BLA 125413 Resubmission - St. Louis Cord Blood Bank

CMC Review of Complete Response letter items

ALLOCORD

HPC, Cord Blood

Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

Reviewed by:	Signature
Brent McCright, Ph.D. ***Review Committee Chairperson***	
Brian Niland, Ph.D.	
Joydeep Ghosh, Ph.D.	
Safa Karandish, B.S., MT (ASCP)	
Concurred by:	
Keith Wonnacott, Ph.D. **Branch Chief**	

Executive Summary

Product overview: The St. Louis Cord Blood Bank (SLCBB) seeks to license cryopreserved Hematopoietic Progenitor Cells (HPCs) that have been derived from cord blood. The BLA is for HPC, Cord Blood intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. SLCBB proposes to license cord blood processed using the PrepaCyte-CB method that enriches the product for white blood cells while depleting red blood cells (RBCs) and plasma.

Previous review findings: The original BLA was submitted October 21, 2011. After review of the BLA submission and inspection of the St. Louis and Kansas City manufacturing facilities, deficiencies were identified. A Complete Response Letter listing the 26 deficiencies was sent to SLCBB on August 16, 2012. The deficiencies related to the following:

1) Outstanding inspection issues
2) Incomplete validation of the CBU collection and manufacturing process
3) Incomplete submission of Standard Operating Procedures for product manufacture and handling
4) Lack of an expiration date determination plan
5) Label and package insert information was incomplete
6) Sterility test parameters needed modification
7) Insufficient lot release testing information for CBUs manufactured at the Kansas City site

The applicant submitted a response to the August 16, 2012 Complete Response Letter (CR) on December 13, 2012. CR letter comments 5, 11, 13, 17 – 23 were addressed by the withdrawal of the Kansas City manufacturing site from this BLA. Responses to all other issues have been addressed in the December 13, 2012 resubmission and subsequent amendments, and are reviewed below.

Responses to Aug 16, 2012 Complete Response Letter

Complete Response Letter Comments:

1. Outstanding inspectional issues identified on the FDA Form 483 for St. Louis Cord Blood Bank (SLCBB), located in St. Louis, Missouri dated April 20, 2012, and the FDA Form 483 for St. Luke's Cancer Institute (SLCI), located in Kansas City, Missouri dated April 27, 2012 issued at the conclusion of each pre-license inspection, have yet to be resolved. You must satisfactorily resolve these issues prior to approval of the application.

SLCBB response: Responses were submitted to all the issues identified on the 483 during the inspection of the St. Louis manufacturing site. The sponsor withdrew the request for the inclusion in this application of the contract manufacturing site located at the St. Luke's Cancer Institute in Kansas City, MO.

Reviewer Comment: The responses for the St. Louis manufacturing site are acceptable. Details of the review are contained in the DMPQ review memo.

2. The collection validation summary that you have submitted is not adequate because it does not include all the relevant aspects of the collection procedures that are currently in use (e.g., completion of donor screening documentation, labeling, collection volume, and transportation) with pre-defined acceptance criteria. Please submit the final validation summary for the collection and transportation of cord blood units from the hospitals to the processing laboratories. The validation must be completed at the SLCBB and SLCI facilities.

SLCBB response: The Collection validation plan, data and the final summary report have been submitted (amendment 12).

Validation parameters:
A total of ------(b)(4)------ cord blood collections were evaluated from 11/13/12 to 11/19/12. The validation was performed following the established procedures for maternal consent and screening, collection of cord blood, labeling of cord blood unit and maternal specimens, temporary storage at the collection hospitals and transportation of collected units to the processing laboratory (list of SOPs were included in the validation plan entitled "Validation of Collection Procedures for Unrelated Umbilical Cord Blood Products"). The parameters shown in Table 1 were chosen to present an adequate evaluation of the overall quality of the collected units:

Table 1: Cord blood collection validation parameters

Parameter	Definition	Rationale
% of units with acceptable volume	Cord Blood volume collected	The collected volume of cord blood is the first factor in determining whether the collected product will proceed to manufacturing. Volume is not a release parameter.
% of units deferred due to technical errors	Technical errors include: mislabeled unit or maternal tubes, compromised collection bag integrity, clotted cord blood unit, or unacceptable elapsed time from collection	The technical expertise of the collection team has direct impact on the quality of the cord blood collection.
Incidence of storage temperature deviations	The temperature of the storage site at each of the 29 hospitals. Target temp range (b)(4) (b)(4)	Storage and transport of Cord Blood units must occur under controlled conditions. Based on historical observations, temperatures within this range are not expected to have an adverse effect on product integrity.
Incidence of transport temperature deviations	The temperature of the environment during transport of the cord blood units to the SLCBB. Target temp range (b)(4) (b)(4)	
Microbial Cultures	The percent of units that are sterile post processing.	Sterility of the cord blood unit is dependent upon both the collection process and the manufacturing process.
Maternal and Donor Safety	Adverse events associated with collection are communicated to the SLCBB	Cord Blood collection should not pose any risk to mother or baby.

Acceptance criteria & results:

SLCBB evaluated historical data for units collected between March 1 and May 31, 2012 to determine the acceptable range and standard deviation. The analysis was performed by breaking the time period into (b)(4) long intervals and calculating the percent per (b)(4). The data tools used included ----------(b)(4)---------- correction. The Table 2 shows the predefined acceptance criteria for each evaluated parameter and the results.

Reviewer comment: In the validation plan or summary report, the sponsor had not indicated the total number of historical units that were evaluated for the validation. In the response letter dated 3/7/13, the sponsor stated that (b)(4) historical units were evaluated for the validation.

Table 2: Collection validation acceptance criteria and results

(b)(4)

Reviewer Comment: The validation data was consistent with the historical data and was within the pre-defined acceptable criteria. SLCBB discards collected units with "technical errors" (e.g. issues with labeling, bag integrity) or positive sterility results.

3. Please submit PrepaCyte-CB processing validation protocols. You will need to establish a validation protocol, with defined acceptance criteria, that is approved by your Quality Unit before performing the validation study. The protocol should be developed using any new standard operating procedures (SOPs) that are implemented in response to the 483 inspection observations.

SLCBB response: SLCBB submitted a new Process Validation Plan on December 14, 2012 in Amendment 12.

The validation plan stated that the CBUs processed for the validation would be handled according to the SOPs that have been modified in response to the observations made during the April 2012 site inspection. SLCBB personnel will no longer perform ----------(b)(4)------ on --(b)(4)-- CBUs in a ------(b)(4)------ and the manufacturing personnel have been trained for consistent aseptic technique. Improvements have been made to the batch record to include the documentation of completed critical steps, identification of major equipment used, and the documentation of critical time and equipment operating parameters. These changes have been evaluated and deemed acceptable, as documented in the DMPQ review.

Validation Plan Parameters: The validation plan proposed the evaluation of ----------(b)(4)--------- processed CBUs. The parameters shown in Table 3 were chosen as relevant determinants of product quality and processing efficiency.

Table 3. Parameters to be measured during process validation.

Parameter	Definition	Rationale
TNC recovery	Total nucleated cells (b)(4) (b)(4) per product: % of recovery with respect to pre-processing. Post-thaw will be evaluated with respect to post-processing values	Assures significant recovery of nucleated cells following volume reduction (plasma and RBC reduction) using PrepaCyte-CB. Significant loss of nucleated cells would impact unit potency and indicate inadequate process control.
(b)(4)		
Nucleated cell viability recovery using (b)(4)	(b)(4)	Assures that processing and thawing according to the standard operating procedure does not result in significant loss of viable nucleated cells.
Sterility %	Absence of microbial contamination in (b)(4) samples	Assures that collection and subsequent aseptic cord blood processing did not introduce microbial contaminants into the product; supports product safety
Post processing viability using (b)(4)	(b)(4)	Assures that cord blood collection, transportation, receipt within (b)(4) from collection time and processing and thawing according to the standard procedure do not significantly compromise nucleated cell viability.
Viable CD34 recovery %	Viable CD34 cells per product: % of recovery with respect to pre-processing. Post-thaw will be evaluated with respect to post-processing values	Assures significant recovery of viable CD34 cells following volume reduction (plasma and RBC reduction) using PrepaCyte-CB. Significant loss of viable CD34 cells would impact unit potency and indicate inadequate process control.

Description of test samples: Pre-processing TNC, (b)(4), Viability and CD34 counts were obtained from the ---(b)(4)--- sample withdrawn ----------(b)(4)----------.

Post-processing TNC, (b)(4), Viability and CD34 counts were obtained from a sample removed ----------(b)(4)----------.

Post-processing sterility was performed on samples on the end process ---(b)(4)---.

Acceptance criteria: SLCBB used historical data from (b)(4) units processed between March 1 and May 31, 2012 to calculate statistically acceptable ranges which they defined as (b)(4) Standard deviations.

For processing validation, two independent samples t-test or Wilcoxon-Mann test (depending on whether data sets conform to normal distribution) will be applied to the data to determine if there are differences from prospective data and historical data. Failure of an individual CBU will not result in validation failure, but when a CBU failure does occur, the failure will be investigated to determine if the process contributed to the failure. If a product failure occurs, the failure will be reported to the Quality Specialist. The Quality Specialist will then review the batch record and evaluate if the process contributed to the failure. During the analysis, the number of overall failures will be assessed to ensure they approximate expected values rather than a trend caused by a processing issue. The organism present in a contaminated culture will be identified to help determine the source of the contamination.

Reviewer Comment: This is an acceptable validation plan.

Validation Report – Attachment 1a of Amendment 12

The process validation began on 11/13/12 and concluded on 11/19/12 after the manufacture of (b)(4) CBUs. Data from the ----(b)(4)---- processed units were statistically compared to the pre-defined acceptance criteria using the Wilcoxon-Mann-Whitney test with ----------(b)(4)---------- correction. The results are shown in Table 4.

Table 4. Summary of Post Processing Results, N = (b)(4)

(b)(4)

Analysis of units that did not pass validation acceptance criteria

----(b)(4)---- units --(b)(4)-- did not pass the sterility test. One CBU had a bacterial culture contaminated with ---(b)(4)--- (species not identified), the other with -------*(b)(4)*-------. The historical data from the (b)(4) units had a (b)(4) sterility failure rate, so this is not significantly different than the historical expectation.

Reviewer comment: The source of the contamination cannot be determined based on the information provided, but given the nature of the collection process, it is likely that the CBUs were contaminated prior to processing.

(b)(4) units did not pass the acceptance criteria for either viability or recovery of viable nucleated cells (Table 5).

Table 5. Investigation of failed units

(b)(4)

SLCBB stated that post-processing nucleated cell viability and recovery are historically related to pre-processing viability and high red blood cell counts. Consistent with these observations, ----------(b)(4)---------- had low pre-processing viability, and -----(b)(4)----- had a relatively high RBC. SLCBB stated that the frequency of failures related to viability observed in the validation data is similar to their historical results. No batch record abnormalities were identified.

Reviewer Comment: The processing validation data was within the acceptance range and did not significantly differ from the historical data. The process validation plan and data are acceptable.

4. The thawing and reconstitution instructions to be provided in the Prescribing Information must be based on validated procedures. Please provide written instructions and data demonstrating that your instructions have been validated.

SLCBB response: In their package insert, SLCBB provides instructions on the use of a "Dilution" reconstitution protocol that adds 50 mLs of an albumin/dextran solution to the cryopreserved CBU. In addition, they have provided instructions for the use of a "Wash" reconstitution protocol to be used when the DMSO dose will be > 1 .0 mL/kg. The "Wash" method includes centrifugation and supernatant expression steps that permit the removal of approximately 75% of the DMSO.

Key aspects of the product handling information include:

A) Receipt instructions that describe the weighing of the dry shipper and specify the storage of the CBU in the liquid or vapor phase of a nitrogen freezer
B) Specification of the reconstitution/wash solution consisting of a 5:1 mix of 10% dextran 40 and 25% human albumin
C) A description of the thawing of CBUs in a 37^{o} C water bath
D) Instructions for the dilution of CBUs with reconstitution solution and transfer to infusion bag
E) A list of recommended quality control assays

Validation of the Dilution reconstitution procedure per Attachment 20 of Amendment 12

Data from (b)(4) thawed and reconstituted CBUs was used to establish the acceptance criteria of (b)(4) standard deviation from the means of this historical data. All post-thaw testing (TNC recovery, ------(b)(4)------, CD34 recovery and Viability) was done on samples removed from the final product after thaw and reconstitution.

Table 6. Historical thaw and reconstitution data

(b)(4)

Validation Report: (b)(4) cryopreserved CBUs were thawed and evaluated immediately (Table 7) after reconstitution and after 4 hours storage at room temperature (Table 8).

Table 7. Data from (b)(4) CBUs reconstituted using the Dilution method – data from immediately after reconstitution

(b)(4)

Table 8. Data from (b)(4) CBUs reconstituted using the Dilution method – after 4 hours

(b)(4)

Data Summary: Both the post-thaw viability and TNC recovery are above the > 70% level recommended in the Cord Blood Guidance for both the initial and 4 hour post thaw time points. The initial post-thaw data for viable CD34+ cells, CFUs, (b)(4) viability, TNC recovery, and ---(b)(4)--- viability were all equal or superior to the control group (Table 6).

Reviewer Comment: SLCBB consistently obtained lower percentages of viable cells when they used the (b)(4) method than when they used the ---(b)(4)--- method. The ---(b)(4)- method for measuring viability is based on -----(b)(4)----- and may be more sensitive to post-thaw cell stress than the ----(b)(4)---- method. Since the -(b)(4)- results are consistent between samples and are also consistent with their historical data, it does not appear the results are an indication of variations in product quality.

Additional validation data for CBU thaw and reconstitution using the Dilution method

SLCBB also provided additional data for the Dilution reconstitution method from ----------(b)(4)---------- manufactured CBUs SLCBB used for process validation (Attachment 1a, Amendment 12). All post-thaw testing (TNC recovery, --(b)(4)-- recovery, CD34 recovery, sterility, and viability) was done on samples ----------(b)(4)----------.

Table 9. Data from (b)(4) CBUs reconstituted using the Dilution method – initial

(b)(4)

Data Summary: The post-thaw viability (determined by ---(b)(4)---) and TNC recovery for all (b)(4) CBUs were both above the > 70% level recommended in the Cord Blood Guidance and the results were all superior to their historical data.

Reviewer comment: The thaw and reconstitution validation data using the Dilution method is acceptable.

Validation of the Wash method per Attachment 21 of Amendment 12.

SLCBB also submitted an SOP and validation data for a Wash reconstitution procedure for use at the clinical site. As in the Dilution reconstitution method, the thawed CBU is diluted with 50 mL of wash buffer consisting of the combination of a 5:1 mix of 10% Dextran 40 and 25% human albumin. However, in the Wash method this is followed by centrifugation to sediment the cells and the removal of about 75% of the supernatent.

Validation Report: (b)(4) CBUs were thawed and evaluated immediately (Table 10) after washing and after 4 hours storage at room temperature (Table 11). The samples for analysis were taken from the resuspended cells after centrifugation.

Table 10. Data from (b)(4) CBUs using the Wash reconstitution method - initial

(b)(4)

Table 11. Data from (b)(4) CBUs using the Wash reconstitution method – after 4 hours

(b)(4)

Data Summary: The post-thaw viability (TB) and TNC recovery for all (b)(4) CBUs are both above the > 70% level recommended in the Cord Blood Guidance and the initial TNC recovery and TB viability were better than the control data (Table 6). The (b)(4) method for determining cell viability consistently measured a lower percentage of viable cells. The (b)(4) method may be a more sensitive method for detecting cell stress and cells in the early stages of apoptosis, especially post-thaw. One CBU had a ---(b)(4)--- recovery (b)(4) of CD34+ cells.

Reviewer comment: The Wash method for CBU reconstitution appears to result in slightly (b)(4) TNC recovery and lower viability than the Dilution method. However, the ---(b)(4)--- viability and TNC recovery values are both greater than the 70% level recommended in the Cord Blood Guidance, even after 4 hours. Therefore, the validation of the Wash reconstitution method is acceptable.

5. Information for training of collection staff for SLCI was not included in the submission. Please provide a description of training of collection personnel for the collection sites providing units to SLCI and a description of the periodic monitoring that occurs to ensure the collections are continually performed on an acceptable basis.

SLCBB response: The SLCI site has been withdrawn from the application.

Reviewer Comment: This is an acceptable response.

6. Please provide the appropriate request for a Categorical Exclusion for the Environmental Assessment.

SLCBB response: They requested a categorical exclusion from environmental assessment because the materials used and by products produced during the CBU manufacturing process are naturally occurring and do not individually or cumulatively have a significant effect on the human environment.

Reviewer Comment: This is an acceptable response.

7. Please identify an appropriate reserve sample that will be retained for each lot in compliance with 21 CFR 211.170. One of the segments attached to the cryopreserved HPC, Cord Blood product may be appropriate.

SLCBB Response: SLCBB agrees to use one of the four integrally attached segments as a reserve sample. The segments are aliquots of the final product and each segment is etched with a unique identifier that relates to the final product container. One segment is used to ----------(b)(4)----------; another is available to ----------(b)(4)----------. The third is ----------(b)(4)----------. The fourth ----------(b)(4)----------.

Reviewer Comment: This is an acceptable response.

8. The data that you have submitted are insufficient to establish a product dating period (expiration date). We note that only summary data were included, and no stability protocol has been established. Please provide a stability protocol and data to establish an expiration date for cryopreserved HPC, Cord Blood units made

using the PrepaCyte-CB process. The stability protocol should contain appropriate predefined acceptance criteria.

SLCBB Response: SLCBB proposes an initial expiration date based on data from (b)(4) CBUs and supported by limited clinical data. They propose an initial expiry date of three years.

Expiry date protocol

(b)(4) randomly selected CBUs processed using the PrepaCyte-CB protocol in Nov 2009 were thawed in Nov 2012 to demonstrate product stability. Post-thaw TNC recovery, viable CD34 recovery, viability, and sterility were used to determine if storage had an effect on product quality.

Stability acceptance criteria

SLCBB is using their historical thaw/reconstitute data from (b)(4) control CBUs (Table 6 above) and recommendations from the Cord Blood Guidance to set the acceptance criteria shown in Table 12. Statistical analysis may be applied to data to determine if a test results represent biological variation versus a trend in loss of stability.

Table 12. Stability acceptance criteria and data

Parameter	**Acceptable ranges**	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Visual inspection	No cracks, leaks, legible labeling	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
TNC recovery %	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Viability, ---(b)(4)---	> 70%	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Viable CD34 recovery %	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

Reviewer comment: SLCBB has set their acceptance levels for the thawed and reconstituted CBUs at greater than 70% viability and TNC recovery as described in the Cord Blood Guidance and as recommended during our Mar 18, 2013 telecon. The CBUs tested for this study all passed these acceptance criteria.

Although a recommended level of viable CD34 cell recovery is not present in the Cord Blood Guidance, FDA requested that SLCBB continue collecting viable CD34 cell recovery data to help evaluate the stability of their cryopreserved CBUs. An acceptance level of (b)(4) was agreed upon during the Mar 18, 2013 telecon. The mean (b)(4) and median (b)(4) for CD34 recovery were above the acceptance criteria but one CBU had a viable CD34 recovery of (b)(4), which is (b)(4) than their target of --------(b)(4)--------.

Because the acceptance criteria were set very near the expected value, the --(b)(4)-- of an individual CBU by a relatively narrow margin was not unexpected. This -(b)(4)- appears to be due to biological variation and does not appear to represent a trend in the stability of the product.

Plans to extend expiration date to greater than 3 years: Further studies on thawed CBUs will be performed to extend the expiration date. An in vitro assessment with acceptance criteria will be performed every -(b)(4)-. Engraftment time and survival time will be analyzed to detect if there are statistically significant differences related to age of CBU used for transplant.

Reviewer comment: The stability data are acceptable to support the setting of an initial 3 year expiration date. The expiry date protocol (QM.21.03) is acceptable for extending the expiration date as data are generated.

9. The submitted validation data do not adequately support a (b)(4) incubation time for the sterility test. For testing the sterility of the licensed product, please incubate all samples for 14 days.

SLCBB response: The sponsor has agreed to a 14 day incubation period and modified their sterility testing SOP MI.05.02 accordingly.

Reviewer Comment: This is an acceptable response.

10. Please update your standard operating procedure (MI.02.01) showing the validated incubation time, temperature, the --(b)(4)-- culture -(b)(4)- used, and how qualification of each lot of --(b)(4)-- culture -(b)(4)- will be performed. Please submit the updated SOP for FDA review.

SLCBB response: The updated SOP MI.05.02 (and MI.02.02) states the following:

- Incubation Temperature: ---(b)(4)---.
- Incubation Time: 14 days.
- Media Bottles: ----------(b)(4)----------.
- The media lots will be qualified for growth promotion quality and sterility by their manufacturer, (b)(4).

Reviewer Comment: This is an acceptable response.

11. No validation data for sterility testing at SLCI were submitted. Please submit these data.

SLCBB response: The SLCI site has been withdrawn form the BLA application.

12. For collected units transported from the hospitals to the SLCBB facility, the transportation SOP should clearly state whether or not you discard units if there is any temperature excursion during transportation of units. Furthermore, we do not feel that your existing measures are adequate to ensure that the appropriate temperature is maintained throughout the shipping procedure. We recommend that a continuous temperature monitor be utilized for each shipment to ensure that the temperature is maintained throughout shipping and storage and that the data be reviewed before units undergo further processing.

SLCBB Response: SLCBB has qualified a temperature monitoring device (data logger) to be used during transit of collected cord blood units from the collection hospitals to SLCBB. The couriers have been trained on the use of the device and associated documentation. SOP CL.17.10 (response letter, attachment #18) describes that the courier starts the data logger (------(b)(4)------) at the first pick-up location. The identification number of the data logger is documented on the Daily Courier Log. The courier delivers the units and the associated data logger to SLCBB. Upon receipt, the laboratory staff stops the data logger after documenting the presence or absence of "out of range" alarm. The data logger temperature recording is downloaded daily or when time permits. The temperature information is reviewed by the quality unit to determine the product disposition.

Reviewer comment: The described procedure for continuous temperature monitoring during transportation is acceptable. However, SOP CL.17.10 and draft SOP TE04.03: Cord Blood Product Disposition Determination (Amendment 9, submitted June 26, 2012) did not explain the process for handling units that did not meet the acceptable transportation temperature. SLCBB submitted the final SOP TE04.03 (amendment 14) which specifies that units that do not meet the acceptable transportation temperature are not qualified for licensure.

13. The SLCI facility SOP SLCI-CTS 4039.01 states that the acceptable transportation temperature is (b)(4). However, it is not clear if a continuous temperature recording device (e.g., data logger) or a thermometer that simply displays the temperature is used in the transport coolers and whether units are discarded if the transportation temperature is outside the defined range. Please provide clarification and describe how you will ensure that the appropriate temperature is maintained during the entire transit time.

SLCBB response: The SLCI site has been withdrawn form the BLA application.

Reviewer Comment: This is an acceptable response.

14. In SOP TE.01.03 (Unrelated Umbilical Cord Blood Processing Using PrepaCyte-CB), you state that if a collection from a single donor is received in (b)(4) bags and ----------(b)(4)----------, the (b)(4) bags may be --(b)(4)----------). The collection procedure (SOP CL.06.07) does not describe collections into (b)(4) bags.

Please confirm whether you perform cord blood collections into (b)(4) bags, and if so, please submit the applicable collection and labeling SOPs.

SLCBB response: When the -(b)(4)- of blood in the umbilical cord exceeds the -(b)(4)- of a (b)(4) bag, collectors are permitted to complete the collection in a -(b)(4)- bag. The procedure has been modified to provide additional instructions (SOP CL.06.08, attachment 27).

Reviewer comment: The revised SOP provides adequate instructions for collection, and labeling of the -(b)(4)- bag. Both collection bags and associated documents are placed in the same package. The response is acceptable.

15. Please submit the final Donor Eligibility (DE) SOPs/forms used at the SLCBB and SLCI facilities. The final SOPs/forms should address the following issues in the draft SOPs in your June 25, 2012 submission:

    a. Please clarify in Draft SOP CL.03.07 whether donors with the listed findings are considered "eligible" or "ineligible" for DE determination purposes and specify that donor conditions such as elevated temperature in mother/infant or receipt of antibiotics during labor are acceptable only in absence of any suspicion related to infection.

SLCBB Response: SLCBB has submitted the revised final SOP CL.03.07.

Reviewer comment: The revised SOP is acceptable.

    b. Please define in Draft SOP CL.06.08 how information regarding the possibility of plasma dilution in the birth mother (e.g., administration of >2000ml IV fluid) is factored in to the DE determination.

SLCBB Response: SLCBB has submitted the revised final SOP CL.06.08 which explains that birth mothers who have received >2000ml of IV fluids 1 hour before the specimen collection are rejected.

Reviewer comment: The revised SOP is acceptable.

    c. There is no category in the Draft Product Documentation/Tech Review form for HPC, Cord Blood units collected from donors for whom DE determination was not completed and it is not clear whether an HPC, Cord Blood unit categorized as “available” is acceptable for licensure or release under IND. Also, please submit the corresponding form used at SLCI.

SLCBB Response: SLCBB submitted the draft “Unit Detail Report” which addressed the above issues. SLCBB clarified that the “Unit Detail Report” would replace the “Product Documentation/Tech Review form” and the final report would be submitted

after the implementation of ISBT 128 labeling. SLCI facility has been withdrawn from the application.

Reviewer comment: On the draft Unit Detail Report, testing for -(b)(4)- disease was listed as optional. The sponsor was informed (phone call and email on 3/12/13) that for the licensed units, the test results for -(b)(4)- could not be listed as optional because in the application, they had indicated that the testing for -(b)(4)- was a release criterion. SLCBB submitted the final Unit Detail Report which lists -(b)(4)- as a required test (amendment 18). SLCBB discards units that test positive for -(b)(4)- disease.

16. You stated in your June 25, 2012 submission that CMV (b)(4) testing is performed on the (b)(4) sample of the unit and you will not release the product if the CMV (b)(4) result is positive. Therefore, we consider this to be a release criterion and the assay must be validated.

SLCBB Response: On October 19, 2012, SLCBB suspended CMV (b)(4) testing on cord blood samples at time of confirmatory testing.

Reviewer comment: SLCBB submitted the revised "Comprehensive Matched Cord Blood Report" and SOP SE.01.09 that reflect the change in testing (amendment 14). The response is acceptable.

Reviewer Comment for items 17 – 23: Since the SLCI site has been withdrawn from the BLA application, these comments are no longer an issue.

17. Please provide information regarding the unique donor identification numbering system that is used at the SLCI facility.

18. Please submit the maternal specimen shipping information for the SLCI facility.

19. We note that no data were provided for the ----------(b)(4)---------- instrument at SLCI. Please submit qualification data on this instrument, including analysis of cord blood samples for relevant parameters (e.g., ----(b)(4)----).

20. Regarding your December 12, 2011 submission that included cell count "linearity data" for the SLCI ----------(b)(4)---------- instrument, please clarify the types of samples tested and clarify your acceptance criteria.

21. Adequate information was not submitted to evaluate SLCI's use of ----(b)(4)---- as a primary method for viability testing. Please submit SLCI's method comparison of cord blood viability using ----------(b)(4)---------- and an evaluation of viability sample stability.

22. Inadequate information was submitted to evaluate SLCI's use of -------(b)(4)------- to enumerate viable CD34+ cells in cord blood samples. Please address the following concerns:

a. Please submit qualification data for the ----------(b)(4)---------- that includes analysis of cord blood samples for relevant parameters (e.g., CD34/----(b)(4)----).

b. Regarding the SLCI report in your December 12, 2011 submission titled, "New Instrument Validation ----------(b)(4)---------- please provide additional description on the type of samples analyzed throughout this report and clarify the acceptance criteria for all parameters.

23. Regarding your December 12, 2011 submission, inadequate information was submitted to evaluate inter-laboratory precision of cord blood -----(b)(4)------ comparison between SLCI and SLCBB. Please clarify your acceptance criteria used for this comparison.

LABELING

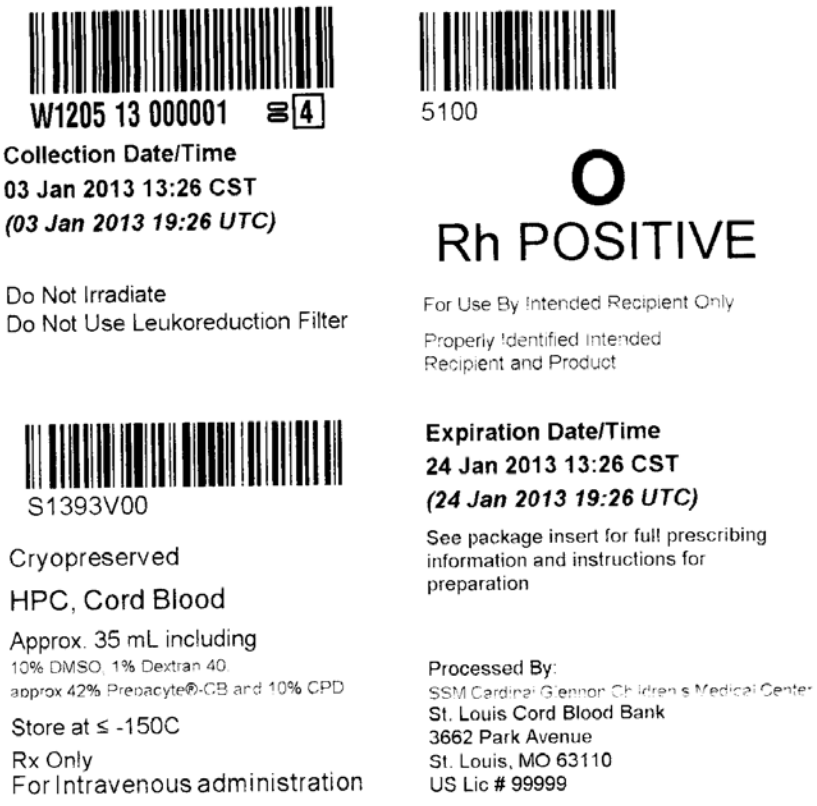
24. During the telephone conversation of July 30, 2012 between you and representatives of this office, you stated your intention to implement a container and package label system according to ISBT128. Please submit revised container and package labels.

SLCBB response: SLCBB submitted sample product labels and an ISBT 128 label sheet (Attachment 15a of Amendment 12. The pre-printed sheets of labels contain bar codes and readable identifier numbers and will be applied during the processing of the CBUs. The partial container label shown below will be folded in half and placed inside the pouch on the freezing bag.

Figure 1. Partial container label

The full container label will be added to the product prior to shipment per the instructions described in Attachment 8 of Amendment 16, Distribution Label Qualification. The label will be applied to a shipping tag and then attached to the product with twine. SLCBB felt that twine was the best choice based on ease of attachment and removal. A sample label is shown below in Figure 2.

Figure 2. Full container label



Package Insert – The package insert was reviewed by the Advertising and Promotional Labeling Branch, as well as the CMC and clinical review team. Changes to the package insert were required for clarity and regulatory compliance. The most significant CMC related changes included the following:

- Detailed procedures for "The Wash Method" were added to the product preparation instructions.

- The amount of time the product may be stored after thawing and reconstitution was changed to an upper limit of 4 hours.

- "Expected Results" and "Limitations" sections were removed from the Package Insert that was originally submitted.

Reviewer Comments: The proposed labeling and package insert provide adequate directions for the safe and effective use of ALLOCORD in the indicated population.

25. We note you have included the name "AlloCORD" on your example of a proposed label to be affixed to the HPC, Cord Blood product. Please submit a proprietary name request according to Guidance for Industry "Contents of a Complete Submission for the Evaluation of Proprietary Names" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

SLCBB response: They submitted a request to use AlloCORD as the proprietary name for their product.

Reviewer Comment: ALLOCORD was reviewed by APLB and determined to be acceptable.

26. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Response: Refer to the prior CR comment 24 labeling discussion shown above.

Additional reviewer comments:

1. SLCBB submitted the finalized version of the following documents (amendment 14):
   a. Saint Louis Cord Blood Bank Nursing Instructions for Cord Blood Collections Using the (b)(4) Sterile Cord Blood Collection Unit for Vaginal and Cesarean Deliveries
   b. Labor and Delivery Data form including Guidelines for Assessment of Mother and Baby

Reviewer comment: The submitted forms are acceptable.

2. In the response letter received on 12/14/12, SLCBB indicated that they have replaced the 8 character donor identification numbering system (Pre-fix "SL" + 6 digit number) with the ISBT 128 Donor Identification number (DIN). They submitted a sample of the DIN label sheet. The ISBT 128 DIN presents the information in both eye and machine readable format. To maintain linkage between the infant donor and the birth mother, identical numbers are assigned to the cord blood unit and the maternal specimens but they are distinguished by the 2 digit extension and color codes.

Example of ISBT 128 DIN:

Cord Blood Unit DIN	Maternal Specimen DIN
	

Facility ID# (W1205) + Year (12) + serialized ID# (000001) + extension code (00 for CBU or 20 for maternal specimen)

The DIN label color and the extension codes are defined in the following table:

Flag Character	Flag Character Color	Designated Use
00	No Color	Cord Blood Samples, Product or product culture vials
00	Tan	Forms
20	Pink	Maternal Samples
21	Yellow	Stored Aliquots
22	Blue	Segments

In addition to the labels on the unit, the DIN is included on the associated documentation and the Comprehensive Matched Cord Blood Unit (amendment 14) that are shipped with each unit to the transplant center.

Reviewer comment: The ISBT 128 DIN and the method for linkage between the cord blood unit and the birth mother are acceptable.

3. Since the sponsor plans to license cord blood units isolated from donors undergoing intrapartum antibiotic prophylaxis without removing any residual antibiotics, a warning should be put in the ALLOCORD label regarding the potential of allergic reactions in β-lactam antibiotic-sensitive ALLOCORD recipients. The PI was revised to include a statement on this issue.

4. Due to inherent limitation of the sampling method used for the sterility test (especially under low bioburden conditions) and the fact that the processed cord blood final product is not suitable for terminal sterilization, the ALLOCORD should not be labeled as sterile and a warning should be put in the label regarding the potential to transmit infectious bacteria or fungi. The PI was revised to include a statement on this issue.