



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: NDA BN110059/0, HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive

From: Ellen Huang, CSO, OCBQ/DMPQ/MRB II, HFM-676

Through: Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II, HFM-676

Cc: Sonday Kelly, RPM, OBRR/DBA/RPMB, HFM-380
Jennifer Schmidt, Consult Reviewer, OCBQ/DMPQ/MRB I, HFM-675

Subject: **Complete Response Review Memo:** Review of the Complete Responses submitted to CBER February 27, 2013 and associated with NDA submitted by Hemerus Medical, LLC, for HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive.

Due Date: April 28, 2013

REVIEW RECOMMENDATIONS

Based on the review of the firm's response, approval is recommended.

REVIEW SUMMARY

Hemerus Medical, LLC (Hemerus) submitted a NDA for HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive. Hemerus is manufacturing the Leukocyte reduction filter and using JMS Singapore PTE LTD (JMSS) as a contract manufacturer for CPD and SOLX® solutions, SOLX® System device assembly, packaging, labeling, and sterilization. The system is terminally sterilized by using a -----
------(b)(4)-----.

CBER issued a complete response (CR) letter on August 31, 2012. Please refer to my review memo dated August 10, 2012 for a complete review of the original NDA submission.

Hemerus submitted a complete response to the CR letter on February 27, 2013. Please refer to the review memo below for a review of the firm's response to the CR letter for CR Issues 5-7. All responses were found acceptable.

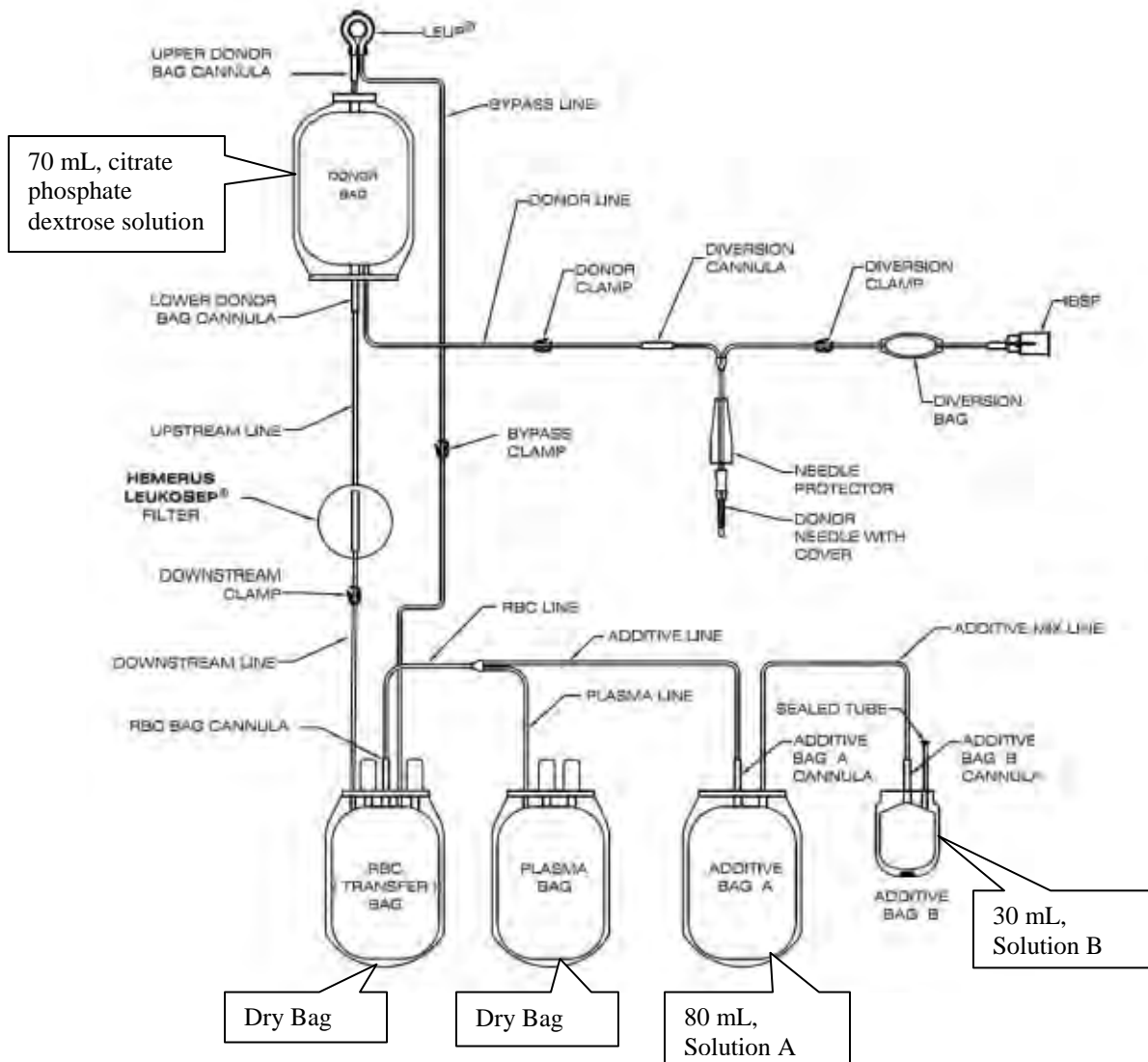
NARRATIVE REVIEW

Items Reviewed

- Items related to sterilization and transportation in NDA BN110059/0 (CR Questions 5-7, excluding the chemical analysis for sterilization and the label peel test)
- Teleconference on March 22, 2013

Background

The HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive is a whole blood collection system containing CPD anticoagulant and SOLX® Red Blood Cell additive solution. It is designed with a donor needle, blood diversion bag with integrated blood sampling port, whole blood collection bag, LEUKOSEP® leukoreduction filter, red blood cell storage bag, plasma storage bag and SOLX® additive solution bags. A schematic of the product is below:



Below is a summary of the manufacturing process overview by facility.

Manufacturing Process	Facility Where Process is Performed
Manufacture of LEUKOSEP® HWB-600-XL Leukocyte Reduction Filter for Whole Blood	Hemerus Medical, LLC St. Paul, MN USA
Manufacture of Blood Storage Container, CPD and SOLX® Solutions, Assembly, Labeling, Packaging and Sterilization of SOLX® System	JMS Singapore PTE LTD Singapore
Inspection and Release of Finished Device	Hemerus Medical, LLC St. Paul, MN USA

To sterilize the system, the firm uses a bioburden/biological indicator sterilization approach. The units are terminally sterilized by using a -----(b)(4)-----

In the original submission, the firm had only conducted one acceptable validation run in Sterilizer (b)(4), which did not demonstrate reproducibility. Additionally, it was not clear how the heat shock studies correlated to actual production sterilization conditions.

Furthermore, in the original submission, the transportation studies were found deficient.

Review of Hemerus' Responses to CBER August 31, 2012 Complete Response Letter

The following are CR Issues 5-7 from the CBER August 31, 2012 CR letter requesting additional information. The firm provided a response to this CR letter on February 27, 2013. The CR questions are in italics; Hemerus' summarized responses are in regular text; and my comments are in bold below.

5. *You have performed one acceptable run in the re-validation of Sterilizer (b)(4), which does not demonstrate reproducibility. Please note that the initial validation (Validation Report LAB/VP/039/06) was performed with a biological indicator (BI) with a D-value which was not determined through a standard referenced method and was not referenced on the certificate of analysis (COA) for the specific sterilization method used in your validation.*

For your validation, please provide additional sterilization runs to demonstrate reproducibility of your final load configuration using a sufficiently resistant BI in comparison to your facility bioburden. The D-value of the BI should be determined by a standard referenced method. Please note that the D-value cited on the BI vendor's COA for your chosen sterilization method will suffice.

A new, ----(b)(4)----- sterilization validation for the SOLX® System was recently conducted by JMSS. The validation incorporated FDA's recommendations and was performed with BIs that were certified by the vendor for use in (b)(4) sterilization.

The protocol and report describing the sterilization validation were provided in Appendices 3 and 4 of the response, respectively. The validation demonstrated the effectiveness and reproducibility of the validated cycle to produce sterile product.

Comparative heat resistance studies were performed with organisms isolated from the facility and -----(b)(4)-----, the BI used for monitoring the

sterilization cycle. Additional information regarding these studies is discussed in the answer to Question 6 below.

According to Validation Protocol and Report VP/058/LAB/12 (LEUKOSEP HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX Additive – (b)(4) Sterilization Using (b)(4) Sterilizer (b)(4), the firm validated the units on Sterilizer (b)(4) at conditions of ----(b)(4)----- (minimum F_0 value = ----(b)(4)-----). The study included:

- -----(b)(4)-----

- -----(b)(4)-----

- -----(b)(4)-----

Operation Qualification (OQ)

OQ activities included -----
----- (b)(4) -----
----- All the criteria for the OQ were met.

Performance Qualification (PQ)

The PQ included -----
----- (b)(4) -----

-----All sensors met the minimum F_0 value of (b)(4) minutes. The actual minimum F_0 value from all three runs was (b)(4) minutes.

For the biological indicator, JMSS used -----(b)(4)----- Spore recovery test was performed by an external laboratory. The table below shows the placement and type of BIs used.

(b)(4)

Reviewer's Comments:

I defer to the product office regarding the chemical tests performed by the firm. Xuan Chi from the product office reviewed the chemical analysis and found no issues.

6. *For the heat shock studies used to evaluate the resistance of organisms at your facility, it is not clear how your study correlates to actual production sterilization conditions. Specifically, the heat shock conditions -----(b)(4)-----
----- than the actual sterilization production cycle for all of the spore formers and mold found in the facility. It is not clear if the heat shock condition or the sterilization production cycle is actually the worst case.*

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Studies were conducted using FDA's recommendations to verify that ----(b)(4)----- is more heat resistant than organisms isolated from the facility. Bacterial and fungal spore formers isolated from the JMSS facility were shown to be less heat resistant than the BI organism -----(b)(4)----- . The protocol and report are attached as Appendices 5 and 6.

If a new heat resistant species is found during routine monitoring, the microorganism will be compared against the BI organism using a similar heat resistance study. The procedure is documented in JMSS SOP LAB/PRO/AE/011 – Heat Shock Test.

According to Test Protocol and Report TP/016/LAB/12 (Comparison Study for Heat Resistance between --(b)(4)-- BI ---(b)(4)-----, Spore Formers & Molds in JMSS Facility the initial resistance test (heat shock test) was a -----

----- (b)(4) -----

----- (b)(4) -----

----- Therefore, the firm concluded that the bacterial and fungal spore-formers isolates at the JMSS Facility were less heat resistant than the BI organism.

Reviewer's Comments:

I reviewed the firm's response and the test protocol and report. The firm's response and the study appear appropriate and the firm fulfilled this CR question. The firm performed additional studies to compare the resistance of spore formers and mold in their facility using test conditions that can be correlated with the sterilization production cycle. The firm also followed our recommendation of using the BI as a control.

7. *The transportation simulation study (Report Number 0706135) evaluated in Report TP/077/PED/2008 did not meet the acceptance criteria (packaging damaged, moisture found in the package, label peel test failed). We noted that the packaging configuration was changed and shipped from Singapore to Hemerus under unknown shipping conditions.*

Please complete additional transportation studies with the new shipping configuration using defined shipping conditions that represent the worst case conditions (e.g. temperature extremes, humidity extremes, time, and etc.).

Hemerus has further modified the shipping carton and packaging configuration for the SOLX® System and has repeated transportation testing using ASTM D4169-09 guidelines. Design modifications include: -----

----- (b)(4) -----

----- (b)(4) -----
-----.

A summary comparison of the previous shipping carton design and the most recent tested design is given in the table below.

[(b)(4)]

The complete protocol and report describing testing of the modified cartons and packaging are in Appendices 7 and 8 (PC412992 and FR412992). The modified packaging configuration met all performance criteria after simulated environmental conditioning performed according to ISTA 2A and transportation testing conducted according to ASTM D4169-09.

Inspection of ---(b)(4)----- ensured (b)(4) confidence and (b)(4) reliability that SOLX® System packaging is capable of withstanding extreme environmental conditioning and distribution simulation. A summary of the testing results in the Table below.

[(b)(4)]

According to protocol and final report PC412992 and FR412992 (Environmental Conditioning and Transportation Simulation Validation of Proposed SOLX System Packaging), the firm changed the shipping carton and packaging configuration again. Per ISTA 2A (2011), the cartons were subjected to the following environmental conditions: -----

----- (b)(4) -----

For the distribution simulation the cartons were subjected to all testing required per -----

----- (b)(4) -----

The firm concluded the proposed redesigned packaging effectively protected the contents throughout the simulated environmental conditioning and distribution testing.

The firm also provided information regarding the label peel test for CR Question 7.

Reviewer's Comments:

I reviewed the firm's response and protocol and final report. I found the response and reports acceptable. The firm completed additional transportation studies with current shipping configuration using simulated shipping conditions.

I defer to the product office to review the label peel testing.

----- (b)(4) -----