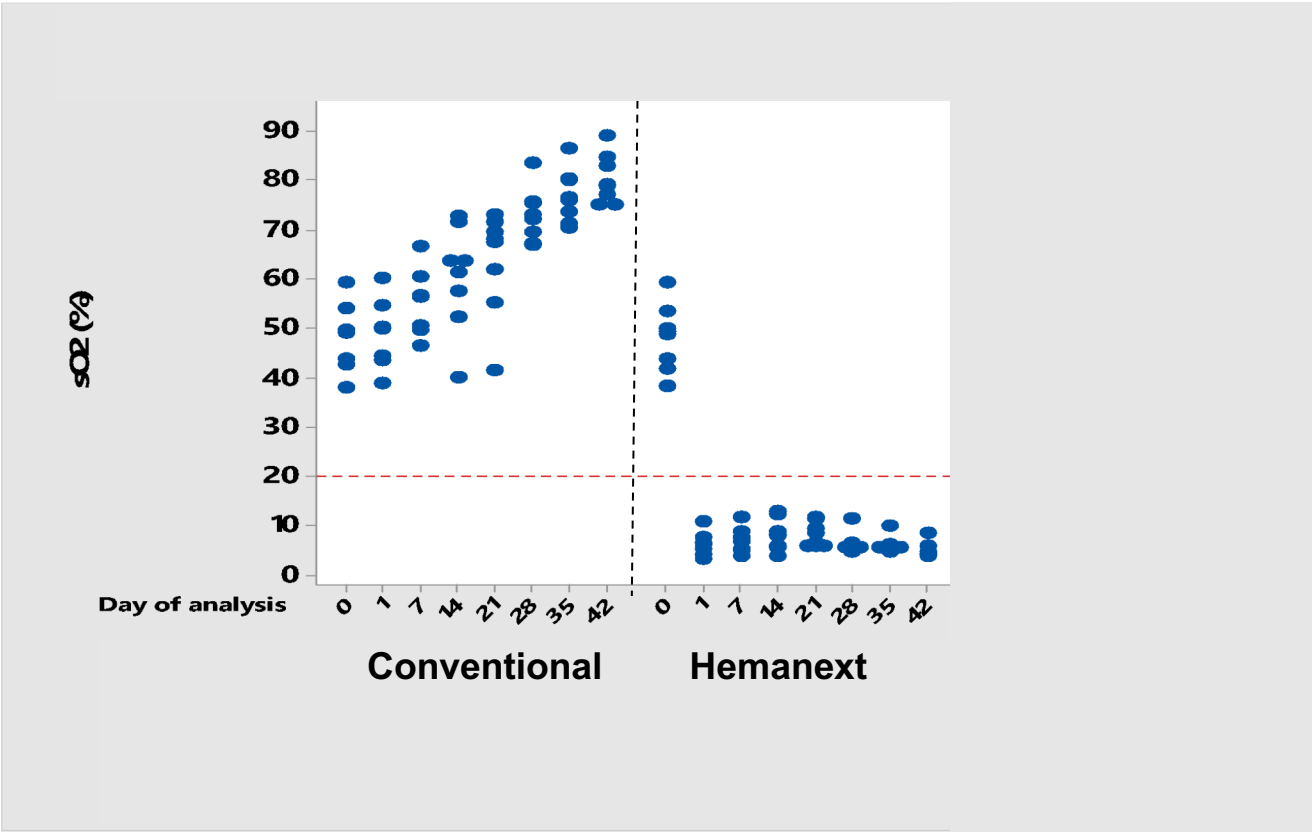
Causes and Consequences: Oxidative Damage

Hemanext®



Tatsuro Yoshida, Michel Prudent, Angelo D'Alessandro. Red blood cell storage lesion: causes and potential clinical consequences. Blood Transfus 2019; 17: 27-52

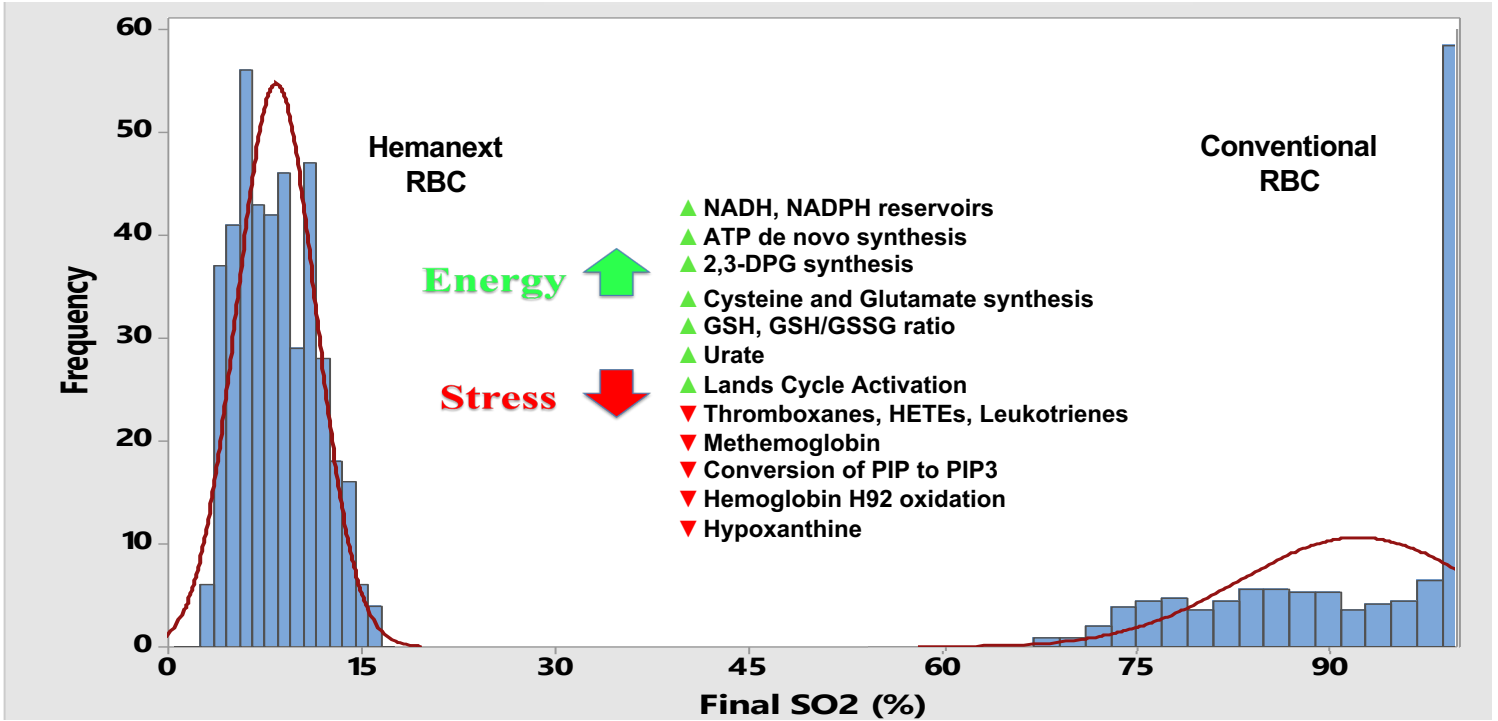
Hemanext Controls Oxygen During Storage



RESPR22: Additive Solution Study at Hema Quebec

%SO_2 optimisation minimises oxidative damage and promotes healthy metabolism

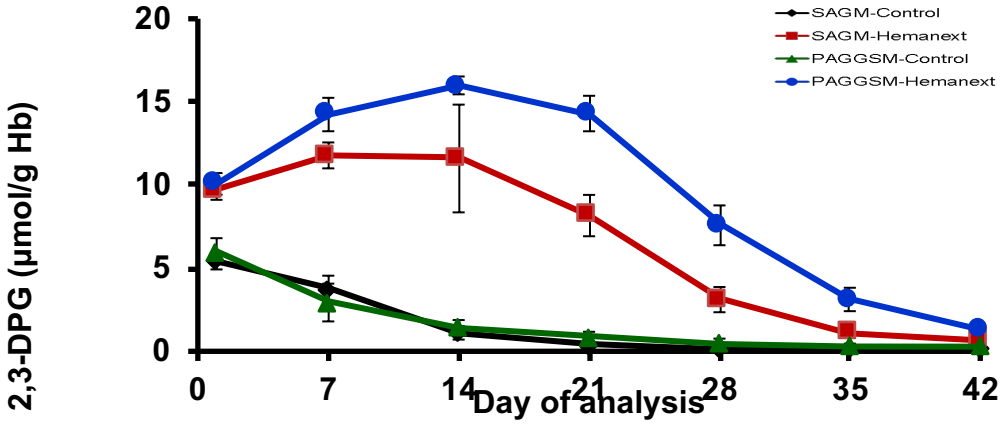
Hemanext®



Oxidative modifications of glyceraldehyde 3-phosphate dehydrogenase regulate metabolic reprogramming of stored red blood cells. Reisz JA, Wither MJ, Dzieciatkowska M, Nemkov T, Issaian A, Yoshida T, Dunham AJ, Hill RC, Hansen KC, D'Alessandro A. Blood. 2016 Sep 22; 128(12):e32-42.

Microvascular Analyser

MVA Video



- Study comparing the in vitro performance characteristics of RBCs stored in SAGM and PAGGSM additive solutions
- Pool and split design
- 2,3 DPG in both Hemanext groups was higher than control throughout storage
- PAGGSM-Hemanext was significantly higher than SAGM-Hemanext
- PAGGSM-Hemanext group 2,3 DPG remained at or above physiologic levels throughout 21 days of storage.

RESPR22: Additive Solution Study at Hema Quebec

CE Mark Study

- Study at Hema-Quebec to support an application to CE mark the Hemanext RBC Processing System
- Evaluate CPD/PAGGSM leucocyte-reduced RBCs stored hypoxically for 49 day using the Hemanext RBC Processing System

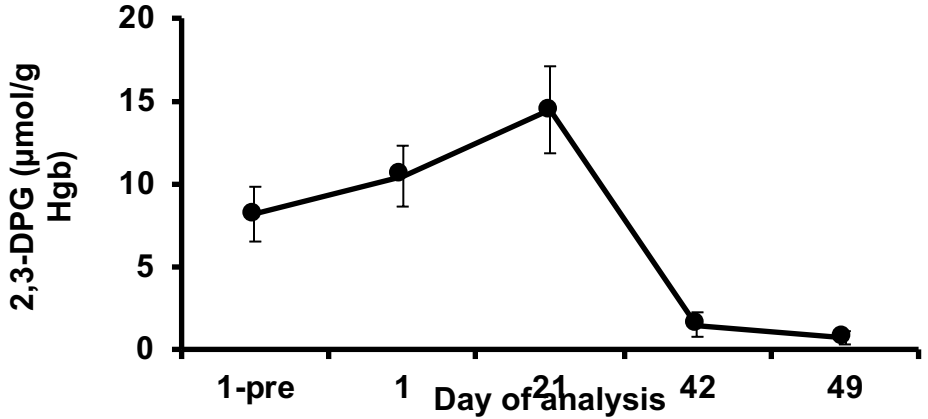
Haemoglobin recovery

Parameter	All Donors	
	n	32
Holdup Volume in ORB + Tubing (ml)	Mean (Std Dev)	4.97 (3.58)
	Min - Max	0.00 - 11.40
Holdup Volume in ORB + Tubing (%)	Mean (Std Dev)	1.87 (1.30)
	Min - Max	0.00 - 4.23
Total Hemoglobin in HSB (g)	Mean (Std Dev)	50.49 (6.27)
	Min - Max	41.33 - 65.25

CLIN-0002: CE Mark study at Hema Quebec

2,3 DPG (n=32)

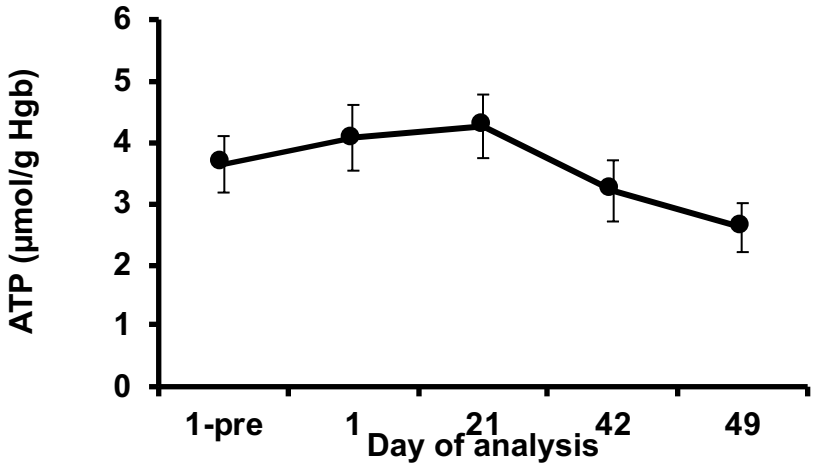
2,3 DPG (µmol/gHb)				
Testing Day	Mean	SD	Min	Max
1-pre	8.2	1.7	5.4	11.2
1	10.5	1.8	6.8	14.6
21	14.5	2.6	6.4	18.1
42	1.5	0.8	0.4	3.1
49	0.7	0.4	0.0	1.8



CLIN-0002: CE Mark study at Hema Quebec

ATP (n=32)

ATP (µmol/gHb)				
Testing Day	Mean	SD	Min	Max
1-pre	3.6	0.5	2.9	4.6
1	4.1	0.5	3.1	5.5
21	4.3	0.5	3.3	5.3
42	3.2	0.5	2.4	4.8
49	2.6	0.4	1.8	3.8



Hypoxic storage maintains ATP levels and increases DPG levels

Red blood cell metabolic responses during blood bank storage under mild and acute hypoxia. D'Alessandro A, Travis N, Hill RC. Vox Sanguinis. 2016 January; 111(S1):7-305.

CLIN-0002: CE Mark study at Hema Quebec

NIH Funded Hemanext Blood Quality Study Results

Preliminary Data – not reviewed by FDA

Study Arm	RBC Yield Post-Hemanext > 85%	Day 42 Hemolysis < 1%	Dual label 24- hour recovery > 75%
Hemanext < 12 hours *	n=95 **89.66%** (±3.42)	n=92 **0.283%** (±0.168)	n=19 **89.34%**** (±5.72)
Control/AS3 < 8 hours	N/A	n=94 **0.289%** (±0.154)	n=21 **85.47%** (±5.82)

- **89.34% recovery is the highest reported for a commercially viable red cell**

*** p < 0.05, * 12 hours vs. 8 hours of processing time**

CLIN-0001: Multicenter US FDA trial

Resuscitation Timeline – Rat Model

Developed pre-clinical model to measure differences in RBC quality

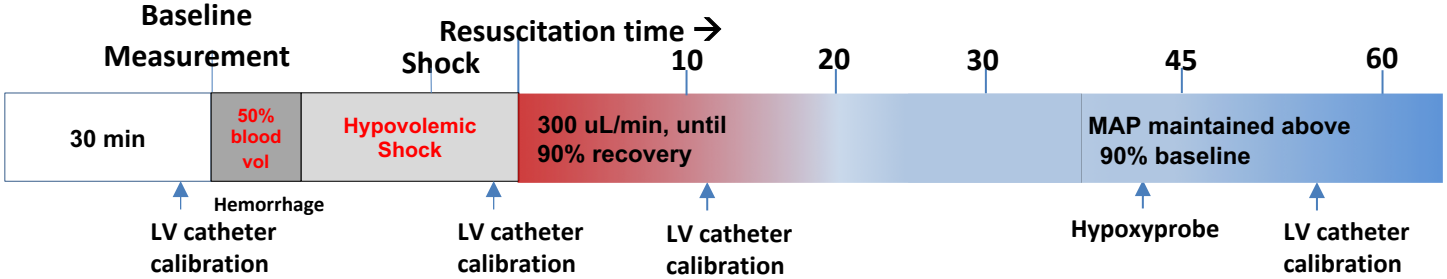
+ Oxygen delivery & vascular management – resuscitation of blood pressure, lactate reduction
+ Marker of blood integrity – post-transfusion intravascular hemolysis
+ Markers of organ inflammation – kidneys, liver, lungs, spleen

Determined relationship between human and rat blood

+ Rat blood behaves similarly to human blood under Hemanext hypoxic conditions
+ Selected 3 week storage duration based on 24-hour recoveries
  + Conventional RBCs 80% 24-hour recovery
  + Hypoxic RBCs 83% 24-hour recovery

Using 3 week old rat blood for resuscitation

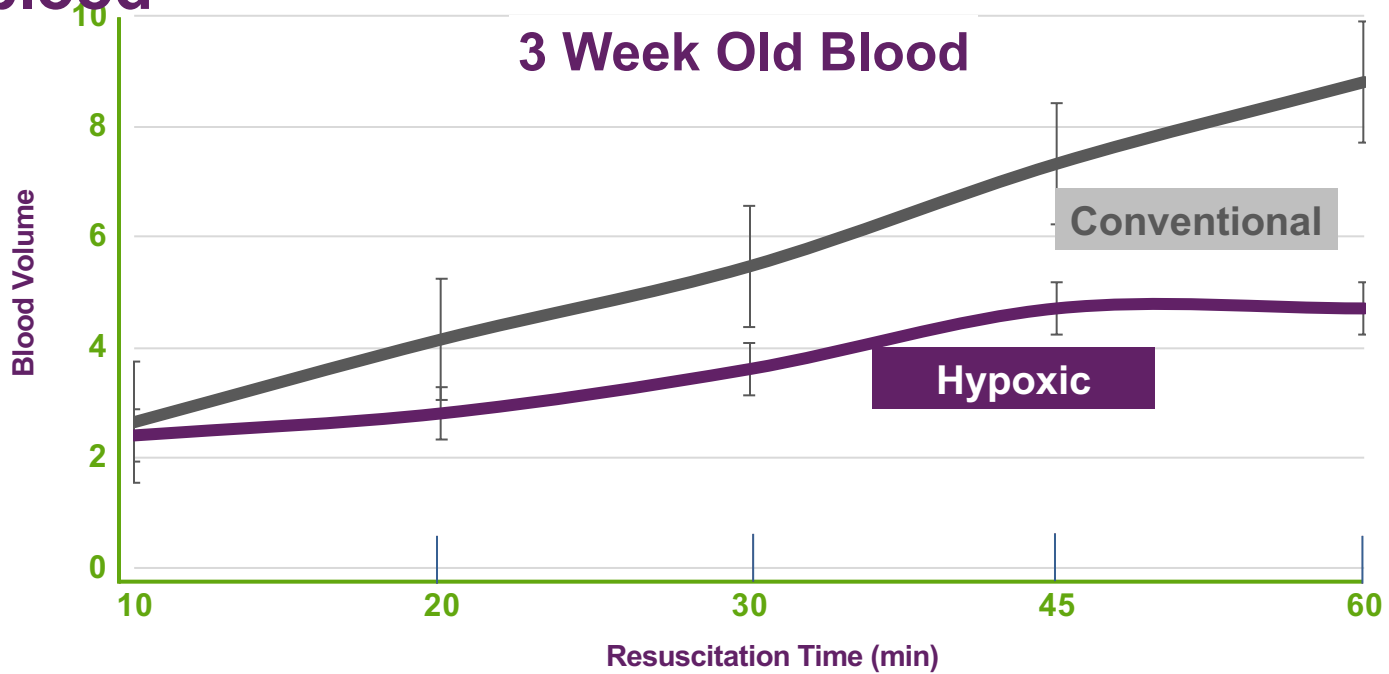
Transfusion of Anaerobically or Conventionally Stored Blood After Hemorrhagic Shock. Shock. 2019 Aug 30. doi: 10.1097/SHK.0000000000001386. [Epub ahead of print]. Williams AT, Jani VP, Nemkov T, Lucas A, Yoshida T, Dunham A, Alessandro A, Cabrales P.



Reduction in blood volume needed to achieve resuscitation after hemorrhagic shock with hypoxically stored blood

Hemanext®

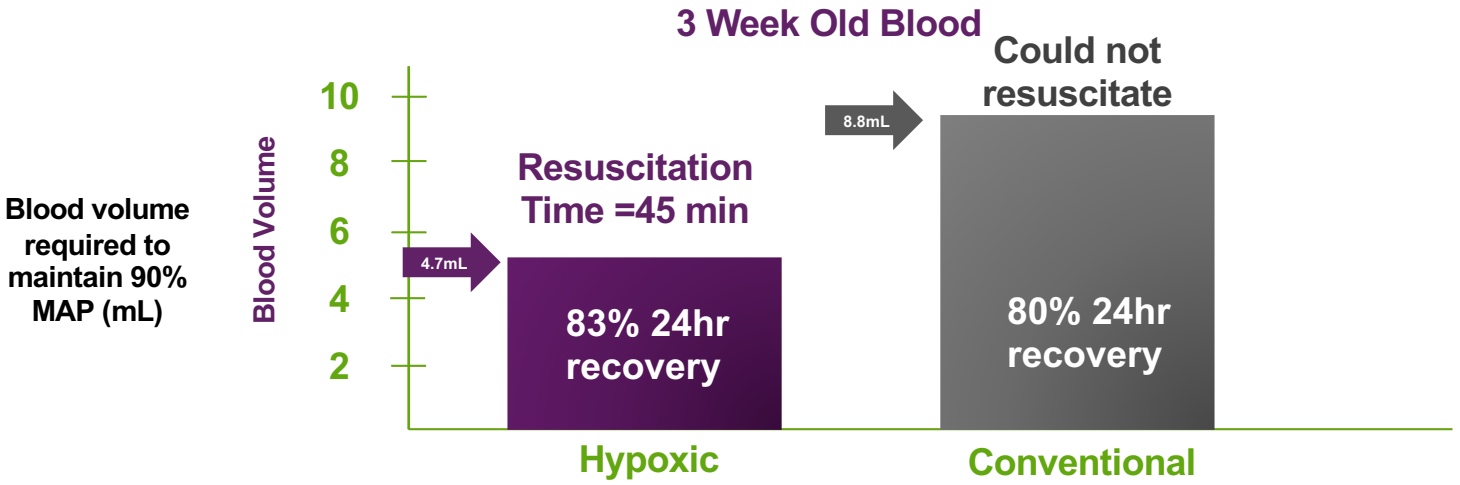
Blood volume required to maintain 90% MAP (mL)



Hypoxic storage dramatically improved resuscitation efficacy and reduced the volume capable of achieving resuscitation.

Reduction in blood volume needed to achieve resuscitation after hemorrhagic shock with hypoxically stored blood

Hemanext®



Hypoxic storage dramatically improved resuscitation efficacy and reduced the volume capable of achieving resuscitation.

Pre-clinical Testing of Hemanext RBC

Hemanext®

Test	Method
Neutrophil Priming Test	Neutrophil activation will be performed with RBC and supernatants from Hemanext products. **Completed** – no evidence of neutrophil activation
Growth and proliferation of facultative and strict anaerobic bacteria	Spike bacteria at different concentrations into leukocyte reduced red cell concentrates. Half of the unit will be processed with Hemanext RBC Processing System and then stored at 4C for 42 days – **Completed – no evidence of increased anaerobic bacterial growth. Will replicate for a manuscript.**
Rate of sickling of sickle red blood cells	Incubate sickle and Hemanext RBC. The change in sickling rate will be measured after mixing with Hemanext RBC – **Completed- no evidence of increased sickling at very extreme oxygen and time variables. Will replicate for a manuscript.**
Endothelial Adherence	Incubate Hemanext RBC with HUVEC at 37ºC under static condition and varying shear stresses – **Completed. Hemanext equivalent or better. Manuscript in process.**
WBC viability and RBC quality post-gamma irradiation	Demonstrate leucocyte inactivation and maintenance of red cell quality post-gamma irradiation - **Hemanext equivalent or better. Completed**
Hemolytic Potential	Subject Hemanext RBC to varying shear stresses measuring hemolysis and red cell fragmentation – **In process**
Neoantigenicity and T-Cell activation tests	Measure expression of surface RBC antigens before and after Hemanext RBC Process – **In process**

Extensive in vitro characterization has not revealed any safety risks

The Hemanext® One Blood Processing and Storage System

Oxygen Reduction Bag (ORB)

Hemanext Storage Bag (HSB)

The **Hemanext® One Blood Processing and Storage System** is *totally compatible* with and *fully integrates* with all current processing and storage systems worldwide.

After centrifugation, RBCs are placed in a conventional storage bag **(LD RBC).**

RBCs are then transferred to a proprietary double layered bag **(ORB)**, which then **removes** up to 95% of the oxygen from the hemoglobin.

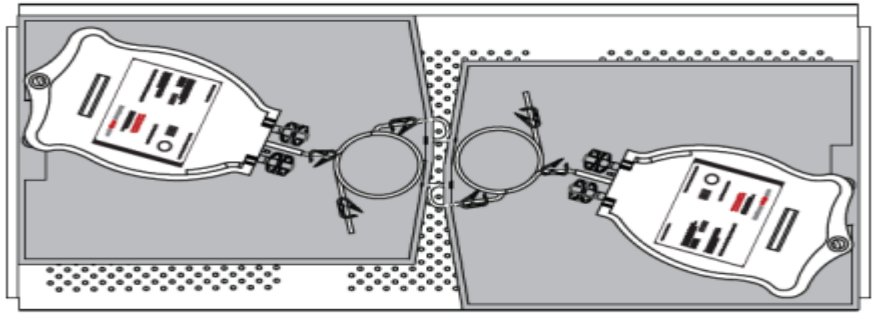
Upon completion of the oxygen transfer, (currently a three hour period), RBCs are transferred to a final proprietary storage bag **(HSB)**, which ensures no further oxygen penetration.

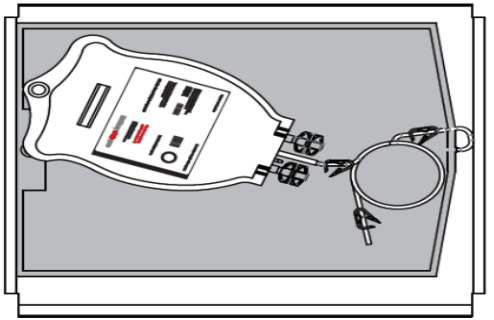
Hemanext Processing

1. Remove from packaging
2. Transfer LR RBC to the Oxygen Reduction Bag
   - + Using a sterile welding connector (SCD), sterile dock the CPD/PAGGSM, LR RBC bag to the LR RBC blood line.
   - + At room temperature (20-26˚ C), hang the LR RBC bag at a head height of no greater than 180 cm (72 inches.)
   - + Separate the LR RBC bag and discard accordingly

Hemanext Processing

3. Agitate in the ORB at room temperature
   - + flatbed platelet agitator shelf at room temperature (20-26˚ C)
   - + No more than two Hemanext RBC Processing Systems per shelf with the ORB parallel to the axis of motion and the HSB on top of the ORB
   - + Ensure that the two Hemanext RBC Processing Systems do not overlap
   - + If flatbed platelet agitator shelf is less than 14.25 x 30 x 1 in (36 x 76 x 2.5 cm), place only one Hemanext RBC Processing System





Hemanext Processing

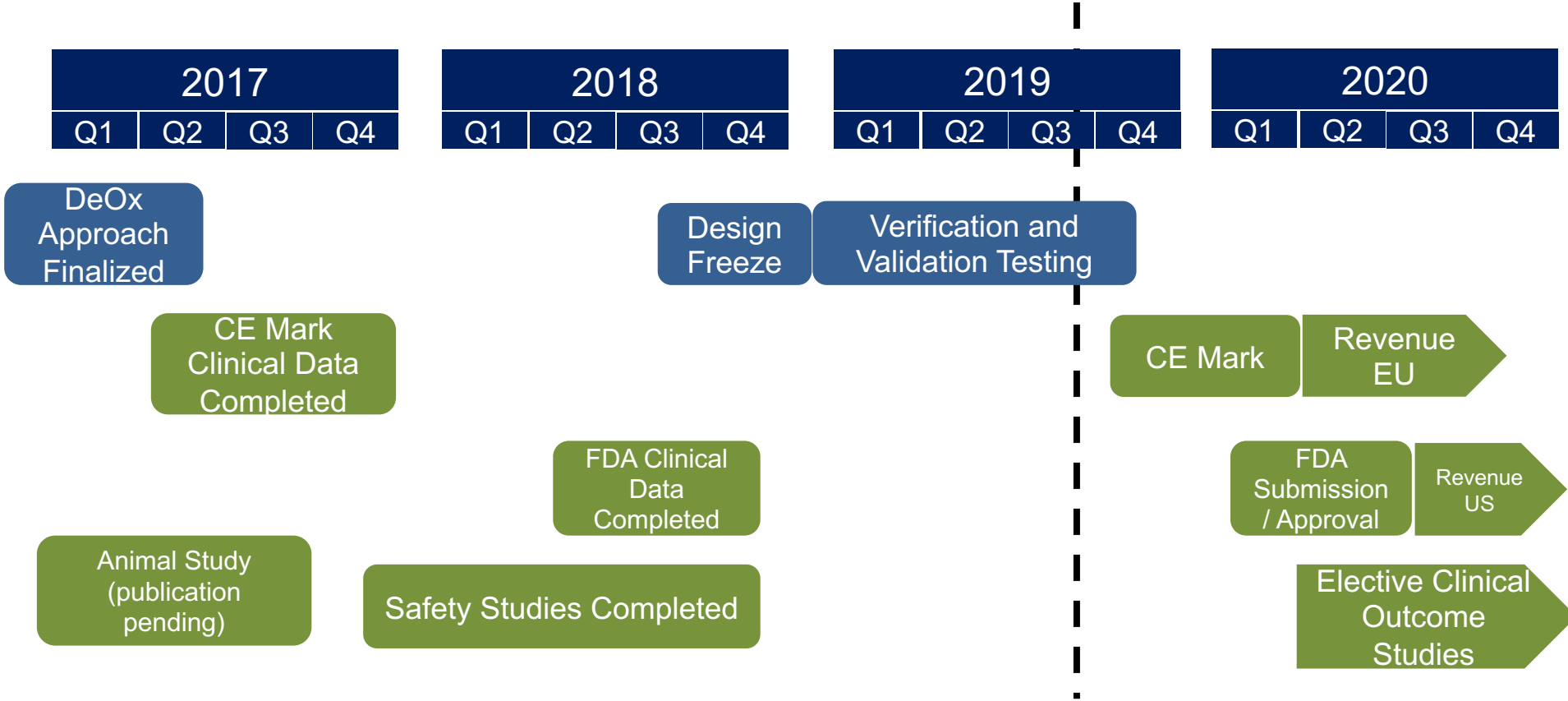
4. Transfer to the Hemanext Storage Bag

- Separate the ORB and dispose accordingly.
- Segment the HSB bloodline as needed.
- Place the HSB into cold storage at1 to 6° C for up to 42 days after collection.
- Prior to transfusion, confirm that the O2 indicator in the HSB is not purple or bluish-gray.

Hemanext Processing

Processing Video

Hemanext Timeline



Plans for Improving Patient Outcomes

Hemanext®

2019	2020	2021	2022	2023	2024
PHASE 1		PHASE 2		PHASE 3	

Clinical Focus

Hematological Disorders:
Oncology /Thalassemia/ Sickle Cell

High Volume Transfusions:
Complex Surgery/ Trauma/ Burn

Other High Volume

Patients and Impacts

SCD
Thalassemia
MDS

+ **Reduced transfusion volume**
+ **Increased transfusion interval**
+ **Reduced iron overload**
+ **Sustained Hb levels**
+ **Reduced sequelae**

Trauma
Burns
Surgeries

+ **Reduced transfusion volume**
+ **Improved oxygen delivery**
+ **Reduced infections**
+ **Reduced length of stay**

Magnitude of Benefit from Improved RBC Quality

Recent Clinical Observations[1,2,3]

- Abdominal surgery[1]
  - RBC age drives extent of Hb loss (18-61% losses) of transfused Hb
- SCD patients[2]
  - Variability of 75.6 – 148.5 days RBC survival after transfusion
- MDS patients[3]
  - Loss of 29 – 52% of transfused red cells <24 hr post-transfusion
  - Hemoglobin loss dependent on inflammatory state of the patient

Post-transfusion variability indicates the magnitude of the opportunity

1 Hunsicker Transfusion, 58(8), 1870-1880, 2018
2 Kim et al., Trans. Aph. Sci, 57, 46-49, 2018
3 Wendelbo et al., Vox Sanguinis, 113, 657–668, 2018

Regulatory clearance activities in progress

Hemanext®

2018:

- ✓ Successful completion of CE Mark and FDA clinical studies
- ✓ FDA confirms clinical study meets submission requirements
- ✓ FDA confirms De Novo 510(k) clearance pathway – based on two communications

2019:

- Submit (Sept ‘19) CE Mark
- File for FDA Clearance (Dec ‘19)

2020

- CE Mark approval
- FDA Clearance (June ‘20)
- US Launch (June ‘20)

“The response to the De Novo pre-submission request was the best I can recall receiving in 22 years dealing with FDA. I am typically realistic, even pessimistic, but I truly believe that FDA is excited about the potential of this product to improve the quality of blood.”

Susan Finneran, President, Regulatory Compliance Experts, Inc.

Thank you

The team at Hemanext and all our collaborators

Mike Dioguardi (Director, Research and Clinical Operations)

Andy Dunham (Chief Scientific Officer)

Bob Haime (Vice President, Commercial Operations)