

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

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2009**

Contains Nonbinding Recommendations

Draft – Not for Implementation

Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	GUIDANCE FOR PREPARING IND APPLICATIONS FOR CERTAIN HPC-CS	3
	A. Non-U.S. HPC-C establishment: Existing and future inventory	3
	B. U.S. HPC-C establishment: Pre-licensure inventory	4
	C. U.S. HPC-C establishment: Prospective manufacture of unlicensed HPC-C .	4
	TABLE A: MINIMAL INFORMATION TO BE INCLUDED IN THE IND*	5

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 providing advice to you, potential sponsors (e.g., generally cord blood banks, or registries, and individual physicians serving as sponsor-investigators) to assist in the submission of an investigational new drug application (IND) for certain hematopoietic progenitor cells, cord (HPC-C)¹, when such HPC-Cs are not licensed in accordance with 21 CFR 601, and when a suitable human leukocyte antigen (HLA) matched cord blood transplant is needed for treatment of a patient with a serious or life-threatening disease or condition and there is no satisfactory alternative treatment. If unlicensed HPC-Cs are made available for clinical use, they must be distributed under an IND meeting the applicable requirements in 21 CFR Part 312.

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.

¹ For the purposes of this guidance, HPC-C refers to minimally manipulated hematopoietic stem/progenitor cells from placental/umbilical cord blood, sourced from an unrelated allogeneic cord blood donor and intended for hematopoietic reconstitution in patients with specified indications.

Contains Nonbinding Recommendations

Draft – Not for Implementation

II. BACKGROUND

This guidance document is applicable to certain unlicensed HPC-Cs that are made available for transplantation in cases when no satisfactory alternative treatments are available. This guidance document is applicable only to HPC-Cs intended for hematopoietic reconstitution in patients with the clinical indications listed in the Guidance for Industry entitled “Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Specified Indications” (HPC-C licensure guidance). Thus, this guidance covers 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 Adrenoleukodystrophy,
 - Primary immunodeficiency diseases
 - Bone marrow failure
 - Beta thalassemia; and
- Intended to be used in recipients unrelated to the donor.

This guidance document provides recommendations for the submission of an IND application (21 CFR Part 312) for such HPC-Cs that are not FDA-licensed but are needed for treatment of patients with the indications specified above and for which there is no satisfactory alternative. Specifically, these HPC-Cs are:

- Manufactured in non-United States (U.S.) cord blood establishments, listed in international cord blood registries, and selected for treatment of a patient in the U.S.;
- Manufactured in U.S. cord blood establishments before a biologics license application (BLA) has been approved and not shown to meet licensing criteria (e.g., not shown to be comparable to other licensed HPC-C in the inventory); or
- Prospectively manufactured in the U.S. and do not meet licensing criteria but for which there is no satisfactory alternative (e.g., for the purpose of assuring patient access to HPC-Cs with diverse HLA phenotypes).

The HPC-C licensure guidance describes ways for cord blood manufacturers to apply for licensure of their HPC-Cs, for specified indications. That guidance document is intended to assist the manufacturers in obtaining a biologics license by following recommendations and applicable requirements in 21 CFR Part 601. It provides guidance on the content and format of information to be submitted in a BLA for HPC-Cs in the chemistry, manufacturing and controls (CMC) section and the establishment description section, and other information about how to comply with applicable regulatory requirements.

Contains Nonbinding Recommendations

Draft – Not for Implementation

FDA recognizes that there will be situations in which there will not be a licensed cord blood unit that provides an appropriate match for a patient in need and that an unlicensed cord blood unit may be the best match. Because each cord blood unit is unique and may be life-saving for a particular patient, we recognize the importance of the availability for transplantation of certain unlicensed cord blood units. This guidance document outlines the minimum information that should be included in an IND application for the HPC-Cs described above. Sponsors who follow this guidance may choose to either submit one IND to cover the use of multiple cord blood units, or submit a separate IND for each single-patient use.

III. GUIDANCE FOR PREPARING IND APPLICATIONS FOR CERTAIN HPC-CS

HPC-Cs described in this section may be made available for clinical use when a sponsor submits an IND application to FDA and the IND goes into effect under 21 CFR 312.40(b). The sponsor of the IND may be the manufacturer (generally a cord blood bank), or a national or international cord blood registry involved in coordinating the distribution of HPC-Cs from participating cord blood banks. Generally, a physician seeking to transplant HPC-Cs described in this section would serve as an investigator under the IND, but a physician also can be a sponsor-investigator.

A. Non-U.S. HPC-C establishment: Existing and future inventory

Some non-U.S. HPC-C establishments may choose not to apply for licensure, therefore, there will need to be an IND in order to import unlicensed HPC-Cs that are listed in international registries. These registries are searched by transplant physicians, including U.S. transplant physicians when such HPC-Cs are needed for treatment of patients with the diseases indicated in the HPC-C licensure guidance. Additionally, products from these establishments often will not meet the criteria for licensure and thus, an IND route would be required if the product were selected for use in a patient in the U.S. Examples of such situations may include, but are not limited to:

1. The donor eligibility determination, including relevant communicable disease screening and testing, was performed in accordance with the standards and industry practices of another country but do not meet all of the requirements in 21 CFR Part 1271 Subpart C; or
2. The HPC-C release criteria are different from those recommended in the HPC-C licensure guidance and insufficient information is available to demonstrate their equivalence; e.g., lower total nucleated cell count (TNC); CD34+ cell count not performed.

The minimal information to be included in an IND for these HPC-Cs is summarized in Table A, Column A.

Contains Nonbinding Recommendations

Draft – Not for Implementation

B. U.S. HPC-C establishment: Pre-licensure inventory

An IND should be submitted for the pre-licensure inventory of unlicensed HPC-Cs that cannot be shown to be comparable to the establishment's licensed HPC-Cs and are needed for treatment of patients with the serious or life-threatening diseases or conditions described in the background section of this guidance. The minimal information to be included in the IND for these HPC-Cs is summarized in Table A, Column B.

C. U.S. HPC-C establishment: Prospective manufacture of unlicensed HPC-C

An IND should be submitted if cord blood establishments seek to include in their inventory HPC-Cs that are not licensable as outlined in the HPC-C licensure guidance due to failure to meet donor eligibility or manufacturing criteria. The agency expects that this will be an uncommon situation. However, we understand that there may be certain situations in which the manufacture of such units is reasonable. For example, some cord blood donors from under-represented populations may test reactive/positive for Hepatitis B virus (HBV) core antibody but test negative for HBV surface antigen and HBV nucleic acid (by nucleic acid amplification testing (NAT)), indicating that the donor most likely has recovered from a previous HBV infection, and HPC-Cs from such donors would be unlikely to transmit the viral infection. Collection of cord blood from these ineligible donors, in order to maintain diversity of HLA phenotypes of units in inventory, may increase the likelihood that patients with serious or life threatening diseases or conditions without satisfactory alternative treatments and with less common HLA types will be able to find suitably matched HPC-Cs for transplantation.

The minimal information to be included in the IND for these HPC-Cs is summarized in Table A, Column C.

Contains Nonbinding Recommendations

Draft – Not for Implementation

Table A: MINIMAL INFORMATION TO BE INCLUDED IN THE IND*

IND Category	A. Non-U.S. HPC-C establishment - Existing and future inventory.	B. U.S. HPC-C establishment - Pre-licensure inventory.	C. U.S. HPC-C establishment - Prospective manufacture of unlicensed HPC-Cs
Labeling (21CFR 312.6, 21 CFR 312.23(a)(7)(iv), 21 CFR 1271.55)	Container label and English language supplemental labeling as described in the regulations, including: • Limited summary of manufacturing information • Donor eligibility summary of records (for HPC-C manufactured on or after 5/25/05) • Directions for use • Caution Statement	Container label and supplemental labeling as described in the regulations, including: • Representative draft labeling • Donor eligibility summary of records (for HPC-C manufactured on or after 5/25/05) • Labeling content described in Section VII.B.12 of HPC-C licensure guidance • Directions for use • Caution Statement	Same as category B.
Promotion and charging (21 CFR 312.7(d))	As described in the regulation.	As described in the regulation.	As described in the regulation.
IND content and format (21 CFR 312.23) Cover sheet (Form FDA 1571)	Sponsor's name, address, and telephone number; Date of the application; Commitment that an Institutional Review Board (IRB) will be responsible for review and approval of the study; Name and title of the person responsible for monitoring the	Same as category A.	Same as category A.

Contains Nonbinding Recommendations

Draft – Not for Implementation

Investigator's Brochure (IB) (21 CFR 312.23(a)(5), if required (21 CFR 312.55; IB not required for sponsor-investigators	clinical investigation; and Signature of the sponsor. Describes the product and its formulation (cell content and additives); including a description of possible risks. Provides recommended instructions for HPC-C thawing and administration	Same as category A.	Same as category A.
Protocol	Provides a brief summary of the study including a description of the cord blood dosing plan, and outlines recipient safety monitoring and reporting during infusion and post-transplant. Outlines plan for review of clinical outcome data. The data should be reviewed to determine whether any adverse experience (e.g., seroconversion or other evidence of relevant communicable disease agent or disease transmission, failure to engraft) or other serious or unexpected outcomes identified may be due to problems with product manufacture, and whether corrective actions are needed.	Same as category A.	Same as category A.

Contains Nonbinding Recommendations

Draft – Not for Implementation

CMC - Donor Eligibility	Describes procedures for donor eligibility determination for HPC-C manufactured on or after 5/25/05: Follow 21 CFR 1271 Subpart C (DE rule) and see DE guidance **; if not all requirements in 21 CFR 1271.75, 21 CFR 1271.80 and 21 CFR 1271.85 were met, label “Not evaluated for infectious substances” and “Warning: Advise patient of communicable disease risks”; in addition, if donor has a risk factor, label “Biohazard” and state risk factor in summary of records; in addition, if donor has a positive test result, label “Biohazard” and “Reactive test results for...” Donor eligibility for HPC-C manufactured before 5/25/05: Describes donor screening and testing performed to prevent spread of communicable disease.	Same as category A.	Same as category A. Additionally, certain HPC-C from ineligible donors could be made available for use, with appropriate labeling and other manufacturing controls. For example, when a donor tests positive for HBV core antibody (and negative for HBV surface antigen and HBV NAT), label with Biohazard legend; “Warning: Advise patient of communicable disease risks” and “Warning: Reactive test results for...”
---------------------------------------	---	----------------------------	--

Contains Nonbinding Recommendations

Draft – Not for Implementation

CMC - Release specifications	• No evidence of contamination (describe sterility testing performed and provide results) • TNC count – define minimal specifications and report • Cell viability – define minimal specifications and report*** • Identity – HLA, ABO/Rh • Hemoglobin testing - report	Same as described in the HPC-C licensure guidance (Section V.B), or provide alternative manufacturing procedures, controls, and/or release criteria.	Same as category B.
-------------------------------------	--	---	----------------------------

* The items listed in the Table are examples of the types of information to be included in the IND application. Regulations in 21 CFR 312 not listed also apply, except where indicated.

** Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) dated August 2007. Available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072929.htm>.

*** For licensed HPC-Cs, the minimum numbers of viable nucleated cells and viable CD34+ cells are recommended in the HPC-C licensure guidance. Alternative specifications for cell viability may be submitted in the IND for consideration by the agency.

****A sponsor-investigator is not required to prepare an investigator brochure.

Contains Nonbinding Recommendations

Draft – Not for Implementation

IV. Responsibilities of sponsors and investigators

The responsibilities of sponsors and investigators set forth in 21 CFR 312 subpart D are applicable to INDs described in this guidance.

- An individual or entity that submits an IND is considered a sponsor and must comply with the responsibilities for sponsors set forth in 21 CFR 312 subpart D to the extent they are applicable to the IND. A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND as described in this guidance, is considered a sponsor-investigator, and must comply with the responsibilities for sponsors and investigators set forth in 21 CFR 312 subpart D to the extent they are applicable to the IND.

Sponsors are responsible for:

- submitting IND safety reports and annual reports (when the IND or protocol continues for one year or longer) to FDA as required by 21 CFR 312.32 and 21 CFR 312.33,
- ensuring that licensed physicians are qualified to administer the investigational drug,
- providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug,
- maintaining an effective IND with respect to the investigations (as set forth in the IND regulations),
- maintaining adequate drug disposition records, and retaining records in a manner consistent with the requirements of 21 CFR 312.57.

Investigators are responsible for:

- reporting adverse drug events to the sponsor,
- ensuring that the informed consent requirements of 21 CFR part 50 are met,
- ensuring that IRB review of the use of the HPC-Cs under the IND is obtained in a manner consistent with the requirements of 21 CFR part 56, and
- maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of 21 CFR 312.62.