BLA #: 125397

Teleconference Date: June 28, 2011

FDA Attendees: Quagraine, Mercy; Karandish, Safa; McCright, Brenton; Bauer, Steven; Ghosh, Joydeep; Joshi, Bharat; Norwood, Laurie; Heidaran, Mohammad; Wang, Gang; Benton, Kimberly; Oh, Steven; Przepiorka, Donna; Hyde, John E; Bryan, Wilson; Bross, Peter; Hoque, Atm S.; Serabian, Mercedes; Rees, Renee;

Sponsor Attendees:
Eva Quinley – Senior Vice President (NYBC), Quality & Regulatory Affairs
Andromachi Scaradavou – Medical Director (NCBP)
Michael Zdanowski – Director of Operations (NCBP)
Rodica Ciubotariu, M.D., Ph.D. – Director of Donor Services (NCBP)
Ludy Dobrila, Ph.D. – Associate Director, Processing (NCBP)
Tao Wang – Manager, Cord Blood Validation (NCBP)
Michael Tarnawski – Director, IT (NCBP)
Susana Albano, Ph.D. – Director, Quality Control Laboratory (NCBP)
Carmelita Carrier, Ph.D. – Director, HLA Laboratory (NYBC)
Jay Valinsky, Ph.D. – Vice President (NYBC) & Director, Flow Cytometry Laboratory
Sarai Paradiso – Supervisor, Flow Cytometry Laboratory (NYBC)
Donna Strauss – Executive Director, Core Operations (NYBC)
Edwin W. Streun – Director, Regulatory Affairs (NYBC)

NCBP point-by-point responses to the FDA questions of June 15, 2011 and June 17, 2011

June 15 Questions

PROCESSING

1. In Table 7 under Process Validation Report, NCBP-VAL-10-012R1, page 15, the mean CD34 cells/HPC value is less than the minimum value. On verification during the pre-approval inspection in April 2011a transcription error was observed. You agreed to revise and resubmit the revisions to the file. Please submit the revisions the agency for review. These discussions were with DR, Tao Wang.

Response:

This was corrected prior to the end of the inspection; we will submit the corrected document electronically.

FDA summary of discussion: Response satisfactory

2. In your Process Validation Protocol, NCBP-VAL-10-012P, page 5, you report that some characterization and testing of HPC-Cs during the execution of the validation were performed at ----------(b)(4)----------. Please clarify what testing was conducted at (b)(4).

Response:

Testing of ABO/Rh typing and IDMs was conducted -(b)(4)-. This is specified in the Processing Flow Chart on page 6 of the Process Validation Protocol, NCBP-VAL-10-012P.

(b)(4) is now operating as --------(b)(4)----------.

FDA summary of discussion: Response satisfactory

3. Please define how long the retentions samples are kept; refer to the Section VII.B.14.f. of the Cord Blood Licensure Guidance for information on how long retains may be kept. We note that you report that they are kept indefinitely.

Response:

In the Amendment 125397.004, submitted 27 May 2011, we presented the information on the reserve samples, as follows: "We describe in this document the different samples stored from the NCBP HPC-C products and propose that the combination of samples and testing results provide sufficient information about the identity and potency of the HPC-C and adequate material for future evaluation (infectious disease, HLA and genetic testing) so that they meet the regulatory requirements."

As we described in section 2.4: "All samples are stored indefinitely"; the case is the same for CD34+ results and CFU images. By "indefinitely", we mean that we will store the plasma, DNA and cell samples ----(b)(4)---- after the expiration of the HPC-C (as described in the Guidance), or until such time as they are used for a justified medical purpose.

Our practice has been not to discard samples, ever.

Please let us know if you require further information.

FDA summary of discussion: Response satisfactory

4. We note that some of your SOPs describe procedures for other samples, e.g. Flow cytometry procedures. We recommend that SOPs for cord blood processing pertain to cord blood alone.

Response:

Our processing SOPs do apply just to cord blood; however, the SOPs in the Flow Cytometry and HLA laboratories may apply to any samples as long as the samples are handled in the same way. These laboratories serve as reference laboratories for the National Cord Blood Program, similar to ----------(b)(4)----------. If there is need for instructions specific for NCBP, these are included in the SOPs, as appropriate.

5. Per the regulations cited in 21 CFR 211.137 and 21 CFR 1271.260, the HPC-C product must bear an expiration date determined by appropriate stability testing. Please describe how the HPC-C expiration date will be attached to the product. We note that you have established a 4 year expiration for HPC-C prepared by manufacturing method 4.

Response:

Section 2 of the BLA Original Application, "Representative Draft Labeling" submitted 07 Jan 2011, described the labels, as follows:

At the time of release for transplantation and shipment, HemaCord™ HPC Cord Blood Product has the following labels:

1. Container Label: The cryopreservation bag has a partial label affixed on it, that

2. Additional information (partial label), described in items 2.1, 2.2, 2.3 and 2.4, accompanies the HPC Cord Blood Product in an envelop

2.1 Report on Matched Cord Blood Unit;

2.2 Licensed HPC Cord Blood label, which will be generated when a licensed HPC product will be released for transplantation, and contains:

- Proper name of the product "Hemacord™, HPC Cord Blood Cell Suspension" and license number ".."
- Name and address of manufacturing facility "National Cord Blood Program, New York Blood Center, 45-01 Vernon Blvd, LIC, NY 11101, USA"
- CB unit ID (eye readable and bar code)
- Intended Recipient name and NCBP search ID
- TNC/Kg (*TNC of the HPC product divided by the recipient's body weight*)
- HLA match with recipient (*HLA matching is assigned considering low resolution typing for HLA class I A and B loci and high resolution typing for HLA DRB1 alleles*)
- HPC Product expiration date
- Instructions for use: "Rx only, For IV administration only"
- Warning: "See Package Insert for full Prescribing Information on Hemacord™"

2.3 Cord Blood Unit Receipt Form

2.4. Procedure for Cord Blood Units Thawing and Preparation for Administration,

3. Shipper Container labels

The licensed HPC Cord Blood label is printed at the time a licensed product is released for transplantation. The information on this label describes TNC and HLA characteristics of the

licensed product with regards to the particular patient, so it cannot be prepared before we know the information of the intended recipient.
The expiration date will be assigned based on the year of manufacturing of the HPC-C product and -(b)(4)- stability studies, as described in the CMC section of the BLA Original Application.
This is a partial label and is not attached to the product but accompanies the unit in an envelope, along with the other three documents.

Given the fact that the unit and the metal canister are cryopreserved, there is no material than can be securely attached to them at the time of shipment. Since the final (and effective) expiration date will be assigned at the time of shipment, it will be shown on the partial label as described above.

Example of Licensed HPC Cord Blood label is attached.

FDA summary of discussion: Based on sponsor's explanation above, CBER indicated that internal discussions were ongoing regarding this issue.

DONOR ELIGIBILITY AND COLLECTION

6. Please resolve the following outstanding issues and provide the revised documents that you had indicated in your responses to the questions discussed at the teleconference on 4/11/11 and the pre-license inspection:

i. "Report on Matched Cord Blood Unit (CBU)" addressing the footnote "FDA approved assays" which is not applicable to the tests performed on the cord blood sample.

Response:

We will modify the footnote on Matched Cord Blood Unit (CBU) to read: "Tested in a CLIA-certified laboratory, using FDA approved assays **for the maternal sample**".

FDA summary of discussion: Revised report will be submitted.

ii. Data Form to capture information regarding ----------(b)(4)---------- prior to the collection of maternal specimens. Also, please provide the revised SOP that explains how this information will be factored into the DE determination.

Response:

a) The NCBP dataform addresses transfusion of blood products but not -----(b)(4)---------- at volume --------(b)(4)----------. We prefer to address the latter rare event in our respective SOP. If mother had that event (i.e., fluid resuscitation), she is seriously ill and it is not appropriate to perform an interview or blood drawing at that time.

Therefore, we are proposing to modify SOP **CB 37.0006** Obtaining Maternal Blood Specimen, as follows: (revised SOP will be submitted electronically).

6.3 Procedure

6.3.1 BEFORE maternal blood draw, review the mother's medical record for the past 24 hours for infusion of ----------(b)(4)----------.

6.3.1.1 DO NOT draw maternal blood sample if the mother received more than ----------(b)(4)----------. Maternal blood sample can be drawn 24 hours later.

If no maternal sample can be obtained, the unit is Non-Qualifying and F37.003 needs to be sent.

b) SOP **CB37.0023.3** Donor Eligibility – Infectious Disease Testing, Maternal and Infant Risk Factors, specifies:

6.2.3 Units that are collected from mother that displayed the following risk factors are declared **ineligible**

6.2.3.2 Mother received during labor and delivery (before maternal blood was drawn) more than --(b)(4)-- of transfused blood products (blood, packed Red Blood Cells, platelets or plasma).

FDA summary of discussion: Sponsor was informed that the proposed plan was acceptable. However, reviewer pointed out that the time frame of –(b)(4)- is only applicable to infusion of -------(b)(4)----------. For -(b)(4)--, time frame is within-–(b)(4)---. Sponsor agreed to make the clarification in the revised SOP.

iii. Donor Eligibility SOP (CB37.0023.3) addressing: 1) DE determination and the proper designation of ineligible units prior to the release of cord units to the search inventory (we understand that this will be completed by August 1, 2011), 2) DE criteria for licensed units.

Response:

SOP **CB37.0023.3** will be revised to clarify that donor eligibility has to be assigned before CB unit is released to Search Inventory (by August 1st).

Donor eligibility is assigned based on FDA criteria for HCT/P donors, for all CB units.

Starting August 1, 2011, the batch record of every unit, which includes eligibility assignment, has to be reviewed and signed by Quality, before the unit is released to search Inventory. Quality will approve that units meet licensing requirements.

7. In your sponsor letter to the questions discussed at the teleconference on 4/11/11, you described the process that is performed at the time of placenta retrieval, for donor identification and labeling in multiple birth settings. However, those details are not included in the Collection of Cord Blood SOP (CB37.0001.1). Current version of the SOP provides labeling instructions for single births only. Please provide the revised SOP.

Response:

We will revise SOP **CB37.0001** to expand section 8.3.2 regarding identification and labeling of units from twin pregnancies, and we will submit the revised document electronically.

FDA summary of discussion: Sponsor will submit the revised SOP.

8. Please provide clarification regarding the documentation of maternal information for maintaining linkage between the birth mother and the cord blood unit. According to the collection and maternal consent SOPs (CB37.0001.1, step 8.4.2 and CB37.0002.1, step 5.8.1), mother's name, medical record number and address is documented on the last page of the Data Form; however, the blank and the completed forms that you have submitted do not include a designated section for documentation of mother's information.

Response:

In the data form, page 16, the page before the last one has the maternal information, and page 17, the very last page, has the information on mother's and baby's physicians. Unfortunately the documents submitted previously were "blank" dataforms, and scanned up to page 15 because the last two pages are empty in the blank forms.

We will provide electronically scanned document of a completed form to clarify this.

FDA summary of discussion: Sponsor will submit all the data form pages.

9. The quarantine procedure that you described in your response to the FDA letter dated 3/9/11, is not sufficient to prevent improper release of units prior to completion of the donor eligibility. Quarantine designation may be accomplished by various methods including automated designation, physical separation or other methods. Please provide additional information regarding your revised procedure.

Response:

This response is covered by Submission 125397.004, response to PLI 483 observations. The revised procedures will be in place by August 1, 2011, and provided to FDA prior to that date.

***FDA summary of discussion*: Sponsor will submit the information by August 1, 2001. Sponsor specified that the quarantine designation method would be used for prospective units, which was acceptable to the reviewer. Sponsor will be submitting the revised documents.**

LOT RELEASE TESTING (Brent may have summaries)

10. Please submit validation data for infectious disease testing performed. We note that the test kits are licensed or cleared, however, you should show at a minimum that the kits work the way they are supposed to in your hands (with various operators). In addition, please describe the samples used for NAT testing for HIV and HCV.

Response:

a) Please note that NCBP outsources all infectious disease testing to CLIA-approved laboratories.. Validations studies for the FDA-approved assays (approved for maternal samples) that (b)(4) is performing have been requested and will be submitted electronically.

b) Since 2008, NCBP is testing the maternal sample of the processed CB unit prospectively for NAT HIV/HCV. The assays used by ----------(b)(4)---------- and since August 2010, ----------(b)(4)----------.

Prior to 2008 maternal samples (stored at or below -(b)(4)- were tested upon request of a unit from a Transplant Center. With the change in the manufacturer's specifications of the –(b)(4) assay (October 2010) samples stored for longer than --(b)(4)--- are tested "not according" to the specifications and the results are reported with a disclaimer "Testing for Research Only, maternal sample stored at ----------(b)(4)----------.

In prior teleconferences/written exchanges FDA referred to units that maternal samples were tested out of manufacturer's specifications as "incomplete" for donor eligibility. Currently, there is no commercially available test for CBU from this period.

We have requested guidance for this situation through our IND mechanism (Annual Report).

11. We note that you retest ---(b)(4)-- Cord Blood unit for HLA type before it is shipped. Data from these re-testings could provide evidence that the test method is reliable and accurate. Please submit data summarizing the frequency the HLA re-testing does not match the original HLA test. Please include a description of the course of action that was taken to resolve the discrepancy.

Response:

Prior to release of a cord blood unit to transplant, the HLA typing is repeated from a sample of a -(b)(4)-- segment in order to verify the initial HLA assignment. A total of (b)(4) cord blood units were retested from segments in 2010 and one discordant antigen assignment was reported representing a concordance of 99.88%. The initial testing on this unit was done in 2006. For 2011 to date, (b)(4)cord blood units have been retested from segments and no discrepancies have been found.

The discordant antigen assignment was noted after completion of the typing by ----------(b)(4)----------. The HLA typing was repeated and reviewed for verification of results. Analysis of the underlying cause of the discordant result showed that it referred to a specificity, HLA---(b)(4)--, not recognized by serologic typing reagents; thus the sample was assigned (b)(4)-- based on the serologic reactions detected.

It is the practice of NCBP to submit confirmatory results when units are shipped.

A detailed report of the discordant case will be sent electronically.

Flow Cytometry Comments (Flow Cytometry issues were not discussed because Steve Bauer was unavailable. A separate telecon was scheduled to discuss these issues)

Instruments for analysis

12. You currently use ---(b)(4)----- flow cytometers for CB analysis. Section 2.2

of your BLA states that equivalent instruments could be used but criteria to establish "equivalency" were not submitted. If you want to use different instruments, you will need to submit to FDA a plan for establishing equivalency for review and approval. Also, you will need to submit data to support this change and await FDA approval before this change can be implemented (see comment on Flow Cytometer New Instrument Validation, #8 below)

Response:

Twice annual comparison studies are conducted with the ------(b)(4)---- instruments. These studies, which are required by the State of New York, demonstrate equivalency of results among the (b)(4) instruments in use. This comparison study was also conducted when the laboratory was using a different flow cytometer, the --(b)(4)--, to demonstrate equivalency of this instrument to the ------(b)(4)----- flow cytometers.

The Flow Cytometry Laboratory has two (2) SOPs in place to cover the eventuality of using a new and different flow cytometer. These are:

27.0011 – New or Relocated Instrument Validation
27.0012 - Comparative Study – Flow Cytometer Workstations (Note: this SOP issued for the twice --(b)(4)-l instrument comparison studies required by NY State Department of health).

If we decide to deploy new equipment, all elements of new instrument validation SOPs will be followed as described and will be submitted to Quality for review. As instrument changes pertain to a licensed cord blood product, procedures will also be submitted to FDA for review as recommended.

Flow cytometry SOPs (SOP 27.0090)
13. Your SOP 27.0090 for analysis of cell samples by flow cytometry includes several types of samples that are not the intended cord-blood product. Please submit a revised SOP that is designed solely for the characterization of your intended clinical cord-blood product.

Response:

The Flow Cytometry Lab is a reference lab that is not within the administrative prevue of NCBP. Rather it reports to NYBC Core Operations. The SOP for CD34 enumeration takes into account that other samples from other consignees may be processed in the laboratory, but that the protocol used is the same. National Cord Blood Program samples are handled in the same manner as are any other samples tested. This would be similar to what ----------(b)(4)---------- does for testing for infectious diseases for multiple customers. Nonetheless, if the agency requires it, we can create a NCBP specific protocol.

Sample quality and age
14. Section 6.4.2.2 of your SOP 27.0090 for analysis of cell samples by flow

cytometry lists several sample age or quality attributes that may result in contacting the submitter of the sample and the need for supervisory review and sign off. Your revised SOP needs to stipulate that any samples that do not meet acceptance criteria will not be further processed for clinical use under the license.

Response:

In cases when sample age exceeds the acceptable time parameter, the sample is considered out of specification and the flow cytometry results will be released with a disclaimer. The Flow Cytometry Laboratory alerts NCBP and notifies Quality. The standard operating procedure being developed to provide instruction to Quality personnel for the review and approval of batch records will include instructions stating that should cord blood samples fail to meet acceptance criteria, the units from which those samples are collected may not be released as licensed products.

----------*(b)(4)*----------
15. ----------(b)(4)----------.

Response:

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

Sample preparation
16. 6.4.4.1 instructs the analysts to add -(b)(4)- of CD45/CD34 -----(b)(4)---- antibody into each sample tube. The reagents listed in Table 1, in Section 4.5.2 refer to antibodies supplied by (b)(4) either singly -----(b)(4)-------. Please submit data to validate that single antibodies or pre-supplied mixtures both result in comparable assay performance. If such a demonstration is suitable, the SOP needs to include procedures for ---(b)(4)---- antibodies.

Response:

The reference is to a notation in the Comment field of this Table. These comments were descriptive and come from the Manufacturer's Package insert. The Table noted that the vendor supplies these reagents in both individual and ----(b)(4)---- formats. However, the captioned section of SOP 27.0090 is explicit, namely, -------(b)(4)---------- are used. For clarity, we have modified the Table in question and added a note.

[(b)(4)]

*As per SOP 27.0090, the Flow Cytometry Laboratory uses -----(b)(4)---- anti-CD34 and ----------(b)(4)------- CD45 ----------(b)(4)----------.

Flow cytometry analysis
17. 6.5.1 refers to several SOPs for instrument quality control and maintenance. These need to be updated to the most current versions of these SOPs. Please update the references to SOPs in your revised flow cytometry SOP.

Response:

In our validation documents, we referenced the actual version number of the SOP. However, it is our practice in writing SOPs to only reference "current" version of another SOP. Our SOPs are reviewed at least annually to insure that references are correct.

18. 6.5.3 instructs the analyst to use the current CD45/CD34 acquisition template and further states that any changes to the template must be documented, approved by the laboratory director and filed in the laboratory. Please note that any changes to template should be subject to QA/QC review. In addition, the process for template generation and qualification of each revised template needs to be documented and supported with validation data.

Response:

We will modify the SOP to reflect the requirement for Quality review if there are template changes. We will also modify the SOP to reference the method for creation of templates which is in the Operator's Manual for the CellQuest software.

Flow Cytometry Validation studies

19. Since accuracy could depend on instrument, set-up, and compensation, this test should be repeated 3 times with different lots of standards, different operators, different machines, and at different times. The different machines should be the -----(b)(4)-------- that you are currently using.

i. Since precision could depend on instrument, set-up, and compensation, this test should be repeated 3 times with the standard preparation and different product lots, different operators, different machines ----(b)(4)---- currently in use), and at different times.

ii. Since linearity could depend on instrument, set-up, and compensation, this test should be repeated 3 times with different standard preparations, different operators, different machines ----(b)(4)---- currently in use), and at different times.

Response:

The reviewer appears to have touched on two different areas. This first relates to instrument set-up (linearity, compensation, etc). The second relates to the robustness of the assay itself.

With regard to the first comment, the flow laboratory performs a daily instrument setup and QC procedures which assure instrument linearity and that appropriate compensation is set. These procedures follow SOP 27.0015 (Cytometer Instrument QC) and 27.0094 (Flow Cytometer Instrument Set-up for CD34 Enumeration and Viability Assays). In addition, a --(b)(4)- linearity ----------(b)(4)---------- is performed following SOP 00.082 ----------(b)(4)----------.

With regard to the second comment, NYBC provided accuracy and precision measurements as part of the BLA (CMC/Method Validation). The Flow Cytometry Laboratory performed accuracy determinations using CD34---(b)(4)---- and determined that the assay performed within manufacturer's specifications. In addition The Flow Cytometry Laboratory performed precision studies in 2006 using ---------(b)(4)---------- cord blood units and again in 2010. In the 2010, (b)(4) technologists performed the assays on (b)(4) different---(b)(4)--- instruments. In addition, studies performed in 2010 also demonstrated that inter-technologist differences relative to their ability to define ----------(b)(4)-------- in complex multi-parameter histograms were non-statistical.

We will perform additional studies if required.

iii. Regarding the --(b)(4)-- studies performed in 2008, more information is needed regarding the number of times this test was done, if there were different lots involved, and if there were different operators involved.

Response:

Current manufacturer's package inserts requires that samples contain --------(b)(4)---------- in order to obtain acceptable results with the antibody -----(b)(4)------ in use.

In order to meet this criterion, we established set ------(b)(4)------ for the analysis of ----(b)(4)---------- cord blood samples. This approach to establishing set ---(b)(4)--- was taken because, in the current process, the Flow Cytometry Laboratory does not have detailed hematology results on CBU samples prior to testing.

The 2008 ----(b)(4)---- studies described in the reviewers' comment were designed specifically to establish these -----(b)(4)-------, but were not explicitly designed to be performed across lots, operators etc. The results provided to the agency, and which are in the SOP, established these --(b)(4)-- and allowed us to determine that >95% of CBU samples would fall within the cell concentration requirements.

Additional studies to verify the conclusions derived from the 2008 evaluations can be done if required.

Flow Cytometer New Instrument Validation

20. Regarding new instrument validation, please note that new instruments should be qualified based on accuracy, precision, and linearity tests using the modifications to these assays described above, in addition to the analysis of ---(b)(4)----.

Response:

We are in agreement and this will be done. Dates for completion will be submitted with our formal submission.

General comment on the flow cytometry assay

21. The descriptions of the flow assay lack any mention of positive and negative assay controls including isotype controls and positive and negative cell controls. These should be included in each assay to insure acceptable analytical performance.

Response:

In documents provided to the Agency, we noted:
"The Flow Cytometry Laboratory has used an --(b)(4)-- approach to CD34+ cell enumeration since 2006. It should be noted that unlike chemistry or other quantitative tests, validation of the

analytical method for the enumeration of CD34+ and CD45+ cells in UCB is hampered by the limited availability of reference standards which are fresh biological samples that could be used to measure assay linearity and accuracy and for testing the viability of samples over a broad range of values. Accordingly, we have used commercially available control materials when possible to meet these requirements. These controls are stabilized whole blood samples, containing or --(b)(4)-- with CD34+ cells"

The concept of the use of positive, negative and isotype controls is explicitly NOT part of the --(b)(4)-- protocol currently in use. We have adapted our protocols to conform to those in the published scientific literature[1,2] . To address the points made by the reviewer:

The use of positive and negative controls in flow cytometric analysis is most useful in those cases where the populations of positive and negative cells are well defined and where analysis can be done with single parameter histograms. Unstained cells are one type of negative control used to establish the threshold between positive and negative cell populations. Most of the current literature indicates that the use of unstained cells as controls in these circumstances is generally inadequate since they will only correct for autofluorescence and will ignore any fluorescence resulting from non-specific binding.

Isotype controls have also been used in some circumstances to assist in distinguishing negative from positive cells, also most effectively in single parameter analysis. Isotype controls work well if the fluorescence intensities of positive and negative cell populations do not overlap significantly. It has also been shown that the use of isotype controls lead to erroneous results unless the fluorescence to protein ratio is the same for the specific antibody and the non-specific control. The situation is even more complex in multi-color analysis of the type used for CD34 determinations.

Based on the literature, our position on the use of such controls is:

1. Positive Controls – Positive controls should not be used in the --(b)(4)-- analysis. Positive controls (CD34 --(b)(4)---- are useful for instrument set-up and as vehicles for evaluating method performance on a daily basis. In addition, the Flow Cytometry Laboratory uses ----------(b)(4)----------.

2. Negative controls – We are unaware of any stabilized, reference negative control materials that are commercially available. Even if such materials were available, their use in establishing gates in the multi-parameter analysis of the type used for CD34+ cells in CBU has been questioned[1]. Therefore, negative control cells are not used in the --(b)(4)-- analysis

3. Isotype controls are explicitly NOT recommended in the current --(b)(4)-- method[1,2]. One reason for this is that from the early years of CD34 testing isotype controls stained more events non-specifically, than were stained specifically by the CD34 conjugates[3]. This position has been endorsed by --------(b)(4)--------- and has been reviewed by the Agency[4].

---

[1] ---------(b)(4)----------.

[2] ----------(b)(4)----------

[3] (See M Keeney et al (1998) Cytometry 34: 280-283).

[4] From (b)(4) web site in reference to document ---(b)(4)- "The U.S. Food and Drug Administration (FDA) has evaluated and recognized this approved-level consensus standard for use in satisfying a regulatory requirement"

4. Accordingly, and in concert with the --(b)(4)-- procedures described in references 1 and 2, we use a series of ----------(b)(4)---------- to remove any non-specifically stained events and debris from the final reported CD34+ cell number.

STERILITY

Sections 4.1.3.1.2 and SOP CB40.0006.1 – Sterility Assay Protocol for Lot Release

22. We note that you have mentioned two ranges of incubation temperatures for your sterility assay: ----(b)(4)----- (under section 4.1.3.1.2) and ----(b)(4)------ (under SOP CB40.0006.1). Please clarify which one will be used for testing the sterility of your product.

Response:

The sterility testing of our CB product is performed using the --------(b)(4)---------. The equipment temperature requirements do follow manufacturer instructions and are ---(b)(4)---- as described in SOP **CB40.0006**. We apologize for the typo error in BLA section 4.1.3.1.2.

23. Please provide representative -(b)(4)- for the following using your ----(b)(4)----- ------(b)4)---:

i. --(b)(4)--
ii. ---(b)(4)---
iii. ----(b)(4)------
iv. ----------(b)(4)----------
v. ----------(b)(4)----------

Response:

Examples of representative **--(b)(4)--** are available and will be submitted electronically.

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

Response:

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

2 pages redacted due to (b)(4)

[(b)(4)]

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

The fact that -(b)(4)- does not identify an organism might reflect a ---(b)(4)---- instead of a contamination of the HPC-C product. Also, it might reflect the presence of an organism that was not alive at the time of the -(b)(4)- processing.
In any case, the product is not in NCBP Search Inventory.

The revised SOP will be submitted electronically.

v. We will submit the data electronically.

vi. The volume of plasma left in the -----(b)(4)---- after processing is used to prepare aliquots for IDM, retention samples and microbiology testing. Based on our experience, after these procedures, it is rare that sufficient volume is left over for repeat microbiology testing, since --(b)(4)- of plasma would be necessary.

NCBP, however, prevents any HPC-C to enter into Search Inventory if there is any indication of an invalid test, unless without doubt, after determination of the identity of the microorganisms isolated from the test, the growth of the species may be ascribed unequivocally to faults with respect to the material and or the technique used in conducting the sterility test procedure.

All tests that are positive follow the algorithm described in the table above and in SOP **CB40.0006**.

If a negative control turns positive, an investigation report is initiated and the incident is reported to QA for further decisions. The test would be considered valid only if the positivity can be attributed without doubt to operator technique and is an isolated event.

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

----------.

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

ii. ----------(b)(4)----------?

Response:

i. ----------(b)(4)----------:

[(b)(4)]

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

(Question 29 was numbered as 1, possible transcription error?)

1. It appears that you will be testing ----(b)(4)------ cord blood samples at a time for sterility. What is the maximum storage time for the respective plasma bags? How are you going to store them before the sterility test?

Response:

Sterility testing does follow the rule -----(b)(4)------- as described in NCBP QC Laboratory Policies **CB40.0001** and SOP **CB40.0006**. In our everyday routine practices, there are no ----------(b)(4)---- CB samples at a time, --(b)(4)---.

FDA Resposne: Will be updated to indicate the maximum holding time and temperature for cord blood samples before they are tested for sterility.

Section 4.3.2.1 and NCBP-VAL-10-003 – Sterility Assay Method Validation, Phase I study

30. We note that during this phase of study samples were shipped from NCBP to a Contract Laboratory at the ----------(b)(4)---------- and a Microbiology Laboratory at the -----(b)(4)--------. Using a table please indicate the conditions, monitoring criteria and average duration of all respective shipments.

Response:

Conditions of respective shipments were consistent for all samples processed for the Phase I study. All were transported at room temperature (RT), immediately after processing and the transportation time from the NCBP laboratory to ---(b)(4)--- took not longer than ---(b)(4)--- due to the proximity of the ----------(b)(4)----------). All samples were transported using a NYBC courier vehicle.
The protocol at that time (2008) did not specify the use of timers or temperature loggers to monitor shipping conditions. However, since the study was performed during the months of October - November, NYC temperatures were not extreme.

31. Table 5 (Section 4.3.2.1.9):

i. Please indicate the actual absolute number of CFUs for each challenge strain used to inoculate the media.
ii. Please explain the difference between NA*4 and NA*5 in Table 5.

Response:

i. The information requested will be submitted electronically.

ii. This was a transcription error. NA*5= not applicable.

32. The ----(b)(4)---- methods recommend a ---(b)(4)--- incubation temperature for molds as many of them would not grow at ---(b)(4)--- please clarify why this temperature is not used with ----(b)(4)-----.

Response:

The ---(b)(4)---. operates using only one temperature range: ---(b)(4)---.. A list of molds detected with this temperature range has been requested from ----(b)(4)-----. and will be submitted electronically.

33. Please submit a list of microorganisms that you have isolated to date from your facilities and the cord blood units using your ----(b)(4)-----. machines.

Response:

Response to item 33 is provided as attachment.

FDA Response: Satisfactory; the list for the environmental isolates is also provided under June 17 question #

Section 4.3.2.1 and NCBP-VAL-10-006 – Sterility Assay Method Validation, Phase II study

1 page redacted to (b)(4)

35. ----------

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

----------.

Response:

We will organize a repeat study.

36. ----------

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

Response:

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

FDA Response: Will be updated along with the table 6 in the original submission.

37. We note that during this phase of study samples are shipped from NCBP to a Contract Laboratory at ----(b)(4)------. Using a table please indicate the conditions, monitoring criteria and average duration of all respective shipments.

Response:

Please see the attached Table describing the shipping conditions. The Table will also be submitted electronically.

38. Please describe how you have assessed the ruggedness and robustness of your proposed test method during the assay validation.

Response:

We do not completely understand how to respond to this question and would appreciate some examples.
Further, we would like to ask whether a retrospective review of -----(b)(4)---- QC results could address the question.

FDA RESPONSE: The sponsor will submit a retrospective analysis of validation data to indicate how the ----------(b)(4)----------

June 17 Questions

1. Please provide a copy of fully executed Disinfectant Efficacy Study and a list of objectionable microorganism found in the Long Island NYBC facility.

Response:

The execution of the disinfectant efficacy study started on May 10, 2011 according to NCBP protocol NCBP-VAL-11-003P and ---(b)(4)--- protocol 11-012442-2611.01. The study is not complete yet. We will submit a copy of fully executed study when the report is approved (expected in early July).

Table below lists the objectionable microorganisms found in the Long Island City NBCP facility.

No	Microorganisms
1	Staphylococcus haemolyticus
2	Micrococcus lylae
3	Brevibacillus brevis
4	Corynebacterium genitalium
5	Micrococcus luteus
6	Bacillus licheniformis
7	Staphylococcus warneri
8	Corynebacterium propinquum

FDA summary of discussion: Response satisfactory

2. Please provide a rationale why the EM program for Rooms 164, 167, 168 and 169 does not include any action limit for viable (air/surfaces) and non-viable particles. Please also indicate why there is no action limits for viable particles (surface and air) in rooms 165 and 140.

The rational for why the EM program for Rooms 164, 167, 168, and 169 do not have action limits for viable and non-viable particles is based upon the following citations to the Code of Federal Regulations:

21 CFR 211, Subpart C – Buildings and Facilities, Sec. 211.46, Ventilation, air filtration, air heating and cooling, Subsection (b) states, "Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product."

21 CFR 211, Subpart C – Building and Facilities, Sec. 211.42, Design and construction features, Subsection (c), (10), iv, requires a "system for monitoring environmental conditions" only for "Aseptic processing".

21 CFR 211, Subpart C – Building and Facilities, Sec. 211.42, Design and construction features, Subsection (c), (9), "Control of Laboratory Operations" requires "specifically defined areas of adequate size", "as are necessary to prevent contamination or mixups".

No manufacture, processing, packing, or holding of an HPC-C product occurs in rooms 164, 167, 168, or 169. No HPC-C product enters these rooms. No Aseptic processing occurs in these rooms. Rooms 164, 167, 168 and 169 are "specifically defined areas of adequate size" physically separated from all rooms in which manufacture, processing, packing, or holding of a drug product occurs. Physical separation includes walls, doors and uni-directional sealed pass-through windows, as well as air handling systems designed to maintain positive pressure in rooms in which manufacture, processing, packing, or holding of a drug product occurs. Such physical separation supports the required controls "necessary to prevent contamination or mixups" with HPC-C product.

In addition, should any bacterial contamination of samples be detected, the finished HPC-C would be discarded (SOP CB40.006, latest revision, section 6.10.8).

Therefore, while there is no requirement for environmental monitoring or any action limit for viable (air/surfaces) and non-viable particles in these rooms, the NCBP EM Program (SOP CB00.0008, latest revision) provides for information-only testing in these rooms as an additional level of facilities controls.

SOP CB00.0008, latest revision, specifies Action Limits for viable particles (surface and air) in rooms 165 and 140.

FDA summary of discussion: Response satisfactory

3. Please provide a rationale for the frequency of environmental monitoring for Rooms 140, 164, 165, 167, 168 and 169.

The frequency of environmental monitoring for rooms 140, 164, 165, 167, 168, and 169 was set based upon the following factors:

1. ----------(b)(4)----------
2. ---------(b)(4)----------
3. ----------(b)(4)----------
4. ----------(b)(4)----------
5. ----------(b)(4)----------
6. ----------(b)(4)----------

A complete description of the rational will be provided electronically.

FDA summary of discussion: Response satisfactory

4. In regard to the procedure followed for release of the final product, please provide a complete and up to date SOP which includes a step by step process and timeline for the release of the product into the searchable inventory.

This SOP will be provided.

FDA summary of discussion: In regard to question 4, NYBC committed to send a revised SOP which details a step by step process and timeline for the release of the product into the searchable inventory by August 1st.

5. In regard to product segregation, please indicate how do you plan to segregate the IND units from licensed products.

Due to the need to maintain HPC-C potency, there is a product specific requirement to cryopreserve HPC-C within --(b)(4)-- of the collection of the HPC-C. The classification of an HPC-C into IND or Licensure status will be performed after all test results are present, donor eligibility has been assigned, and Quality reviews the completed Batch Record. Therefore, the HPC-C must be cryo-preserved prior to classificiation as IND or License.

Furthermore, also in order to maintain potency, there is a requirement to minimize the exposure, post-cryopreservation, of the HPC-C to transient warming events (TWE's). In order to minimize

TWE's, a product-specific Liquid Nitrogen Freezer System was designed (BioArchive). The BioArchive is a combination of a controlled rate freezer, long term storage dewar, and an electronic inventory control system. Prior to classification as IND or License HPC-C, the HPC-C is stored in the BioArchive. The HPC-C will not be physically removed from Liquid Nitrogen until it is needed for a specific patient, in order to minimize TWEs. Therefore, there will be IND and License HPC-C's stored in the same BioArchive, in order to maintain HPC-C potency.

License and IND HPC-C's are segregated within the BioArchive in two ways. Physical separation includes the use of a sealed Teflon overwrap bag, and a barcoded metal canister. Electronic segregation includes the BioArchive Inventory Control Systems, which controls the location of each individual HPC-C by unique Barcode ID.

In addition, the completed Batch Record, reviewed by Quality, will identify each HPC-C product as "License" or "IND". The status as "License" or "IND" will be electronically associated with the unique Barcode ID, providing additional electronic segregation.

FDA summary of discussion: Response satisfactory

6. In regard to line clearance, please provide an updated SOP which you follow to prevent cross contamination between different units being processed.

The response to this item will be provided electronically.

FDA summary of discussion: In regard to question 6, NYBC committed to send an SOP for the line clearance in room 165 by August 1st.