Date: _____

Dear Doctor:

Miltenyi Biotec's CliniMACS® CD34 Reagent System is approved as a Humanitarian Use Device (HUD) by the U.S. FDA following Miltenyi's submission pursuant to regulations outlined in the Humanitarian Device Exemption (HDE) regulations. The approved label indication is as follows:

HUMANITARIAN DEVICE: Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this indication has not been demonstrated.

INDICATIONS AND USAGE

The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

What does "the effectiveness of the device for this indication has not been demonstrated" mean?

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. The number of patients diagnosed with AML in CR1, and indicated for allogeneic transplantation, enables the CliniMACS® CD34 Reagent System to be regulated and approved as an HUD.

The Humanitarian Device Exemption (HDE) regulatory submission is similar in both format and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. Given the low patient numbers, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is ***effective*** for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. Furthermore, the clinical data must support a premise of "probable benefit"; in that the risk to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The CliniMACS® CD34 Reagent System was shown to meet this requirement.

What does this mean for me?

The CliniMACS® CD34 Reagent System is now available for sale under the HDE regulations. The following components now have the HDE indication on their package insert:

CliniMACS® CD34 Reagent (200-070-103)
CliniMACS® PBS/EDTA Buffer (200-070-026)
CliniMACS® Tubing Set TS (200-073-105) and Tubing Set LS (200-070-205)
CliniMACS® plus Instrument (200-029-101)

What is required in order for me to use the CliniMACS® CD34 Reagent System?

Unlike our procedures surrounding the distribution of other Investigational Products, the purchase of the above components will no longer require documentation from FDA. However, as the holder of the HDE for the CliniMACS® CD34 Reagent System, Miltenyi Biotec is responsible for ensuring that the CliniMACS® CD34 Reagent System is:

1. **used under physician order, only in Institutions having a properly constituted and functioning Institutional Review Board (IRB) and**
2. **The IRB has approved the use of this Humanitarian Use Device in treating patients within the Institution.**

Documentation confirming both of these requirements must be in place at Miltenyi Biotec in order for the CliniMACS® CD34 Reagent System components to be shipped to your Institution.

Requirement #1: How does Miltenyi plan to ascertain that Institutions have a properly constituted IRB?

Pursuant to 45 CFR Part 46, the U.S. Department of Health and Human Services (www.hhs.gov) has oversight of "Office for Human Research Protection" (OHRP) which assigns **Federal-wide Assurance (FWA) numbers.** Through the FWA, an Institution commits to HHS that it will comply with the requirements for the Protection of Human Subjects per 21 CFR Parts 50 and 56. Thus, Miltenyi Biotec intends to use the FWA numbers to certify that each Institution that receives HDE product operates under a properly constituted and functioning IRB.

All existing, and future sites wishing to utilize the CliniMACS® CD34 Reagent System as a Humanitarian Use Device will be asked to provide their FWA number to Miltenyi Biotec to satisfy that they operate under a properly constituted and functioning IRB. The information supplied in **Attachment A** will be filed by Miltenyi Biotec in order to satisfy requirement #1 listed above. If the IRB which oversees the use of the CliniMACS® CD34 Reagent System site does **not** have an FWA number, the Institution will be required instead, to submit responses to the questions listed under Item #2 of **Attachment A or provide an equivalent formal written attestation of this information**. Miltenyi Biotec must receive the information listed under #1 or #2 of **Attachment A** in order for the CliniMACS® CD34 Reagent System components to be provided to your Institution without an FDA assigned IND or IDE number.

Requirement #2: What must my IRB do to review and approve the use of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device?

The CliniMACS® CD34 Reagent System has been approved for marketing within the indication listed above. This FDA approval is based on evidence of safety and probable benefit within the patient population treated in the clinical study. Therefore, the use of the System to treat the patients meeting the approved indication is not deemed "clinical investigation". Even though the device is not considered investigational, IRB review is required per the Humanitarian Use Device Regulations, with the exception of emergency use. The initial review must be performed by the full Institutional Review Board, although continuations may be performed by expedited review.

The health care provider(s) at the Institution continue to be responsible for obtaining IRB approval before using the CliniMACS® CD34 Reagent System as a Humanitarian Use Device (HUD), except in certain emergencies where prior IRB approval is not required. Specifically, FDA recommends reviewing the following materials during initial review of the HUD. The first **TWO** items will be provided by Miltenyi Biotec:

- A copy of the HDE approval letter;
- The CliniMACS® CD34 Reagent System Instructions for Use (IFU)
- A summary of how the physician(s) within the Institution propose to use the System, including a description of the inclusion criteria.

Currently, many IRBs provide guidance and/or forms for HUD or HDE applications to the IRB. While the HDE regulations do not require informed consent for treating patients within the label indication, it is up to your Institution as to whether a patient consent will be required.

In reviewing the use of the CliniMACS® CD34 Reagent System as a HUD, your IRB should understand that the FDA has made a determination of safety and probable benefit for use of the HUD within its approved indication. The IRB is not required to review and approve each individual use. Your IRB may use its discretion to determine how to approve use of a HUD. When a HUD is used to treat patients, i.e., not for research, the FDA does not require submission of a protocol to the IRB for review. However, your IRB or Institution may require one under its own policies and procedures.

There is no regulatory requirement for committees other than the IRB to approve the use of a HUD. However, this is left to the discretion of your Institution. Similarly, the FDA does not require you to audit medical records of patients who have been treated using a HUD.

Am I required to obtain IRB Approval for use of the HUD if our Institution already has an approved protocol for the use of the CliniMACS® CD34 Reagent System under the Investigational Device Exemption (IDE) Regulations ?

Yes. The labeling has changed on all components of the CliniMACS® CD34 Reagent System to reflect the new Indication as a Humanitarian Use Device. According to the FDA requirements if the initial review was performed using the full panel, IRBs may use the expedited review procedure as outlined in 21CFR 56.110. FDA recommends the use of an expedited procedure because a HUD is a legally marketed device and no safety and effectiveness information is being collected, as is required for research protocols. An expedited review does not mean a less than substantive review. During the expedited review, the Chair or the Chair's designated member(s) should thoughtfully consider the risk and benefit information. IRBs may develop their own policies and procedures for continuing review of a HUD and may perform this review at a convened meeting.

In accordance with this FDA Guidance, Miltenyi is required to document proof that your Institution's IRB has approved the use of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device in order for product to be shipped to your Institution without documented proof of an FDA sanctioned protocol. Once you have obtained IRB Approval to use the System, please complete Attachment B or an equivalent attestation, and forward this information to your Clinical Applications Manager or myself. Taken with the Information provided in Attachment A, you will then be able to routinely order the CliniMACS® CD34 Reagent, Tubing Sets and Buffer.

Will Miltenyi ship product if I have a patient requiring emergent therapy and I do not yet have IRB approval?

Yes. If you as a physician are treating in an emergency situation and determine that IRB approval for the use of the CliniMACS® CD34 Reagent System cannot be obtained in time to prevent serious harm or death to a patient, the CliniMACS® CD34 Reagent System may be used without prior IRB approval. You should contact your Clinical Applications Manager, or myself and we will arrange for product to be shipped for you on a "emergency" basis. You must however, provide written notification regarding the emergency use to your IRB Chairman within five days; including identification of the patient involved, the date of the use, and the reason for the emergency use.

Please refer to the FDA Guidance: "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" for additional information regarding IRB review of Humanitarian Use Devices:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm#7

We are anxious to support the integration of the newly approved CliniMACS® CD34 Reagent System into your clinical practice! Please do not hesitate to contact your Miltenyi Clinical Applications Manager at our toll free number, 1-800-FOR-MACS (1-530-888-8871) Prompt #5, or myself if we can provide additional information in support of your IRB application.

Sincerely,

_____

Regulatory Affairs
Miltenyi Biotec, Inc.
120 Beacon Street
Somerville, MA 02143

Attachments: A: Institutional Review Board (IRB) Information
B: Notice of IRB Approval for the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

ATTACHMENT A

Institutional Review Board (IRB) Information

1. Please Provide the FWA Number assigned to the IRB that oversees clinical trial activities within your Institution:

   FWA Number: _____

   No further information is necessary if an FWA Number is provided.

2. ***If your Institution does not have an FWA Number***, please provide the following information:

a. The IRB name, if any, used by the institution or organization (e.g., State University Behavioral IRB or University Healthcare Biomedical IRB):

   _____

b. Complete Mailing Address of the IRB, including City, State and Zip; plus country if outside the USA:

   _____

   _____

   _____

   _____

c. Telephone Number(s) for IRB:

   _____

   _____

d. Fax Number for IRB:

   _____

e. IRB Chairperson

   a. Full Name: _____

   b. Title or Position: _____

   c. Earned Degree(s): _____

f. In lieu of providing IRB Member information in the table below, the Chairperson of the IRB may attest that the IRB is duly constituted and complies with 21 CFR parts 50 and 56. Links are as follows:

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1

As Chairperson for the Institutional IRB referenced above in Section 2, I attest that our Institutional Review Board complies with the FDA 21 CFR Parts 50 and 56.

RESEARCH INSTITUTION _____

DATE: _____

READ AND ACKNOWLEDGED:

INSTITUTIONAL REVIEW BOARD CHAIRMAN: (PRINT NAME) _____

INSTITUTIONAL REVIEW BOARD CHAIRMAN (SIGNATURE) _____

If section 2.f. is <u>not</u> completed by the Chairman, please complete the table below to identify all IRB Members approving the use of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device:

Member Name (Last, First)	Earned Degree(s)	Scientist (S) or Nonscientist (N)	Primary Scientific or Nonscientific Specialty	Affiliation with Institution(s) Y/N
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				

Please return this form to your Clinical Applications Manager, or Fax to 1-831-417-9621

ATTACHMENT B

Notice of IRB Approval for the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

Date: _____

Miltenyi Biotec Incorporated
120 Beacon Street
Somerville, MA 02143
Phone: 1-800-810-3135
Fax: 1-617-218-0060

Regarding: IRB Approval of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

To Whom It May Concern:

The letter certifies that the CliniMACS® CD34 Reagent System has been reviewed and approved by our Institutional Review Board (IRB) for Use as a Humanitarian Use Device. During the review of this Project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

It is agreed that any and all adverse event(s) that occur when using the CliniMACS® CD34 Reagent System will be reported in accordance with the Medical Device Reporting Regulations, including notification to Miltenyi Biotec Incorporated at the address and/or fax number listed above.

Signed: _____

Print Name: _____

IRB Chairman or Treating Physician: _____

Institution: _____

Address: _____
_____
_____

Email Address: _____

Phone: _____