DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File STN 125397/0, Hematopoietic Progenitor Cells, Cord (HPC-C)

From: Mohammad Heidaran, Ph.D., Biologist, OCBQ/DMPQ/MRB II, HFM-676

CC: Gang Wang, Ph.D., Expert Biologist, OCBQ/DMPQ/MRB II, HFM-676
Mercy Quagraine, Biologist, OCTGT/DCGT/CTB, HFM-715
Thomas Terrolyn, CSO, RPM, OCTGT/RMS, HFM-705

Through: Chiang Syin, Ph.D., Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review of the Chemistry, Manufacturing, and Controls sections of the Biological License Application (BLA) STN 125397/0 submitted by New York Blood Center, Inc. (License # 0465).

Action Due Date: November 10, 2011

Recommendation

I have completed my review of all the information related to chemistry manufacturing and controls (CMC) and facility issues pertaining to DMPQ's review responsibility in BLA STN 125397/0. The following manufacturing facility related items were reviewed:

- Heating, Ventilation, and Air Conditioning (HVAC) System (15.3.2)
- Control of Aseptic Manipulation and Cross Contamination (15.3.2.1)
- Facility Controls (15.3.3)
    i. Cleaning and Sanitization Procedure (15.3.3.3)
    ii. Environmental Monitoring Programs(15.3.3.4)
- Computer / Software Validation (15.3.4.4)
- Manufacturing Process and Process Controls (4.1.5.1.4)
- Container Closure and Packaging Systems (5.1.6.1)
- Manufacturing Equipment Qualification
- Utility Qualification
- Others:
    i. Work Station Clearance and Product Changeover
    ii. Chain of Identity
    iii. Other products
    iv. Long Island City Maximal Production Capacity

Based on my review of the content submitted, the submission package appears to be complete, the validation studies appear to be properly designed and executed and the information and data appear to be adequately reported. My review questions and the issues identified during the pre-license inspection, of New York Blood Center (NYBC) have been adequately addressed. The inspectional issues were discussed in more details in the Establishment Inspectional Report (EIR).

A pre-license inspection (PLI) of NYBC manufacturing facility in Long Island, New York took place from April 25, 2011 to April 29, 2011. A Form FDA 483 containing seven objectionable conditions was issued to the firm at the conclusion of this PLI on April 29, 2011. NYBC has adequately addressed all seven observations. Based on the inspection and the CMC information reviewed, I recommend prospective licensure of units processed in this NYBC facility.

Summary

NYBC submitted this Biological License Application (BLA) to seek retrospective and prospective licensure of placental-derived Cord Blood Units (CBU) which were manufactured in the NYBC Long Island and -----(b)(4)---- facilities, located at 310 East 67th Street – New York since August of 2006. The manufacturing of CBU is performed according to Method 4 which involves the use of AXP AutoXpress Platform (AXP system) that was cleared by FDA on October 5th, 2007. Only the DMPQ-related information in the CMC section has been reviewed. These sections include: Heating, Ventilation, and Air Conditioning (HVAC) System; Control of Aseptic Manipulation and Cross Contamination; Facility Controls which include Cleaning and Sanitization Procedure and Environmental Monitoring Programs and Computer / Software Validation. In addition, I also reviewed the critical Manufacturing Process and Process Controls including shipping validation and procedures for quarantine and release of CB units; Container Closure and Packaging Systems; Manufacturing Equipment Qualification and Utility Qualification. Clinical, product, pharmacological, statistical and other non-DMPQ-related issues are not subjects of this review memo.

Information requests (IR) were submitted as part of the filing letter to NYBC on March 9th, 2011 and June 17, 2011. Additional information was also collected during inspection of the Long Island facility located at 45-01 Vernon Blvd., Long Island City, NY. The responses received from IR and information collected during the inspection were found to be acceptable.

In response to the 483 observations identified during the inspection, NYBC agreed to a --(b)(4)-- environmental monitoring of Room 165 (processing room) and 140 (cryopreservation room) with action limit consistent with –(b)(4)-- classification. In addition, NYBC agreed to conduct --(b)(4)--- EM monitoring of BSCs located in cryopreservation room at both static and dynamic (rest and operational) conditions consistent with ---(b)(4)----- requirements.

The maximal production capacity of --------(b)(4)---------- shift within the current facility appears to be acceptable based on the approximate time required for processing and cryopreservation of cord blood units at the time of inspection and in view of the aseptic process validation study results.

Background (Proposed Licensure of Cord Blood Units):

NYBC indicated in Section 4.1 of the original BLA submission that they propose licensure of all HPC-C manufactured according to Method 4 beginning in August of 2006. Based on the information provided in the original application, it was not clear if these units were processed in compliance with the Current Good Manufacturing Practices (CGMP).

Reviewer Comment:

1) *Please provide a detailed table indicating the following information for all HPC-C you propose to be licensed:*
   a) *Date of processing;*
   b) *Location/facility of processing;*
   c) *Methods of collection, processing and cryopreservation;*
   d) *Equipment or devices used in collection, processing, testing and cryopreservation (indicate if a non 510(k) cleared equipment/device is used);*
   e) *Testing methods (including donor eligibility testing);*
   f) *Demonstration of Conformance to CGMPs.*

NYBC Response:

NYBC provided information about the date of processing, location or facility used for processing each unit, method used for collection, processing and cryopreservation of the units proposed to be licensed and container closures used for collection, processing and storage of these units (see Table I) . The proposed CBU to be licensed, were all manufactured according to Method 4 which involves the use of an AXP functionally closed system. Since the AXP system was 510(k)-cleared by FDA on 10/2007, the units prior to this date were processed using a functionally closed system which was not cleared. CBUs processed from 8/2/2006 to 4/30/2009 were processed in the ---(b)(4)--------- facility.

Table I: Summary of Manufacturing Facility Qualification:

Processing Date	**Facility**	**Collection Bag**	**Auto AXP Device**	**Facility Qualification**	**Equipment Qualification**
8/2/2006-4/30/2009	--(b)(4)---Facility (b)(4)	----(b)(4)----------	Cleared; 10/2007	Not Done	Not Done
5/12/2009-7/6/2009	Long Island City (LIC)	----(b)(4)----------	Cleared	Not Done	Not Done

Processing Date	Facility	Collection Bag	Auto AXP Device	Facility Qualification	Equipment Qualification
7/7/2009-present	LIC	----(b)(4)----------	Cleared	Facility & HVAC Commission (4/5/2009) EMPQ (12/21/2010)	6/18/2009

Reviewer Comments:

There is no documented evidence that the previous facility in ----(b)(4)--- operated under CGMP conditions for units manufactured from 8/2/2006 to 4/30/2009. Cord Blood Units manufactured from 5/12/2009 to present were processed in the Long Island facility. This facility was not fully qualified and commissioned until 12/21/2010. The CBUs processed after 12/21/2010 to present are processed using 1) approved/cleared functionally closed system for HPC-C processing, 2) approved/cleared contained closures for collection and storage of the final product; 3) fully qualified and commissioned facility and equipment. However, several deficiencies were identified during the review process (**see the addendum to this memo for the list of questions**) and during the pre-license inspection. These deficiencies were not fully addressed until October 31 of 2011 **(see also the Establishment Inspection report (EIR).**

Specific Systems:

The following systems are described in this section: Heating, Ventilation, and Air Conditioning (HVAC) System; Control of Aseptic Manipulation and Cross Contamination; Facility Controls and Computer / Software Validation.

Heating, Ventilation, and Air Conditioning (HVAC) System

The NCBP areas are served by 4 air-handling units (AHU), AHU-1 through AHU----------(b)(4)----------AHU-2 provides services to the area immediately adjacent to the GMP process area including BioArchive Storage Room (121), Receiving and Accessioning (161/163), In process testing Room (162) and entry corridor. AHU 2A provides dedicated, -----(b)(4)--- air to the GMP Process Area including 1) Gowning Room and Interlock; 2) Processing and Processing Supervisor Office; 3) Cryopreservation; 4) Quality Control lab - Plasma Processing and 5) Quality Control lab - Sample Prep. The entire CGMP Process Area receives filtered air from ----------(b)(4)----------. In addition, all rooms within the GMP area are designed with a minimum ----------(b)(4)----------

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

Reviewer Comment:

2) *In regard to the NYBC facility qualification located in Long Island, NY. It is not clear from the submission when the NYBC facility was fully qualified and/or commissioned* ***(see also response to question 1 of the addendum to this review or question 11 of the filing letter dated March 9th, 2011).***

Reviewed on Inspection:

I reviewed the timeline for the facility qualification and commissioning during the inspection. Based on the document provided by NYBC, it was determined that NYBC facility qualification was completed in December of 2010 **(for detailed information see the EIR).**

Reviewer Comment:

3) *In regard to HVAC qualification/commissioning please provide a detailed summary of HVAC qualification and system commissioning plan, (NCBP-CQP-CB-HVAC-001).*

Reviewed on Inspection:

A dedicated AHU provides ---(b)(4)---- air to the GMP Process Area including 1) Gowning Room and Interlock; 2) Processing and Processing Supervisor Office; 3) Cryopreservation; 4) Quality Control Lab - Plasma Processing and 5) Quality Control Lab - Sample Prep. ----------(b)(4)----------. During inspection, I was able to review the HVAC commissioning plan and all relevant documents pertaining to the HVAC qualification. NYBC fulfilled the requirement for HVAC qualification as part of the facility commissioning documentation and environmental monitoring performance qualification. I reviewed the relevant documents and found it to be acceptable **(see also the EIR)**

Control of Aseptic Manipulation and Contamination/Cross-Contamination Controls

The control of aseptic manipulation verifies that CBUs are not contaminated with adventitious materials and is processed and stored in manner that prevents cross-contamination. The control of aseptic manipulation is performed at 1) Collection Step (SOP CB37.0001.1); 2) Transport of Collected CBU to NYBC (SOPs CB37.0011.1 and CB37.0012.1); 3) Receiving CBU at NYBC and 4) Processing Steps. NYBC provided the following SOPs that cover key manufacturing steps. All SOPs for CBU collection, transport and processing were reviewed at the time of inspection and found to be acceptable.

NYBC stated in Section 4.1.4.3, that the overall containment strategy for the LIC facility is based ----------(b)(4)---------- ----------(b)(4)----------. Transfer of cord blood is performed using an -----(b)(4)---------- process thereby maintaining the integrity of the system. The DMSO cryoprotectant is the only addition to the CBU which is performed under aseptic conditions in biological safety cabinet (BSC) workstations within the cryopreservation area. The integrity of the cryopreservation process was validated during media fills (section 4.1.5.4) by ----------(b)(4)----------.

Aseptic Process Validation:

The Aseptic Process Validation (APV) simulated all ----------(b)(4)---------- ---------- The APV studies adequately demonstrated that the manufacturing steps for the CBU processing and cryopreservation can be performed by NYBC staff in a manner that maintains the integrity of the functionally closed system utilized under maximal operation capacity and worst case scenario.

Product Segregation

NYBC states that the manufacturing steps including processing and cryopreservation are performed in well defined segregated working space, using a functionally closed system and based on the ----------(b)(4)--------- rule to reduce the chance of cross contamination and error. However, it is not clear what the exact work flow is for each personnel. For example, if each unit is processed by -------(b)(4)----------

Reviewer Comment:

14) Please provide a detailed description of the process used to manufacture cord blood product including whether or not one operator may handle multiple units one at the time.

Reviewed on Inspection:

During inspection, I reviewed the step by step process for manufacturing CBU and observed the process in operation. While each operator is allowed to handle -----(b)(4)--------, each operator in the processing room can handle ----------(b)(4)---------- so long as it is not at the same time. The practice of each operator handling --------(b)(4)--------- minimizes possible error in processing and cryopreservation.

Personnel and Waste flow:

Waste is handled after normal working hours when processing is complete. Waste materials exit the CGMP Process Area through the airlock: Personnel and Waste flow diagram indicates that the flow of materials, waste and personnel is temporally and physically segregated to prevent cross contamination.

Facility Controls

The NCBP facility is controlled by the following SOPs: CB44.0003.1: General Use of the NCBP Facility; CB44.0004.1: Access Control for the GMP Process Area; CB00.0004.1: Cleaning of the NCBP GMP Process Area; CB0005.1: Gowning Requirements for the NCBP GMP Process Area and CB00.0008.1: Environmental Monitoring of the NCBP GMP Process Area.

Unauthorized Access Prevention:

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

Gowning Practices

The Gowning requirements for entry to the GMP Process Area are defined in SOP CB00.0005.1, “Gowning Requirements for the NCBP Process Area”. Table 2 of the submission summarizes the gowning requirements by room. Lab coat, hair net/ beard cover, shoe cover and gloves are required in Room 140, 164, 165, 167, 168, 169, and 170. Room 169 is the Gowning Room, which is divided into a “dirty” and a clean” side separated by a line marked on the floor. NYBC describes in detail the entry procedure for the GMP Process Area. For entry into Room 170 which is not part of the CGMP processing area the minimum requirement is a lab coat and employees follow safety requirements.

Cleaning and Sanitization Procedure

The cleaning procedure consists of ---------- NCBP CGMP Process Area. Cleaning of the facility is defined in CB00.0004.1 entitled “Cleaning of the NCBP GMP Process Area”. NYBC uses a ----------
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----------(b)(4)----------

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

Reviewer Comment:

4) In regard to facility cleaning please provide a detailed summary of Disinfectant Efficacy Studies and a list of objectionable microorganisms found in the facility ***(see also question 4 of the addendum or question 13 of the filing letter dated March 9th, 2011)***.

Reviewed on Inspection:

During inspection, I reviewed these documentations and determined that NYBC did not have a list of objectionable microorganisms and did not complete the Disinfectant Efficacy Study. Additional information request submitted to NYBC **(see response to question 16 of the addendum to this file)**.

Environmental Monitoring Programs

Room Differential Pressure Verification:

The EM program is defined in SOP CB00.0008.1 entitled "Environmental Monitoring of the NCBP GMP Process Area". The EM programs cover the controlled but unclassified area of the CGMP Process Area and involve 1) Room Differential Pressure Verification; 2) Room Temperature and Humidity Monitoring and 3) Viable/Non-Viable Monitoring. Table 5 of the submission provides a summary of the room's differential pressure.

Room Temperature and Humidity Monitoring

The temperature and humidity of the facility is monitored according to SOP CB00.0006.1 entitled "NCBP----------(b)(4)----------. NYBC states that --(b)(4)--- system is a continuous, self diagnostic, remote monitoring system, which provides reporting, alarm and remote notification of excursion from specified criteria. The exact location of sensors is summarized in Table 6 of the submission. Sensors are located in Room Number ------(b)(4)----------. The Room Temp and Relative Humidity (RH) alarm limits are defined to be from ---(b)(4)------ for temperature in all rooms and ---(b)(4)--- RH for Room ----------(b)(4)----------.

Viable/ Non-Viable Environmental Monitoring

Table 8 of the submission indicates that all rooms in the GMP processing area are classified as "Controlled but Unclassified". According to NYBC the entire CGMP area is monitored for

viable (air and surfaces) and non-viable particles for information only, but rooms where the product is processed and cryopreserved (Room 165 and 140) have action limits consistent with ----------(b)(4)---------- for non-viable particles. Viable particles are monitored for background information only (see Table II below).

Table II: Summary of CGMP Area Classification:

Room Number	**Scope of Use**	**Frequency**	**Viable Air/Surface**	**Non-Viable Air of particles---(b)(4)---**
165, 140	Processing and Cryopreservation	Quarterly	Information Only	----(b)(4)-------
164, 167, 168, 169	In-process Testing, Plasma Processing, Gowning/Airlock	Quarterly	Information Only	------(b)(4)---------

According to NYBC the sampling program for viable and non-viable particles was developed in three stages over a period of 1 year. The EM program stage 1 involved –(b)(4)-- monitoring for 1 year, followed by an Environmental Monitoring Performance Qualification (EMPQ), Stage II, and a routine environmental monitoring program (Stage III).

Stage 1: --(b)(4)-- Monitoring for 1 year:

NYBC states that a year of the --(b)(4)--- environmental monitoring results could be found in NCBP-S-003 report approved on 10-18-2010. This report covers the results of viable air, viable surface and non-viable particulate samples obtained in the cord blood CGMP Processing Area during the 12-month period from May 2009 through May 2010. NYBC also stated that a detailed map of the sample locations can be found in the sample location section of the Environmental Monitoring (EM) Program Evaluation Study binder, NCBP-S-003.

Reviewer Comment:

5) *In regard to NCBP-S-003 report summarizing the results of –(b)(4)--- EM, please provide the results of viable air, viable surface and non-viable particulate samples obtained in the cord blood CGMP processing area during the 12-month period from May 2009 through May 2010. Please also provide the study binder NCBP-S-003 including the sample location and rationale for choosing these sample locations.*

Reviewed on Inspection:

I reviewed at the time of inspection the document entitled NCBP-S-003 which included the EM results for viable air, viable surface and non-viable particulate samples obtained in the cord blood CGMP Processing Area during the 12-month period. The data indicated that no significant excursion was observed in the CGMP areas. I also reviewed the sampling plan, sampling size and rationale for choosing the selected locations. NYBC stated that the location for sampling and

number of samples were determined based on ----------(b)(4)----------.

Following stage I, NYBC executed the Clean Room Environmental Monitoring Performance Qualification (NCBP-VAL-09-017P). The EMPQ includes environmental testing performed for viable and non-viable particles collected under static and dynamic conditions.

Reviewer Comment:

6) In regard to EMPQ please provide the SOP number CB0008.1 "Environmental Monitoring of the NCBP GMP Process Area' and a copy of EMPQ protocol and results.

Reviewed on Inspection:

During inspection I reviewed the SOP CB0008.1 "Environmental Monitoring of the NCBP GMP Process Area' and a copy of qualification protocol and the results collected for EMPQ studies. The results were evaluated and found to be acceptable **(see also the EIR).**

Routine Monitoring:

NYBC also stated that the CGMP Process Area, Processing and Cryopreservation (Rooms 165 and 140), is routinely monitored quarterly for viable (surface and air) and non-viable particles. In rooms, 165 and 140, the non-viable particle count has an action limit consistent with ---(b)(4)---------- environment. However, the viable particles (surface and air) are monitored for background information only. In response to question 17 of the addendum NYBC agreed to include action and alert limits for monitoring viable particles in rooms 165 and 140. The data for viable (surface and air) and non-viable particles, collected quarterly in other rooms, will be used for information only (see also Table II).

Reviewer Comment:

7) In regard to ---(b)(4)-- EM, please provide a detailed sampling plan for data collected in the CGMP area. In regard to routine EM please also specify if you plan to monitor the Biosafety Cabinet (BSC) located in the cryopreservation room.

Reviewed on Inspection:

During inspection, I reviewed the sampling plan for routine environmental monitoring for the CGMP areas which did not include a regular monitoring of the (b)(4)BSCs where DMSO is added to the final product under aseptic conditions.. For routine monitoring NYBC is expected, at certain frequency, to monitor the BSC where aseptic addition of DMSO to the product is performed **(see also the EIR objectionable item 6).**

Computer / Software Qualification

Section 15.3.4 provides a summary of manufacturing steps which are computer controlled, NYBC states that major computer controlled steps include collection, processing, quality control,

HLA typing, CBU product selection and distribution (see schematic below for the NYBC cross functional data flow description).

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Computer System Validation:

Table 1 in section 15.3.4 provides a summary of the NCBP computer subsystems: The subsystems include:

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[(b)(4)]

Reviewer Comments:

NYBC provided validation studies for major subsystems outlined above. In addition they indicated that the Computer System is verified to be Part 11 compliant. However, it is not clear when the entire computer system was fully validated and if the system is fully compliant with part 11 requirements.

Review Comment:

12) Please provide documentation supporting that the current computer system used at NYBC is fully validated and it is Part 11 compliant.

Reviewed on Inspection:

During inspection I reviewed the validation studies for computer systems controlling the processing steps. I confirmed that NYBC has a change control procedure in place and there is an audit trail for changes made to the system. The overall security of the Computer System was also verified. I also confirmed that the system was Part 11 compliant with respect to record keeping but not for electronic signature. The computer system appears to be fully validated.

Manufacturing Process and Process Controls

Allogeneic CBUs are manufactured from donated CBU collected in 8 contracting hospitals and shipped to the facility in Long Island, NY for processing. The entire process includes 1) Collection; 2) Shipment from collection site to the processing center; 3) CBU processing; 4) Cryopreservation; 5) Shipment to point of care transplant centers; 6) Thawing and preparation of the product for administration.

This section of BLA is reviewed in depth by product reviewers. I only briefly evaluate and comment on those DMPQ-related issues, especially those related to shipping validation and SOPP used for review and removal of non-conforming CBUs.

Shipping: The shipping of the CBU product is performed using dry-shipper (cryo-shipper) from Long Island facility to transplant centers worldwide. The dry-shippers are vacuum-insulated metal containers filled with liquid nitrogen dispersed in absorbent materials that allows for steady flow of cold vapor nitrogen into the cryostorage space, in upright position the dry-shippers are designed to maintain lower than 150 ^{o}C for a period of ---(b)(4)---. Based on their experience and the defined delivery schedule of HPC-C to the NCBP's client transplant centers worldwide, it has been determined that the temperature of dry-shippers were able to maintain at below -150 ^{o}C for at least --(b)(4)-- which -------(b)(4)--------- stipulated as the maximum time of effective cooling (**see also the EIR**)..

Reviewer Comments:

NYBC provided the validation study for shipment of the final product. However, it is not clear how the dry shippers are charged and whether the temperature of the liquid nitrogen is monitored during the shipment using the data loggers.

Review Comment:

9) Please provide a detailed description of how the dry shippers are charged and the method by which the temperature of dry shippers is monitored. Please also provide SOP for maintenance and calibration of data loggers.

Reviewed on Inspection:

During inspection I reviewed the protocol for charging the dry shippers and use of data loggers to monitor the temperature of dry shippers. I also reviewed the documentation for data logger's preventive maintenance and calibration. It appears that the shipping from the firm to the transplant centers is fully validated **(see also the EIR).**

Review and removal of non-conforming CBU from Inventory

According to SOP CB38.0011.1, CB units with positive infectious disease tests (if the infectious risk is identified before completion of processing) must not enter the inventory. If either the cord blood or maternal blood samples are determined to be positive for infectious disease the unit is physically removed from freezer and discarded. The unit is also deleted from the inventory and will not become available for transplantation.

Review Comments:

10) In regard to review and removal of non-conforming CBU, please provide a copy of the SOP CB38.0011.1 CB, and a detailed SOP for quarantine and release of the final product into the inventory.

Reviewed on Inspection:

During inspection I was able to review the SOP # CB41.0002.1 for removal of non-conforming units and the SOP for final release of the product. According to these documents the processed CBU is initially released into the searchable inventory while the units are still in quarantine. Once a suitable matched unit is identified, the selected unit is finally released by the NYBC Medical Director. We recommended to NYBC during inspection that the release of product into the searchable inventory should be performed within a reasonable amount of time following the initial storage of the final product. In addition, the final release of the product should also be performed by NYBC Quality Unit. It also appeared that the NYBC has no procedure in place to segregate the units intended for licensing from the investigative units **(see the EIR and addendum to this file, questions 19 and 20).**

Container Closure and Packaging Systems

NYBC provided a list of container closures used for collection, processing and storage of the final product. The collection bags include: 1) ----------(b)(4)---------- and 2) AXP AutoXpress Bag manufactured by ThermoGenesis Corp (Rancho Cordova, CA) which is used for cryopreservation of the final product. However, it is not clear when each container was used for CBU manufacturing and when each container was either approved or cleared by FDA?

Review Comments:

13) Please provide a complete list of all bags used for collection, processing and storage of the final product and specific date of each container closure approval or clearance.

Reviewed on Inspection:

During inspection I confirmed that all container closure used for CBU collection, processing and storage are either cleared and/or approved. I also documented the date by which each container was cleared or approved The Container Closure Integrity, Biocompatibility and Leachable and Extractable study results were not included in the submission. However the relevant information was previously evaluated as part of NDA and/or 510(k) applications (see Table III below).

Table III: Summary of Container Closure Approval or Clearance Date:

Container Closure	**Manufacturer**	**Approval/Clearance Type and Number**	**Approval and Clearance Date**
Collection ---(b)(4)-----	------(b)(4)----------	---------(b)(4)----------	---------(b)(4)----------
Collection ---(b)(4)-----	----------(b)(4)----------	---------(b)(4)----------	---------(b)(4)----------
Collection ---(b)(4)-----	------(b)(4)---------	---------(b)(4)----------	---------(b)(4)----------
Sterile Tube Welder	------(b)(4)---------	---------(b)(4)----------	---------(b)(4)----------
AXP AutoXpress Platform with processing kit	Thermogenesis Corp.	BK070006-CBER 510(k)	Cleared 10/5/2007

Key Manufacturing Equipment and Equipment Cleaning

For processing CBU, NYBC uses several pieces of equipment which include:

Biological Safety Cabinets

For processing of cord blood, the BSC located in cryopreservation rooms are used to perform the following aseptic manipulation which involves the addition----(b)(4)---------- volume of DMSO to the final product through a 0.2 µ filter. I reviewed the Equipment Qualification Plan & Protocol entitled: Installation and Operational Qualification for ----------(b)(4)---------- Biological Safety Cabinets document number NCBP-QPP-BSC-001. The document outlines installation and performance qualification of –(b)(4)---- Bio Safety Cabinets which were installed in the ---------(b)(4)---------- I the Long Island facility. (b)(4) of BSC's are used as work stationed in the QC laboratory. (b)(4) were installed in cryopreservation Room 140 and used as work station to add DMSO to the final product. Biological Safety Cabinets are designed to protect contents from airborne contaminants and protect personnel from the cabinet contents. This isolation is achieved by creating a critical work area supported by the ----------(b)(4)----------. The qualification of BSC's was conducted on the ----------

-------(b)(4)------ in the cryopreservation Room 140 of the --------(b)(4)---------- in the Long Island Facility according to protocol NCBP-QPP-BSC-01 which included the test procedures, documentation, references, specifications and acceptance criteria. Results of verification tasks and operational test were reviewed as part of NCBP-RQPP-BSC-001R met the predetermined acceptance criteria. Verification tasks and operational tests included 1) technical documentation; 2) Drawing verification; Equipment identification; verification of equipment utilities, instrument calibration; operational testing and operational qualification including BSC Certification and documentation. NYBC also provided me with a copy of the most up-to-date certification of all BSC's. The BSCs used in cryopreservation room as a workstation for addition of DMSO, are cleaned before and after each unit being processed (see also workstation clearance section).

Reviewer Comments:

NYBC did not provide a comprehensive list of all equipment used for manufacturing and testing of the product. Qualification studies for major equipment were also missing.

11) Please provide a comprehensive list of equipment used in testing and manufacturing of the processed CBU. Please also provide a summary report on the major equipment and/or device qualifications ***(see also question 10 of the filing letter dated March 9th, 2011).***

Reviewed on Inspection:

A comprehensive list of equipment including model number, how it is used and if it is 510(k) cleared was provided by NYBC (see Table IV below). In addition, I also reviewed equipment qualification documentation for the following equipment: 1) ----(b)(4)--- Centrifuges; 2) - Sterile Tubing Welder;--(b)(4)---------- Flow Cytometer; 6) BioArchive - System and 7) ----------(b)(4)----------. Installation and Operational Qualification of major equipment were reviewed at the time of inspection. Performance Qualification of critical equipment was verified as part of aseptic process validation and cord blood processing validation **(see the EIR).**

Equipment Cleaning:

Processing of CBUs is performed using a single use functionally closed system. As a result, the risk of possible cross contamination from one unit to another or due to contaminated equipment surfaces is reduced or eliminated. In addition, NYBC has a program in place for routine cleaning of major equipment as part of their ----(b)(4)------ facility cleaning protocol. The overall cleaning procedures used for common equipment is acceptable.

Table IV: List of Major Equipment:

[(b)(4)]

[(b)(4)]

Utility Qualification

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

The commissioning and qualification of the NCBP utilities system was based on the ----------(b)(4)----------. According to this document a system level impact assessment

(SLIA, NCBP-SLIA-CB-001) was performed on each of the utilities that were defined as part of the NCBP establishment. SLIA was used to determine whether a system has direct, indirect or no impact on product quality. Only utilities with direct impact were commissioned and qualified.

Reviewer Comments:

NYBC did not provide detailed summary qualification for the ----------(b)(4)---------- system. In regard to water source, NYBC stated that no water was used in the manufacturing steps. However they did not indicate what type of water used for cleaning and dilution of reagents for testing.

8) In regard to water used in the facility please provide the type of water used for cleaning of equipment and facility and dilution of testing reagents? In regard to the utilities qualification, please provide a detailed summary of the liquid nitrogen qualification.

Reviewed on Inspection:

According to NYBC no water is used for CBUs processing. The water used for testing is ------(b)(4)-------. However, the water used for cleaning is produced in house by a ------(b)(4)----------. In regard to ----------(b)(4)---------- during inspection as part of the commission plan NCBP-CQP-CB-001 dated 6/33/2008 I was able to review the summary of data verifying that the ---------(b)(4)---------- was installed properly and performs according to a predefined set of acceptance criteria **(see also the EIR).**

Work Station Clearance and Product Changeover

NYBC did not provide any information related to the work station clearance and product changeover.

Review Comment:

15) Please provide a detailed summary of SOP used for work station clearance and changeover ***(see question 12 of the filing letter dated March 9th, 2011).***

Reviewed on Inspection:

NYBC did not have a SOP for work station clearance and changeover. However, during inspection I observed several operators cleaning their work areas after each unit was processed. This practice was not followed in the processing rooms. The firm stated that the processing room is routinely cleaned and the risk to the product is not existent since the units are processed using a functionally closed system. In the cryopreservation room the operators did in fact follow proper procedure for the workstation clearance and changeover. NYBC committed to provide a

detailed SOP for workstation clearance and changeover **(see the EIR and addendum to this file, questions 15 and 21)**.

Chain of Identity (COI) Procedures

The COI is maintained through extensive use of labeling, operator verification and a barcode system. The barcode system maintains traceability of all manufacturing documentation, in-process containers, and final product back to the starting material and to the patient. Under this system, all in-process containers and samples are labeled and controlled to prevent mistaken identity or product mix-up.

Other Products

Other products processed in the facility include blood or blood-derived products. It is important to note that Blood or Blood related products are not processed in the NCBP area of the NYBC located in Long Island facility.

Long Island City Facility Maximal Production Capacity

The major critical steps in UCB manufacturing, processing and cryopreservation are performed in Rooms 165 and 140 respectively. Room 165 does not contain any BSCs but houses several ---(b)(4)---- which have capacity to process (b)(4) cord blood units per run with each run taking approximately --(b)(4)--. Room 140, the cryopreservation room, has (b)(4) BSCs which are used to perform aseptic addition of DMSO to the final product. While the processing of the cord blood in Room 165 is performed -----(b)(4)-----, the addition of cryopreservation solution to the final product ----------(b)(4)----------. During inspection we observed successful processing and cryopreservation of --(b)(4)- requiring approximately -(b)(4)--. Based on the approximate time required for processing and cryopreservation of --(b)(4)- and in view of the aseptic process validation studies showing successful media fill results for -----(b)(4)--------, the maximal production capacity of -----(b)(4)----- shift appears to be adequate. Further increase in the production capacity may require additional shift of operation and/or changes in the manufacturing facility footprint.

Addendum to NYBC STN 125397/0, Hematopoietic Progenitor Cells, Cord for Additional Information:

The following questions were sent to NYBC on March 9, 2011. NYBC provided their response in an amendment on April 21 of 2011.

1) *Please provide a detailed table indicating the following information for all HPC-C you propose to be licensed:*
    a. *Date of processing;*
    b. *Location/facility of processing;*
    c. *Methods of collection, processing and cryopreservation;*
    d. *Equipment or devices used in collection, processing, testing and cryopreservation (indicate if a non 510(k) cleared equipment/device is used);*
    e. *Testing methods (including donor eligibility testing).*
    f. *Demonstration of Conformance to CGMPs*

NYBC Response:

NYBC provided information about the date of processing, location or facility used for processing each unit, method used for collection, processing and cryopreservation of the units proposed to be licensed and container closures used for collection, processing and storage of these units. The proposed CBU to be licensed, were all manufactured according to Method 4 which involves the use of an AXP functionally closed system. Since the AXP system was cleared by FDA on 10/2007, the units prior to this date were processed using un-approved or cleared functionally closed system. CBUs processed from 8/2/2006 to 4/30/2009 were processed in the ---(b)(4)--- facility. There is no documented evidence that the facility in ---(b)(4)--- operated under CGMP conditions for units manufactured from 8/2/2006 to 4/30/2009. Cord Blood Units manufactured from 5/12/2009 to present were processed in the Long Island facility. This facility was not fully qualified and commissioned until 12/21/2010. The CBUs processed after 12/21/2010 to present are processed using 1) approved/cleared functionally closed system for HPC-C processing, 2) approved/cleared contained closures for collection and storage of the final product; 3) fully qualified and commissioned facility and equipment. However, several deficiencies were identified during the review process and during the pre-license inspection. These deficiencies were not fully addressed until October 31 of 2011.

The following questions were addressed during inspection:

2) *In regard to the NYBC facility qualification located in Long Island, NY. It is not clear from the submission when the NYBC facility was fully qualified and/or commissioned.*

NYBC Response:

I reviewed the timeline for facility qualification and commissioning during the inspection. Based on the document provided to me by NYBC, and interview with Director of Operation it was determined that NYBC facility qualification was completed in December of 2010 **(see also the EIR).**

3) In regard to HVAC qualification/commissioning please provide a detailed summary of HVAC qualification and/or system commissioning plan (NCBP-CQP-CB-HVAC-001).

NYBC Response:

During inspection I was able to review the HVAC commissioning plan and all relevant documents pertaining to the HVAC qualification. NYBC fulfilled the requirement for HVAC qualification as part of the facility commissioning documentation and environmental monitoring performance qualification. I reviewed the relevant documents and found it to be acceptable

4) In regard to facility cleaning please provide a detailed summary of Disinfectant Efficacy Studies and a list of objectionable microorganisms found in the facility.

NYBC response:

During inspection I reviewed these documentations and determined that NYBC did not have a list of objectionable microorganisms and did not complete the Disinfectant Efficacy Study **(see the EIR and also addendum to this file, question 16).**

5) In regard to NCBP-S-003 report summarizing the results of --(b)(4)--- EM, please provide the results of viable air, viable surface and non-viable particulate samples obtained in the cord blood CGMP processing area during the 12 month period from May 2009 through May 2010. Please also provide the study binder NCBP-S-003 including the sample location and rationale for choosing these sample locations.

NYBC response:

I reviewed at the time of inspection the document entitled NCBP-S-003 which included the EM results for viable air, viable surface and non-viable particulate samples obtained in the cord blood CGMP processing area during the 12 month period. The data indicated no excursion was observed in the BSCs located in the CGMP area **(see also the EIR).**

6) In regard to EMPQ, please provide SOP number CB0008.1 "Environmental Monitoring of the NCBP GMP Process Area' and a copy of EMPQ protocol and results.

NYBC Response:

During inspection I reviewed the CB0008.1 "Environmental Monitoring of the NCBP GMP Process Area' and a copy of qualification protocol and the results collected for EMPQ studies. EMPQ performed in the Processing and Cryopreservation rooms under both static and dynamic conditions. The Media Fill Studies performed by ----------(b)(4)----------. All results met the predetermined acceptance criteria. In support of EM studies and EMPQ, I also reviewed the media growth promotion studies which were performed by ------(b)(4)-----. The deficiencies observed in growth promotion studies were addressed as part of the EIR.

7) In regard to –(b)(4)--- EM, please provide a detailed sampling plan for data collected in the CGMP area including the processing and cryopreservation rooms. In regard to routine EM please also specify if you plan to monitor the BSC located in the cryopreservation room.

NYBC Response:

During inspection I was able to review the sampling plan for routine environmental monitoring for the CGMP areas which did not include a regular monitoring of the BSC where DMSO is added to the final product under aseptic conditions **(see the EIR observation and addendum to this file, questions 17 and 18).**

8) In regard to water used in the facility please provide the type of water used for cleaning of equipment and facility and dilution of testing reagents. In regard to the utilities qualification, please provide a detailed summary of the liquid nitrogen qualification.

NYBC response:

According to NYBC no water is used for CBU processing. The water used for testing is --------(b)(4)-------. However, the water used for cleaning is produced in house by a ------(b)(4)----------. In regard to ----------(b)(4)---------- during inspection as part of the commission plan NCBP-CQP-CB-001 dated 6/33/2008 I was able to review the summary of data verifying that the ----------(b)(4)--------- was installed properly and performs according to a predefined set of acceptance criteria **(see also the EIR).**

9) Please provide a detailed description of how the dry shippers are charged and the method by which the temperature of dry shippers is monitored. Please also provide SOP for maintenance and calibration of data loggers.

NYBC response:

During inspection I reviewed the protocol for charging the dry shippers and use of data loggers to monitor the temperature of dry shippers. I also reviewed the documentation for data logger's preventive maintenance and calibration. It appears that the shipping from the firm to the transplant centers is fully validated **(see also the EIR).**

10) In regard to review and removal of non-conforming CBU please provide a copy of the SOP CB38.0011.1 CB, and a detailed SOP for quarantine and release of the final product into the inventory

NYBC response:

During inspection I was able to review the SOP # CB41.0002.1 for removal of non conforming units and the SOP for final release of the product. According to these documents the processed CBU is released into the inventory while the units are still in quarantine. Once a suitable unit is identified, the selected unit is finally released by the NYBC Medical Director. According to NYBC the final release of product is not finalized until a suitable match is identified. It was noted at the time of inspection that the final release of the product should be performed by the NYBC quality unit. In addition we expect that the processed units are released into the

searchable inventory within a reasonable amount of time following the initial storage of the product. Following the release of the product, it appears that the NYBC has no procedure in place to segregate the licensed units from the IND units **(see the EIR and addendum to this file, questions 19 and 20).**

11) Please provide a comprehensive list of equipments used in testing and manufacturing of the processed CBU. Please also provide a summary report on the major equipment and/or device qualifications.

NYBC response:

A comprehensive list of equipment, model number, how it is used and if it is 510(k) cleared was provided by NYBC. In addition I also reviewed equipment qualification documentation for the following equipment: 1) --(b)(4)-- Centrifuges; 2) Sterile Tubing Welder; 3) ----(b)(4)---------- ---------- Flow Cytometer; 6) BioArchive System and 7) ------(b)(4)---------- ----------. Installation and performance of the major equipment were verified at the time of inspection **(see also the EIR).**

12) Please provide documentation supporting that the current computer system used at NYBC is fully validated and if it is Part 11 compliant.

NYBC response:

During inspection I reviewed the validation studies for computer systems controlling the processing steps. I confirmed that NYBC has a change control and there is an audit trail for changes made to the system. The overall security of the Computer System was also verified. I also confirmed that the system was Part 11 compliant with respect to record keeping but not for electronic signature. The computer system appears to be fully validated.

13) Please provide a complete list of all bags used for collection, processing and storage of the final product and specific date of each container closure's approval or clearance.

NYBC response:

During inspection I confirmed that all container closures used for CBU collection, processing and storage are either cleared and/or approved. I also documented the date by which each container was cleared or approved (see Table III of this memo).

14) Please provide a detailed description of the process used to manufacture cord blood product including whether or not one operator may handle multiple units one at a time.

NYBC response:

During inspection I reviewed the step by step process for manufacturing CBU and observed the process. While each operator is allowed to handle --------(b)(4)-------, each operator in the processing room can handle ----------(b)(4)---------- ----------. The practice of each operator

handling ------(b)(4)----- is acceptable since it minimizes possible error in processing and cryopreservation.

15) Please provide a detailed summary of SOP used for work station clearance and changeover.

NYBC response:

NYBC did not provide an SOP for work station clearance and changeover. **(see the EIR and response to questions 21)**.

The following questions were submitted to NYBC on June 17, 2011. NYBC responses were received on June 22, August 15 and 29 of 2011.

16) Please provide a copy of an executed Disinfectant Efficacy Study and a list of objectionable microorganism found in the Long Island NCBP facility.

NYBC Response:

NYBC provided a copy of disinfectant Efficacy study report for protocol # 11-012442-2611.01 performed by ----------(b)(4)---------- on July 15th. NYBC also provided a list of objectionable microorganism identified in the Long Island facility.

The response is acceptable

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

NYBC Response:

NYBC stated that no manufacturing, processing, packing or holding of HPC-Cs products is performed in rooms 164, 167, 168 or 169. NYBC provide updated SOP (CB00.0008.2) to include alert and action limit for viable surface and air for the processing and cryopreservation rooms (rooms 165 and 140). I verified that the revised SOP included the alert and action limit consistent with the ----(b)(4)---- environment.

The response is acceptable

18) Please provide a rationale for the frequency of environmental monitoring for rooms 140, 164, 165, 167, 168 and 169.

NYBC stated that the frequency of environmental monitoring for rooms 140, 164, 165, 167, 168 and 169 was based on 1) 12 month EM study data (NCBP-S-003); 2) Analysis of the risk to the product; 3) HPC-C contamination results; and ------(b)(4)-------- standards.

The response is acceptable

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

NYBC provided updated SOPs, SOP CB41.0002.2 (Release of Cord Blood Unit for Transplant); SOP CB44.0008.1 (CBU status assignment and stepwise transition to the NCBP Search Inventory) and SOP CB00.0013.2 (Quality review and release of Cord Blood Units). According to the revised SOP the units are released into the searchable inventory through a stepwise process in a timely fashion following the final processing and cryopreservation of the units. I have reviewed the revised SOP submitted and found the NYBC response to be acceptable**.**

The response is acceptable

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

NYBC Response:

NYBC stated that the segregation between IND and licensed units will be done in two ways: Physical segregation 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 located of each HPC-C by a 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.

The response is acceptable.

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

NYBC Response:

The firm stated that the processing room is routinely cleaned and the risk to the product is non existent since the units are processed using a functionally closed system. In the cryopreservation room the operators did in fact follow good manufacturing practices for the workstation clearance and changeover. NYBC submitted a new SOP CB00.0003.2 entitled “Operations Line Clearance, Opening and Cleaning. The SOP clearly outlines the procedure for line clearance in the cryopreservation room.

The response is acceptable