

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: Chiang Syin, Ph.D., Branch Chief, OCBQ/DMPQ/MRB II, HFM-676
Cc: Sondag Kelly, RPM, OBRR/DBA/RPMB, HFM-380
Jennifer Schmidt, Consult Reviewer, OCBQ/DMPQ/MRB I, HFM-675
Subject: Review of the 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: August 31, 2012

REVIEW RECOMMENDATIONS

Based on information submitted in the supplement, amendments, and teleconferences, I recommend a Complete Response (CR) Letter containing the following comments be issued to Hemerus Medical, LLC:

- 1. 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.
2. 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)----- 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.

- Please perform additional studies to compare the resistance of spore formers and mold in your facility using test conditions that can be correlated with your sterilization production cycle. To facilitate comparison to your chosen validation biological indicator, we recommend that your thermal studies also include the biological indicator as a control.
3. 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 worse case conditions (e.g. temperature extremes, humidity extremes, time, and etc).

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

The NDA submission included the validation of the (b)(4)- sterilization process, a re-validation of the (b)(4) sterilization process, the Drug Master File (DMF) on the container and closure for blood bag system, and transportation studies.

Information Requests (IR) from DMPQ was communicated to the firm on April 16, May 23, June 29, and July 12, 2012 and the firm provided a response on May 3, June 8, July 18, and July 23, 2012, respectively. Additionally, a teleconference was held with the firm July 26, 2012 and the firm provided comments regarding the teleconference in a response on July 27, 2012.

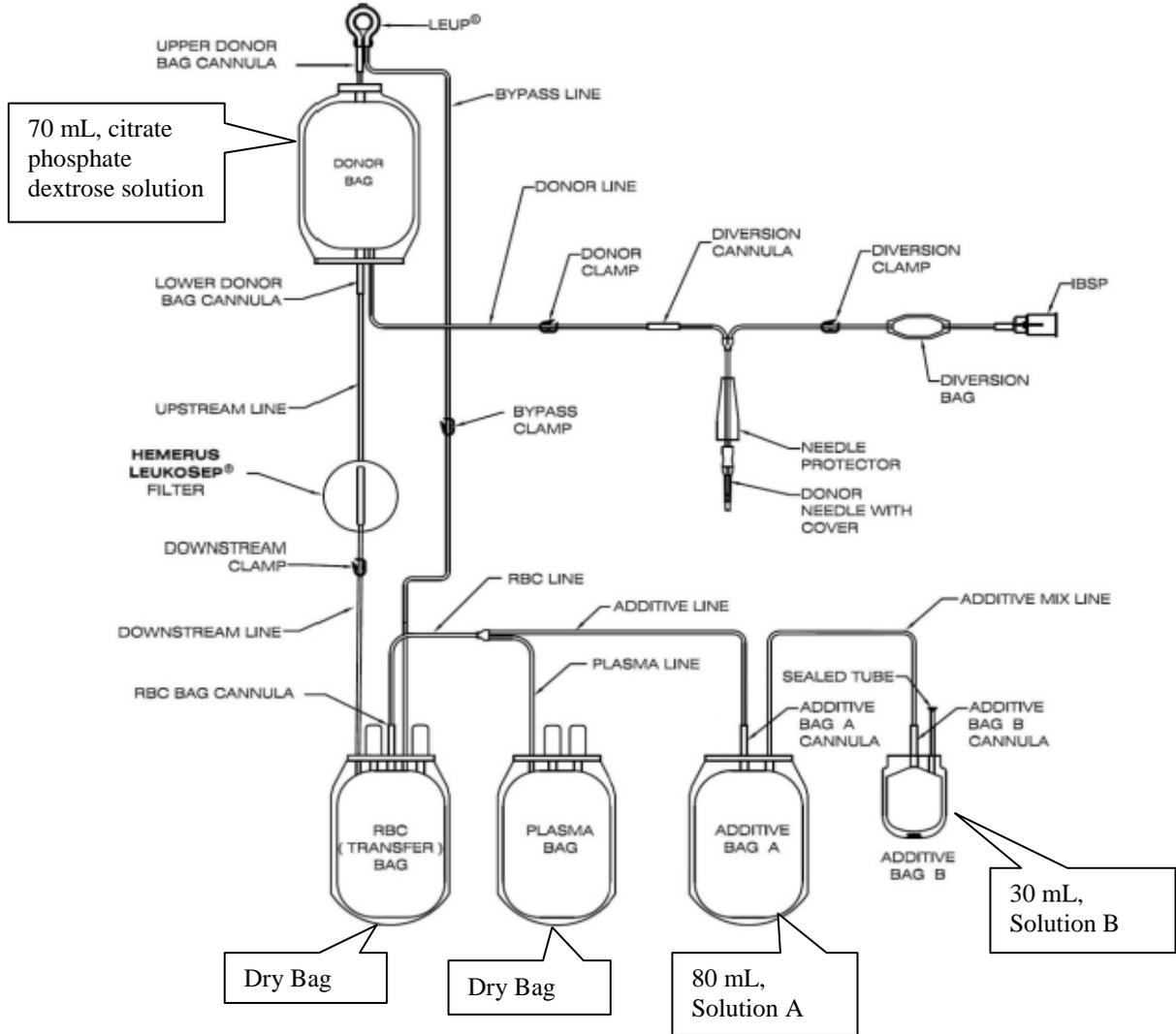
NARRATIVE REVIEW

Items Reviewed

- Items related to sterilization, container closure integrity on final container, and transportation in NDA BN110059/0
- Amendments 9 (responses to IR dated April 16, 2012), Amendment 11 (responses to IR dated May 23, 2012), Amendment 12 (responses to IR dated June 29, 2012), and Amendment 13 (responses to IR dated July 12, 2012), and Amendment 14 (responses to a telecon on July 26, 2012)

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:



JMS Singapore PTE LTD (JMS) is the contract manufacturer for CPD and SOLX® solutions, SOLX® System device assembly, packaging, labeling, and sterilization.

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

Sterilization

JMS initially validated the LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX™ Additive on Sterilizer (b)(4) under report number LAB/VP/039/06 in 2007. Subsequently, JMS revalidated the system on Sterilizer (b)(4) in 2009 under report number VP/031/LAB/09. The system is terminally sterilized by using a------(b)(4)------. The submission also states that a -----(b)(4)-----.

Validation: Report LAB/VP/039/06

Report LAB/VP/039/06, *JMS(S) Validation Protocol and Report: LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX™ Additive: -----(b)(4)-----*, included:

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

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

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

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

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

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

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

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

1 page redacted due to (b)(4)

concerning raw materials, manufacturing processes, facilities, equipment, and process controls and specifications used during manufacture of the PVC containers.

Integrity testing on portions of the system was found in the submission. For example, the filter was tested by an ----(b)(4)----- test (Report PC400210 and FR400210)

Reviewer’s Comments:

- It was not clear if the complete system was evaluated for container closure integrity testing. Clarification was sought from the firm. Refer to **IR Question 60** in the “Review Questions” section below for the firm’s response.
- The firm was also asked to explain what package testing has been completed to ensure sterility for the lifetime of the product. Refer to **IR Question 61** in the “Review Questions” section below for the firm’s response.

Transportation

Hemerus provided transportation simulation tests, which were performed by ---(b)(4)----. (Report Number 0706135 Rev. C: Transportation Simulation Testing for the Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX™ Additive). The purpose of these tests were to evaluate the capacity of package design when exposed to conditions representative of the product and shipping and handling stresses likely to occur during products life. The units were tested for -----(b)(4)-----
----- . The tests performed by (b)(4) were based on ASTM D 4169-05, DC 13, Assurance Level I Truck/Air Spectrum and (b)(4) procedures. Tests included manual handling, vehicle stacking, loose load vibration, low pressure (high altitude) hazard, and vehicle vibration. The test specimens sustained some creasing and denting during the drop tests (manual handling), which may have caused the shippers to loose some stacking strength.

Hemerus also provided JMS’s testing protocol and report, TP/077/PED/2008: Transportation Testing for SOLX. JMS performed designed verification in general appearance (visual inspection) and packaging testing (foil peel strength, tub peel strength, and label peel) after transportation. The foil peel strength and tub peel strength passed the acceptance criteria. However, the general appearance and label peel testing did not meet the acceptance criteria. The outer box was compressed and the label on the outer box was torn. Dampness was noticed in the inner box and divider. The moisture led to deformed inner boxes, tape peeling off the inner boxes, flaky interior surfaces of the inner boxes, and flaky labels on the aluminum foil pack. Additionally, kinked tubes were noted and attributed to wrong placement of the tub, harsh transportation testing, and divider losing its integrity. Furthermore, air bubbles within the label were found.

In addition, Hemerus provided protocol report PC407240 and final report FR407240 (Verification of Foil Pack Integrity of Hemerus LEUKOSEP/SOLX System Following Shipment). In this report, it was noted that Hemerus modified the packaging -----
----- (b)(4) ----- . The changes are summarized in the table below.

[(b)(4)]

Per PC/FR407240, cartons were shipped from Singapore to Hemerus. The cartons were shipped to a clinical site and shipped back to Hemerus. Thirty foil packs were visually inspected for pinholes, tears, and other unacceptable damages and were found acceptable.

Reviewer's Comments:

- It was unclear how the units would be routinely transported. Therefore, the SOP for transportation was requested. Refer to **IR Question 63** in the “Review Questions” section below for summary of the procedure.
- Hemerus had several transportation studies performed. The relationship between these studies was unclear. Additionally, it was not clear if the worse case shipping conditions were represented. Refer to **IR Question 64** in the “Review Questions” section below for the firm’s response.
- According to TP/077/PED/2008, moisture was found in the inner box. The firm was asked to address the moisture. Refer to **IR Question 65** in the “Review Questions” section below for a review of the firm’s response.
- The firm mentioned that modifications were made to the packaging. It was not clear if the modifications were made before or after the transportation validation. Refer to **IR Question 66** in the “Review Questions” section below for the firm’s response.

REVIEW QUESTIONS

Review questions were communicated to the sponsor on April 16, May 23, June 29, July 12, and July 26, 2012. CBER received responses from the sponsor on May 4 in amendment 9, June 8 in amendment 11, July 23 in amendment 12, July 23, 2012 amendment 13, and July 27, 2012 in amendment 14. A summary of my review questions (in *Italics*), Hemerus’ responses (in regular text) and my comments (in **bold**) are below:

(b)(4) Sterilization

Amendment 9 (May 4, 2012)

1. *Please provide the design approach utilized for your autoclave (i.e. overkill).*

The design method used for the sterilization validations was a combined bioburden/biological indicator approach.

Reviewer’s Comment: Using the bioburden/biological indicator approach is acceptable. The firm’s acceptance criterion for the sterilization validation was a

Reviewer’s Comment: Response is acceptable.

- 6. *You stated that all thermal sensors are calibrated ----(b)(4)----- . Please explain why the sensors were not calibrated before and after each validation run.*

The thermal sensors had valid calibration certificates traceable to a national standard at the time of the validation activities meeting the requirement of ISO 17665-1 Sterilization of health care products – Moist heat Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.

Reviewer’s Comment: Typically thermal sensors used to measure temperature in validations are calibrated before and after each use. However, it is the firm’s risk if the chose not to calibrate before and after each use. Therefore, the firm was asked if the thermal sensors were within calibrated after the validation. Refer to IR Question 32 below.

- 7. *Please clarify if there were any sensors in the drain.*

There were no sensors placed in the drain.

Reviewer’s Comment: Response is acceptable. Sensors are typically placed in the drain but it is not required.

- 8. *One empty chamber cycle was performed in Study LAB/VR/039/06. -----*

Reviewer’s Comment: Response is acceptable.

- 9. *For the PQ, please clarify where the thermal sensors were placed the system (i.e. in the anticoagulant solution) and a rationale for the placement.*

Reviewer’s Comment: Response is acceptable.

- 10. *The validation states that -----*

- a. *Please provide as side-by-side comparison of --(b)(4)-- bag and SOLA bag (dimensions, materials, etc). Please also provide a diagram of each bag.*

The side-by-side comparison is listed in the table below.

[(b)(4)]

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

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

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

Reviewer's Comment: Response is acceptable. Using the bag with the largest fluid volume is the worse case location.

11. In Study LAB/VR/039/06 several thermal sensors did not reach (b)(4) when sterilization dwell time started. Please justify why this deviation is acceptable.

14. *In Study VP/031/LAB/09 ---(b)(4)----- was used as a biological indicator. Please explain why the bioburden test method and biological indicator sterility test method was not revalidated with ---(b)(4)-----.*

The bioburden test is conducted to determine the bioburden count before (b)(4) sterilization. The bioburden count is typically controlled ----(b)(4)----- and normally JMS observes counts -----(b)(4)----- . Positive and negative controls are put in place during the biological indicator test and are considered substantial for the biological indicator test.

Reviewer’s Comment: Response is acceptable. ---(b)(4)-----, the BI used in the test method, was a surrogate. However, I requested the recovery rate from the test methods from the firm (Refer to IR Question 49 below).

15. *Please explain how you decided to place the BIs in the studies.*

The selection of BI locations was based on (b)(4) coldest spots identified from the temperature profile study.

Reviewer’s Comment: Response is acceptable.

16. *Please provide the certificate of analysis for the BIs in Study LAB/VR/039/06 and their D₁₁₅-values.*

The firm attached the COA for -----(b)(4)-----, which was used in LAB/VR/039/06. D₁₁₅-values were not included on the certificate. The COA for -----(b)(4)-----.

Reviewer’s Comment: Since the COA did not have the D-value for (b)(4) sterilization, the firm was asked again to provide the D-value in IR Questions 36 and 40 below.

17. *Please provide the D₁₁₅ values for all of the BIs used in Study VP/031/LAB/09.*

The firm provided the COA for ----(b)(4)-----, which was used in study VP/031/LAB/09. D₁₁₅-values -----(b)(4)-----, which were calculated from the provided graphs. The D₁₂₁-value was ---(b)(4)---

Reviewer’s Comment: Response is acceptable.

18. *In Appendix V of Study LAB/VR/039/06 a drawing with the BI sample arrangement was provided. Please explain the acronyms (i.e. DBI, LF, etc). It is not clear where Solution B is placed in the arrangement. A photo of the arrangement or a larger drawing may be helpful.*

The acronyms are explained below and a conceptual drawing is provided. The -----(b)(4)-----.

[(b)(4)]

Reviewer’s Comment: Response acceptable.

19. *Please explain if there were any changes to the autoclave of the load configuration between the initial validation and the revalidation.*

There was no change in load configuration between initial validation and revalidation.

Reviewer’s Comment: The response did not appear consistent with the firm’s response to IR Question 20 below. The firm stated that they changed the bag configuration. Please refer to IR Question 20 for my comments regarding the bag configuration change.

20. *In Module 4 it states that a “new bag arrangement during sterilization” occurred. Please elaborate on this change and if this new bag arrangement was included in any of the sterilization studies.*

The bag positioning was modified prior to the re-validation performed in 2009. For the modification, the -----(b)(4)-----.

SOLX® System product lot -----(b)(4)--- was tested using the new bag arrangement during sterilization re-validation VP/031/LAB/09. The previous and modified bag arrangements are given below. The SOL B bag is not depicted -----(b)(4)-----.

[(b)(4)]

Reviewer’s Comment: The new bag arrangement could be considered a load configuration. Given that the initial validation is considered invalid since the D-value of the BIs are unknown (refer to comment to IR Question 40), that in the revalidation only one run was performed, and that the firm has not correlated the BI with the facility’s organisms (refer to comment to IR Question 34), the firm was asked to provide additional runs with the new bag arrangement. Please refer to IR Question 44 for the firm’s response.

21. *In Study LAB/VR/039/06 one of the top 3 cold spots was location (b)(4). However in Study VP/031/LAB/09 location (b)(4) was one of the top 3 hot spots. Please explain this change.*

Conditions within the sterilizer were adequately controlled for each study to pass the sterilization validation requirements. All F₀ values of the sensors recorded in both validations were able to meet the minimum of ---(b)(4)---. It is unknown why the change in cold or hot locations was observed.

Reviewer’s Comment: The firm was asked to elaborate on this response. Refer to IR Question 45 below.

22. *In several of your runs kinked tubes were found. Please clarify if you evaluated if the kink affected sterilization process such as causing water to become pooled at the kinked areas. Please explain if this any water becomes trapped in the kinks or if the kinks -----(b)(4)-----.*

There was no water observed in the kinked area after the sterilization process and the kinked region of the tubing was not completely flattened. -----
----- (b)(4) -----
-----.

Reviewer's Comment: The firm was asked if they inspect the system for kinked tubes during routine production. Refer to IR Question 30.

23. *It was noted that several positive controls in the BI sterility test results were negative in Study LAB/VR/039/06. Additionally, several positive controls in the bacteriostasis and fugistasis results were negative in Study VP/031/LAB/09. Please explain why this is acceptable.*

This phenomenon is commonly encountered for positive controls during the initial incubation period when growth may not produce visual turbidity. All sterility test results passed acceptance criteria at the end of the incubation date.

Reviewer's Comment: Response is acceptable.

Amendment 11 (June 8, 2012)

24. *Please clarify if the complete system is autoclaved and if the system is over-pouched/packaged when sterilized.*

The complete system is autoclaved. There is no over-pouch or package when sterilized.

Reviewer's Comment: Response is acceptable.

25. *Please provide how many systems are in each tray and trolley. Please clarify how many systems are in a full load.*

Refer to the table below for the breakdown of each tray and trolley.

[(b)(4)]

Reviewer's Comment: Response is acceptable.

26. *Please explain if each tray is configured in the same way and do they have the same number of systems.*

Each tray is configured in the same way and has one set per tray.

Reviewer's Comment: Response is acceptable.

27. *Please provide a picture/diagram of how the system is configured in a trolley.*

Refer to the diagrams below for a top and front view of the trolley.

[(b)(4)]

[(b)(4)]

Reviewer’s Comment: Response is acceptable.

28. *Please explain how the system is coiled and packed for sterilization and if this is clearly defined in a SOP.*

The coiling performed prior to sterilization is defined in JMS document MI 0126-P036 – Blood Bag Manufacturing for LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive. -----(b)(4)-----
-----.

Reviewer’s Comment: Response is acceptable.

29. *Please provide a picture of the configuration of the system for sterilization (including how the tubing is configured along with the bags and filter).*

[(b)(4)]

Reviewer’s Comment: Response is acceptable.

30. *Please clarify if the systems are visually inspected for kinked tubes after sterilization during routine operations.*

Yes, the systems are visually inspected for kinked tubes after sterilization during routine operations.

Reviewer’s Comment: Response is acceptable.

No.	Bacteria	2010	2011
1	<i>Bacillus megaterium</i>	√	
2	<i>Bacillus firmus</i>	√	
3	<i>Bacillus lentus</i>		√
4	<i>Bacillus pumillus</i>	√	√
5	<i>Brevibacterium spp.</i>		√
6	<i>Brevibacillus non-reactive</i>	√	√
7	<i>Bacillus cereus 1</i>	√	
8	<i>Cellulomonas sp</i>	√	
9	<i>Kocuria varians/rosea</i>	√	√
10	<i>Kocuria kristinae / Micrococcus kristinae</i>	√	√
11	<i>Micrococcus spp</i>	√	√
12	<i>Pseudomonas stutzeri</i>	√	
13	<i>Pseudomonas oryzihabitans</i>	√	
14	<i>Rhodococcus spp</i>	√	
15	<i>Staphylococcus sciuri</i>		√
16	<i>Staphylococcus cohnii ssp cohnii</i>	√	
17	<i>Staphylococcus cohnii ssp urealyticum</i>	√	
18	<i>Staphylococcus epidermidis</i>	√	
19	<i>Staphylococcus xylosus</i>	√	
20	<i>Stenotrophomonas maltophilia</i>	√	

No.	Fungus	2010	2011
1	<i>Aspergillus fumigatus</i>	√	√
2	<i>Aspergillus niger</i>	√	√
3	<i>Aspergillus versicolor</i>	√	
4	<i>Candida sp</i>	√	
5	<i>Chaetomium globosum</i>	√	
6	<i>Fonsecaea compacta</i>		√
7	<i>Fusarium spp</i>	√	
8	<i>Geomyces pannorum</i>		√
9	<i>Gliocladium sp</i>		√
10	<i>Malbranchea</i>		√
11	<i>Microsporium ferrugineum</i>		√
12	<i>Microsporium nanum</i>	√	
13	<i>Monilia sitophila</i>		√
14	<i>Penicillium sp</i>	√	√
15	<i>Rhizopus sp.</i>		√
16	<i>Trichophyton rubum</i>		√
17	<i>Verticillium</i>	√	
18	<i>Yeast sp</i>		√

Reviewer’s Comment: Since the D-value of the organisms found on the product and at JMS’ facility was not provided, it is not clear how the BIs used during the validation correlate with the organisms found on the product and at their facility. The firm needs to demonstrate that the BIs are more resistant than the facility isolates. Refer to IR Question 48 below.

Additionally, I asked the firm to verify all organisms found on the product and in their facility were not heat resistant ----(b)(4)----- by providing the data for all organisms tested (refer to IR Question 50).

35. *Please provide the population and resistance of the bioburden on your product and at your facility.*

The bioburden count is controlled ----(b)(4)----- and normally counts in the order of (b)(4) are observed. The bioburden organisms are subjected to a resistance test of -----(b)(4)----- . To date, we have not found any bioburden organisms resistant to this condition.

Reviewer's Comment: As per the my comments to IR Question 34 above, it is not clear how the BIs selected correlate with the organisms found on their product and at their facility since the D-value was not provided.

36. *Please provide the population and resistance of the BIs.*

The BI population is ----(b)(4)----- with D-value range from ---(b)(4)-----.

Reviewer's Comment: Response from the firm is not consistent with their response to IR Question 40 below. According to the firm's response to IR Question 40, the D-value of ---(b)(4)----- is unknown. The ---(b)(4)----- D_{115} -value is ---(b)(4)----- and D_{121} -value is ---(b)(4)-----.

37. *Are you performing periodic resistance testing?*

JMS does not conduct periodic resistance testing of the BIs. BIs are purchased from an external supplier and are accompanied with a Certificate of Analysis stating the D-value.

Reviewer's Comment: Reponses is acceptable. Per the original submission, spore recovery test was performed by an external laboratory.

38. *In the validation and revalidation the minimum F_0 values were ---(b)(4)----- minutes, respectively. Please clarify if there were any BIs in those systems.*

Yes, there were BIs in the systems and passing results were obtained.

Reviewer's Comment: Response is acceptable.

39. *In Study LAB/VR/039/06, several thermal sensors did not reach (b)(4) when sterilization dwell time started. Those locations could be indicative of a cold spot. Locations ---(b)(4)--- did not have BIs at those locations. Please address this concern.*

The F_0 value for locations ---(b)(4)----- showed that they were not the coldest spots. Location (b)(4) was identified as the coldest spot and a BI placed at location (b)(4) passed criteria.

Reviewer's Comment: Response is acceptable.

40. *The BIs used in LAB/VR/039/06 did not have a D-value for (b)(4) sterilization on the COA. Please explain how resistance can be evaluated.*

The verification of D-value for (b)(4) sterilization on COA for BI used in LAB/VR/039/06 was inadvertently not checked. JMS has implemented a process for checking BIs D-value on each COA since March 23, 2009.

Reviewer’s Comment: Response is not acceptable. Without the D-value, the resistance cannot be evaluated and the BIs used in the validation cannot be correlated to the bioburden on the product or in the facility. Therefore, this initial validation LAB/VR/039/06 is not valid. This was communicated to the firm via a telecon on June 29, 2012. Additionally, refer to IR Question 48 below.

41. *Please clarify if you had any sterility failures of the final product. If so provide a summary report of the investigation, root cause and corrective and preventative action associated with these failures.*

No, there were no sterility failures encountered for the SOLX® final product during validation and revalidation.

Reviewer’s Comment: Response is acceptable.

42. *Please provide the firm’s sterility release criteria. Will you be using parametric release?*

The product sterility release criteria are based on BI sterility and product sterility results. JMS do not use parametric release. The firm monitors the critical sterilization process parameters for each sterilization lot including: -----
------(b)(4)-----.

Reviewer’s Comment: Response is acceptable.

43. *During your validations, please clarify if there are any other changes (besides -----
-(b)(4)-----) from the actual system that is being validated. For example, are all the other bags, connections, tubes, and etc the same (material, dimensions, etc).*

All the other characteristics are the same for the system that was validated except for the ---(b)(4)---

Reviewer’s Comment: Response is acceptable.

44. *The new bag arrangement is considered a new load configuration. Additional runs need to be performed at the new load configuration for the Agency to be able to evaluate the effectiveness of your sterilization cycle.*

The new bag arrangement was not considered a substantial change to the load configuration and therefore a complete three-cycle sterilization validation was not performed. During the revalidation there were no changes to product including weight, dimension, material, size or surface area. There were also no changes to the cycle parameters, equipment or total number of devices per trolley and load. Monitoring and release testing also remained the same.

Reviewer’s Comment: Given that the initial validation is invalid since the D-value is unknown and that the revalidation only included one run, additional validation runs will be required to demonstrate repeatability. The firm was asked to perform additional runs with the new bag configuration. Refer to telecon on June 29, 2012 where this was communicated to the firm and IR Question 48 below.

indicators. To address these concerns, please provide the following additional information:

Hemerus stated that JMS performed in-house studies to determine the D-value for -----(b)(4)----- . A D₁₁₅ value of ---(b)(4)--- was found using the -----(b)(4)-----.

Studies at JMS demonstrated that the usage of -----(b)(4)----- as a microbial challenge in (b)(4) sterilization was able to represent total destruction of natural bioburden observed in product.

Reviewer’s Comment: The firm’s response is not consistent. Previously, per IR Question 40, the D-value for ---(b)(4)--- was unknown. It was not clear what method the firm used to determine the D-value for ---(b)(4)----- . Refer to IR Question 51 below. The firm was also mentioned that they were using a process-challenge device and the firm was asked to explain this device is IR Question 52.

a) Please provide additional studies to compare the resistance of representative organisms in your facility. To facilitate comparison to your chosen validation biological indicator, we recommend that your thermal studies also include the biological indicator. Please note, if your thermal resistance studies indicate a facilitate isolate more resistant than----- (b)(4)---- then additional validation runs with a new, more resistant biological indicators should be provided.

JMS performed in-house testing with ----(b)(4)----- in a process-challenge device and found a D₁₁₅ value of ---(b)(4)----- . Comparison of -----(b)(4)----- demonstrated the ---(b)(4)----- was more resistant. In 2009, the BI organism for (b)(4) sterilization was changed to ----(b)(4)-----.

JMS performs routine monitoring of bioburden in pre-sterilized products and the environment, and conducts post-sterilized product sterility testing. All microorganisms isolated in routine monitoring of bioburden at JMS are subjected to a ----(b)(4)----- heat shock treatment. The heat shock treatment is intended to confirm that the bioburden isolated will not survive the (b)(4) sterilization condition of ----(b)(4)-----.

As discussed in a previous response to FDA (BN110059/A11 dated 6/6/2012 page 5) all the organisms identified from the JMS facility during bioburden monitoring in 2010 and 2011 were not heat resistant to ----(b)(4)-----.

Additionally, product sterility testing is conducted on post-sterilized products before product release and has never yielded spore-forming organisms. During Out of Specification (OOS) instances from 2010 and 2011, none of the isolated microorganisms survived the heat shock treatment --- (b)(4)---- and were not spore-formers.

Reviewer’s Comment: The firm did clarify that all organisms were heat shocked and not heat resistant to ----(b)(4)----- . Refer to IR Question 50 below where the firm was asked to provide the data for all of the organisms tested.

- b) *Additional runs to demonstrate reproducibility need to be performed with the new bag arrangement using a sufficiently resistant biological indicator for the Agency to be able to evaluate the effectiveness of your sterilization cycle.*

The firm continues to believe that the new bag arrangement was not considered a substantial change to the load configuration. During the revalidation there were no changes to product including weight, dimension, material, size or surface area. There were also no changes to the cycle parameters, equipment or total number of devices per trolley and load. Monitoring and release testing also remained the same.

The -----(b)(4)----- biological indicator used in the re-validation was demonstrated to be more resistant than previously used -----(b)(4)-----.

Sterilization re-validation is required --(b)(4)---; therefore, re-validation will be performed during the next SOLX® System production lot. The re-validation will be conducted using the -----(b)(4)----- biological indicator and the bag arrangement used in VP/031/LAB/09.

As noted in the response provided in Appendix 1, the sterilization process at JMS has been validated for sterilizing blood bag anticoagulants from 1994 (about 18 years). During these years JMS has not encountered any sterility issues in products sterilized using the sterilization condition of -----(b)(4)-----.

Reviewer’s Comment: Additional information regarding the D-value is needed to determine if additional runs are required. Refer to IR Question 51.

Amendment 13 (July 23, 2012)

- 49. *In LAB/VP/044/06 you evaluated the bioburden test method for Hemerus SOLX filter system. Please provide the recovery rate and correction factor calculated from this study. Please clarify if the correction factor was used in the test results provided in the revalidation report VP/031/LAB/09.*

From the study, the recovery rate calculated is (b)(4) and correction factor calculated is (b)(4). Yes, the correction factor was used in the test results provided in the revalidation report VP/031/LAB/09.

Reviewer’s Comment: The recovery rate is low and the firm was asked about this. Refer to IR Question 53.

- 50. *You stated that all organisms found in the JMS facility during environmental monitoring were not heat resistant to ---(b)(4)----- . Please provide the data for all organisms tested.*

The heat resistance data for testing performed in years 2010 and 2011 were provided. All microorganisms tested were not heat resistant when treated up to -----(b)(4)----- . It should be noted that six microorganisms found in the JMS facility were inadvertently omitted from lists previously submitted with BN110059 Amendment 11. The following bacteria and fungus should have been included.

	Bacteria	2010	2011
1	<i>Staphylococcus lugdunensis</i>	√	
2	<i>Brevibacterium spp</i>	√	
3	<i>Staphylococcus caprae</i>	√	
4	<i>B. non-reactive</i>		√
5	<i>S. warneri</i>		√
	Fungus		
6	<i>Mucor ramosissimus</i>	√	

Per Validation Reports VR/072/LAB/10 and VR/067/LAB/11, the organisms identified were heat shocked -----(b)(4)-----
 -----The organisms were tested through the condition that produced no growth. All of the organisms were tested at -----(b)(4)-----
 -----.

Reviewer’s Comment: Upon reviewing the reports, it was noted that most of the organisms were only tested at ---(b)(4)-----. The exception was the bacterium species from 2011. The actual sterilization production cycle is ----(b)(4)-----
 ----- . The firm was asked to clarify the correlation of the initial screening (longer time conditions at a lower temperature) with the actual sterilization production cycle (shorter time conditions at a higher temperature). The firm provided a response in IR Question 54 below.

Telecon on July 26, 2012 and Amendment 14 (July 27, 2012)

51. You stated that JMS performed in-house studies to determine the D-value for -----
 -----(b)(4)----- and that the D₁₁₅ value for the spore strips was ---(b)(4)----.

a) Please clarify that the D₁₁₅ value of ---(b)(4)--- is for (b)(4) sterilization.

During the telecon, JMS stated that the D₁₁₅ value of ---(b)(4)----- is for (b)(4) sterilization.

Reviewer’s Comment: Response is acceptable.

b) Please explain what method was used in the studies

JMS stated during the telecon that they used a -----(b)(4)----- to define the D-value.

Reviewer’s Comment: Response is not acceptable. The reference standard for determining the D-value is a resistometer. A resistometer is capable of square-wave heating that can quickly reach sterilization dwell conditions, has a quick cool-down, and is highly accurate. An -----(b)(4)-- is not as accurate as a resistometer and is not capable of a square-wave heating. Therefore an ---(b)(4)--- is not appropriate to be used to determine the D-value of BIs being used for a validation. Since the D-value of the BIs were not determined through a standard referenced method and was not referenced on the certificate of analysis (COA) for the specific sterilization method used

in the validation, additional validation runs are required. Refer to CR deficiencies under “Review Recommendation” section above.

52. *You indicated that you have performed in-house testing with ---(b)(4)-- in a process-challenge device. Please clarify if this process-challenge device is used for routine production load. If so, is this part of the release criteria.*

JMS said in the telecon that the process-challenge device is used for routine production load and is part of the release criteria. The process-challenge device is a PVC bag and is not used in lieu of sterility test.

Reviewer’s Comment: Response is acceptable.

53. *You stated that your recovery rate was (b)(4) for the bioburden test method. We are concern that your low recovery rate may not be able to adequately detect the low presence of viable organisms in your final release sterility testing.*

- a) *Please clarify if the test method for bioburden is the same for sterility.*

JMS indicated in the telecon that methods are different. Both methods cover all fluid pathways, but the order of the flow is different.

- b) *What is the recovery rate for the sterility test method?*

JMS said that the recovery rate for the sterility test method was not determined.

- c) *What is the pore size of the filter on the unit?*

Hemerus said the filter is approximately (b)(4).

- d) *Please clarify if the fluid pathway for sterility test method has the same pathway as clinical use.*

Hemerus said that they are not the same but, they are similar

Reviewer’s Comment: Responses is acceptable regarding the bioburden recovery rate is acceptable. The bioburden test method is used to test units prior to sterilization (non-sterile product) and was used as a baseline in the validation. During the initial validation, all bioburden results were ----(b)(4)----- and during the revalidation, all bioburden results were -----(b)(4)-----. Although the recovery rate for removing bioburden from the system is low, the actual bioburden found on the units are much lower then the population of the BIs used in the sterilization validation.

Additionally, although there recovery rate for the sterility test method has not been determined, the validation is to demonstrate that the firm is capable of reproducibly sterilizing the system. Since there was only one valid validation run, I have recommended the firm perform additional runs with a sufficiently resistant BI in comparison to the facility bioburden and that the D-value of the BI should be determined by a standard referenced method. Refer to my comments to IR Question 51 above.

54. *From the review of your bioburden screening data (heat shock studies), we noted that some studies did initial testing at ----(b)(4)-----.* If a positive result was obtained, the organism would then be subjected at ---(b)(4)-----.

of your initial screening (i.e. -----(b)(4)-----) with your sterilization production cycle (-----(b)(4)-----) and which condition is actually the worst case.

During the telecon JMS stated that ---(b)(4)----- is not as effective as -----(b)(4)----- . The Agency asked if they have any published literature explaining this correlation.

In Amendment 14, the firm explained that organisms undergoing heat shock treatment are tested -----(b)(4)----- . The organisms are tested only through the condition that produces no growth.

In order to demonstrate that the treatment progression is representative of increasing lethality conditions, sterilization times were calculated for each condition for equivalency at -(b)(4)- in the table below.

[(b)(4)]

From the equivalency results calculated for each progressive condition, it was demonstrated that the ---(b)(4)----- treatment conditions provide increasing lethality when standardized to lethality at --(b)(4)-.

Reviewer’s Comment: The response is not acceptable. The F₀ formula that the firm used from the reference is to determine F₀ for (b)(4) sterilization. The firm is using this calculation to determine the F₀ for the heat shock method, which is not appropriate.

Additional studies is needed to compare the resistance of representative organisms at their facility using test conditions that can be correlated with the sterilization production cycle. I also recommend that the thermal studies include BIs to facilitate comparison the chosen validation BI with the heat shock study. Refer to CR deficiencies under “Review Recommendation” section above.

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

Amendment 11 (June 8, 2012)

55. Please explain the purpose of the -----(b)(4)-----.

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

1 page redacted due to (b)(4)

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

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

Container Closure

Amendment 9 (May 4, 2012)

60. Please clarify if any container closure integrity testing has been performed on the complete system (LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive). If so, please provide the study or the location of this study in the submission or DMF. Additionally, provide a reference to any standards you use for this testing.

Design verification testing (DVT) for the SOLX® System was based on ISO 3826-1 (Plastics collapsible containers for human blood and blood components – Part 1: Conventional containers). Integrity testing for collection and transfer tubing comprising the complete device system was performed according to ISO 3826-1 Section 5.6.

(b)(4) devices were tested at multiple tubing joints during the original design verification testing were provided in the original NDA. No leakage was observed at the tubing junctions and no visual defects were observed. All points tested successfully passed the applied tensile force of -----(b)(4)-----.

Integrity testing for device system tubing was also conducted after ---(b)(4)--- real-time aging of SOLX® System devices. The protocol and report summarizing this testing were submitted in the amendment (TP/284/PED/2010, Design Verification Testing of ---(b)(4)--- Real Time Aged SOLX Blood Bag System).

After ---(b)(4)--- real time aging, ---(b)(4)--- devices were tested for joint and tubing integrity before and after thermal stability conditioning as described in ISO 3826-1 Section 6.2.5. No leakage was observed at the tubing junctions and no visual defects were observed.

All points tested successfully passed the applied tensile force of -----
 -----(b)(4)----- locations were tested prior to thermal conditioning and (b)(4) locations were tested after conditioning.

Reviewer’s Comment: I reviewed TP/284/PED/2010 and the report appeared adequate regarding container closure. -----

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

However, I was not certain if these testing were performed after sterilization and ---(b)(4)-----. Refer to **IR Question 62** below for clarification.

----- Subsequent transportation simulation was conducted using guidelines of *ASTM D 4169-05 Performance Testing of Shipping Containers and Systems DC13 Assurance Level 1 Truck/Air Spectrum*. The simulated testing included manual handling, stacking, loose load vibration, low pressure and vehicle vibration. DVT Testing of packages undergoing this conditioning and simulated shipping is summarized in NDA BN110059 Module 4 Appendices 4-24 and 4-25.

Slight packaging modifications were implemented during product development as described in Protocol PC407240 and Report FR407240 submitted with original NDA BN110059 Module 4. After the packaging modifications, the packages underwent actual shipping conditions from Singapore to Hemerus (St. Paul, MN) to a U.S. site and back to Hemerus.

Reviewer’s Comment: The simulated transportation testing performed appears to be worse case conditions. However, the firm made modifications to the packaging and it is unclear what conditions the new packaging configuration was shipped in. Please refer to IR Question 67 below for clarification.

65. *Per Study TR/077/PED/2008, moisture was found in the inner box.*

- a. *Please clarify if you have assessed how the moisture impacts your product.*
- b. *Please clarify if your package inserts instructs the customer how to handle if the packaging or product is damp.*

The conditioning cycle conducted prior to testing was considered “worst-case” for moisture exposure and is not expected to be encountered during typical storage and shipment. The SOLX® System packaging is specifically designed to protect devices from external moisture. Each individual collection set is packaged in a casted polypropylene tub sealed with a top layer of polypropylene. Four packaged sets are sealed within one sealed outer aluminum pouch designed to prevent moisture transfer.

Additionally, SOLX® System printed labels were tested according to ISO 2836:2004 Graphic technology – Prints and printing inks - assessment of resistance of prints to various agents. The printed labels remained legible and intact for all agents tested, including water. The results of this testing were submitted to FDA as part of Amendment 8 to BN110059.

The carton label, foil pack label and Instructions for Use each contain the statement, “Do Not Use if Package is Damaged”.

Reviewer’s Comment: The firm does not address the root cause and corrective action. I requested the deviation report regarding the moisture. Refer to IR Question 67e below for clarification.

66. *Module 4 stated that “packaging modifications” were made. Please clarify if the transportation testing ^{(b)(4)} Report 0706135 Rev C and TP/077/PED/2008/JMS was completed before or after packaging modifications were made. If it was completed prior to the packaging modifications, please clarify if transportation testing was evaluated after the packaging modifications. If transportation testing was not evaluated after the packaging modification, please provide a justification for not completing one.*

Minor packaging modifications were implemented and Hemerus did not repeat the (b)(4) transportation testing after the modification but choose to perform actual shipping testing. The packaging modifications were designed to be comparable or an improvement to the original design previously tested under the worst-case simulated conditions.

Reviewer's Comment: As mentioned in my comments for IR Question 64 above, the firm did not provide the shipping conditions and was requested.

Telecon on June 29, 2012 and Amendment 12 (July 18, 2012)

67. *You performed a transportation simulation study (Report Number 0706135) and evaluated the results in Report TP/077/PED/2008. The general appearance and label peel testing did not meet the acceptance criteria. The outer boxes, inner boxes, labels, and dividers were damaged and moisture was found in the package. Per Report PC407240 and FR407240 you subsequently changed the packaging configuration and shipped cartons from Singapore to Hemerus. In PC407240 and FR407240, you only evaluated the foil and failed to evaluate the general appearance of the outer boxes, inner boxes, divers, tubs, and labels and failed to evaluate the label peel testing. Please address the following questions.*

- a. *Please provide the shipping conditions (i.e. time, temperature, etc), how many carton were shipped, and if the study represented the worse case shipping conditions (i.e. time, temperature, etc.).*

The cartons were shipped on pallets from Singapore to Hemerus. Subsequently single cartons were air shipped from Hemerus to a site in the US and then shipped back to Hemerus by air. Specific time and temperature were not documented. Single carton shipping is considered a worst case shipping condition as compared to a wrapped stack of boxes secured on a pallet.

Hemerus has generated a supplemental protocol and report to document inspection of outer boxes, inner boxes, labels and dividers associated with PC/FR407240. Protocol and Report 410931 provided. Per Report 410931, the outer carton, inner carton, divider, and foil pack label were visually inspected and all acceptance criteria were met. Follow up testing with regards to label peel had previously been performed and documented in a separate report, TP/119/PED/2009.

- b. *Please clarify how many runs were performed in this study.*

The study documented in PC/FR407240 involved 4 cartons individually shipped to three different domestic sites.

- c. *Please clarify if the packaging of the cartons in this study reflects routine manufacturing conditions.*

Yes, the packaging cartons used routine manufacturing materials and processes.

- d. *The transportation SOP you provided does not include how the inner box, outer box, and dividers are assembled in the carton. Please explain how the cartons are packaged and if this information is captured in a different SOP.*

Each outer carton contains two inner cartons. Each inner carton contains four foil pouches with a divider placed vertically in the middle separating 2 foil packages from the other 2 foil packages. Four individually packaged sets are sealed within one foil pack for a total of 32 units in each shipping carton.

- e. *Please provide the investigation report (root cause) for the failed acceptance criteria in Report TP/077/PED/2008, what changes were made to address these failures (corrective action), and how you ensure the effectiveness of the corrective action (i.e. SOP changes).*

The modifications were made during the design and development stage of the project and a formal investigation was not documented. The Hemerus design team, in collaboration with the manufacturing facility, worked together to propose corrective actions within the development process.

The root cause was attributed to handling of the cartons, high humidity conditions during testing, friction with the foil packages, and a non-optimized label adhesive application process. As a corrective action, the firm will put shipment units on pallets to improve handling, boxes will be shrink wrapped to prevent moisture damage, smaller boxes and stronger dividers will be used to prevent shifting of foil packages, and increasing the label adhesive application process.

- f. *Please provide the justification for changing the packaging configuration.*

As discussed above, the boxes were modified to be slightly smaller to help prevent units from shifting during transport. In addition, changes were made to the divider to further protect foil packages.

- g. *Provide the shipping criteria during routine operation (i.e. time, temperature, etc).*

Hemerus has not defined specific shipping criteria (time and temperature) for shipping but has incorporated the following information on the inner and outer carton labels and foil packages: Protect From Freezing, Store at Room Temperature, Avoid Excess Heat and Direct Sunlight, and Do Not Use if Package is Damaged.

Hemerus is not aware of a regulatory requirement to define specific time and temperature criteria for shipping currently marketed systems similar to the SOLX® System. Standard shipping practices, combined with observance and compliance with labeling statements, should be followed.

Reviewer's Comment: Response is not acceptable. The initial transportation study did not meet the validation acceptance criteria and a formal investigation should have been performed. The subsequent study using the new packaging configuration (PC/FR407240) did not subject the units to worse case conditions (i.e. temperature and humidity extremes). Additional transportation studies need to be performed using worse case shipping conditions. This was communicated to the firm again during a telecon on July 26, 2012. Refer to IR Question 68 below.

Telecon on July 26, 2012 and Amendment 14 (July 27, 2012)

68. *Your initial transportation validation (TR/077/PED/2008) did not meet your acceptance criteria and a formal investigation was not performed. Subsequently, the packaging configuration was changed, shipped from Singapore to Hemerus and evaluated in FR410931. However, the shipping conditions with the new configuration were not under the worse case conditions (temperature, time, etc). Additional runs are needed using the new configuration under worse case conditions.*

During the telecon, Hemerus maintained that they believe their study under PC/FR410931 (new packaging configuration) was sufficient. In Amendment 14, the firm provided the root cause investigation and corrective action to the initial study. They also provided the visual inspection results of the shipped units with the new packaging configuration.

Reviewer's Comment: Response is not acceptable. The initial transportation study did not meet the validation acceptance criteria and a formal investigation should have been performed. The subsequent study using the new packaging configuration (PC/FR407240) did not subject the units to worse case conditions (i.e. temperature and humidity extremes). Therefore, additional transportation studies need to be performed using worse case shipping conditions. Refer to CR deficiencies under "Review Recommendation" section above.

h:\dmpq\nda\bn 110059-0 hemerus leukosep\revmemo hemerus nda bn110059-0 v6.doc