



January 7, 2009

**National Marrow  
Donor Program®**

Entrusted to operate the  
C.W. Bill Young  
Cell Transplantation Program

**National Coordinating Center**  
3001 Broadway St. N.E.  
Suite 100  
Minneapolis, MN 55413-1753

Toll Free: 1 (800) 526-7809  
Phone: (612) 627-5800  
marrow.org

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Docket 2008-D-0520, October 9, 2008 “Draft Guidance for Industry:  
Potency Tests for Cellular and Gene Therapy Products”**

Dear FDA Dockets Manager:

We are writing to submit comments in reference to the Guidance Document for Industry: *Potency Tests for Cellular Therapy Products*, the draft guidance for developing potency tests for submission of an Investigational New Drug Application (IND) or Biologics License Application (BLA). The comments relate only to the field of cord blood banking and collection and use of Peripheral Blood Stem Cells (PBSCs) for transplantation. This document is a summary of reviews conducted by a working group, consisting of representatives of a number of cord blood banks that participate in the National Marrow Donor Program (NMDP) network and staff from the NMDP. These comments address a number of issues that we believe are important to consider in developing potency measurements that may be applied to release criteria in these settings.

The group made the following comments:

**1. Page 1, section I. Introduction, second paragraph:** This document states that it applies only to CGT products regulated under section 351 of the Public Health Service Act. As such, we understand that this guidance applies to the development of potency and / or release criteria for 351 HCT/Ps for which there is not yet a published FDA document with more specific potency guidance. In the context of allogeneic cord blood collected for transplantation, we understand that this guidance document would not apply because there is more specific potency guidance published in the Guidance Document for Industry: *Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies*. For allogeneic peripheral blood stem cells (PBSCs) for transplantation, we understand this document to be applicable because more specific FDA guidance has not yet been developed. Please verify this is an appropriate interpretation. However, if this guidance does apply to HPC-Cs, please provide more specific guidance about what would be an acceptable approach to demonstrate potency and cGMP comparability between current units and those that were manufactured prior to this guidance so that those units could be made available for routine use.



Division of Dockets Management (HFA-305)  
Food and Drug Administration  
January 7, 2009  
Page 2

**2. Page 3, Section II. A. Background, 8<sup>th</sup> bullet regarding dating periods:**

The use of potency data to assign an expiration date for cord blood units (HPC-C) or PBSCs that may be cryopreserved is problematic. Current data shows that HPC-C units can be stored for extended periods of time and result in successful transplants. Broxmeyer and Cooper (*Clinical Experimental Immunology* 107(Suppl 1):45-53, 1997) reported 74-91% recovery of CFU-GM, BFU-E and CFU-GEMM 10 years after cryopreservation. Kobylka et al (*Transplantation* 65(9): 1275-1278, May 15, 1998) reported 80% nucleated cell recovery on cord blood cryopreserved in liquid nitrogen for 15 years. These samples also grew progenitor cell colonies in culture. Additional unpublished data support efficient stem cell recovery following cord blood cryopreservation for over 20 years (H. Broxmeyer, personal communication). We do not believe the data adequately support the definition of an expiration date for cryopreserved HPC-C or PBSCs at this time. Similarly, the use of potency data to define expiration dates in the context of the collection of PBSCs for immediate transplantation is not relevant to this clinical setting.

**3. Page 4, Section C., 4<sup>th</sup> sentence** With regard to relationship of potency measurements and correlation to clinical efficacy in context of HPC-Cs or PBSCs, we wish to highlight the following limitations. Based on current data, the clinical efficacy is most positively correlated with the Total Nucleated Cells (TNC) and the HLA match between the donor and recipient (data previously submitted in docket number 1997N-0497). However, the clinical efficacy is also related to the dose that is needed for a particular recipient. The TNC and HLA type are determined as part of the manufacturing process for both HPC-Cs and PBSCs. However, the HLA match and dose are not known at the time of manufacture of HPC-Cs. Additionally, in the context of HPC-Cs, the clinical effectiveness of the product is affected by the conditions of transport and, more importantly, thawing practices at the transplant center. Neither of these is under control of the manufacturer. Similarly, the transport and handling of PBSCs after their manufacture impacts the clinical efficacy and is not in the control of the manufacturer. It is our understanding that the manufacturer's responsibility includes packing for transport. In the context of cryopreserved HPC-Cs or PBSCs, instructions for thawing are part of the materials provided to the transplant center, as well. Please verify that the manufacturer's responsibility and potential impact to potency does not include transport or thawing.



Division of Dockets Management (HFA-305)  
Food and Drug Administration  
January 7, 2009  
Page 3

4. **Page 6, Section III.B. 1 Biological assays;** While the results of a number of bioassays are part of the data collected routinely for HPC-Cs and PBSCs to evaluate product characteristics (TNC, viable nucleated cells, CFCs, viable CD34+ cells, etc), we believe that TNC is the best and most consistent bioassay for potency across the industry currently. Recent inter-laboratory proficiency testing data show that there is significant variability between labs using current methods to determine CFC and CD34+ values. The NMDP member cord blood banks participate in an annual proficiency testing program that uses fresh cord blood samples. This program is conducted in partnership with StemCell Technologies, an industry leader in proficiency program and colony forming unit assays. The outcome of three years of testing has documented a high degree of variability for CFU identification. The CV for total colonies in the CFU assay is approximately 36%, with higher degree of variation on specific colony identification. Based on more limited data for CD34 enumeration, a similar pattern of variation was seen. The CV for CD34 can be as high as 40%. Although these tests were performed by trained, experienced technicians, these assays are subjective and are prone to technician bias. Because of this variability, we would suggest that potency measures to be used for potential release criteria be limited at this time to TNC. It is also important to note that potency of cryopreserved HPC products is defined on the pre-cryopreserved product. As such, potency is different than release criteria. Additionally, for PBSCs, the results of some of the bioassays referenced above are not available to the manufacturer at the point of release of the unit for subsequent transport. By definition, these potency assay results cannot be used as release criteria in this setting. Transplant centers consistently view TNC as the most critical value in combination with the HLA match of the donor-recipient pair in clinical practice, as well.

We greatly appreciate the FDA's willingness to consider these comments. We look forward to seeing a finalized document for industry use. Please address any questions related to these comments to John Miller, M.D., Ph.D, Senior Medical Director at [jmiller@nmdp.org](mailto:jmiller@nmdp.org) or (612) 884-8534.

Sincerely,

A handwritten signature in blue ink, appearing to read "J. Miller", is written over a horizontal line.

John Miller, M.D., Ph.D.  
Vice President and Senior Medical Director