Official Planning/Kick Off Meeting Agenda (6/7/12)

Sponsor: **LifeSouth**
BLA #: **BLA 125432**
Product: **HPC, Cord Blood**

1. Introduction of Review Team

Discipline	Name	Phone
Product Reviewer/Chair	Mohammed Heidaran/Ramjay Vatsan	301-827-6230/301-827-6041
	Karoll Cortez/ Safa Karandish	301-827-6849
	Jalel Sheikh/ Joydeep Ghosh	301-827-6037/301-827-5346
Pharm/Tox Reviewer	Atm S. Hoque	301-827-9071
Clinical Reviewer	Mark Borigini	301-827-3940
Statistical Reviewer	Stan Lin	301-827-9177
RPM	Candace Jarvis	301-827-5357
Labeling Reviewer	Loan Nguyen/Angela Hall/Lisa Stockbridge	301-827-6333/301-827-2585
DMPQ Reviewer	Grace Deneke/ Marion Michaelis	301-827-7059/301-827-7095
BIMO Reviewer	Lillian Ortega	301-827-6335

2. Administrative (Sponsor Communication)

A. Secure email has been established with the sponsor
Point of Contact: Jill Evans: JAEvans@lifesouth.org

B. For email correspondence, please cc me on all emails

C. For phone correspondence **w/o** RPM, please document **ALL** conversations, pdf the record and forward to me for archiving

D. For phone correspondence w/ RPM, I will generate minutes and archive them

3. Official Milestones and Monthly Goals

The current due date**: March 18, 2013 (10 month clock)**

Filing Meeting: Monday, July 2, 2012
Filing Letter Action/Comments: COB, Tuesday, July 10, 2012

Filing Letter: Tuesday, July 17, 2012
Mid-cycle Review Meeting: Thursday, October 18, 2012
Monthly Team Meetings: June 25, 2012, (On a as need basis)
Wrap-up Meeting: Tueday, February 19, 2013
Labeling Meeting: TBD

4. Regulatory history/review of agreements with sponsor Mohammed Heidaran/Ramjay Vatsan

5. Review Expectations

A. ***Sponsor Communications***

How often? : *As Needed*

Who initiates? : *The reviewer that need clarification. (Please see Administrative Section)*

Who participates? : *TBD*

How are they documented? : *See Administrative Section*

B. ***Inspections***
Timing for DMPQ and BiMo Inspections:

C. ***Team Meetings***
Please be prepared to provide an update on the progress of your review for this application and discuss any issues that may have surfaced since the last meeting.

6. Review Updates
Please bring review updates to committee meetings. If additional meetings are needed, please notify the RPM.

7. Next Steps

A. ***Filing Meeting***

Filing meeting for BLA #**125432** for **LifeSouth Blood Center** is scheduled for **Monday, July 2, 2012**. While preparing your presentations for the meeting, please ensure the following are addressed:

- Summary of the application

- Any major issues (RTF or non RTF comments)
- A description of any material needed for the review not included in the application to be requested from the Sponsor.
- Deficiencies to be included in the 74 day letter

Please keep your presentations to no more than **5 minutes, or let me know if additional time is required.**

****Note:** Attached are the filing checklists that are to be used when making your filing determination.

8. Attachments

A. Cord Blood BLA Guidance

B. Good review Management Principles and Practices (*document i includes detailed deadlines*)

C. Cord Blood Guidance Checklists (Discipline Specific)

D. Pre-BLA Minutes

Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications

Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products

Date: December 22, 2010

Meeting Date: November 22**,** 2010
Time: 2:00 PM-3:30 PM
Meeting type: Pre-BLA
Meeting Priority: B
Meeting ID # PTS **001196**
Product name: Hematopoietic Progenitor Cells-Cord (HPC-C)
Proposed Use: Treatment of malignancies and graft versus tumor effect
Sponsor: LifeCord
Meeting format: face-to-face
Meeting Chair/Recorder: Debra Vause, RN, BSN

FDA Participants:

ATM Shamsul Hoque, Ph.D., Pharmacology/Toxicology Reviewer, Division of Clinical Evaluation & Pharmacology/Toxicology
Donna Przepiorka, M.D., Ph.D., Clinical Reviewer, Division of Clinical Evaluation & Pharmacology/Toxicology
Debra Vause, RN, BSN, Regulatory Project Manager, Regulatory Management Staff, Office of Cellular, Tissue, and Gene Therapies
Kevin Shannon, M.D., Oncology Reviewer, Division of Clinical Evaluation & Pharmacology/Toxicology
Keith Wonnacott, Ph.D. – Cell Therapy Branch Chief, Division of Cell and Gene Therapy
Mercy Quagraine, Ph.D., Product Reviewer, Division of Cell and Gene Therapy
Stephanie Simek, Ph.D., Deputy Director, Office of Cellular, Tissue, and Gene Therapies
Kimberly Benton, Ph.D., Deputy Director, Division of Cell and Gene Therapy
Patrick Riggins, Ph.D., Branch Chief, Regulatory Management Staff, Office of Cellular, Tissue, and Gene Therapies
Bindu George, M.D., Clinical Team Leader, Division of Clinical Evaluation & Pharmacology/Toxicology
Wilson Bryan, M.D., Clinical Branch Chief, Division of Clinical Evaluation and Pharmacology/Toxicology
Mohammad Heidaran, Ph.D., Biologist, Office of Compliance and Product Quality, Division of Manufacturing and Product Quality
Nancy Waites, Consumer Safety Officer, Office of Compliance and Product Quality, Division of Manufacturing and Product Quality
Gang Wang, Ph.D., Expert Biologist, Office of Compliance and Product Quality, Division of Manufacturing and Product Quality
Ellen Lazarus, M.D., Director, CBER/OCTGT/DHT
Safa Karandish, Consumer Safety Officer, CBER/OCTGT/DHT

Sponsor Participants

Kristy Unold, MT (ASCP) SBB, Collection, Medical Office/Cellular Therapy Director

Kathleen Sazama, M.D., J.D., Medical Director LifeCord Collections
Diann Fisk, MT, BS, LifeCord Cell Processing Manager
John Wingard, M.D., LifeCord Medical Director

Background and Objectives:
On August 24, 2010, the sponsor submitted via facsimile a request for a pre-BLA meeting with FDA in mid October, 2010. The purpose of this meeting, as defined by the sponsor, is to discuss a BLA submission. The FDA responded to the meeting request on September 13, 2010 establishing the date and time of the face-to-face meeting. The sponsor submitted 22 copies of the briefing package on October 25, 2010. The FDA sent draft comments to the sponsor by facsimile transmission on Friday, November 19, 2010. The FDA met with the sponsor on Monday, November 22, 2010. The sponsor gave a brief introduction with a slide presentation and mock demonstration of the system they propose to use. The system includes functionally closed system with no open steps in the process. They will manufacture the product using a collection bag which is sterilely welded with a (b)(4) Tubing Welder to a sampling pouch, which is aseptically removed, then a (b)(4) is sterilely welded to a (b)(4) Freezing Container. Hetastarch is added via a (b)(4) filter to maintain a functionally closed system. These are then loaded into the (b)(4) system.

The following steps take place in the BSC: (b)(4) (b)(4) (b)(4). The remainder of processing takes place on an open bench in a processing laboratory that is environmentally non-classified. The finished product is labeled.

SPONSOR:

LifeCord proposes to meet biologics license application requirements, prevent contamination and cross-contamination, and ensure the safety, purity and potency of our HPC-C units by manufacturing them in a functionally closed system with no open steps in the process.

a) The system consists of:

- The (b)(4) (see Attachment 1a).
- The (b)(4) single use disposable processing kit, connected to a cryopreservation container (b)(4) see Attachment 1b) in a sterile manner using a (b)(4) Tubing Welder.(See Attachment 1c).
- Reagents (listed in #3), added in a manner to maintain a functionally closed system.

Processing and cryopreservation procedures are described in Attachment 2.

b) Our manufacturing system takes place in an indoor processing laboratory space that is non-classified. The freeze media will be prepared in a (b)(4) and will be added to the (b)(4) (b)(4) Cell Separation through a (b)(4) filter to maintain the functionally closed system.

c) Gowning and de-gowning requirements are listed in the processing and cryopreservation procedures described in Attachment 2.

d) Environmental monitoring will ensure that environmental pollutants and contaminants do not compromise the unit's safety, purity, and potency. Work areas will be cleaned (b)(4) according to validated cleaning procedures. See Attachment 3 for the Environmental Monitoring Plan.

1. Does our proposed HPC-C manufacturing process meet licensure requirements?

FDA Response

The final decision on the manufacturing process meeting licensure requirements cannot be made until the application is submitted, reviewed and an inspection is performed. Licensure requirements do not only consist of the manufacturing process, but also facility and equipment qualification, environmental monitoring, and raw material control, etc.

The FDA has the following questions / comments in relation to this question:

1. You state you will be using a functionally closed system with no open steps in the process. Please keep in mind that you will need to demonstrate through qualification studies such as media simulation, or other applicable process, that you are capable of aseptically processing the cord blood units following your SOPs and maintaining the closed, sterile system. The qualification runs should include all aseptic manipulations and environmental / personnel monitoring.

Summary of Discussion: The firm should perform studies that simulate UCB processing in order to show that the system is a functionally closed system. Typically, process simulations are performed using a type of microbiological growth media instead of the actual cord blood unit. Each processing step is performed, including all steps such as aseptic additions and use of the tube welder to make connections. The firm should be following established processes and procedures for the manufacturing and taking applicable environmental monitoring samples throughout the process. The simulation is typically performed under worst case conditions such as the presence of maximum number of personnel allowed in the processing area, maximum manufacturing capacity, and major equipment being used in operation. The firm also has to show as a positive control that the media used for process simulation can support the growth of representative microorganisms including bacteria, yeast and fungus. FDA also mentioned that we expect the firm to qualify the tube welder and show that the LifeCord personnel can successfully use the equipment to make a sterile connection between the (b)(4) closed system and UCB bag. Most firms perform a minimum of three consecutive successful media runs to qualify aseptic processing.

The FDA stated we did not expect to see media spiked with organisms to show that an addition is sterile after it passes through a filter.

2. On page 15 of the pre-read package under the description of the “CBU Processing” section at step A, you state that personnel will use the appropriate gowning / PPE to evaluate the CBU upon receipt. Please clarify where this evaluation is taking place. On page 16, under “Receive CBU into Processing Area” you do not describe any type of gowning /PPE required by the personnel. Please clarify what type of gowning is required for this step. In addition, please describe the type of gowning / PPE required for

personnel working in the hood and how often it needs to be changed. Do the personnel wear sterile gloves or sterile sleeves, if applicable, in the hood?

3. In regard to the Environmental Monitoring (EM) procedures, we would also like to point out that the type and frequency of your EM within the Class (b)(4) i.e., measuring viable/nonviable airborne particulates and viable surface monitoring (b)(4) per year do not meet current good manufacturing practices (CGMP) for aseptic processing of sterile drugs. Please be aware that CGMP requirements for EM frequency and alert/action levels are different from (b)(4) requirements. Please reference the following documents in order to better understand the Agency's expectations for EM:

   - Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004
   - Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications, October 2009
   - USP <1116>

4. Please be aware that EM will also need to be conducted under dynamic conditions and should include appropriate personnel monitoring with appropriate alert/action levels based on dynamic monitoring.

5. We recommend that you establish a comprehensive EM program and have SOPs and controls in place to routinely monitor the manufacturing facility and the (b)(4) BSCs. The EM SOP will need to include sampling locations, duration of sampling, frequency of sampling, and type of material used for sampling, etc. A rationale for the sampling locations will need to be included in the BLA along with EM data to show that critical manufacturing areas and support areas meet pre-determined specifications. We recommend that you review your process flow and determine the steps within the process where the product is most vulnerable to contamination and ensure those areas are under tight control. This can be done through some type of risk assessment.

6. The area surrounding the hood does not have to be monitored as frequently as critical areas used for aseptic processing including the BSC, however, it will have to be monitored. Usually during the environmental monitoring qualifications, a greater number of samples are taken to determine critical sample areas and room classification. Critical sample areas in the hood and surrounding areas will depend on the manufacturing flow pattern. It is usually any point where the product is either open or there is an increased risk of contamination. After qualification is completed, the number of samples and possibly the frequency of sampling may be reduced and only the critical sample points may be monitored in each area. Depending on the controls in place, the area surrounding the hood may only need to be monitored on a weekly or monthly basis.

7. In regard to Routine Surveillance Monitoring you state that it will take place after cleaning. For (b)(4) environment we recommend that you perform EM during the operation and before any cleaning steps are performed for the next operation.

8. On page 4 of 6 attachment 3 you define Post Clean as "the condition of the area after being appropriately cleaned, used to monitor effectiveness of the cleaning agent" or Post Use which is defined as "the condition of area being appropriately cleaned and having cell processing performed in the area , used to monitor effectiveness of the cleaning agent". Please clarify what you meant by Post Use Environmental Monitoring? Do you plan to perform EM after having cell processing performed in the area and prior to any subsequent scheduled cleaning steps?

9. We recommend that you perform a disinfectant effectiveness study to validate the disinfectant agents used in your facility. Then SOPs for use of the agents will be written based on these studies.

10. On Page 3 of 6 of the attachment 3 you state that you plan to perform (b)(4) monitoring in designated areas for both viable and nonviable airborne particulates. Please provide additional information about the location of the designated areas?

11. Personnel Monitoring: Please also provide more information about how personnel who perform critical aseptic tasks are monitored after each operation.

12. Section 8 of the EM SOP, Related SOPs, does not reference an area cleaning SOP. An SOP needs to be in place and documentation must be kept that the area and equipment are cleaned as specified in the appropriate SOP and record the type of cleaning / disinfectant agent used.

Summary of Discussion: The sponsor proposes to maintain Biological Safety Cabinet (BSC) as a (b)(4) and remainder of processing space as non-classified (b)(4). The sponsor asked if FDA considers the handling of solutions in the BSC which are subsequently filtered “critical processing” step that necessitates environmental monitoring (EM) during each processing run in the BSC?

FDA requested clarification of LifeCord’s statement that they are performing “100% sampling of the solutions”. Sponsor stated this means that samples from every preparation of solution are sampled and tested using the (b)(4) method.

Based on the limited information provided by LifeCord, FDA would consider the handling of the solutions in the BSC a critical processing step. FDA expects the firm to validate the above aseptic processing performed in the BSC. The validation process should demonstrate that the process does not introduce any contaminants to the sterile solutions prepared in the BSC. After initial qualification or validation the firm should requalify their aseptic processing on a periodic basis, typically semi-annually.

Please note that the adequacy of the EM procedures including the location, sampling size and frequency for viable and non-viable airborne particles, floors, walls, surfaces, and personnel within the manufacturing facility and the (b)(4) BSCs should be established based on the risks associated with the products and Environmental Monitoring Performance Qualification (EMPQ) studies.

ADDITIONAL COMMENTS

13. Please clarify if you seek licensure for only the RBC-reduced method (b)(4) of processing; you state elsewhere in the package that two manufacturing procedures (RBC-reduced (b)(4) are used in preparing HPC-C, but only one procedure is described.

14. Please clarify if more than one facility will be used to manufacture the HPC-C. If so, then you would need to demonstrate comparability of products manufactured in those facilities.

15. If you intend to seek licensure for banked units in inventory, then please clarify which procedures have been used to prepare these units, and indicate the nature of any revisions made to these procedures over time.

The only non-FDA approved reagent used in manufacture is DMSO (Dimethyl Sulfoxide). LifeCord proposes to ensure that purchased DMSO conforms to specified identity using a USP-approved method, which assesses (b)(4) (See Attachment 4 for a copy of the monograph for DMSO). The identity assay will be performed by (b)(4) (b)(4) This process will take place for each manufactured lot of this reagent prior to use.

2. Does our proposed identity assay for DMSO meet licensure requirements?

FDA Response

The use of (b)(4) for DMSO identity assay is acceptable. We note that a b(4) b(4) however, it is not completely clear if in addition to (b)(4) HSA (b)(4) DMSO, other solutions are added, because the percentages of the composition do not add up. Please clarify.

FDA additional comments after the meeting: We do not expect that it will be necessary for LifeCord to perform a full chemical analysis on each bottle of DMSO. Please see our response below regarding qualification programs for components/materials and vendors.

3. Other FDA-approved reagents used in manufacture are (b)(4) (b)(4), .in the collection bag, (b)(4), Hetastarch (b)(4)), and (b)(4).

LifeCord proposes to establish and maintain quality requirements of suppliers by performing the following at the time of supply receipt:

- ***Reviewing Certificate of Analysis (if applicable), and maintaining review records.***
- ***Examining solution/reagent label and expiration date for acceptability.***
- ***Examining solution/reagent container for breaks, leaks, and other abnormalities.***

- ***Examining solution/reagent for acceptable appearance, noting any potential impurities, discoloration, turbidity, and other abnormalities.***
- ***Verifying solution/reagent matches specifications of the purchase order.***
- ***Reviewing package inserts to ensure that no changes in manufacture have been made that would affect the use of materials. Comparing the package insert against the existing version on file, and maintaining a copy of current package inserts in records.***

If a change were made in reagent or manufacturer, a validation protocol would be created, approved, conducted, and accepted prior to using the new supply.

Do our proposed purchasing controls meet licensure requirements?

FDA Response

All reagents should meet written specifications as described in your standard operating procedures (SOPs), before released for use. You should examine the certificate of analysis (COA) and/or other documentation on each lot of component to ensure that it meets established acceptance criteria for specified attributes. If documentation for a component is incomplete, testing for the incomplete attribute of the component is recommended. Please refer to Section VII.B.9. of the guidance for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for information on component used in manufacturing as stated below:

> "Each component must be tested for conformance with appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d). For example, components that come into direct contact with an HPC-C should be sterile. Acceptance may be based on a Certificate of Analysis, as long as at least one specific identity test is performed and the reliability of the vendor's result has been established"

Please be aware that the product license holder has ultimate responsibility to ensure the quality of the incoming materials, reagents, and components that they purchase from the vendors. We recommend that you have adequate procedures in place to qualify the vendors and to ensure the incoming materials, components and reagents that you receive from vendors consistently meet the pre-determined specifications.

On Page 46 of the pre-read package you provide a high level description of your Supplier and Vendor Qualification program. Please be aware that SOPs will need to be in place and the qualification of suppliers and vendors should be documented. Testing of critical materials must also be performed per SOP and meet pre-determined specifications. The results should be documented.

Summary of Discussion: The sponsor requested clarification about FDA's response "Acceptance may be based on Certificate of Analysis, as long as at least one specific identity test is performed and the reliability of the vendor's result has been established"
Does this mean that we are required to do sterility & specific identity testing of each lot?

Discussion focused on whether an identity test had to be performed on each lot of components/materials. FDA clarified that for components and materials, sterility and identity testing *may not* be necessary on each lot, but this will depend on the system that the sponsor establishes for qualification of their vendors. The sponsor should qualify their vendor, and establish procedures for reviewing the COAs, establish SOPs with regards to storage, expiration, etc.

FDA additional comments after meeting:

The regulations in 21 CFR 211.84(d) do not specify what type of identity testing must be performed on a component/material. We do not expect that a full chemical analysis will be necessary. We encourage you to consider how you will establish a qualification program for your components/materials and the vendors from which you will purchase.

Questions you may consider in your qualification program may include: Do you periodically assess that components/materials are performing as expected? Is DMSO protecting cyropreserved cells from lysis? If you need to switch vendors in the future, how will you assess the new components/materials?

4. LifeCord performs HPC-C unit sterility testing using the (b)(4) Instrumented b(4)

LifeCord proposes to validate the (b)(4) method using the validation protocol included as Attachment 5.

Does our proposed validation meet licensure requirements?

FDA Response

It is acceptable to use (b)(4) as long as you have fully validated this method and demonstrated comparability of the (b)(4) method to the USP methods or according to 21 CFR 610.12. However, we cannot make a determination whether your validation protocol will be acceptable based on the information provided. The following comments, when addressed, should help in the design of the validation:

1. Please describe how the study will be conducted, including how time to detection is determined and the cord blood test sample volume.

2. Your proposed panel of (b)(4) test organisms includes (b)(4) that you refer to as "local" source, (b)(4) (b)(4). Were these recovered from prior testing of HPC-C in your bank?

3. We recommend the inclusion of facility isolates, such as those recovered from your environmental monitoring. Please comment.

4. Under the heading "Incubation Times," we note that you state "cultures with no growth detected will be retained for (b)(4) …" Please clarify if the (b)(4) incubation will also be in effect for sterility testing of HPC-C, and not only for this validation protocol. If

you are planning to reduce the incubation time you should add slow growers (we recommend *Propionibacterium acnes* and *Penicillium chrysogenum*) in your current panel of test microorganisms.

5. Concentrations of organisms used to spike, regardless of sample volume, should be between 10 – 99 CFUs. We note that several times in your protocol you refer to (b)(4) (b)(4) with different sample volumes. We strongly recommend that you reconsider these proposed spike levels, because to compare to the sensitivity of the CFR method we require that you can detect less than 100 CFU *per bottle/vial*.

6. Identity of positive growth should be confirmed to be the organism inoculated.

7. We note that you plan to evaluate robustness in part by comparing the time of detection for the (b)(4) spike inoculum levels. Do you intend to compare the CFR and (b)(4) methods this way? If so, how frequently do you intend to visually examine the CFR bottle?

8. You should carefully consider the composition of the test sample so that it is representative of product samples that you intend to test with the (b)(4) automated culture system. Among the items you should consider are cell concentration, media and additives, and preservation agents or antimicrobial agents that may have a bacteriostatic or fungistatic effect.

9. We note that your proposed incubation temperature for all (b)(4). We note that several published studies of this method showed that an incubation temperature (b)(4) was necessary for detection of some organisms.

10. For more information on your validation protocol, please refer to "Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products" from February 2008. (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072612.htm).

Summary of Discussion: FDA's primary concern with the proposal is the inocula of (b)(4) (b)(4) Your study needs to demonstrate that your system can detect (b)(4). We are concerned that a (b)(4) will make both of your inocula above (b)(4) and you will need to repeat the study. LifeCord acknowledged this concern and indicated that the goal is to have at least one of the inocula fall in the (b)(4)

Regarding the incubation temperature, LifeCord asked FDA if there are specific organisms that require testing at lower temperatures. FDA agreed to provide references to published studies that the sponsor may wish to review (listed below). LifeCord stated that adding an incubation temperature will not be feasible because their clinical microbiology laboratory uses (b)(4) only.

LifeCord indicated that they intended to use the b(4) test method as the comparator.

FDA asked if LifeCord has a back-up system in place in the event of equipment problems. LifeCord replied that the hospital clinical microbiology laboratory has multiple (b)(4)

FDA Additional Comments after the meeting:
For the purposes of demonstrating that your proposed use of (b)(4) for sterility testing of HPC-C is suitable for its intended purpose, performance of "parallel" testing with CFR 610.12 (or (b)(4) as part of your validation will not be required.

Please be aware that the facility, such as a hospital clinical micro lab, that performs your HPC-C sterility testing for product release will be considered a testing lab, will be required to register with FDA, and will be subject to GMP inspection.

At the meeting you presented your reasoning for not including an incubation temp of (b)(4) in your validation; however we continue to have concerns that this may affect your ability to detect Aspergillus niger and other common environmental isolates that do not grow well at higher temperatures. This will be a BLA review issue. References you may wish to review are listed below.

- G Kielpinski, S Prinzi, J Duguid and G du Moulin. Roadmap to approval: use of an automated sterility test method as a lot release test for Carticel, autologous cultured chondrocytes. Cytotherapy (2005) Vol. 7, No. 6, 531_ 541

- HM Khuu, F Stock, M McGann, CS Carter, JW Atkins, PR Murray and EJ Read. Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products. Cytotherapy (2004) Vol. 6, No. 3, 183_ 195

The lack of certain information about your HPC-C facility and process impedes our ability to fully advise you on aspects of your validation proposal such as challenge strain panel, incubation temperature, and length of incubation. We do not have information on your environmental monitoring results or product isolates, and we cannot assess whether your system is functionally closed until we review your aseptic processing validation in your BLA.

5. Does our proposed thawing procedure meet licensure requirements?

FDA Response

Please clarify if the procedure outlined in Attachment 6 is in use at the clinical site and if you have received any comments on it. Based on our reading, it appears it would be difficult to follow the step by step instruction for equilibrating and washing. For example one will add (b)(4) (b)(4) (b)(4) The sequence of performing the various steps should be clear for personnel who perform these procedures. Please comment on the following:

1. The description for preparing the equilibrating/wash solution results in final concentrations of (b)(4) Dextran 40 concentration, but the narrative describes a (b)(4) and 10% Dextran 40.

2. Per Section V.D.1.d of the cord blood licensure guidance, the sponsor should have detailed SOPs for emergency product recovery in the event of container failure; this includes plans for sterility testing and notification of FDA and appropriate persons. It is not clear if there is one in place.

3. (b)(4) (b)(4). Please describe the management of this repeat procedure in terms of resuspension volumes, containers used and time involved in relation to the expiry of the thawed HPC-C.

4. Describe the time limits for each step and the conditions for holding the thawed/washed units prior to infusion. What is the expiry for the thawed HPC-C?

5. Please clarify your statement in this Attachment 6 that "Transplant centers should use a thawing procedure that has been validated at their institution", page 1/7.

Summary of Discussion: The agency explained that the license holder was responsible for providing validated thawing instructions to the end user, regardless of whether the end user follows or does not follow the instructions. LifeCord also indicated that they intended to establish a post-thaw expiration of (b)(4) for the HPC-C.

Regarding procedures for emergency product recovery, LifeCord indicated that in situations of container failures, they intended to discard the product. This will be described in SOPs in place for emergency product recovery, as required by the licensure guidance, along with procedures for reporting such incidents to the agency.

6. Does our proposed storage of retention samples meet licensure requirements?

FDA Response

1. We are unable to provide a complete response to this question based on the high level of information provided in the pre-read package. Please note that equipment used for storage will need to be qualified (included IQ, OQ and PQ) and samples will need to be properly labeled and stored in a designated area and tracked appropriately.

2. We note that aliquots of DNA (maternal and cord blood) are stored at (b)(4); and aliquots of maternal and donor plasma and serum are stored at (b)(4). However, it is unclear what viable cells refer to e.g. cord blood or processed HPC-C, and at what temperature the viable cells are stored. Please clarify. Aliquots of plasma, serum, nucleated cells, and DNA used for tests other than potency, may be stored as described, but a sample representative of the HPC-C which is stored under the same conditions as the HPC-C should be stored for potency testing.

3. Please refer to Section VII.B.14.f of the cord blood licensure guidance for information on retention samples.

7. Do our proposed equipment qualification policies meet licensure requirements?

FDA Response

Based on the high level information you provided in your pre-read package, your equipment qualification plan appears to be acceptable. We will not be able to make the final determination if your equipment qualification meets licensure requirements until we receive your final BLA submission and review the equipment qualifications. SOPs need to be in place for equipment maintenance / calibration, equipment qualification, and utilities qualification, etc.

8. Do our proposed HPC-C release criteria meet licensure requirements?

FDA Response

HPC-Cs for licensure should meet the criteria listed in Table A (Section V.B) of the licensure guidance. We assume that your question is in regard to whether the procedures you follow to release a HPC-C are acceptable. We cannot make a determination based on the forms submitted (Attachment 9) without a narrative explanation of the procedures. Please provide a narrative description of the step by step procedures that are followed, making references to forms/SOPs that are used, where applicable. The forms and SOPs should cover only HPC-C that you intend to license. We also note some conflicting information in some of the forms which may need explanation. For example, please comment on the following:

1. CD34 assessment is performed on the day mother of donor is consented (CB.10.4). What sample is used for testing maternal sample or donor cord blood?

2. HLA testing is performed on b(4) (CB.10.4). The Cord Blood Licensure Guidance recommends the use of cord blood, however, the use of an alternate sample is acceptable if you demonstrate with data that you can use the red cell fraction to consistently obtain results.

3. It is unclear what samples are used for confirmatory HLA typing, after a request for HPC-C is made by (b)(4) (Attachment 9b); whole blood, buffy coat, or leukocyte enriched samples may be shipped to (b)(4) for confirmatory HLA typing. Please note that an attached segment should be used for confirmatory HLA typing.

4. Please describe how you manage a second request for a HPC-C in situations where confirmatory HLA typing was done on a previous request, but HPC-C was not released (UCB.13.1).

5. It appears infectious disease testing may not be completed on some units, yet these units are listed in the registry (UCB.13.1). In general, this should not apply to HPC-Cs for licensure. Please describe the donor screening and testing procedures in place at the time of manufacture for all of the HPC-C that you intend to be included under the license, and provide examples of the relevant labeling, including the Donor Eligibility summary of records, that will be applied to HPC-C from each time period. Also see comment #16, below.

6. Please explain the 'follow-up' procedure for maternal donors before releasing HPC-Cs for transplant (UCB.13.2).

7. Please describe documentation that accompanies HPC-C at shipping (CB.13.3).

8. You state that b(4) may be used to assess viability when the unit is requested. If viability was performed within the last 12 months, it is not repeated. HPC-Cs collected before March 2004 do not have b(4) Some units have post thaw viabilities of (b)(4) Please clarify.

9. Does our proposed procedure to enumerate viable (CD34+ cells meet licensure requirements?

FDA Response

1. We cannot make a determination based on the information provided in the meeting package. Please note that the viable CD34+ cell content is part of the release testing that is performed on the HPC-C prior to cryopreservation; you are performing this testing on b(4) Please explain how you calculate the content of viable CD34+ cells in the HPC-C.

2. Regarding the incubation conditions used, (b)(4), please specify which conditions are used and provide temperature limits. You also indicated that the stained cells may be stored up to (b)(4) before analyzing; please submit data to show that the different conditions yield equivalent results.

3. We also have the following additional comments for your attention:

    a. Please specify the model of flow cytometer used

    b. Please discuss the following:

        i. maintenance of the instrument
        ii. QC of the instrument performance
        iii. calibration of the instrument
        iv. training of the operators
        v. qualification of the assay including repeat measurements, proficiency testing, etc.
        vi. software used and indicate if it has been cleared by CDRH

10. Does our proposal meet licensure requirements?

The storage stability/expiration date will change over time as the validation described in attachment 12 is continuously performed. Labels cannot securely be affixed after cryopreservation. We propose to attach the current stability/expiration data at the time of release with a tie tag.

FDA Response

1. The stability or expiration date of the product should be determined based on real time validation studies. It is also your responsibility to determine what methodology for affixing labels works best for the CB cryopreserved product manufactured in the facility.

2. The use of a tie tag to attach the expiry at the time of release is acceptable.

3. The stability protocol submitted in attachment 12 is not very clear. We request that you give a brief presentation of your stability program at the pre-meeting on November 22, 2010. After review of Attachment 12 we do have the following comments for clarification:

   a. The (b)(4) expiry that you propose should be supported by data presented in your BLA application.

   b. The use of transplant outcome data from HPC-Cs from your inventory is acceptable.

   c. The product characterization (sterility, TNC, viability, and viable CD34 cell counts) that you propose to perform using a minimum of three HPC-Cs representatives of units used for transplantation is acceptable. However, your protocol does not take into account any manufacturing methods that have been used over the life of your inventory, the (b)(4) manufacturing methods you intend to use for licensure, the years that these methods were used (if any changes occurred), and any facility changes that have occurred.

   d. It is unclear how a (b)(4) sampling time point for (b)(4) will yield any meaningful information to extend product expiry, but analysis of samples of your inventory based of manufacturing method and year of manufacture may be meaningful. For on-going studies used to extend expiry, we recommend that you choose a sampling time point that will help extend the expiry of the HPC-C for at least one year.

   e. The purpose of testing retains of (b)(4) in addition to the final HPC-C is unclear.

4. Please note that expiration dates related to storage conditions, as determined by stability studies should include both cryopreserved and post-thaw expirations dates (and times when appropriate).

5. You may want to consider including a Stability Protocol in your BLA submission. If approved, the protocol would be an agreement on your protocol for testing the stability of your cord blood units and extending the expiration date

6. Additionally, LifeCord should verify the storage container and the adhesive and ink on the labels will not adversely affect the product over the expiry date of the product.

7. We can also discuss the potential that older HPC-C may be used under IND if they do not meet the expiry criteria that is approved in your BLA.

Summary of Discussion: LifeCord presented an overview of their stability program as requested by the agency. As part of their stability program, they intended to assess parameters including TNC, CD34+ cell count, and cell viability. They proposed to analyze 3 HPC-Cs at (b)(4) intervals for the (b)(4), at (b)(4) intervals for the (b)(4), and (b)(4) testing thereafter. The results from these studies will be used to advance the expiry of the HPC-C. The agency found this proposal acceptable. The stability protocol will be submitted in the BLA for review. They also clarified that they intend to only include red blood cell reduced HPC-C in their license application; also HPC-Cs in inventory manufactured before obtaining licensure will not be included in the application for licensure

11. Does this package insert meet licensure requirements?

FDA Response

No, we have the following comments on your draft of the package insert:

1. Please limit the "Highlights" section to no more that ½ page.

2. The section you have entitled "Adverse Reactions" (Section 6) is primarily comprised of information that belongs in Section 5, "Warning and Precautions". Further guidance for the "Adverse Reactions" section can be found in "Guidance for Industry. Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

3. For requirements regarding font, format, and content, please see FDA publication "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

4. Additional resources may be found at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

5. At this time, we are unable to further address specifics of the details in the draft Label you have provided as this would require review of the information you will be submitting in your BLA. Further guidance for the details of the content of each section is available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm213055.htm

12. Does our post-marketing assessment meet licensure requirements?

FDA Response

1. No, your plan for safety review and outcomes assessment does not completely meet licensure requirements.

2. For an approved BLA, the safety and outcomes assessment information will be submitted by the BLA holder as a supplement to the BLA. How the data are gathered from the clinical site(s) is up to the BLA holder, but the data should be readily available for the BLA holder to be able to assess whether any adverse experiences or other unexpected outcomes identified may be due to problems with product manufacture, and whether corrective actions are needed.

3. The expected follow-up information and the timeline for reporting outcomes assessments will be established during the BLA approval process. You will need to submit your SOP for collection and assessment of clinical outcomes. In addition to the items you have listed in your Question #12, please also include infection transmission events among the parameters monitored. With respect to your comment that collected clinical parameters may not be reflective of the cord unit which ultimately results in long-term implantation, FDA emphasizes that a primary purpose for data collection is for safety evaluation. For that goal, post-thaw information, infusion reactions, early adverse experiences, and early transplant outcomes may relate to the cord which does not persist. Therefore, it is essential to follow safety and outcome parameters on all units released and used.

4. The timeline for BLA safety reports is described in 21 CFR 600.80. These adverse experiences must be reviewed promptly once they are received by the BLA holder and reported to FDA using the FDA Form 3500A. You will need to submit your SOP for review and report of such safety events. Please include in your label instructions to the user for how to identify and report adverse experiences**.** You may find clarification of what to report in the guidance document entitled "Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" found at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm

Summary of Discussion: The sponsor expressed understanding that clinical data should be readily available for the BLA holder to be able to assess whether any adverse experiences or other unexpected outcomes may be due to problems with product manufacture. The sponsor stated that reporting of data by transplant centers is mostly voluntary, and the sponsor has no control over what data are reported by transplant centers. FDA acknowledged that in some cases privacy laws of other countries prohibit reporting of data to the sponsor.

FDA requested the inclusion of infection transmission events. The sponsor responded that most transplant recipients experience infections that are unrelated to the stem cell product. Infections possibly due to the stem cell product are rare events, and many transplant centers do not report their infections. The sponsor proposes if a transplant center identifies an infection believed to be related to the HPC product, then that infection must be reported to the sponsor who will report it to the FDA. The FDA recommends the sponsor use explicit instructions to the user on how to identify and report infections of interest.

13. Would it be acceptable to screen HPC-C for abnormal hemoglobin(s) using this method?

FDA Response

The intended use of the (b)(4)' system is to separate and determine the percent amounts of (b)(4) and as an aid to identifying abnormal hemoglobins in whole blood. If the system can be validated with appropriate controls to detect at least (b)(4) in cord blood, it is acceptable.

ADDITIONAL CLINICAL COMMENTS

1. On the Form 356h that you submit, please specify the diagnoses for which your product is indicated. If you are limiting your diagnoses to those supported by docket 1997N-0497, you may make reference to the docket for the integrated summary of efficacy and the supporting efficacy data (the actual data need not be submitted by you). If the diagnoses in your label go beyond those supported by the docket, you will also need to submit evidence of efficacy for each additional diagnosis. For additional information about the indications supported by data in the docket, please see "Guidance for Industry. Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications" available at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf

2. In addition to the documents in your pre-BLA package, please also include in your submission the following information:

    a. Copies of all versions of the family history questionnaire, maternal risk questionnaire, and the list of maternal tests with the dates of implementation for each revision. Please ensure that the dates of implementation of each span the period of collection for which you seek licensure.

    b. Written procedures for:

        i. Maternal screening
        ii. Maternal testing
        iii. Donor eligibility determination
        iv. Notification of mothers or their responsible physicians of positive or indeterminate test results according to local or national regulations
        v. Elicitation and handling of post donation information
        vi. Elicitation and handling of recipient adverse events

3. You will need to provide clinical safety data in your submission. Module 2 should include the overview of safety evaluation plan used to generate the data, demographics of the patients in the safety dataset, and a summary of the safety experience. Module 5 should include narratives for all adverse events that have been reported to you and detailed results of any clinical outcomes analyses for your products.

4. This product may be subject to the Pediatric Research Equity Act and if the data to support your intended indications do not cover all pediatric age groups (including neonates), you may need to include in your submission a request for a waiver or deferral of the pediatric assessment. For further information, please see "Guidance for Industry - How to Comply with the Pediatric Research Equity Act" at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

Action Items

The Office of Cellular, Tissue and Gene Therapies (OCTGT) encourages sponsors/applicants to submit applications via the Food and Drug Administration (FDA) Electronic Submissions Gateway (ESG). The ESG is an Agency-wide solution for accepting electronic regulatory submissions that enables the secure submission of regulatory information for review. Instructions for setting up an ESG account can be found at http://www.fda.gov/esg/webtrader_checklist.htm.

OCTGT strongly encourages the use of secure email. Secure email makes use of encryption during transmission and the messages are decrypted upon receipt using the certificate. To establish secure email, please follow the instructions found in Appendix A.

OCTGT may communicate via non-secure email if a sponsor/applicant provides written authorization to do so. If you would like to communicate via non-secure email, please include a statement to this effect in the cover letter of your IND. In your cover letter, please also include the names and email addresses of those individuals with whom FDA may communicate. If you would like to communicate via non-secure email prior to submitting your IND, please send a fax or email to the attention of Debra Vause with a statement to this effect. In your fax or email, please include the names and email addresses of those individuals with whom FDA may communicate. You may send the fax to the attention of Debra Vause at 301-827-9796.

Please note that OCTGT will only use email in place of telephone communications for general discussions, to relay regulatory issues and to request information. OCTGT will not provide copies of letters or meeting minutes by email and will not accept amendments via email.

Appendix A

Exchanging Certificates with the External Individual and FDA

1. The external user must obtain his or her own certificate from a Certificate Authority (CA) like Digital Signature Trust Co., Thawte Consulting, (Pty) Ltd., or VeriSign, Inc. (Instructions on how to obtain certificates are located at the end of this document.)
2. After he or she has obtained a commercial grade U.S. Domestic 1024-bit key certificate, the user will need to send a signed message to the address cert-query@fda.hhs.gov. The message must have a subject of Wendy.Lee@fda.hhs.gov. The body of the E-mail may be blank because the certificate exchange process ignores it.

   By digitally signing this message, the user is providing his or her certificate to the Tumbleweed E-mail Firewall (EMF) system/server. The address in the "To" field directs the message to an auto-responder built into the Tumbleweed EMF server. EMF responds to the cert-query@fda.hhs.gov by returning the proxy certificate of the person specified in the "Subject" field, according to the alias name or username. Initially all secure testing is completed with Wendy.Lee@fda.hhs.gov. **However, all external users will need to complete these same steps with each person they need to correspond with at FDA to enable secure e-mail communications. Please make sure that you use the firstname.lastname@fda.hhs.gov ONLY.**

A. The external user should simply double-click on Tumbleweed EMF's certificate. This will open the "Certificate" window. Click on the "Details" tab to view this certificate's details.

B. Click the "Install Certificate..." button at the bottom of this window's "General" tab. This will begin the Certificate Manager Import Window. Click the "Next" button to continue.

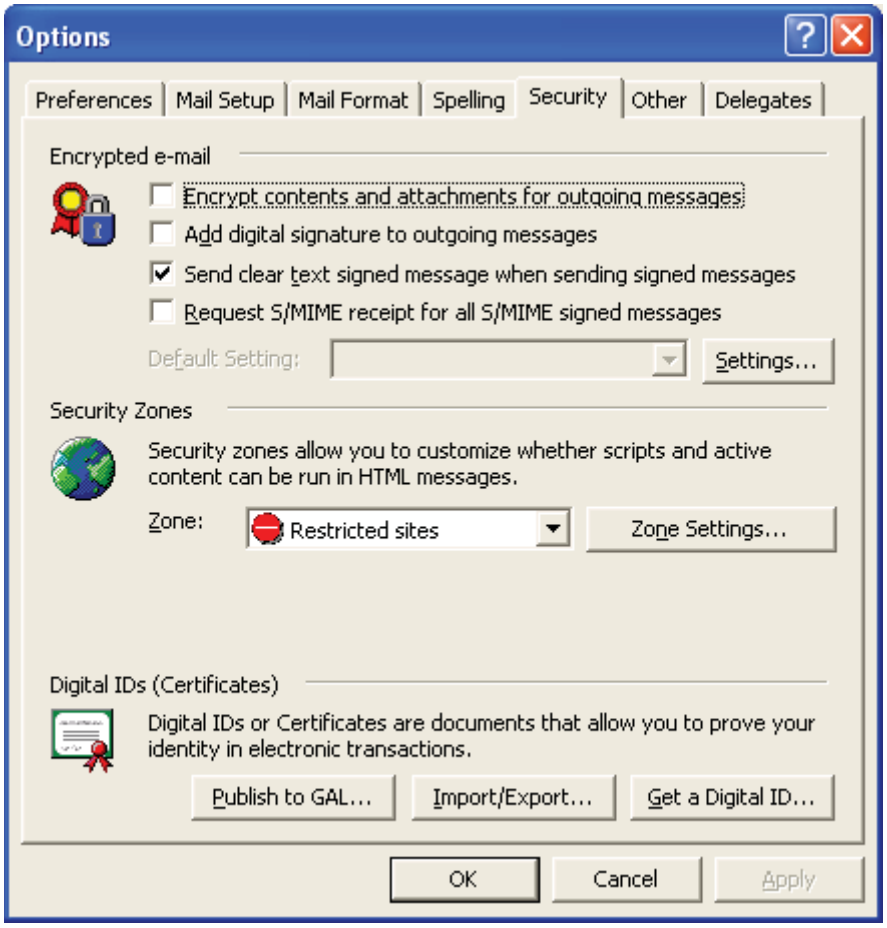
C. Choose to "Automatically select the certificate store based on the type of certificate" when prompted.

D. Click the "Finish" button to complete the wizard. A warning will appear, asking if you want to add the certificate to the root store. Click "Yes" to add it. A message saying that the certificate has been added should appear. Close the "Certificate" window by clicking "OK."

1. By this time, the external user should have gotten a response to his or her certificate query. The query response should appear to have come from the user that was queried. In Outlook, a reddish ribbon and a blue lock will appear on the e-mail message showing that the message has been digitally signed and contains the sender's certificate. The user should right-click on the "From" address to add this sender (and his or her certificate) to the contacts list. The external user should make sure to EXPLICITLY TRUST the certificate. This is a very important PROCEDURE. If this step is not completed, any message sent to this user will not be readable.
2. Now that the certificate exchange has been done, the external user must e-mail Wendy.Lee@fda.hhs.gov. At this point the external user should be sending a SIGNED AND ENCRYPTED message.
3. Now that both the Tumbleweed EMF root certificate and the external user's certificate have been exchanged and verified, the external user and the EMF administrator (through the Wendy.Lee@fda.hhs.gov account) will VERIFY that the exchange test messages are being signed/encrypted and decrypted/verified. A final message will be sent when the process is COMPLETED.

   When sending E-mail to Wendy.Lee@fda.hhs.gov, the external user must click on the "To..." button and choose Wendy.Lee@fda.hhs.gov from the contacts list. Outlook will not associate Wendy.Lee@fda.hhs.gov proxy certificate with the E-mail if the external user just types Wendy.Lee@fda.hhs.gov address in the "To..." field. E-mail addressed by typing the address in will not go out encrypted. (A "Non-Secure Recipients" alert will be displayed.) **PLEASE NOTE: WENDY LEE IS NOT RESPONSIBLE FOR ANY APPLICATION REQUESTS/PROCEDURES OR NUMBERS FOR eCTD REQUESTS!!!!**

A. For the external user to view his or her certificate, he or she must select "Options..." from the Tools menu of Outlook main window. He or she will have to view the "Security" tab under the Options window. Finally, he or she will click the button labeled "Encrypted e-mail..." in this section the external user will need to select either "add digital signature or encrypt contents and attachments or both."

B. 

C. A new window titled "Change Security Settings" will appear. A section called "Digital Signature" will be a little more than halfway down the window. In this section is a button labeled "Choose..." The external user will have to click on this button to bring up a list of his or her certificates. (Note: there is another section called "Encryption." This should contain the same certificate that the "Digital Signature" section has.)

D. In the new window, the external user must choose the certificate he or she is working with by double-clicking it. This opens the "Certificate" window. The certificate's thumbprint is under the "Details" tab. (Note: Microsoft products display the thumb/fingerprint using the SHA1 algorithm while EMF uses the MD5 algorithm. The external user should explicitly state to the EMF administrator that the thumb/fingerprint being read is from SHA1.)

HOW OUTLOOK USERS OBTAIN CERTIFICATES

External users of S/MIME clients must obtain a certificate from a CA and import it into their E-mail client. This client must be configured for commercial grade 3DES encryption when communicating with FDA/HHS, as that is a specification

mandated by FIPS 140-1. Although a certificate may be obtained from any CA, these instructions show how to acquire one from VeriSign, Inc. and import it into Outlook with Internet Explorer.

1. Open the Outlook client program.
2. Pull down the "Tools" menu and select "Options."
3. Click on the "Security" tab in the "Options window."
4. Select "Get a Digital ID." This will automatically load VeriSign's web page.
5. From VeriSign's web page, select "Class 1 Digital ID."
6. Fill out the form with payment information. Press the "Submit" button.
7. E-mail from VeriSign Inc. should shortly arrive. This E-mail has embedded hypertext markup language so that it looks like a web page. Links in this E-mail will lead one through the final steps in importing the certificate.
8. FDA NOW SUPPORTS TLS. PLEASE LET ME KNOW IF YOU WOULD LIKE TO ESTABLISH A TLS CONNECTION.

Wendy Lee
Wendy.Lee@fda.hhs.gov
FDA E-mail Administrator
FDA/OITSS/DIO
- Phone: 301-827-3080

SPECIAL NOTE: FDA USERS ARE TO USE THE firstname.lastname@FDA.HHS.GOV E-MAIL ADDRESS FOR SECURE MESSAGING UNTIL FURTHER NOTICE. PLEASE DO NOT ADDRESS A MESSAGE USING ANY OTHER E-MAIL ADDRESS.

Chronology
OCTGT/IOD/Vause:11/22/10;12/2/10;12/3/10;12/10/10;12/13/10;12/14/10;12/15/10;12/16/10;12/17/10;12/21/10
(N:\IOD\Vause\Meetings\LifeCord_PBLA_12/15/10.doc)

APPROVED
By Debra Vause at 6:46 pm, Dec 22, 2010

Brief Summary of LifeSouth Community Blood Center's LifeCord Product:

Regulatory History:

- Pre BLA meeting held on November 22nd 2010
- The previous BLA# 125412 was submitted on October 5, 2011 and received on November 7, 2011. We received their request for withdrawal by fax on December 28, 2011
- Resubmission BLA #125432 dated May 18, 2012

Application Summary:

1. The firm is asking for licensure of unit processed after March of 2012
2. The collection of CB is performed in utero
3. 8 collection centers have been identified
4. Processing performed using -----(b)(4)----------
5. Cryopreservation and storage is performed using --------(b)(4)---------- from ----(b)(4)-----
6. The facility is located at 4039 Newberry Road in Gainsville, FL (FEI # 3003707120)
7. The facility includes an (b)(4) processing room, receiving room, Gowning room and a room for unit storage.

Validation Studies Included:

- Cord Blood Collection Process Validation
- ---(b)(4)--------- Cell Processing System Using ------(b)(4)---------- Biomedical Dry Shipper Model (b)(4) Shipper
- Unprocessed Umbilical Cord Blood Transport Containers
- ----------(b)(4)---------- ---------- Validation Cryopreservation (Thawing and Washing of HPC-C) Validation Document
- Use of DMSO for Cord Blood Preservation
- ----------(b)(4)---------- Injection Validation for Sterility
- ----------(b)(4)---------- System Method Validation
- Validation of ----(b)(4)--------- Hematology Analyzer for TNC Counts
- Enumeration of CD34 Cells with --------(b)(4)---------- Reagents Using --(b)(4)-- .
- Viability Testing of Cryopreserved CB Samples by Flow Cytometry
- ----------(b)(4)---------- Assay Using (b)(4)
- nRBC Method Re-Validation by –(b)(4)----
- Sterility Protocol for Hematopoietic Progenitor Cell, Cord Blood
- HVAC Clean Room Test and Certification Report
- Environmental Monitoring Plan and Validation Document

- ----(b)(4)------ Overwrap Bag, validation from vendor

Company History:

- LifeCord, a program of LifeSouth Community Blood Centers, Inc. (LifeSouth), was established in 1997 by collaborative agreement between three entities - the University of Florida (UP) faculty of the department of medicine, Shands at UF (the teaching hospital for the University of Florida).

- (Shands), and LifeSouth - has operated under IND BB-7520 approved by the UF IRB to collect, process, bank and distribute cord blood units for transplantation since that time (1997).

- In the 14 years of its existence, LifeCord has collected more than (b)(4) cord blood units, of which (b)(4) met all criteria for banking and are stored and listed for transplant in the NMDP registry, as of October 19, 2011.

Manufacturing History:

- ----(b)(4)----- units have been distributed for transplant by LifeCord into 81 patients needing hematopoietic reconstitution for malignancy and other diseases. Data from 77 of these transplants have been reported back to LifeCord through the CIBMTR and NMDP as of October 31, 2011.

- LifeCord representatives met with the FDA for a pre-biologics license application meeting in November 2010. Information shared during that meeting resulted in a decision to change manufacturing from manual to more fully automated methods and to create a new manufacturing facility to meet FDA requirements for licensure.

- Life South submitted BLA# 125412 on October 5, 2011. LifeSouth withdrew the BLA by fax on December 28, 2011

- Previous BLA submission lacked validation results for CBU collection, CBU processing (volume reduction/cryopreservation) using their then new -(b)(4) based manufacturing process, shipping and storage.

- Other CMC information that were not complete in the previous BLA submission from LifeSouth include validation results of test methods for: sterility testing, lot release testing, Absence/incomplete SOPs for critical methods such as CBU collection, Vendor qualification, Production control records, Inventory management etc.