Guidance for Industry

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

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U.S. Department of Health and Human Services
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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, the Center for Biologics Evaluation and Research (CBER), FDA, are recommending ways that would allow you, the manufacturer, generally a cord blood bank, to apply for licensure of minimally manipulated, unrelated allogeneic placental/umbilical cord blood, for specified indications. This guidance document is intended to assist you in obtaining a biologics license. It contains information about the manufacture of minimally manipulated, unrelated, allogeneic placental/umbilical cord blood and how to comply with applicable regulatory requirements.

This guidance finalizes the draft guidance entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies," dated December 2006.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Scope

1. What Products does this Guidance Cover?

This guidance document provides recommendations for the submission of a biologics license application (BLA) (21 CFR Part 601) for placental/umbilical cord blood products that are:

- Manipulated minimally; and
- Intended for hematopoietic reconstitution in patients with any of the following diseases:
  - Hematological malignancies
  - Certain lysosomal storage and peroxisomal enzyme deficiency disorders
    - Hurler Syndrome (MPS I)
    - Krabbe Disease (Globoid Leukodystrophy)
    - X-linked Adrenoleukodystropy
  - Primary immunodeficiency diseases
  - Bone marrow failure
  - Beta thalassemia; and
- Intended to be used in recipients unrelated to the donor.

For the purpose of this guidance, these minimally manipulated allogeneic products for the above stated indications will hereafter be referred to as hematopoietic progenitor cells, cord (HPC-C).[1]

2. What Products are Not Covered?

This guidance applies only to those HPC-Cs described in Section II.A.1 above. If you manufacture peripheral blood or placental/umbilical cord hematopoietic stem/progenitor cells other than those described, (e.g., more than minimally manipulated, or for other indications) you may need to submit an IND or other premarketing application appropriate for that product.

[1] This guidance applies to HPC-Cs manufactured by U.S. cord blood establishments and non-U.S. cord blood establishments that distribute cord blood in the U.S. However, some non-U.S. cord blood establishments that participate in international registries may not apply for licensure of their products. Importation and use of unlicensed placental/umbilical cord stem/progenitor cell products from non-U.S. cord blood establishments would be acceptable under an Investigational New Drug (IND) application held by the non-U.S. establishment, an affiliated U.S. establishment, the U.S. transplant center, or a registry. Also, certain HPC-Cs manufactured in the U.S. may not be licensed but could be listed in registries and made available for clinical use under an IND. Additional recommendations regarding submission of INDs for certain unlicensed HPC-Cs are provided in the companion draft guidance entitled "Guidance for Industry and FDA Staff: Investigational New Drug Applications (INDs) for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications)."

We encourage manufacturers of cord hematopoietic stem/progenitor cells for autologous use, or use in a first- or second-degree blood relative, to follow the recommendations concerning the manufacture of these products and how to comply with applicable regulatory requirements, even though their products may not require premarket review.

B. How do I use this Guidance to Apply for a Biologics License?

You may demonstrate in your license application that you have followed the recommendations in this guidance in order to meet the applicable regulatory requirements for a license application. We intend to grant a license for products shown to follow these recommendations and that meet applicable regulatory requirements in Title 21 of the CFR. Also, you may modify any particular procedure in this guidance, provided that you present evidence in your application demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of your product.

The license would apply to all HPC-Cs manufactured after approval of the license application as well as HPC-Cs previously manufactured in accordance with the information provided in the license application, where documentation is provided to demonstrate their comparability.

C. Am I Required to use this Guidance when I Apply for a Biologics License Application?

No, you are not required to use this guidance. However, you must submit a BLA for your HPC-Cs containing data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency (21 CFR 601.2). This guidance provides specific recommendations for those manufacturers who wish to rely on data in docket number 1997N-0497 (formerly docket number 97N-0497)[2]. If you choose not to rely on these data, you should consult with us about alternative approaches to satisfying applicable regulatory requirements.

D. Historical Background

In 1997, we proposed a new regulatory framework for human cellular and tissue-based products, including hematopoietic stem/progenitor cells. The proposed framework provided a tiered approach to the regulation of human cellular and tissue-based products, now referred to as human cells, tissues, and cellular and tissue-based products (HCT/Ps). We implemented this approach by promulgating three final rules, which comprise 21 CFR Part 1271.

[2] "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products" (63 FR 2985) January 20, 1998.

On January 19, 2001, we published the first final rule entitled "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" (66 FR 5447) (the "registration and listing final rule"). The registration and listing final rule requires establishments that manufacture HCT/Ps to register and list their products with the agency.

On May 25, 2004, we published the second final rule entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (69 FR 29786) (the "donor eligibility final rule"). This final rule requires, with certain exceptions, that a donor eligibility determination be made based on the results of HCT/P donor screening and testing for relevant communicable disease agents and diseases.

On November 24, 2004, we published the third final rule entitled "Current Good Tissue Practice for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products; Inspection and Enforcement" (69 FR 68612). The Current Good Tissue Practice (CGTP) final rule provides requirements for the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery (collection), donor screening, donor testing, processing, storage, labeling, packaging, and distribution.

On May 25, 2005, the three final rules became effective. As described in the registration and listing final rule,[3] we are regulating as biological drugs or devices those HCT/Ps that:

- Are more than minimally manipulated (processing alters the biological characteristics of the cells);
- Are for a use other than homologous use as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- Involve for their manufacture the combination of the cell or tissues with another article, excluding water, crystalloids, or a sterilizing, preserving, or storage agent that does not raise new clinical safety concerns with respect to the HCT/P; or
- Have a systemic effect or are dependent upon the metabolic activity of living cells for their primary function, and are not for:
  - Autologous use;
  - Allogeneic use in a first- or second-degree blood relative; or
  - Reproductive use.

We consider unrelated allogeneic hematopoietic stem/progenitor cells to have a systemic effect and are therefore regulating them as biological products and drugs under the Public Health Service (PHS) Act and the Federal Food, Drug, and Cosmetic Act (FDCA).

On January 20, 1998 (63 FR 2985), we issued a notice in the Federal Register entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments." In the notice, we explained that it may be possible to develop product

[3] 66 FR 5447 at 5467, January 19, 2001. See also, 21 CFR 1271.10.

standards and establishment and processing controls of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products intended for hematopoietic reconstitution, based on existing clinical trial data, or data developed shortly thereafter, demonstrating the safety and effectiveness of the cells. We further explained that if adequate information were submitted to the docket, we intended to issue guidance in accordance with good guidance practice regulations, 21 CFR 10.115, for establishment controls, processing controls, and product standards. If such standards could be developed, we suggested that, in lieu of reviewing individual applications containing clinical data, we would propose granting licensure for products shown to meet the issued standards.

To provide a scientific basis for the proposed standards, we requested the submission of comments proposing establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. To allow sufficient time for the development of data and standards for these products, the notice also announced our intention to phase in implementation of an IND and license application requirements for these products. We provided a period of two years, until January 20, 2000, for interested persons to submit proposed product standards and establishment and processing controls with supporting clinical and nonclinical data. At the request of industry, we reopened the comment period for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

The Biological Response Modifiers Advisory Committee met on February 27, 2003, to discuss issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution. At the meeting, FDA provided an analysis of clinical outcome data submitted to FDA regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. Guest experts provided the most recent data on clinical studies of unrelated donor umbilical cord blood transplantation in children and adults.

The committee's deliberations focused on:

1. Factors the agency should consider in determining the safety and effectiveness of placental/umbilical cord blood transplantation for hematopoietic reconstitution;
2. The role of CD34+ cell count in selection of cord blood units for transplantation; and
3. Other measures of quality that should be considered.[4]

We have reviewed and assessed the submitted information as well as the large body of published literature on this subject, and have determined that the data are sufficient to establish the safety and effectiveness of HPC-Cs for the indications described earlier in

[4] Summary minutes of the meeting are available at our website at http://www.fda.gov/ohrms/dockets/ac/03/minutes/3924M1.htm.

this guidance. The data permit the development of recommendations for establishment and processing controls and product characteristics for these products. Accordingly, this document provides guidance on the content and format of information to be submitted in your BLA for HPC-Cs in the chemistry, manufacturing, and controls (CMC) section, and the establishment description section.

III. APPLICABLE REGULATORY REQUIREMENTS

You and your HPC-Cs are subject to all applicable regulatory requirements; and, when applying for a biologics license, this includes a prelicense inspection (42 U.S.C. § 262). Because we regulate HPC-Cs for unrelated allogeneic use as drugs under the FDCA and as biological products under the PHS Act, you must follow the applicable regulations promulgated under these acts.

Regulations applicable to HPC-Cs include, but are not limited to, the following sections of the CFR:

- 21 CFR Parts 201, and 610 Subpart G – Labeling;
- 21 CFR Part 202 – Prescription Drug Advertising;
- 21 CFR Parts 210 and 211 – Current Good Manufacturing Practice Regulations (CGMP);
- 21 CFR Part 600 – Biological Products: General; and
- 21 CFR Part 610 – General Biological Products Standards.

Cord blood and HPC-Cs are considered HCT/Ps, defined in 21 CFR 1271.3(d). In the collection of cord blood and the manufacture of HPC-Cs, the regulations promulgated for HCT/Ps in 21 CFR Part 1271 apply. These regulations encompass registration and listing, donor eligibility, and good tissue practices. For the manufacture of HPC-Cs, in the event that a regulation in 21 CFR Part 1271 is in conflict with a requirement in 21 CFR Parts 210, 211, 600, or 610, the regulations more specifically applicable to an HPC-C will supersede the more general.

The Current Good Tissue Practice (CGTP) requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (21 CFR 1271.150(a)). Because cord blood and HPC-Cs are HCT/Ps, these provisions are applicable to both cord blood and HPC-Cs.

The CGMP requirements, in 21 CFR Parts 210 and 211, govern the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to ensure that such drug meets the requirements of the FDCA as to safety, has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess. Due to the broader scope of these regulations, most of the CGMP regulations under 21 CFR Parts 210 and 211 would be applicable to your HPC-Cs. Additionally, due to the broad scope of the regulations, for the most part, CGTP would be subsumed under the broader CGMP requirements. Compliance with these CGMP requirements would result in compliance with applicable CGTP requirements.

Section VII of this guidance contains recommendations for application of the appropriate regulations for establishment registration and listing, and specific recommendations for manufacturing HPC-Cs. We recommend that you use Section VII as a reference for compiling information for submission of your BLA. We have referenced the appropriate CGMP sections of the regulations that apply to biologic products. We have indicated a section from 21 CFR Part 1271 only when there is not a corresponding section in the CGMP requirements, in order to bring that CGTP section to your attention.

IV. LICENSE APPLICATION PROCEDURE

A. What Form do I Submit with My Application?

You should submit a Form FDA 356h - Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use.[5]

B. Where Should I Submit My License Application?

You should submit your completed application to: Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, Suite 200N, 1401 Rockville Pike, Rockville, MD 20852-1448. (21 CFR 600.2(a)).

C. What Information Do I Need to Include in My Application?

In accordance with Form FDA 356h, you must include, at a minimum, the following information: (*Numbers in parentheses refer to items listed in Form FDA 356h*)

1. Index (see item 1 on Form FDA 356h);
2. Representative draft labeling for the product for which licensing is being sought (item 2);
3. A summary of the information submitted in the application (item 3);
4. Chemistry, manufacturing and controls information (21 CFR 314.50(d); 21 CFR 601.2). Include a full description of your manufacturing process and copies of standard operating procedures (SOPs) for critical procedures and assays as listed in this guidance, Section V.D (item 4A);
5. Summary data demonstrating validation of critical processes and assays as listed in this guidance, Section V.F (item 4C);
6. A description of your facility including personnel, physical establishment, and equipment (21 CFR 600.10) as described in this guidance, Section VI (item 15); and
7. Other attachments, including a citation to the data submitted to docket number 1997N-0497 (formerly docket number 97N-0497), which may be incorporated by reference (item 20).

[5] See http://www.fda.gov/opacom/morechoices/fdaforms/FDA-356h.pdf.

Under Establishment Information on page one of Form FDA 356h, please indicate if you are ready for inspection.

You may consider submitting to FDA a validation plan for review prior to submitting your application. You may also request a pre-BLA meeting with the Office of Cellular, Tissue, and Gene Therapies, to discuss your validation plan.

D. What Action will FDA Take?

Upon receiving your submission we will review your license application, including the submitted SOPs and validation data. As soon as possible after receiving a complete application, we will schedule a prelicense inspection to verify that you are in compliance with the applicable regulations. If the submitted application is not complete, we will identify/advise you of the additional information that you will need to submit.

V. CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

A. Introduction

This Section provides guidance on the content and format of information to be submitted in the CMC section of your BLA.

B. HPC-C Description and Characterization

This section of the application should contain a description of the specific tests and expected results that will provide information regarding the safety, purity, potency, and identity of the product. Table A provides the description and characteristics of the cord blood and HPC-Cs (i.e., tests performed and the results) used to obtain the clinical data submitted to FDA in docket number 1997N-0497 (formerly docket number 97N-0497). These clinical data demonstrate the safety, purity, and potency of HPC-Cs. You would be expected to obtain similar test results using the recommended or other appropriate tests in order to rely on these clinical data in support of your BLA.

Table A. Required and Recommended Tests and Test Results [1]

Product Characteristics [2]	Testing	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases – Testing Required. (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection – Type and Timing Required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative. (Cytomegalovirus (CMV) results are recorded).
			CMV - Report
	Sterility - Bacterial and fungal cultures – Testing Required. (21 CFR 211.165(b), and 21 CFR 610.12)	HPC-C (pre-cryopreservation) *	No growth
	Hemoglobin	Cord blood** or appropriate donor sample obtained at time of cord blood recovery	No homozygous hemoglobinopathy
Purity and Potency[3]	Total nucleated cells (TNC)	HPC-C (pre-cryopreservation)	$\geq 5.0 \times 10^8$ TNC ***/ unit HPC-C
	Viable nucleated cells	HPC-C (pre-cryopreservation)	≥ 85% viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	$\geq 1.25 \times 10^6$ viable CD34+ cells ****/ unit HPC-C
Identity	Human leukocyte antigen (HLA) Typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment of HPC-C	Confirms initial typing
	Blood Group and Rh Type	Cord blood	Report

[1] Testing, Sample (Type and Timing), and Results are recommended unless specifically noted as required.

[2] The PHS Act requires a demonstration that the product is safe, pure, and potent.

[3] Other purity and potency assays may be considered under the BLA

* Sample may be obtained before or after addition of the cryoprotectant.

** Cord blood = a sample of unmanipulated cord blood. A red cell sample or other cord blood aliquot obtained after volume reduction may be used for testing with appropriately validated reagents or test systems.

*** Based on 20 kg recipient, a target dose of $\geq 2.5 \times 10^7$ nucleated cells/kg and ≥ 70% post-thaw recovery = 1.7×10^7 nucleated cells/kg.

****Based on CD34+ cells ≥ 0.25% of TNC prior to freezing.

C. Manufacturer(s)

1. Identification

This section should include the name(s), address(es), telephone number(s), FDA registration number(s), and other pertinent organizational information for each manufacturer, including those under contract, agreement, or other arrangement with you to perform a manufacturing step. These organizations include, but are not limited to, all collection sites that act as your agent(s) and laboratory(ies) performing testing of donor samples for relevant communicable disease agents and product sterility testing.

2. Floor Diagram(s)

For each processing location, a description of the area(s) used for processing of HPC-Cs should be provided. A floor diagram of the general layout of the facility should be submitted along with the narrative description. The floor diagram(s) should be sufficiently clear to enable the visualization of the production flow and to identify adjacent operations that may create particular concerns (potential impact on product quality). Submission of a floor diagram is not necessary for collection sites.

3. Contamination Precautions

For all areas in which operations for the processing of HPC-Cs are performed, you should provide the following information concerning precautions taken to prevent contamination or cross-contamination:

- A description of the in-process controls performed to prevent or to identify contamination or cross-contamination. You should take appropriate precautions to prevent cross-contamination when the same area or equipment is used to process more than one HPC-C at a time (e.g., several HPC-Cs in a centrifuge simultaneously).
- A brief, narrative description of the procedures and/or facility/equipment design features for the control of contamination, cross-contamination, and aseptic manipulations.
- A brief, narrative description of the area where the manufacturing is performed, including collection, volume reduction, packaging, labeling, cryopreservation, storage, and shipping.

D. Methods of Manufacturing

In accordance with 21 CFR 601.2, you must submit a detailed description of the manufacturing and controls. In this section of Form FDA 356(h), you should submit all relevant SOPs, including donor selection and cord blood collection, cord blood transport to the processing facility, processing, testing, storage, registry listing and HPC-C selection management, and HPC-C shipping and handling.

1. SOPs to Submit with License Application

   You should submit with your license application detailed SOPs for performance of the following critical operations:

   a. Collection

      - Maternal screening[6] and obtaining informed consent;
      - Donor eligibility – donor screening and donor testing;
      - Notification of mothers or their responsible physicians of positive or indeterminate test results according to local or national regulations;
      - Positive identification of birth mother and donor;
      - Cord blood collection, storage, and transport to the processing facility; and
      - Criteria for accepting cord blood for further processing.

   b. Processing

      - Plasma reduction, red cell sedimentation, and/or other nucleated cell concentration methods;
      - Cryopreservation;
      - Frozen storage; and
      - Lot release.

   c. Selection

      - Registry listing; and
      - Search and selection request management.

[6] For further information on CDC maternal screening recommendations see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm and http://www.cdc.gov/hepatitis/HBV/PerinatalXmtn.htm.

d. HPC-C Shipping and Handling

- Shipping to transplant center;
- Thawing and preparation for administration; and
- Emergency product recovery in the event of a container failure, including plans for sterility testing of the compromised product and notification of the appropriate individuals and regulatory authorities.

2. Validation

We recommend that you submit a validation data summary for the following manufacturing and administration steps:

- Cord blood collection;
- Cord blood processing, including volume reduction and cryopreservation;
- Storage;
- Shipping;
- Thawing; and
- Cryoprotectant removal (for use in transplant centers that perform this step)

We recommend that the validation summary include data from the manufacture, as well as the thawing and cryoprotectant removal of a minimum of three consecutive, separate HPC-Cs to demonstrate that you are able to consistently manufacture and thaw those HPC-Cs that meet the product characteristics described previously in section V.B of this guidance.

A separate validation summary should be submitted for those HPC-Cs in inventory that were manufactured using different procedures than those you use currently. The summary should include data demonstrating comparability between the previously manufactured HPC-Cs and HPC-Cs manufactured currently and evidence that the methods, facilities, and controls used for manufacture of these products were operated in conformance with CGMP and other applicable regulatory requirements. The comparability data may include product characteristics such as:

- TNC count;
- Viable CD34+ cell content; and
- Colony forming unit content.

Establishments may include data describing other product attributes obtained from stability or other studies. Information from the medical literature may also be cited to support comparability, if available. Additionally, we recommend that

you submit any available clinical outcome data to support comparability of your HPC-Cs manufactured using different procedures than those you use currently.[7]

3. Flow Charts

In this section, a complete visual representation of the manufacturing process flow should be provided. The flow chart should show the steps in production, equipment and materials used; room or area where the processing is performed (may make reference to diagrams in other sections of the application); and a complete list of the in-process controls and tests performed on the product at each step. In-process holding steps should be included, with time and temperature limits indicated.

The flow chart should also include information (or be accompanied by a descriptive narrative) on the methods used to transfer the product between steps, such as open transfers under laminar flow units. Reference may be made to other sections of the application for more detailed process information. If equipment is dedicated to specific areas, it should be identified.

4. Microbiology

If presterilized equipment and containers are going to be used, you should provide a description of the item, whether it is single-use, and how the item is sterilized.

If equipment is going to be sterilized in-house, you should provide a description and documentation of the validation studies for any processes used for equipment sterilization. The procedures followed should be listed. Information should be submitted as described in the "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (Ref. 1).

5. Control of Aseptic Manipulations

This section should contain descriptions of:

[7] You may find additional information on comparability in the following publications:

- Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, June 2005 (June 30, 2005, 70 FR 37861) (http://www.fda.gov/RegulatoryInformation/Guidances/ucm128059.htm).
- Draft Guidance for Industry; Comparability Protocols - Chemistry, Manufacturing, and Controls Information, February 2003 (February 25, 2003, 68 FR 8772) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070262.htm). When finalized, this guidance will represent FDA's current thinking on the topic.
- Draft Guidance for Industry; Comparability Protocols Protein Drug Products and Biological Products - Chemistry, Manufacturing and Controls Information, September 2003 (September 5, 2003, 68 FR 52776) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070262.htm). When finalized, this guidance will represent FDA's current thinking on the topic.

- How transfers and additions are performed;
- Precautions to control contamination; and
- In-process testing.

You should provide a brief description of all process parameters that are monitored. A description should be provided of the precautions taken to maintain aseptic conditions and prevent contamination during collection, concentration, and cryopreservation. A description of the procedures used to monitor bioburden/sterility should be included. You should also provide a description of the conditions and time limits for process steps.

E. Container Closure System (21 CFR 211.94)

The container closure system refers to the packaging components that together contain and protect the product, including, but not limited to, storage bags, seals, stoppers and administration ports, overwraps, administration accessories, and container labels (Ref. 2).

You should submit a description of the container and closure system, and its compatibility with the HPC-C. The license application should include detailed information concerning the supplier(s), address(es), and the results of compatibility, toxicity, and biological tests. Alternately, a new drug application, 510(k) premarket notification, or drug master file may be referenced for this information. Evidence of container and closure integrity should be provided for the duration of the proposed dating period.

F. Methods Validation/Verification

1. Infectious Disease Test Methods

Appropriate FDA licensed, approved, or cleared donor screening tests must be used to test for relevant communicable disease agents and diseases in accordance with the manufacturer's instructions (21 CFR 1271.80(c)). In this section of your application, you should list the assays that you (or your contract laboratory) perform to test the maternal sample for relevant communicable disease agents and diseases, including the name and manufacturer of the FDA licensed, approved, or cleared test kits used.

2. Other Test Methods

In this section of your application, you should provide a description of all other test methods selected to ensure the identity, purity, strength and/or potency, as well as the lot-to-lot consistency of the finished product and the specifications used for the HPC-C. Certificates of analysis and analytical results for at least three consecutive batches should be provided. We recommend that you use FDA approved, licensed, or cleared test kits and reagents, where available. Examples of the other test methods that you should describe in your application include:

- Sterility (bacterial and fungal cultures): You should provide a description of the 21 CFR 610.12, United States Pharmacopeia, or alternative methodologies used, sample types tested, and if applicable, include a description of your validation protocol and summary validation data for alternative methods, such as automated microbiologic testing systems adapted for this use[8];
- Hemoglobin testing: provide a description of the tests used to evaluate the cord blood donor for hemoglobinopathies;
- TNC counts;
- Nucleated cell viability assay(s);
- CD34+ cell viability (flow cytometry);
- HLA typing: Provide a description of the serologic and DNA-based testing performed, sample types used (e.g., cord blood, processed cord blood discard fractions, and maternal samples, if used) and the name and location of the laboratory that performs the initial and the confirmatory HLA typing of the final product;
- ABO blood group and Rh type; and
- Other tests you may perform to evaluate your HPC-Cs, such as colony-forming unit assays, nucleated red blood cell counts, and cell phenotype analysis.

3. Validation Results

You should provide the results of studies validating the specificity, sensitivity, and variability of each method used for determining whether a product can be made available for distribution. Where applicable, this should include descriptions of reference standards and their validation. For analytical methods in compendial sources, you should provide the appropriate citations.

G. Labeling

In this section you should provide representative draft labeling for your HPC-Cs. A description of the required labels and labeling for HPC-Cs is provided in this guidance in Section VII.B.12.

[8] You may find additional information on alternative methods for sterility testing in the FDA guidance entitled "Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products" dated February 2008 (February 11, 2008 73 FR 7746). Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078696.htm. When finalized, this guidance will represent FDA's current thinking on this topic.

H. Environmental Assessment

An environmental assessment, as outlined in 21 CFR Part 25, or a request for a categorical exclusion with the basis for the exclusion, should be submitted. If an environmental assessment is appropriate, it should include a description of the action that is being considered and should address all the components involved in the manufacture and disposal of the product.

VI. ESTABLISHMENT DESCRIPTION SECTION

A. Introduction

This Section provides guidance on the content and format of information to be submitted in the establishment description section of your BLA.

B. General Information

For each manufacturing location, a floor diagram should be included that indicates the general layout of the facility. The following information should be provided on each floor diagram and/or in an accompanying narrative:

- A layout of the physical facility and the processing that takes place in each area, including receipt and testing activities. A floor diagram should be submitted, indicating the room number and location of major equipment;
- A general description of the processing areas, including a description of the floor, ceiling, and equipment surfaces used for cord blood processing;
- Activities in adjacent areas to the processing areas; and
- Product, personnel, equipment and waste flows.

A floor diagram of the collection site(s) is not necessary.

C. Specific Systems

1. Source of Water Used in Processing (if applicable)

   If the water for production is being purchased for manufacturing, you should provide a description of the water quality used in manufacturing (at each stage in the process) and rinsing of product contact equipment and containers/closures. This includes bottled/packaged water.

   If the water is being manufactured on site, you should provide a general description of the water system(s), including the validation summary and routine monitoring program.

2. Heating, Ventilation, and Air Conditioning

You should include the following information:

- A description of the controls used to prevent contamination and cross-contamination, including air handling units, pressure differentials, whether air is once-through or recirculated, and air changes per hour;
- A description of the environmental quality of each room and each aseptic processing area (laminar flow unit); and
- A validation summary for the system, including a narrative on the validation utilized, acceptance criteria, and explanation of failures and excursions, including deviation reports and results of investigations.

3. Facility Controls

This section should contain information on the various controls and monitoring for the collection and processing of cord blood at the manufacturing locations, including:

- A description of the area and cleaning/sanitization procedures;
- A description of the personnel gowning practices for the manufacturing areas;
- A description of the measures used to prevent unauthorized access into the manufacturing areas (card key readers, etc.); and
- A brief description of any environmental monitoring program, including monitoring for airborne viable and nonviable particles, surface sampling, frequency of the monitoring, and alert and action levels that have been established for each area.

4. Computer Systems

This section should contain information on computer systems that control critical manufacturing processes. For example, you should provide information for computer systems used for recording results of donor eligibility screening and testing; tracking the distribution of HPC-Cs and associated samples; automated systems for controlled-rate freezing, storage, and retrieval; and any other automated systems you use to manufacture your HPC-Cs. The developer of the system should be identified, whether in-house or contractor/vendor. The information provided should also include a brief description of procedures for making changes to the computer system. For each of these systems a list of manufacturing steps that are computer-controlled should be provided.

This section should also contain a validation/verification summary for each of these systems, which includes:

- A narrative description of the validation/verification process or protocol, including acceptance criteria;
- Certification that installation qualification and operation qualification have been completed;
- An explanation of the parameters monitored and tests performed;
- A validation/verification data summary; and
- An explanation of all excursions or failures, deviation reports, and result of investigations for all excursions or failures.

For information on software regulation and validation, we recommend you refer to "Guidance for Industry and FDA Staff: General Principles of Software Validation" (January 11, 2002, 67 FR 1482). Available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126954.htm. Section 6 of this guidance "Validation of Automated Process Equipment and Quality System Software" may be particularly helpful to you in validating the software for use in your establishment. In addition, the Current Good Manufacturing Practice regulations at 21 CFR 211.168(a), (b), and (c) describe your responsibilities regarding automatic, mechanical, and electronic equipment, including computers.

D. Contamination/Cross-Contamination Issues

The following information regarding methods to prevent contamination and cross-contamination should be provided to supplement the information requested in the CMC section of the application.

1. Equipment Cleaning Procedures and Validation

You should provide a brief description of the cleaning procedures and cleaning reagents used. This section should also contain a certification that the cleaning validation for removal of product residues has been successfully completed.

2. Containment Features

This section should contain a description of segregation and containment procedures for areas, manufacturing operations, personnel, equipment and waste materials designed to prevent contamination of products. You should discuss the features that are employed to maintain segregation and containment. These features might include but are not limited to:

a. Air Handling (where appropriate)

- Air pressure differentials between adjacent manufacturing areas;
- Segregation of air handling units;
- Air supply and return (recirculated, once-through, high efficiency particulate air (HEPA) filters, etc.); and
- Use of airlocks.

b. Decontamination and Equipment Cleaning

Procedures for decontamination and cleaning of equipment used to process material in closed containers when there is a breach in the container integrity and leakage of product onto the equipment.

VII. GUIDANCE ON APPLICABLE REGULATIONS

A. Establishment Registration and Listing

Within five days after beginning of operations, you must register and submit a list of every HCT/P that your establishment manufactures, following the registration and listing procedures in 21 CFR Part 1271, Subpart B (see 21 CFR 1271.21). If you, the registered establishment, contract with or have an agreement or other arrangement with an individual to collect and send to you cord blood for processing, that individual does not have to register or list independently; however, that individual must comply with all other applicable requirements (21 CFR 1271.15(f)).

B. Current Good Manufacturing Practice and Current Good Tissue Practice

As previously noted in this guidance, you, the manufacturer, must follow all regulations applicable to cord blood collection and manufacture of HPC-Cs. FDA considers umbilical cord blood collected for further processing into HPC-Cs to be an intermediate product. While there are no specific regulations governing the manufacture of intermediates, drug substances or what are termed active pharmaceutical ingredients, compliance with statutory CGMP (section 501(a)(2)(B) of the FDCA) is required. Accordingly, for collection of cord blood for further processing into HPC-Cs, section 501(a)(2)(B) or statutory CGMP would be applied. This section of the FDCA mandates that methods used in, or the facilities or controls used for the manufacture, processing, packing, or holding of a drug must conform or be administered in conformity with CGMP. Though not specifically applicable to HPC-Cs, the "Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (Ref. 3), provides recommendations for good manufacturing practices for the manufacture of intermediates, drug substances, and active pharmaceutical ingredients.

For the collection of cord blood as well as manufacture of HPC-Cs, the CGTP and other applicable provisions in 21 CFR 1271 apply. The CGMP regulations in 21 CFR Parts 210 and 211 are applicable to the manufacture of a drug product, which is defined as the finished dosage form (21 CFR 210.3(b)(4)). Accordingly, for the manufacture of HPC-Cs, applicable regulations include, but are not limited to, the CGMP in 21 CFR Parts 210 and 211, CGTP and other applicable provisions in 21 CFR 1271, and applicable regulations for biologics contained in 21 CFR Parts 600 through 680. For the most part, in the manufacture of HPC-Cs, the CGMP regulations will be applied because they are more broadly drafted and subsume the CGTP regulations.

The CGMP regulations applicable to the manufacture of your HPC-Cs are contained in eleven subparts in 21 CFR Part 211, and this section of the guidance is formatted to follow these subparts:

Subpart A – General Provisions
Subpart B – Organization and Personnel
Subpart C – Buildings and Facilities
Subpart D – Equipment
Subpart E – Control of Components and Drug Product Containers and Closures
Subpart F – Production and Process Controls
Subpart G – Packaging and Labeling Controls
Subpart H – Holding and Distribution
Subpart I – Laboratory Controls
Subpart J – Records and Reports
Subpart K – Returned and Salvaged Drug Products

The CGTP regulations applicable to the collection of the cord blood as well as the manufacture of HPC-Cs are contained in two subparts in 21 CFR Part 1271, and this section of the guidance is formatted to follow these subparts:

Subpart C – Donor Eligibility
Subpart D – Current Good Tissue Practice

In addition, 21 CFR Part 1271 Subpart A – General Provisions, and Subpart B – Procedures for Registration and Listing, are applicable to HPC-Cs. However, 21 CFR Part 1271 Subpart E – Additional Requirements for Establishments Described in § 1271.10 (reporting requirements and labeling), and Subpart F – Inspection and Enforcement of Establishments Described in § 1271.10, are not applicable to HPC-C products described in this guidance.

As the applicable regulations contain many requirements for written procedures (hereafter "SOPs" for standard operating procedures), you may consider establishing an SOP manual so that all SOPs are found in one location available to personnel.

The following recommendations are provided to assist you in complying with section 501(a)(2)(B) of the FDCA, as well as regulations applicable to the manufacture of your HPC-Cs. This guidance may not include all the regulations that would apply to you, so we recommend that you carefully review all the regulations to ensure that you are in compliance.

1. Donor Eligibility

You must comply with the donor eligibility requirements contained in 21 CFR 1271.45 through 1271.90. You must perform communicable disease testing using

a peripheral blood sample taken from the mother of the cord blood donor within seven days of collection (21 CFR 1271.80(b)).

Once a donor eligibility determination has been made, you must create and retain specific records (21 CFR 1271.55).

2. Prevention of the Introduction, Transmission, or Spread of Communicable Diseases

You must recover, process, store, label, package, and distribute your HPC-Cs, and screen and test donors in a way that prevents the introduction, transmission, or spread of communicable diseases (21 CFR 1271.145).

3. Manufacturing Arrangements

If you engage another establishment under a contract, agreement, or other arrangement to perform any step in the manufacture, then that establishment must comply with applicable requirements for that manufacturing step (21 CFR 1271.150(c)(1)(ii)).

4. Exemptions and Alternatives

You may request an exemption from or alternative to any requirement in Subparts C and D of Part 1271 that apply (21 CFR 1271.155).

5. Quality Control Unit (21 CFR 211.22)

a. You must have a Quality Control Unit (QCU). The QCU may be any person or organizational element responsible for the duties relating to quality control (21 CFR 210.3(b)(15)).

b. The QCU must have:

- Adequate laboratory facilities for testing (21 CFR 211.22(b)); and
- Responsibilities and procedures in writing and the written procedures must be followed (21 CFR 211.22(d)).

c. The QCU has the following responsibilities:

- Responsibility and authority to approve/reject all components, drug product containers and closures, in-process materials, packaging, labeling, and HPC-Cs (21 CFR 211.22(a));

- Authority to review records to ensure that no errors have occurred and that those that do occur are fully investigated (21 CFR 211.22(a));
- Responsibility to approve/reject procedures/specifications affecting identity, strength, quality, and purity of the HPC-Cs (21 CFR 211.22(c);
- Responsibility to review and approve written procedures for production and process control, including any changes to these procedures (21 CFR 211.100(a));
- Responsibility to review and approve the establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including any changes in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms (21 CFR 211.160(a));
- Responsibility to review and approve all HPC-C production and control records to determine compliance with all established, approved, written procedures before a lot is released or distributed. Any discrepancies must be thoroughly investigated (21 CFR 211.192);
- Responsibility to establish and follow written procedures describing the handling of all written or oral complaints, including provisions for QCU review of any complaint related to HPC-C failures; investigation of any complaint; evaluation of whether the complaint represents an adverse drug experience and, if so properly reporting it (21 CFR 211.198); and
- Responsibility for periodically conducting an internal quality audit for management review. You should document these independent reviews (21 CFR 1271.160(c)). Quality audit is defined in 21 CFR 1271.3(gg), and must be performed for activities of core CGTP requirements relating to communicable disease transmission, such as donor eligibility determination. For HPC-Cs, we recommend audits be performed more broadly to encompass CGMP.

6. Personnel

a. General

You must have an adequate number of personnel with the education, training, and experience, or any combination thereof, required to perform their assigned functions. Personnel must be trained in the specific operations they perform and the CGMP that relate to their functions (21 CFR 211.25 and 21 CFR 600.10(b)).

Personnel should be properly gowned and practice good sanitation practices. Only personnel authorized by supervisory personnel should enter limited access areas of your facility. Anyone with an apparent illness that could adversely affect the product should report the condition to their supervisor and be excluded from direct product contact (21 CFR 211.28, and 21 CFR 600.10(c)).

Personnel who perform cord blood collection as your agents must be trained according to the applicable CGMP and CGTP requirements (21 CFR 211.25(a)). (See also 21 CFR 1271.170).

We recommend that you develop a system for providing information and other resources that could be used for education and training of transplant center personnel to ensure appropriate handling, testing, and administration of the HPC-C.

b. Medical Director

We recommend that you have a medical director who is qualified by education, training and/or experience to have responsibility and authority for all medical aspects of the cord blood bank. Where a remote collection facility ships cord blood to a central cord blood bank, the medical director of the central cord blood bank may serve as medical director of the remote collection facility.

c. Laboratory Director

We recommend that you have a laboratory director who is qualified by education, training and/or experience and is responsible for all technical aspects of the cord blood bank.

If you choose to designate a medical or laboratory director to perform any authorization activities, we remind you that the QCU has the ultimate responsibility for approval and/or rejection of the product, in addition to its other responsibilities (see Section VII.B.5 of this guidance).

7. Buildings and Facilities

You should design and maintain your buildings and facilities to provide adequate environmental conditions for the manufacture of HPC-Cs, adequate segregation of operations to prevent mix-ups, and adequate sanitation SOPs to prevent contamination and cross contamination. The following should be considered:

a. Maintenance

Buildings used in the manufacture of HPC-Cs must be maintained in a state of good repair (21 CFR 211.58).

b. Facility Design and Air Handling Systems for Prevention of Cross-Contamination

- Building(s) used in the manufacture of HPC-Cs must be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations (21 CFR 211.42(a)); and
- Operations must be performed within specifically defined areas of adequate size (21 CFR 211.42(c)).

c. General Air Handling Systems

- Adequate ventilation must be provided (21 CFR 211.46(a));
- Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature must be provided, when appropriate (21 CFR 211.46(b), and 21 CFR 600.11(a)); and
- Air filtration systems must be used, when appropriate, on air supplies to manufacturing areas (21 CFR 211.46(c)).

d. Prevention of Mix-ups, Contamination and Cross-Contamination

- Buildings must have adequate space for the orderly placement of equipment and materials to prevent mix-ups and/or contamination between different components, product containers, closures, labeling, in-process materials, and/or products (21 CFR 211.42(b)); and
- Separate or defined areas or other control systems must be in place for the operations as necessary to prevent contamination or mix-ups, including:
    - Receipt, identification, storage, and withholding from use of components, product containers, closures, and labeling pending sampling, testing, or examination by the QCU before release for manufacturing;
    - Holding of rejected, and storage of released components, product containers, closures, and labeling before disposition;
    - Storage of in-process materials;
    - Manufacturing and processing operations;

- Quarantine storage before release of products;
- Control and laboratory operations; and
- Aseptic processing, including, when appropriate, an environmental monitoring system, a room and equipment cleaning/disinfecting system, and a maintenance system for equipment used to maintain aseptic conditions (21 CFR 211.42(c)).

e. Sanitation of the Building; Cleaning and Sanitizing Agents

Buildings used in the manufacture of HPC-Cs must be maintained in a clean and sanitary condition (21 CFR 211.56(a)). There must be SOPs for facility sanitation designed to prevent the contamination of equipment, components, product containers, closures, packaging, labeling materials, or products (21 CFR 211.56(c)).

8. Equipment

a. Adequacy of Equipment Design, Size, and Location

Equipment used in the manufacture of HPC-Cs must be of appropriate design, adequate size, and suitably located for its intended use and for its cleaning and maintenance (21 CFR 211.63).

b. Cleaning and Maintenance

- Equipment and/or utensils must be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the HPC-C (21 CFR 211.67(a));
- SOPs for cleaning and maintenance of equipment, including utensils, must be established and followed (21 CFR 211.67(b)); and
- Records of equipment maintenance, cleaning, sanitizing, and inspection must be kept (21 CFR 211.67(c)).

c. Automatic, Mechanical and Electronic Equipment

- Equipment must be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance (21 CFR 211.68(a));
- SOPs for calibration and maintenance should conform to the equipment manufacturers' recommendations and/or user's manual;

- Written records of calibration checks and inspections must be maintained (21 CFR 211.68(a));
- The liquid nitrogen freezers you use for storage of HPC-Cs should be qualified to maintain the desired temperature and to permit insertion and removal of HPC-Cs without compromising the quality of other HPC-Cs stored in the same freezer;
- Input to and output from the computer or related system of formulas or other records or data must be checked for accuracy (21 CFR 211.68(b));
- Appropriate controls must be exercised over computer or related systems to ensure that only authorized personnel institute changes in records (21 CFR 211.68(b)); and
- Hard copy or alternative systems, such as duplicates, tapes, or microfilm, must be designed to ensure that backup data are exact and complete and that they are secure from alteration, inadvertent erasures, or loss (21 CFR 211.68(b)).

d. Equipment Identification Practices (where appropriate)

Major equipment must be properly identified in the production records to show the specific equipment used in the manufacture (21 CFR 211.105(b)).

9. Predistribution Shipments and Control of Components, Containers, and Closures

You must have SOPs describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components (including cord blood that you receive for processing) and HPC-C containers and closures. These procedures must be followed (21 CFR 211.80(a)).

a. Predistribution Shipments

If you ship cord blood within your establishment or between establishments (e.g., collector to processor) and the cord blood is not available for distribution as described in 21 CFR 1271.265(c), you must first determine and document whether pre-established criteria designed to prevent communicable disease transmission have been met, and you must ship the cord blood in quarantine (21 CFR 1271.265(b)).

b. Identification, Inventory, and Storage of Components, Containers and Closures

- The components and HPC-C containers and closures must be handled and stored in a manner to prevent

contamination. Bags and boxes should be stored above the floor and in such a way as to permit cleaning and inspection (21 CFR 211.80(b) and (c)); and

- Each container or grouping of containers for components or HPC-C containers or closures must be identified with a distinctive code for each lot in each shipment received. You must use this code in recording disposition of the lot. Each lot must be properly identified as to its status (e.g., quarantined, released) (21 CFR 211.80(d)).

c. Storage of Components, Containers, and Closures under Quarantine until Tested or Examined, and Released

- The components, product containers, and/or closures must be stored under quarantine until they have been tested or examined, whichever is appropriate, and released (21 CFR 211.82(b)); and
- The product containers and/or closures must be sampled and tested by the quality control unit before release (21 CFR 211.84(a)).

d. Representative Samples Collected, Tested, or Examined Using Appropriate Means; Approval and Rejection Activities

- The product containers and/or closures must be visually inspected for container damage or broken seals upon receipt and before acceptance (21 CFR 211.82(a));
- A representative sample of each shipment of each lot of components must be collected for testing or examination (21 CFR 211.84(b)). The testing performed should be based on the intended use of the component and the reliability of the vendor;
- Each component must be tested for conformance with appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)). For example, components that come into direct contact with an HPC-C should be sterile. Acceptance may be based on a Certificate of Analysis, as long as at least one specific identity test is performed and the reliability of the vendor's results has been established;
- Lots of components, and product containers and closures that meet the appropriate written specifications may be released for use. Those that do not must be rejected (21 CFR 211.84(e));
- Components, and product containers and closures released for use must be used on a first in first out basis, i.e., the oldest lots used first (21 CFR 211.86);

- If components and product containers and closures are stored for long periods of time under conditions that may adversely affect their performance, they must be re-tested and/or re-examined and approved or rejected by the quality control unit (21 CFR 211.87); and
- Rejected components and product containers and closures must be identified and controlled under a quarantine system intended to prevent their use in manufacturing (21 CFR 211.89).

e. Containers and Closures

- Product containers and closures must not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the HPC-C (21 CFR 211.94(a));
- The container closure system used for HPC-Cs must provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the product (21 CFR 211.94(b));
- Containers and closures used for HPC-Cs must be clean and must be sterilized and processed to remove pyrogenic properties to ensure they are suitable for the intended use. Such depyrogenation processes must be validated. (21 CFR 211.94(c));
- Specifications for the containers and closures, testing and/or examination methods, and, where applicable, the methods for cleaning, sterilization, and depyrogenation must be contained in SOPs and followed (21 CFR 211.94(d));
- During collection of cord blood, we recommend that you use an appropriate closed, sterile container sealed in a manner that prevents cell loss and contamination. We recommend that you use only citrate-based anticoagulants;
- We recommend that you transport cord blood in a shipping container designed to contain any leakage from the collection container and to minimize temperature changes during transportation; and
- We recommend that you store unprocessed cord blood in a secure location and in containers monitored to maintain the desired temperature range.

10. Production and Process Controls (Process Validation)

You should validate the processes used to manufacture HPC-Cs and establish in-process controls and final product specifications to ensure that your HPC-Cs have

the identity, strength, quality, and purity necessary for the products to be safe and effective. Whenever an established, validated procedure is modified, you should perform new validation studies. Because HPC-Cs are subject to microbiological contamination, you should have procedures in place to ensure that sterility of the product is maintained.

a. Written Procedures; Deviations

- You must have SOPs for production and process controls designed to assure that HPC-Cs have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a));
- SOPs, including changes to SOPs, must be approved by the appropriate organizational units and by the quality control unit (21 CFR 211.100(a)); and
- SOPs must be followed and deviations from the SOPs must be recorded and justified. Documentation must be done at the time of performance (21 CFR 211.100(b)).

b. Pre-Cryopreservation Processing

- We recommend that your manipulation of the cord blood be restricted to volume reduction by depletion of red cells and plasma, followed by cryopreservation by controlled rate freezing or an alternative validated technique; and
- You should use an aseptic method of reducing cord blood volume known to preserve viability and potency and to allow acceptable recovery of the original number of hematopoietic progenitor cells.

c. Cryopreservation

- Your cryopreservation SOPs should specify the cryoprotectant to be used and its final concentration, as well as the nucleated cell concentration, method of freezing, endpoint temperature of cooling, cooling rate, and storage temperature; and
- You should use a cryopreservation process validated to preserve potency and to permit recovery of at least 70% of the viable nucleated cells present in the product before cryopreservation.

d. Thawing

- You should validate a thawing process demonstrated to permit recovery of at least 70% of the viable nucleated cells present in the product before freezing; and
- If thawing is to be performed at a separate facility, you should provide that facility with instructions for performing the validated thawing process.

e. Implementation and Documentation of In-Process Controls, Tests, and Examinations

- You must have SOPs that describe the in-process controls, and tests or examinations to be conducted on appropriate samples of in-process materials of each batch (21 CFR 211.110(a)); and
- In-process controls must be consistent with product final specifications (21 CFR 211.110(b)).

f. Time Limitations on Production

- When appropriate, you must establish time limits for the completion of each phase of production to assure the quality of the HPC-C. Deviations from these limits may be acceptable if the deviation does not compromise the quality of the HPC-C. Deviations must be justified and documented (21 CFR 211.111);
- We recommend that you begin processing of HPC-Cs within 48 hours of collection; and
- Your SOPs should be designed to minimize the transit time of the HPC-C between freezing and storage devices.

g. Prevention of Microorganisms in Sterile Products

- Appropriate written procedures (SOPs) designed to prevent microbiological contamination must be established and followed (21 CFR 211.113(a)). Such procedures must include validation of all aseptic and sterilization processes (21 CFR 211.113(b)). (See also 21 CFR 600.11(b));
- During collection, we recommend that you use validated aseptic methods to provide maximum assurance of sterile products (Ref. 4); and
- Your cryopreservation process should employ aseptic techniques and not permit introduction of microbial contaminants or other adventitious agents.

h. Pooling

Cord blood from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing (21 CFR 1271.220(b)).

11. Packaging and Labeling Control

a. Acceptance Operations for Packaging and Labeling Materials; Examination, Storage, and Usage

- SOPs describing the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials must be written and followed (21 CFR 211.122(a));
- Labeling and packaging materials must be representatively sampled, examined, and/or tested upon receipt and before use in packaging or labeling of the product (21 CFR 211.122(a)); and
- Labeling and/or packaging materials not meeting appropriate written specifications must not be approved and released for use (21 CFR 211.122(b)).

b. Control of Labeling Issuance, Examination of Issued Labels, and Reconciliation of Used Labels

- Labeling issued for use in product labeling operations must be strictly controlled (21 CFR 211.125(a)) and must be carefully examined for identity and conformity to the labeling specified in the master or HPC-C production records (21 CFR 211.125(b));
- The quantities of labeling issued, used, and returned must be reconciled, and discrepancies between the quantity of finished product and the quantity of labeling issued must be evaluated (21 CFR 211.125(c)); and
- All excess labeling bearing lot or control numbers must be destroyed (21 CFR 211.125(d)).

c. Packaging and Labeling Operations, Line Clearance, Inspection and Documentation Including Validation and Security of Computerized Processes

- SOPs designed to ensure that correct labels, labeling, and packaging materials are used must be established and followed (21 CFR 211.130). Such procedures must incorporate the following features:

- Prevention of mixups and/or cross-contamination by physical or spatial separation from operations on other products (21 CFR 211.130(a));
- HPC-Cs must be labeled with a distinct identification code (e.g., alphanumeric, that relates the product to the donor and to all records pertaining to the product) (21 CFR 1271.290(c)); and
- The label must include information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Except in the case of autologous or donations as described in 21 CFR 1271.55(a)(1), you must create such a code specifically for tracking, and it may not include an individual's name, social security number, or medical record number. You may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process or you may assign a new code. If you assign a new code to an HPC-C, you must establish and maintain procedures for relating the new code to the old code (21 CFR 1271.290(c)).

- Equipment used in computerized packaging and/or labeling processes must be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance (21 CFR 211.68(a));
- Changes in the computers and related systems must be appropriately controlled to ensure only authorized personnel perform them (21 CFR 211.68(b)); and
- We recommend that the following information accompany the HPC-C during shipping:

  - Emergency contact information; and
  - Instructions for receiving and handling the HPC-C, including interim storage, thawing, and cryoprotectant removal.

d. Expiration Dating (21 CFR 211.137(a through d)); and 21 CFR 1271.260(c))

The HPC-C container label or other labeling must:

- Bear an expiration date determined by appropriate stability testing; and

- Have expiration dates related to any storage conditions stated in the labeling, as determined by stability studies; for example, cryopreserved and post-thaw expiration dates (and times, when appropriate).

e. Examination of the Labeled Finished Product (21 CFR 211.134(a) and (c))

Labeled HPC-Cs must be examined during the finishing operations to ensure that the containers and/or packages have the correct label. The results of the examination must be documented in the production or control records.

f. Packaging and Shipping (21 CFR 1271.265(d))

Packaging and shipping containers must be designed and constructed to protect the HPC-C from contamination and other harmful effects of environmental exposure.

You must establish appropriate shipping conditions to be maintained during transit. We recommend that cryopreserved HPC-Cs be transported in a liquid nitrogen-cooled dry shipper validated to maintain temperature for the appropriate time period.

12. Label and Labeling Content to be Submitted with Your Application

a. Prescription Drug Labeling (21 CFR 201.56 and 201.57)

HPC-C is a prescription drug product subject to the labeling requirements in 21 CFR 201.56 and 201.57. Clearly inapplicable sections, subsections, or specific information may be omitted from the labeling (21 CFR 201.56(d)(4)). The January 2006 draft guidance entitled "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements" contains guidance for implementing these labeling provisions (Ref. 5).

b. Package Label (21 CFR 610.60 and 610.61)

In addition to the labeling requirements in 21 CFR 201.56 and 201.57, your HPC-Cs are subject to the label requirements in 21 CFR 610.60 – Container label; and 610.61 – Package label. A full container label is the label affixed to the immediate container of a product capable of bearing a full label (21 CFR 610.60). A partial label may be used if the immediate container is incapable of bearing a full label (21 CFR 610.60(c)). Partial labels must bear at a minimum specific information described in 21 CFR 610.60(c). Immediate containers bearing partial labels must be placed in a

package that bears all of the items required for a package label (21 CFR 610.60(c)). The package label must bear the items listed in 21 CFR 610.61. This label must be affixed to each package containing an HPC-C product.

c. Bar Code (21 CFR 201.25)

Because HPC-C is a prescription drug product, it is subject to the bar code label requirements in 21 CFR 201.25. You may request, in writing, an exemption from the bar code label requirements (see 21 CFR 201.25(d)).

d. Current Good Tissue Practice – Labeling (21 CFR 1271.55)

CGTPs require that cord blood and HPC-Cs be accompanied by certain records at all times after a donor eligibility determination has been made (21 CFR 1271.55(a)). These accompanying records, a statement of donor eligibility or ineligibility, and a summary of the records used to make the donor eligibility determination (21 CFR 1271.55(b)), must not contain the donor's name or other personal information that might identify the donor (21 CFR 1271.55(c)).

The recommended extent of HLA match between the donor and recipient and the recommended HPC-C cell dose are important considerations for HPC-C dosage and administration and therefore, this information should be provided in the labeling.

13. Holding and Distribution

SOPs describing the distribution of HPC-Cs must be established and followed and include a system by which the distribution of each lot of HPC-Cs can be readily determined to facilitate its recall if necessary (21 CFR 211.150). We recommend that you:

- Store unprocessed cord blood in a secure location and in containers monitored to maintain the desired temperature range;
- Visually examine the final product containers and all attached containers for damage or possible contamination prior to use and immediately after filling;
- Cryopreserve and store the HPC-C in liquid nitrogen in containers appropriate for long-term storage;
- Place the cryopreserved final product in metal canisters, or use a validated alternative method to protect the HPC-C from damage due to mechanical trauma during cryopreservation, transport within the laboratory, removal from storage, transfer to a shipping container, and shipping to the transplant center;

- Store the cryopreserved HPC-C in a device that has been qualified to maintain the desired temperature and that permits insertion and removal of an HPC-C without compromising the quality of other HPC-Cs stored in the same freezer;
- Store HPC-Cs at the following temperatures or at other acceptable temperatures validated to maintain equivalent product quality:
  - liquid: 15 - 25˚C
  - frozen: ≤ -150˚C (liquid or vapor phase of liquid nitrogen)
- Confirm that temperature controls were maintained throughout the storage period prior to product release. Excursions in storage temperature should be investigated; and
- Not store HPC-Cs with nonhuman material.

You must maintain and record storage temperatures and periodically review recorded temperatures to ensure that HPC-C storage temperatures are consistently within acceptable limits (21 CFR 1271.260(e));

14. Laboratory Controls

You should establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers and closures, in-process materials, labeling, and HPC-C products conform to appropriate standards of identity, strength, quality, and purity. All such procedures must be reviewed and approved by your QCU, and any deviation should be recorded and justified (21 CFR 211.160(a) and (b)).

a. Availability for Distribution and Testing and Release for Distribution

You must not make available for distribution an HPC-C that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under 21 CFR 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission (21 CFR 1271.265(c)(2)).

For each lot of HPC-Cs, there must be appropriate laboratory determination of satisfactory conformance to final specifications (21 CFR 211.165).

- Any sampling and testing plans must be described in written procedures that must include the method of sampling and the volume to be tested; such written procedure must be followed (21 CFR 211.165(c));

- Acceptance criteria for the sampling and testing conducted by the quality control unit must be adequate to assure that HPC-Cs meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release (21 CFR 211.165(d));
- The statistical quality control criteria must include appropriate acceptance levels and/or appropriate rejection levels (21 CFR 211.165(d));
- The accuracy, sensitivity, specificity, and reproducibility of test methods must be established and documented (21 CFR 211.165(e)). The methods validation and documentation may be accomplished in accordance with 21 CFR 211.194(a)(2).
- Results of release testing on HPC-Cs must meet established specifications or acceptance criteria before the unit is released for patient administration (21 CFR 211.165(d), 1271.265(c), and 1271.50(a)); and
- HPC-Cs failing to meet established specifications and any other relevant quality control criteria must be rejected (21 CFR 211.165(f)).

b. Product Safety (21 CFR 610.11, and 21 CFR Part 1271, Subpart C)

i. Infectious Disease Testing

- You may not release an HPC-C for transplantation unless all infectious disease testing has been completed and the test results are negative, or in the case of syphilis testing, the appropriate confirmatory test is negative, except for conditions of documented urgent medical need (21 CFR 1271.60(d)) with a signature of the establishment's medical director and appropriate labeling, as described in 21 CFR Part 1271, Subpart C;
- You must establish and maintain a procedure governing the release of an HPC-C from a donor whose maternal blood sample tests reactive for CMV (see 21 CFR 1271.85(b)(2));
- You should perform sterility testing on a sample of the HPC-C taken before cryopreservation. Testing must be performed as specified in 21 CFR 610.12 or with an equivalent method that has been validated or verified for use with your HPC-C (21 CFR 610.9); and

- You must not release an HPC-C for transplantation that fails sterility testing (21 CFR 1271.265(c)(2), and 21 CFR 211.165(f)).

ii. Hemoglobin Testing

You should obtain hemoglobin screening results that indicate whether an HPC-C donor expresses a homozygous hemoglobinopathy, and you should not release for transplantation an HPC-C with this abnormality. In some situations it may be appropriate to include testing for heterozygous hemoglobinopathies, at the request of the transplant physician.

c. Product Potency (21 CFR 610.10)

i. Total Nucleated Cells

- The total number of nucleated cells in the HPC-C should be adequate to provide, after thawing, at least 1.7×10^7 nucleated cells/kg of body weight of the prospective recipient; and
- Because the weight of the prospective recipient is unknown at the time of storage, we recommend that you store HPC-Cs that contain at least 5.0×10^8 total nucleated cells per product.[9]

ii. Viable Nucleated Cells

You should demonstrate by a validated assay that at least 85% of the nucleated cells in the HPC-C are viable after volume reduction and before cryopreservation (see 21 CFR 211.165(a) and (e)).

iii. Viable CD34+ Cells

The percent of viable nucleated cells expressing the hematopoietic progenitor cell marker CD34+ in a normal HPC-C should be at least 0.25% of the total viable nucleated cell content after volume reduction and before cryopreservation.

[9] We base this number upon a hypothetical recipient of 20 kg and a minimum nucleated cell recovery of 70% after freezing and thawing.

d. Product Identity (21 CFR 610.14)

i. Histocompatibility Testing

- Accredited Laboratory – We recommend that the cord blood bank utilize an HLA testing laboratory certified by CLIA (Clinical Laboratory Improvement Amendments of 1988) and accredited by the American Society for Histocompatibility and Immunogenetics or equivalent accrediting body for initial and confirmatory typing of HPC-Cs;
- Typing Methods – HPC-Cs should be typed by serologic or DNA-based methods for HLA Class I (A and B) loci, and by DNA-based methods for HLA Class II (DRB1) loci. A precryopreservation sample should be used for the initial HLA typing if serologic methods are used;
- HLA Confirmatory Testing of Potential Recipient – Prior to releasing an HPC-C for transplantation, we recommend that you obtain or perform confirmatory HLA typing of the potential recipient's blood, unless this typing has been confirmed and updated on an independent sample by the original laboratory or by an independent HLA laboratory; and
- HLA Confirmatory Testing of HPC-Cs – Once an HPC-C is identified for potential use, we recommend that you test a sample of that unit to confirm the HLA type using a contiguous segment. The confirmatory testing record should include a list of the alleles tested and methodology used.

ii. Blood Grouping and Rh Typing

You should identify and record the ABO and Rh of the HPC-C.

e. Stability Testing (21 CFR 211.166)

You must establish a written testing program designed to assess the stability characteristics of HPC-Cs (21 CFR 211.166(a)). Stability programs should include, but are not limited to, analyses of product potency, integrity, and sterility. These studies should also include analyses of products stored at appropriate temperatures and at specific time intervals. Non-clinical laboratory data, such as in vitro colony forming assays, may be used as part of your stability testing program, supported by clinical transplant data where available. The results of such stability testing must be used in determining appropriate storage

conditions and expiration dates (21 CFR 211.166(a)). The written program must be followed and must include:

- Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability (21 CFR 211.166(a)(1));
- Storage conditions for HPC-Cs and other product samples retained for testing (21 CFR 211.166(a)(2));
- Reliable, meaningful, and specific test methods (21 CFR 211.166(a)(3));
- Testing of the HPC-C in the same container-closure system as that in which the HPC-C is marketed (21 CFR 211.166(a)(4)); and
- An adequate number of HPC-Cs must be tested to determine an appropriate expiration date and a record of such data must be maintained (21 CFR 211.166(b)).

f. Reserve Samples (21 CFR 211.170)

An appropriately identified reserve sample that is representative of each HPC-C must be retained (21 CFR 211.170(a)). You may retain multiple samples. The reserve sample or samples taken together consist of at least twice the quantity necessary for all tests required to determine whether the HPC-C meets its established specifications, except for sterility testing.

While reserve samples consisting of small aliquots of plasma, serum, nucleated cells, and genomic DNA are appropriate for most infectious disease tests, HLA typing, and genetic testing, they may not be optimal for testing product potency (e.g., viability assays) because the results of such assays performed on small aliquots of various cord blood fractions may not directly correlate with results of potency tests performed using samples obtained directly from the original product. Where possible, we recommend that you reserve product aliquots determined to yield results comparable to those obtained using thawed samples of an entire HPC-C for each potency specification tested.

You must retain appropriately identified representative samples of the HPC-C for one year after the expiration of the HPC-C (21 CFR 211.170(b)(1)). You may use the post-thaw expiration date to determine the length of time the reserve samples must be retained. These samples must be retained and stored at temperatures and under conditions that will maintain their identity and integrity and are consistent with product labeling (21 CFR 211.170(b)).

15. Records and Reports

a. General Requirements

You are required to maintain all records for 10 years after their creation (21 CFR 1271.270(d)), with the exception of facility cleaning records, which are to be maintained for 3 years (21 CFR 1271.190(d)(2)). You are required, however, to retain records pertaining to a particular HPC-C at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of distribution, disposition or expiration, whichever is latest (21 CFR 1271.270(d)).

Records must be maintained concurrently with the performance of each step of manufacture (21 CFR 211.188, and 21 CFR 1271.270), including donor screening and testing and recovery (collection) (21 CFR 1271.270(a); see 21 CFR 1271.150(a)) and must be accurate, indelible, and legible (21 CFR 1271.270(a)). The records must include the identity of the individual performing the work and the dates of the various entries (21 CFR 1271.270(a)). The records must be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular HPC-C involved (21 CFR 1271.270(a)).

All required records or copies of the records must be readily available for FDA inspection at the establishment where the activities described in such records occurred, or must be immediately retrieved from another location by computer or other electronic means for review during inspection (21 CFR 211.180(c)). Paper records retrieved via fax or courier from another location are acceptable. If you are under contract, agreement, or other arrangement with a collection facility that acts as your agent and is covered under your registration, the collection records should be made available for review at your establishment (21 CFR 1271.270(b)).

Required records may be maintained electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm (21 CFR 1271.270(c)). Suitable equipment to retrieve these documents must be readily available (21 CFR 211.180(d)).

Written records required by 21 CFR Part 211 must be maintained so that data therein can be used for evaluating, at least annually, the quality standards of HPC-Cs to determine the need for changes in product specifications or manufacturing or control procedures (21 CFR 211.180(e)). SOPs must be established and followed for such evaluations and must include provisions for:

- A review of a representative number of batches of HPC-Cs, whether approved or rejected, and, where applicable, records associated with the batch (21 CFR 211.180(e)(1)); and
- A review of complaints, recalls, returned or salvaged HPC-Cs, and investigations conducted under 21 CFR 211.192 for each product (21 CFR 211.180(e)(2)).

Procedures must be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 21 CFR 211.198, 211.204, or 211.208, any recalls, reports of inspectional observations issued by the FDA, or any regulatory actions relating to good manufacturing practices brought by the FDA (21 CFR 211.180(f)).

b. Equipment Cleaning and Use Logs

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use must be included in individual equipment logs that show the date, time, product, and lot number of each batch processed (21 CFR 211.182). For example, equipment logs must include the date, time, product, and lot number of each HPC-C manufactured.

c. Master Production and Control Records

Under 21 CFR 211.186(b)(9), master production and control records must include, among others:

- Complete manufacturing and control instructions;
- Sampling and testing procedures;
- Specifications; and
- Special notations and precautions to be followed.

You must have SOPs for preparing the master production and control records (21 CFR 211.186(a)).

d. Batch Production and Control Records

Batch production and control records must be prepared for each HPC-C and must include complete information relating to the manufacture and control of each HPC-C (21 CFR 211.188, 21 CFR 600.12(a), and 21 CFR 1271.270). These records must include, among others:

- Documentation that each significant step in the manufacture, processing, packing, or holding of the HPC-C was accomplished (21 CFR 211.188(b));

- Complete labeling control records, including specimens or copies of all labeling used (21 CFR 211.188(b)(8));
- Accompanying records (21 CFR 1271.55(a)(1) through (3)); and
- If applicable, documentation of the urgent medical need when an HPC-C is released before the donor eligibility determination is complete, or an HPC-C from an ineligible donor is released (21 CFR 1271.60(d)(1), and 21 CFR 1271.65(b)(1)(iii)).

16. Failure Investigations

Any unexplained discrepancy or the failure of an HPC-C or any of its components to meet any of its specifications must be thoroughly investigated, whether or not the HPC-C has already been distributed. All HPC-C production and control records, including those for packaging and labeling, must be reviewed and approved by the QCU to determine compliance with all established, approved SOPs before the HPC-C is released or distributed. The investigation must extend to other HPC-Cs that may have been associated with the specific failure or discrepancy. A written record of the investigation must be made and must include the conclusions and follow-up (21 CFR 211.192).

17. Tracking

a. Product Handling

If you perform any step in the manufacture of an HPC-C in which you handle the HPC-C, you must track each such HPC-C in accordance with 21 CFR 1271.290, to facilitate the investigation of actual or suspected transmission of communicable disease and take appropriate and timely corrective action.

You must establish and maintain a system of tracking that enables the tracking of all HPC-Cs from:

- The donor to the consignee or final disposition (21 CFR 1271.290(b)(1)(i)); and
- The consignee or final disposition to the donor (21 CFR 1271.290(b)(1)(ii)).

Alternatively, if you perform some but not all of the steps in the manufacture of an HPC-C in which you handle the product, you may participate in a system of tracking established and maintained by another establishment responsible for other steps in the manufacture of the same HPC-C, provided that the tracking system complies with all the requirements of 21 CFR 1271.290.

b. Distinct Identification Code (21 CFR 1271.290(c))

As part of your tracking system, you must ensure that each HPC-C that you manufacture is assigned and labeled with a distinct identification code (e.g., alphanumeric) that relates the HPC-C to the donor and to all records pertaining to the HPC-C. This labeling must include information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Except in the case of autologous or directed donations, you must create such a code specifically for tracking, and it may not include an individual's name, social security number, or medical record number. You may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or you may assign a new code. If you assign a new code to an HPC-C, you must establish and maintain procedures for relating the new code to the old code (21 CFR 1271.290(c)).

c. Tracking from Consignee to Donor

As part of your tracking system, you must establish and maintain a method for recording the distinct identification code and type of each HPC-C distributed to a consignee to enable tracking from the consignee to the donor (21 CFR 1271.290(d)).

d. Tracking from Donor to Consignee or Final Disposition

As part of your tracking system, you must establish and maintain a method for documenting the disposition of each of your HPC-Cs, to enable tracking from the donor to the consignee or final disposition. The information you maintain must permit the prompt identification of the consignee of the HPC-C, if any (21 CFR 1271.290(e)).

e. Written Confirmation of Requirements

At or before the time of distribution of an HPC-C to a consignee, you must inform the consignee in writing of the requirements in 21 CFR 1271.290 and of the tracking system that you have established and are maintaining to comply with the regulations (21 CFR 1271.290(f)).

18. Complaints

a. SOPs for Handling Complaints

SOPs describing the handling of all written and oral complaints regarding an HPC-C must be established and followed (21 CFR 211.198(a)). SOPs must include:

- Provisions for review by the QCU of any complaint involving the possible failure of an HPC-C to meet any of its specifications (21 CFR 211.198(a)); and
- Provisions for review to determine whether the complaint represents a serious and unexpected adverse experience that is required to be reported to the FDA in accordance with 21 CFR 600.80 (21 CFR 211.198(a)).

b. File for Written HPC-C Complaints

A written record of each complaint must be maintained in a file designated for HPC-C complaints. The file regarding HPC-C complaints must be maintained at the establishment where the HPC-C involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility (21 CFR 211.198(b)).

c. Findings of Investigation and Follow-Up

Where an investigation under 21 CFR 211.192 is conducted, the written record must include the findings of the investigation and follow-up. The record or copy of the record of the investigation must be maintained at the establishment where the investigation occurred in accordance with 21 CFR 211.180(c) (21 CFR 211.198(b)(2)).

d. Reasons for Not Investigating

Where an investigation under 21 CFR 211.192 is not conducted, the written record must include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination (21 CFR 211.198(b)(3)).

19. Returned and Salvaged HPC-Cs

- We recommend that you have a procedure for product recovery in the event of a container failure;
- We recommend that you have a plan for sterility testing of the compromised product and notification of the appropriate individuals and regulatory authorities; and
- You must establish and maintain procedures to determine if a unit of HPC-C that is returned to your establishment is suitable to be returned to inventory (21 CFR 1271.265(f)).

VIII. POSTMARKETING ACTIVITIES

A. Clinical Outcome Data Collection

As an indicator of the quality of your products, we recommend that you analyze information that you receive from the transplant centers on clinical outcomes of individuals who receive from your facility HPC-Cs released for transplantation. You should evaluate these data to determine whether any adverse experiences or other unexpected outcomes identified may be due to problems with product manufacture, and whether corrective actions are needed.

B. Changes to be Reported

Requirements for reporting changes to your approved BLA are contained in 21 CFR 601.12.

C. Adverse Experience Reporting

You must report to FDA adverse experiences that are both serious and unexpected that result in any outcomes such as death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization (21 CFR 600.80). These adverse experiences must be promptly reviewed and reported to FDA as explained in 21 CFR 600.80 using the FDA Form 3500A.[10] You may find clarification of what to report in the guidance document entitled "Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products – Clarification of What to Report" dated August 1997 (August 27, 1997, 62 FR 45425).[11]

You must maintain for a period of 10 years records of all adverse experiences (21 CFR 600.80(i)). This includes toxicity associated with infusion of the HPC-C, and delayed or failed engraftment that may relate to the HPC-C manufacturing.

D. Biologic Product Deviation Reporting

Product deviations from CGMP, applicable regulations, applicable standards or established specifications that may affect the safety, purity, or potency of a distributed product should be reported to FDA as soon as possible but you must report at a date not to exceed 45 calendar days from the date you acquire information reasonably suggesting that a reportable event occurred (21 CFR 600.14(c)). You must report on Form FDA 3486 as described in 21 CFR 600.14(d). These product deviations can be due to testing, processing, packing, labeling, or storage, or withholding or distribution. Product deviations can be reported electronically on CBER's website at http://www.fda.gov/cber/biodev/biodev.htm.

[10] Available at: www.fda.gov/medwatch.

[11] Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071981.htm.

IX. DEFINITIONS

CFR: Code of Federal Regulations.

Cord blood: A unit of blood collected generally by venipuncture of the placental and umbilical cord vessels under aseptic conditions into a sterile container.

CGMP: Current good manufacturing practice.

CGTP: Current good tissue practice.

Histocompatibility: Refers to the similarity of tissues between different individuals. The best-known histocompatibility antigens are those of the major histocompatibility complex, termed HLA in humans.

HLA: Human leukocyte antigen.

HPC-C: Minimally manipulated hematopoietic stem/progenitor cells from placental/umbilical cord blood. For the purposes of this guidance, HPC-C refers to the final drug product (cryopreserved or thawed), sourced from an unrelated allogeneic cord blood donor and intended for hematopoietic reconstitution in patients with specified indications.

Manufacture: Means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

Minimal manipulation: For cells or nonstructural tissue - Processing that does not alter the relevant biological characteristics of cells or tissues.

TNC: Total nucleated cells.

Validation: The confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Verification: The confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

X. REFERENCES

1. Guidance for Industry: For the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, November 1994 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.htm).

2. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, May 1999 (July 7, 1999, 64 FR 36694) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.htm).

3. Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, August 2001 (September 25, 2001, 66 FR 49028) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073497.htm).

4. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004 (October 4, 2004, 69 FR 59258) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.htm).

5. Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements, January 2006 (January 24, 2006, 71 FR 3998) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.htm). When finalized, this guidance will represent FDA's thinking on this topic.