

August 23, 2004

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

Re: *Docket No. 2004D-0193: Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products*

Dear Sir/Madam:

Cord Blood Registry® (“CBR”) respectfully submits these comments to the Food and Drug Administration (“FDA”) in response to the notice requesting comments on the Agency’s draft guidance on eligibility determination for donors of human cells, tissues, and cellular and tissue-based products (“HCT/Ps”), including donor screening and testing (“FDA’s Draft Guidance”).^{1/}

CBR is the oldest family cord blood bank in the world, and has been processing and storing cord blood stem cells since 1992. More than 60,000 families have stored cord blood samples in CBR’s facility, which is accredited by the American Association of Blood Banks (“AABB”). More than 18,000 caregivers have collected cord blood for our clients at over 2,500 birthing centers throughout the United States and in more than 50 countries. CBR also provides extensive educational resources for obstetricians,

midwives, and hospitals, and is the largest contracted service provider to some of the nations leading HMOs and health insurance companies.

As a family cord blood bank, CBR's primary service provides parents of newborns with the collection, processing, and long-term cryopreservation of stem cells found in the umbilical cord blood, which are otherwise routinely discarded along with the placenta. These unique newborn stem cells are then available for use by the family and genetically related extended family members (second-degree blood relatives), where transplant results are superior to genetically unrelated cord blood transplants. CBR believes in the value of cord blood stem cells, and sets high standards for storing and processing samples. CBR welcomes development of regulations by FDA that will ensure that quality and safety guidelines are met by all operating cord blood banks.

However, CBR believes that FDA's Draft Guidance should recognize the important differences between family cord blood banks and public banks in the context of donor eligibility. Family banks maintain a long term relationship with the donor, and the birth mother, and the cord blood is intended to be used by the donor, and/or the donor's family. In contrast, a public bank's contact with the donor, and donor's family, is usually limited to the time of cord blood collection. A public bank sample will be stored anonymously,

^{1/} Draft "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" Availability, 69 Fed. Reg. 29835 (May 25, 2004).

and the mother and child will not be available for testing or screening at a later date. Additionally, the donation may be used for any matching recipient. Specific examples of differing regulatory concerns between family cord blood banking and public banking, that should be made in FDA's Draft Guidance, are provided in CBR's comments below.

I. FDA's Draft Guidance Fails To Recognize That Infectious Disease Marker Testing Is Less Reliable In Pregnant Women

FDA's Draft Guidance fails to recognize that Infectious Disease Marker ("IDM") testing is less reliable in pregnant women. FDA's regulations on virus testing in the case of a neonate specify that the mother's specimen is acceptable for testing.^{2/} However, because IDM testing is less reliable in pregnant women, a high rate of false positives for maternal blood can be generated, which causes unnecessary distress to the mother and family of the donor.

As shown in Table 1, using FDA approved kits for IDM testing, we report a higher incidence of false positive or indeterminate test results in pregnant women, and believe that these results demonstrate that these tests have not been optimized for use in this population.

^{2/} 21 C.F.R. § 1270.21 (a) (2004).

Table 1. Infectious Disease Marker Repeat Reactive Rates for Cord Blood Registry (“CBR”) and Blood Systems Laboratories (“BSL”) Testing

Infectious Disease Marker	CBR Reactive Rate (%)	BSL Reactive Rate (%)	CBR Retest Negative^a (%)
Anti-HBc ^c	2.72	0.689	58
HbsAg ^c	0.55	0.097	N/A
HCV	0.24	0.219	83
HIV-1,2	0.11	0.136	100
HTLV I/II	0.34	0.136	100
<i>Treponema pallidum</i> ^b	0.61	0.136	90
NAT HIV and HCV (Multiplex)	0.13	0.11	100

^a Based on clients providing retest results

^b *T. pallidum*, the causative agent of syphilis, is killed at temperatures below 4°C. Storage of stem cells at -195°C would eliminate the possibility of transmission of this agent.

^c Higher rate may be due to the large number of Asian clients, e.g., HBV is endemic in Asia.

The manufacturers of the kits for IDM testing have confirmed that the kits have not been validated in serum or plasma from pregnant female, and Blood Systems Laboratories (“BSL”), which is a non-profit health care service,^{3/} believes that the higher than normal false positive rate is probably due to the fact that the sample is taken from a pregnant female at a time when hormone levels, and circulating proteins, are outside of the “normal” range, and cause interference in the assays.

FDA’s recommendation to conduct IDM testing on maternal blood for family cord blood banking is frequently the cause of unnecessary distress to the mother and family. It is alarming to a breast-feeding mother to receive a letter that she is positive for HIV, hepatitis virus, or HTLV. Many women stop breast-feeding upon receiving such a letter only to find out that the results were incorrect, or a false positive. By simply allowing testing to occur upon release of the sample for use in medical therapies, instead of testing at the time of storage, families can avoid distress of receiving false positive testing results.

The high false positive rate for maternal blood is inconsistent with FDA’s prohibition of collecting cord blood if the maternal sample is reactive for HBsAg.^{4/} If subsequent

^{3/} BSL, formed in 1991, has 2 donor testing service laboratories, which are licensed by FDA, hold current CLIA certification, and are accredited by AABB and the New York State Department of Health.

^{4/} FDA’s Draft Guidance, at 31.

testing, for example by nucleic acid testing (NAT) for HBV, indicates that the sample is negative, a false positive should not prohibit collection of the cord blood.

Therefore, FDA's Draft Guidance should recognize the high false positive rate of IDM testing for maternal blood, and should not make prohibitions that preclude determining the true status for infectious disease testing.

II. FDA's Draft Guidance Should Specify Expressly That Inclusion Of The Donor's Name For Autologous Or Directed Donation Includes Family Cord Blood Banking

FDA's Draft Guidance should specify expressly that inclusion of the donor's name and personal information is permitted for family cord blood banking. FDA's Draft Guidance requires that the HCT/P, and the accompanying records, identify the donor by a distinct identification code, "but not by name (except in the case of an autologous or directed donation)."^{5/} CBR requests that FDA emphasize in FDA's Draft Guidance that autologous or directed donation includes family cord blood banking. The donor's name is an important identifier on the cord blood sample, as well as all accompanying records. In addition to the unique identification number, the donor's name is important in the

^{5/} FDA's Draft Guidance, at 13.

family donation setting. It is an important second identifier, and would give assurance to the family and transplant physician that they are receiving the intended product.

Inclusion of the donor's name is expected by, and part of the consent from, the donor's family, and, thus, would not be a violation of privacy protections.

Therefore, CBR strongly supports inclusion of the donor's name for autologous or directed donation, and requests further emphasis by including family banking in the language in FDA's Draft Guidance. Specifically, we recommend that the Guidance be modified to read as follows: "(except in the case of an autologous or directed donation, such as family cord blood banking)."^{6/}

III. FDA's Draft Guidance Should Provide For Sample Testing At The Time A Cord Blood Sample Is Released For Transplant Instead Of The Time Of Donation For Family Banking

FDA's Draft Guidance should provide for sample testing at the time a cord blood sample is released for transplant instead of the time of donation for family banking. FDA's Draft Guidance requires that tissue banks "must collect the donor specimen for testing at the

^{6/} FDA's Draft Guidance, at 13.

same times as cells or tissue are recovered from the donor, or, if this is not feasible, within seven days before or after the recovery of cells and tissue.”^{7/}

For family banking, it is more appropriate that a sample intended for donor testing be tested at the time of release of the sample for transplantation, and not at the time of donation. Testing performed at the time of release will be more accurate, and allow for screening for the most relevant diseases using the most current testing methodology. Testing technology is rapidly changing, as is the panel of diseases that must be identified. Twenty five years ago, we did not test for Hepatitis C or West Nile viruses nor did we have nucleic acid testing. Accordingly, FDA’s Draft Guidance should accommodate and allow for technological innovations, and the evolution of infectious diseases. A maternal blood sample could be submitted at the time of collection, and stored for future testing. Agency concerns for any potential cross-contamination can be addressed by ensuring that there are adequate safeguards in place, such as storage conditions that include physical separation and preclude any contact among samples.

Another basis for permitting donor testing at the time of release is that family banking has established and maintains a long-term relationship with the donor and the donor’s family. This ongoing contact permits donor screening at the time of transplant to detect conditions that may not have been apparent or present at birth.

^{7/} FDA’s Draft Guidance, at 26.

For all these reasons, FDA's Draft Guidance should provide for sample testing at the time a cord blood sample is released for transplant instead of the time of donation in the context of family banking.

IV. FDA's Draft Guidance Fails To Address Full Disclosure Regarding Cord Blood Banking Options For Expectant Parents

Finally, the concept of donor eligibility for cord blood donations should incorporate protections for the donor afforded by the broad regulatory principles of informed decisionmaking.^{8/} Informed decisions by law require that eligible donors be fully informed of the benefits as well as any risks involved. Under this broad premise, CBR believes that all potentially eligible donors be afforded an opportunity to understand collection, both private and public, through a regulated informed consent, or similar disclosure process.

Although FDA's Draft Guidance addresses cord blood donor criteria in regards to medical health history, it does nothing to ensure that expectant parents fully understand the value the stem cells may have to their own families, such as higher survival rates, and fewer complications when used in transplants compared to unrelated samples, or public

^{8/} 21 C.F.R. Part 50, and 45 C.F.R. Part 46.

benefits for patients in need. Stem cells currently can be used to treat over 70 life-threatening diseases, including cancer, genetic diseases, and blood and immune disorders, and the future promise of stem cell use is phenomenal. Newborn cord blood is recognized as a rich and powerful source of stems cells, and provides an uncontaminated, less invasive, and less costly solution than other stem cell sources. There is extensive medical literature documenting that transplants using a family members cord blood provide twice the survival rate over unrelated donor transplants (from a public bank), and have a 4 times lower incidence of Graft vs. Host Disease, a potentially fatal transplant condition common in transplants with unrelated donors.

Given the unique benefits of treatment by a family member's blood, and the limited opportunity for cord blood collection at the time of birth, CBR strongly recommends that the donor process should be regulated both as to risks, i.e., screening, and as to a balanced presentation of benefits through informed consent or similar form of regulated disclosure.

Thank you for the opportunity to comment on these important issues.

Sincerely,

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Tom Moore/PM

Thomas E. Moore, CEO
Cord Blood Registry