



OurReference : BN110059

Hemerus Medical, LLC
Attention: Ms. Lynn Jensen
5000 Township Parkway
Saint Paul, MN 55110

Dear Ms. Jensen:

Please refer to your October 28, 2011 New Drug Application (NDA), submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act, for the HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive.

We determined that the following information is necessary to continue our review.

Please note that the review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Clinical Studies:

1. You indicated that the study met the acceptance criteria for leukocyte reduction with a residual leukocyte content of less than 5×10^6 cells per unit, with a one-sided 95% lower confidence limit of the true proportion of successful units greater than 95%. However, we identified a leukocyte reduction failure for one unit (Hemerus ID DG3T10, subject ID 002653) which showed the residual WBC count of 6.22×10^6 (please see your data.xlsx, under G3 Calc, Postfiltration, line 49 and 50). This unit failed the endpoint criteria that leukocyte reduced components should contain less than 5×10^6 residual WBC per each whole blood unit (See Figure1). The processed RBC derived from the whole blood unit after a hard-spin should contain most of the WBCs, as shown by the majority of data points in Figure 1. However, the WBC count in DG3T10 RBC unit was 3.7×10^6 WBC/unit (59.3% of the WBCs in the whole blood), which passed the acceptance criteria and was used in the end-point calculations. WBC content in the processed plasma derived from that whole blood unit was only 7.02×10^4 /unit. Please comment.
 - a. Please note the results presented in “Table 5-22 Processed RBC Leukoreduction Filtration Results” are misleading. Your LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System with CPD Anticoagulant and SOLX® Additive is a Whole Blood leukocyte reduction filtration system. The residual leukocytes present in the “Postfiltration” product should be used for evaluation of the filter performance. Please recalculate the results listed under Table 5-22.

b. Please explain the loss of around 40% of residual WBCs in the blood components after processing.

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

[(b)(4)]

Figure 1: Comparative analysis of unit WBC count in postfiltration whole blood (WB) and postfiltration Red Blood Cells (RBC) in -----

2. -----

a. -----

b. -----

3. -----(b)(4)-----:

[(b)(4)]

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

-----.

Chemistry Manufacturing and Controls (CMC):

5. Please provide a summary of accelerated stability studies for at least 6 months for lot # ---(b)(4)----- and lot # ---(b)(4)----- .
6. Were there any significant changes at any time during the 6 month testing at the accelerated storage condition? Please also provide a summary of real-time stability data upon completion.
7. The 14-Day Repeat Dose Intravenous Toxicity Study (Module 4, Appendix 4-5):

- a. As shown by Table 2, there were 3 blood clotting events in test groups (2 specimens in the female test group and 1 specimen in male test group) and 0 clotting event in control specimens. Please explain this result.
 - b. Both male and female test animals were observed to have significantly lower platelet counts ($p=0.0033$ and $p=0.0440$ respectively) when compared to controls. The presence of clots within 2 specimens from female mice contributed to the decrease observed in female test group, but in the male test group, the specimen with clots was excluded from the platelet count. Please explain the decrease in the platelet count in the male test group.
8. The Prothrombin Time Assay study (Module 4, Appendix 4-8) and sister studies:
- a. Regarding the Prothrombin Time Assay study (Appendix 4-8), Complement Activation Assay (Appendix 4-9) and Unactivated PTT Assay (Appendix 4-10), we note that a serious deviation from the study protocol occurred which resulted in the plasma passing through the donor bag and mixing with citrate. Since high amounts of citrate are known to change the outcome of coagulation tests PT and NaPTT (Unactivated PTT), and since citrate also dilutes the plasma, all 3 studies were compromised. In addition, $n = 3$ is not sufficient for the above coagulation tests. Please repeat these 3 tests following the specifics of the protocol, especially those related to the preparation of the test plasma, using a sample size that is statistically sound.
 - b. Regarding the Prothrombin Time Assay study, the plasma used for the test article was from multiple donors and the plasma used for the controls was from one of these donors. This is a problematic because donor-to-donor variability will hide potential effects of the tested article on plasma. Both test and control should have been tested using the same lot of plasma/plasmas.
 - c. Regarding the Complement Activation Assay (Appendix 4-9), please explain the negative concentrations of SC5b-9 protein described on Page 17 of the study report 09-3504-G4.

9. Physicochemical test for plastics-USP (Module 4, Appendix 4-16):

DEHP is not soluble in water and therefore water should not be used as an extractant. More relevant solvent such as plasma should be used as solvent to extract DEHP.

10. Microscopic Particle Count Test (Module 4, Appendix 4-18):

Please specify what guidance was followed for the Evaluation Criteria for the Microscopic Particle Count test, or otherwise provide justification of the Evaluation Criteria.

11. Transportation Testing Report (Module 4, Appendix 4-25):

There are a number of issues identified in this report (Inner box cartons and divider damaged, visual inspection of aluminum foil pack label failed, kinking of collection tubes/connecting tubes, label peel test failed for all (b)(4) groups of blood bags examined). Please provide a summary of corrective actions taken for these issues.

12. Regarding Module 3 – Page 1469 and elsewhere – there are reports of kinks being found in the tubing at the time of inspection after sterilization.

- a. What is the current rate of visible kinks and what changes have you and JMS made to reduce/prevent the occurrence of these kinks? Were similar kinks reported during the post sterilization inspection of your 510(k) product?
- b. In addition, there is discussion in an email between JMS and Hemerus asking whether JMS is inspecting the containers for ‘bag adhesions’ similar to those experienced previously. Has that issue been resolved?

Pharmacology/Toxicology:

13. Regarding label stocks from (b)(4):

The composition of the adhesive, called (b)(4), used on label stocks manufactured by (b)(4) was described as an acrylic, but the full formulation of the material was not provided and should be submitted as an amendment to ---(b)(4)--.

14. Regarding the formulation for acrylate ink manufactured by ----(b)(4)----:

- a. Results previously provided in Report TP/119/PED/2009, submitted in the original NDA BN110059/0, suggest labels printed with acrylate ink maintain their integrity and stability under a variety of conditions and are therefore fully polymerized. While these previous data are acceptable, the cytotoxic potential of labels printed with acrylate ink manufactured by ---(b)(4)---- should be determined using the -----(b)(4)-----.
- b. Please confirm that (b)(4) will be used to polymerize acrylate ink to label stocks and also provide the name and location of the vendor responsible for performing the polymerization procedure.

15. Regarding ribbon ink from Armor,--(b)(4)-- please provide the following for review:

- a. The formulation for ribbon ink, called (b)(4), manufactured by ----(b)(4)-----
----- This was not provided in ----(b)(4)-----.

- b. An assessment of the potential cytotoxicity of ribbon ink (b)(4) used on Hemerus blood bag labels using the MEM Elution assay <USP 87>.
- c. The name and location of the printer responsible for applying ribbon ink (b)(4).
- d. The results from ---(b)(4)--- performed by -----(b)(4)-----.

16. Regarding additional toxicity test results reported by JMS:

The toxicity of PVC manufactured by JMS has not been evaluated by an *in vivo* implantation assay <USP 88>, or by direct contact and agar diffusion <USP 87> *in vitro* assays. Please submit results from these.

17. Regarding physicochemical testing:

- a. Please submit results on buffer capacity, residue contact on ignition and non-volatile residue content in bag extracts.
- b. Please identify the components in PVC extracts used in the toxicity studies by mass spectrometry or at a minimum for total organic carbon (ToC) content.

18. Regarding toxicity testing based on standards described in Japanese MHLW, please do the following:

- a. Clarify what the (b)(4) concentration of (b)(4) means in the cytotoxicity results table. Describe the toxicity observed at concentrations above (b)(4) using morphological and reactivity grades referenced in ISO 10993-5.
- b. Indicate which of the following PVC pellets -----(b)(4)----- will be used to manufacture Hemerus bags.
- c. Indicate the dose of PVC extract used in the acute toxicity studies.
- d. Indicate the extract concentration used in the hemolysis and intracutaneous reactivity assays.

19. Regarding Resistance study, FR409400, March 6, 2012:

- a. Please justify why the stability of label inks was not evaluated against detergents, denatured alcohols, acids, and other solvents specified in ISO 2836 as exposure to these liquids may represent a worst case leaching scenario.
- b. Please confirm labels evaluated in the resistance study were printed with the ribbon ink (b)(4) manufactured by -----(b)(4)----- and with red and black

acrylate inks manufactured by -----(b)(4)----- . Please also confirm that label stocks used in this study were manufactured by (b)(4).

- c. The ink used to print the letter “T” on the label presented in Appendix A (located in the image on the right side at the bottom of page 13 of 17) was significantly reduced following treatment. Please quantify this reduction in ink intensity according to spectrophotometric method ISO 105-A03 referenced in ISO 2836.

20. Regarding the Agar diffusion study-ISO, 12-603-G1:

Please confirm both the ribbon and acrylate inks were present on the label strips and came into direct contact with cells during the study.

21. Regarding extraction procedures used on LeukoSep filters and SOLX circuits:

- a. Please confirm the LeukoSep filter was included in the SOLX circuit when the -----(b)(4)----- were performed.
- b. Please justify why an extraction of the LeukoSep filtration unit using an appropriate solvent followed by analysis of the extracts by GC/MS and HPLC/MS was not performed.
- c. Based on the total surface area of the SOLX circuit and an established extraction ratio of -(b)(4)--, please confirm:
 - 1) The extract volumes of 500 mL used in the biocompatibility studies was the appropriate amount.
 - 2) The extract volume of (b)(4)- used in the metal analyses (Study 06-5803-N2) was also the appropriate amount.

22. Regarding (b)(4) MEM elution assay, 09-3504-G1:

A (b)(4) amount of SOLX extract was applied to (b)(4) cells, but the total volume of media used during incubation of the cells was not indicated. Please provide the SOLX extract dilution factor and final SOLX extract concentrations used during these experiments.

23. Regarding Chemical and physicochemical characterization of extracts, 10-1868-G1:

Please justify why total organic carbon, GC/MS and HPLC/MS analyses were not conducted to further identify and quantify chemical components, in addition to metals and non-volatiles, in SOLX extracts.

24. Regarding the Repeat-dose toxicity study, 09-5442-G1:

- a. Platelet counts in male mice administered SOLX extract following repeat dosing were reduced to 1075 ± 147 K/ μ L compared with 1374 ± 45 K/ μ L in saline-treated male mice. Platelets were also reduced to 489 ± 348 in female mice administered SOLX extracts compared with 983 ± 306 in female mice administered saline controls. Although sample clotting was observed during this study, please still provide an explanation for decreased platelet counts and perform histopathology on splenic tissues to rule out any potential immunotoxicity.
- b. The potential of DEHP and other plasticizers present in SOLX extracts to disrupt endocrine function is a safety concern. However, results from the histological examination of rat testes tissues were not reported. If available, please provide these data.
- c. Please explain why a recovery period, to monitor the possible occurrence of delayed toxicity, was not included in the experimental design.

25. Regarding Verification tests of SOLX blood bags with a focus on blood bag labels, TP/119/PED/2009, please do the following:

- a. Submit a Master File to FDA describing the composition of the ink used on SOLX blood bag labels and indicate where the printing process will be performed.
- b. Submit a Master File describing the composition of the adhesives used on SOLX blood bag label stocks.
- c. Perform a MEM elution, USP <87>, or comparable assay on printed labels to rule out any cytotoxicity associated with ink used on SOLX blood bag labels.

General CMC comments:

26. Configuration Information:

- a. Please identify the source of the needle and needle guard.
- b. Please clarify whether the materials used for the whole blood filter are the same as the 510k LRF with respect LRF media, treatments, etc. Please provide a list of suppliers for the materials used to manufacture the LEUKOSEP® HWB-600-XL filter.
- c. Is a solvent/adhesive used to bond the polycarbonate housing of the leukocyte reduction filter? Where is it defined/described?

- d. The whole blood collection set contains a sample diversion pouch. Did the IND test sites perform testing to demonstrate that hemolysis does not occur when vacutainer tubes are filled? If not, studies should be performed to demonstrate lack of hemolysis. Please note hemolysis may interfere with disease marker testing performed at blood centers.
- e. What solvent is used to bond the tubing to the LRF housing?
- f. Provide complete information on the whole blood leukocyte reduction filter, materials, layers, etc., so a consult materials review can be requested from CDRH or within CBER in the toxicology group.
- g. Can folds occur in the filter media? If so, how is this reduced/prevented?
- h. Under the COMMENTS spread sheet the following issues are of concern:
 - 1) BUBBLES – what was root cause? Was it operator error/product handling or was it related to a filter issue? Are there instructions regarding bubbles in the IFU to the operator? What is the effect of bubbles on the filtration process? Provide data to support your response.
 - 2) Filter issues – please fully explain.
 - 3) Were any donors with SCT collected and processed?
- i. What labeling is on the LEUKOSEP HWB-600-XL filter itself? Please submit a photo or drawing that illustrates the filter and its label.

General comments regarding the Labeling:

- 27. We suggest revising the product name to read as follows: HEMERUS LEUKOSEP HWB-600-XL Whole Blood Leukocyte Reduction Filter for Collection and Filtration of Whole Blood collected in CPD/SOLX Red Blood Cell Preservative Solution.
- 28. Please note labeling may change depending on the final outcome of the approval process.
- 29. Please note that this is a new drug application (NDA) rather than a device application. Throughout the labeling and discussion references are made to the “device” system. Please remove references referring to the collection set as a “device.”
- 30. You did not submit a label for -----(b)(4)-----
----- . Please provide one for our review.

31. The container labels do not follow ISBT consensus standard 2.0. Please review the ISBT standards and revise the labels. The labels will also need an appropriate drug name assigned for the additive solution. Please refer to the ICCBA website for standards. <http://iccbba.org/>. The labels should be resubmitted for review after corrections are made. There may be other revisions requested based on additional information that may be submitted in support of this application. ISBT codes will need to be established for the following:

- a. SOLX RBCs – placed at 1-6 °C within 8 hours of collection.
- b. -----(b)(4)-----

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

32. 4069501 Draft – CPD Whole Blood Container:

- a. Storage temperature (1 to 6 °C) for whole blood product should be on the label.
- b. JMS Singapore, the location of manufacturing, should be included on the labels.
- c. Please confer with ICCBBA to determine whether the symbol ‘consult instructions for use’ is acceptable. Previous labels state ‘See circular of information for indications, contraindications, cautions, and methods of infusion.’

33. 4069502 Draft – CPD RBC Container:

- a. Storage temperature (1 to 6 °C) for SOLX RBC product should be on the label.
- b. JMS Singapore, the location of manufacturing, should be included on the labels.
- c. Please confer with ICCBBA to determine whether the symbol ‘consult instructions for use’ is acceptable. Previous labels state ‘See circular of information for indications, contraindications, cautions, and methods of infusion’. Consult instructions could be referring to the IFU for the SOLX System.

34. 4069503 Draft – CPD Plasma Container:

- a. _____mL from CPD Whole Blood should be on the label.
- b. Store at -18 °C or colder should be on the label.
- c. JMS Singapore, the location of manufacturing, should be included on the labels.

- d. Please confer with ICCBBA to determine whether the symbol ‘consult instructions for use’ is acceptable. Previous labels state ‘See circular of information for indications, contraindications, cautions, and methods of infusion’.

35. 4069504 Draft – SOLX A Additive Solution, 4069505 Draft – SOLX B Additive Solution:

JMS Singapore, the location of manufacturing, should be included on the labels.

36. 4069506 Draft – Container Label for XX Units:

- a. We suggest the wording be revised to define the anticoagulant and product first then to describe the LRF.

Current: LEUKOSEP HWB-600-XL Leukocyte Reduction System for Whole Blood with CPD Anticoagulant and SOLX Additive.

Suggested: Anticoagulant Citrate Phosphate Dextrose Solution, USP (CPD) with an Integral LEUKOSEP HWB-600-XL Leukocyte Reduction System for Whole Blood and SOLX Additive Solution (Parts A and B) USP.

- b. The number of units per package should be defined.
- c. The collection volume should be defined; i.e., for collection of 500 mL of Blood.
- d. JMS Singapore, the location of manufacturing (except for filter) and assembly, should be included on the labels. The draft states the product is “Assembled” in Singapore.
- e. The following statements should appear on this label:
 - 1) Protect from freezing.
 - 2) Avoid excess heat and direct sun light.
- f. A box label for multiple containers, if there is one, was not submitted for our review.

37. 4069507 Draft – Instructions for Use (IFU):

- a. Please revise the Indications for Use to include the following:

“SOLX[®] System” is intended for the manufacture of:

- CPD/XXX Red Blood Cells(RBC), Leukocytes Reduced prepared at ambient temperature and placed at 1 to 6 °C within 8 hours of collection. CPD/XXX Red Blood Cells, Leukocytes Reduced may be stored at 1 to 6 °C for up to 42 days after collection.

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

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- Fresh Frozen Plasma (FFP), Leukocytes Reduced prepared and frozen at -18 °C or colder within 8 hours of collection. Fresh Frozen Plasma (FFP), Leukocytes Reduced may be stored at -18 °C or colder for up to one year after collection.

- -----

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

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b. ----- (b)(4) -----
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c. Please note that you have not included a scenario where the whole blood is collected, filtered, and processed within 8 hours of collection. Currently, FFP must be prepared from whole blood that has been stored less than 8 hours at ambient temperature prior to placing it in a freezer at minus 18 °C or colder with the corresponding SOLX RBCs placed at 1-6 °C within 8 hours of collection.

d. Please clarify what happens to non-leukoreduced units.

e. Please clarify if (b)(4) will be manufactured using this blood bag.

f. Please include the following statement “Studies have not been performed to allow irradiation and/or freezing of SOLX RBCs.”

g. Please revise the statement to include the non-trade name for the additive solution (AS-‘X’) after you have received the additive solution designation for your SOLX System. Please submit the revised IFU for our review.

h. Caution:

- 1) Please remove the word “device” from this statement and others. This is an NDA submission.
- 2) We suggest Rx Only as a Caution statement.

i. Description:

- 1) Remove the phrase “single use device” from the Device Description.
- 2) This collection system includes an integrated sample diversion pouch (IBSP). It should be included in product description.
- 3) Please revise the statement to include the word “solution” after “SOLX Additive.”
- 4) Whole Blood should be capitalized. Please revise the product to include capitalization.
- 5) Consider removing the word “manual” from the description. We do not believe it is necessary.
- 6) Remove the word “device” the statement that reads “Each device unit consists of:”

j. For consistency please consider using the term “container” throughout the IFU rather than switching between “container” and “bag.”

k. Indications for Use:

- 1) The labeling should include a statement that platelets and Cryoprecipitated AHF cannot be prepared from this whole blood collection system.
- 2) Please revise each statement that reads “and frozen at -18 °C or below” to read “placed in a freezer at -18 °C or colder.”
- 3) Please include a statement that allows for pre-storage leukocyte reduction of the CPD whole blood followed by preparation of SOLX Red Blood Cells at ambient temperature within 8 hours of collection. SOLX Red Blood Cells must be placed at 1-6 °C within 8 hours of collection. Plasma must be placed in a freezer at -18 °C or colder within 8 hours of collection.

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

l. Warnings:

1) Please add the following statement: Do not squeeze the Diversion Bag during donation to avoid risk of air embolism.

2) -----

m. Precautions:

1) Consider removing the single use statement. All whole blood collection systems are single use and are not re-used or re-sterilized.

2) Remove the word “device” from the second statement.

3) Please add the following statement: Whole blood collected from certain donors may have extended filtration times and the potential for ineffective filtration and leukoreduction.

n. Removal from Packaging:

1) Remove the word “device” from the title and each of the instructions.

2) Consider revising the first sentence to read “Remove individually packaged collection sets (or units) from the outer foil package and inspect for damage.”

3) -----

4) The instructions in number 1 state that the foil pack should be sealed with an air-tight sealing method. Please clarify how to perform this step or indicate where the instructions are located.

5) Protocol#PC387580 (Revision 11/22/2010) also included an instruction to smooth out any kinks in the tubing. Please comment on its removal from the Draft IFU. We suggest modifying your IFU to include a statement that

directs the operator as to what they should do if they find kinks in the tubing. Examples include the following:

- i. Manufacturer 1 - CPD label - under Warnings and Cautions – includes ‘do not use if the collection set: the tubing has severe kinks’.
- ii. Manufacturer 2 – Check for kinks in the tubing prior to collection and filtration.

o. Blood Collection:

- 1) Number 5: Please revise to include that the arm scrub should be performed with an approved method.
- 2) Number 7: Please revise to include that the blood collection tubes should be appropriately labeled.
- 3) Number 10: Please instruct the user to periodically mix the blood product. Please more clearly define periodically and how often it should be done during the collection process.
- 4) Please consider using the term “upper arm” instead of brachium.

p. Leukoreduction:

- 1) Please revise the instructions to include the time frames and temperatures that should be followed in the manufacturing procedure.
- 2) Please include another step in the procedure to have the user check the blood bag to ensure that the entire unit was filtered and there is no additional volume in the primary bag.
- 3) Please revise the package insert to include the procedure for Quality Control of the products.
- 4) Please revise the package insert to include the procedure to be followed when the entire unit is not leukoreduced (e.g. check volume, residual WBC count etc.).

5) -----
----- (b)(4) -----

q. Processing Blood Components:

-----~~(b)(4)~~-----
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r. Preparing Plasma:

- 1) Note: Please revise the product name to ~~---(b)(4)--~~ as described above.
- 2) Note: Please clarify if (b)(4) will not be manufactured with this blood bag set.
- 3) Please revise each statement that reads “and frozen at -18 °C or below” to read “placed in a freezer at -18 °C or colder.”
- 4) Please consider separating the two statements.

s. Preparing SOLX Red Blood Cells:

1) -----
-----~~(b)(4)~~-----
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2) -----
-----~~(b)(4)~~-----

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- 3) Please revise statement 5 to include the number of days that the product may be stored at 1-6 °C.
- 4) Please add “in a properly designated container” to statement 6.
- 5) If production of excessive bubbles is a continuing problem, the IFU should instruct the operator regarding excess bubble prior to filtration.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application

The action due date for this file is August 31, 2012.

If you have any questions, please call Sunday L. Kelly, Regulatory Project Manager, at (240) 507-8446.

Sincerely,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research