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REVIEW ARTICLE

Placental Cord Blood as a Biological Product: Challenges and Opportunities

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Since the first successful umbilical cord blood transplantation was reported in 1989, more than 513,000 donated cord blood units have been stored worldwide in public cord blood banks for unrelated allogeneic hematopoietic stem cell transplantation. In addition, more than 900,000 cord blood units have been stored in private cord blood banks for potential autologous or allogeneic family use. In November 2011, the United States Food and Drug Administration (FDA) approved the first biologics license for hematopoietic progenitor cells from cord blood (Hemacord) submitted by the New York Blood Center, the first and largest public cord blood bank. Hemacord is intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, are acquired, or result from myeloablative treatment. Currently, US public cord blood banks are required to submit to the FDA a Biologics License Application (BLA) or an Investigational New Drug (IND) application for unlicensed cord blood products. Private cord blood banks in the United States are not required to file an IND or BLA with the FDA. Instead, US private cord blood banks register with the FDA and follow the US federal regulations for human cells, tissues, and cellular and tissue-based products (tissue rules). The regulatory requirements for the FDA tissue rules and IND applications allow cord blood banks to store cord blood units that may not qualify for FDA BLA approval because of positive infectious disease markers or low cell yield collections. This article reviews the current US FDA regulatory requirements for cord blood banks and some challenges and opportunities in working with a diverse cord blood unit inventory.

1. Introduction

Public and private cord blood banks were actively collecting umbilical cord blood from the placenta after newborn delivery and banking the cord blood units for hematopoietic stem cell transplantation when the US Food and Drug Administration (FDA) announced the Proposed Approach to the Regulation of Cellular and Tissue-based Products in February 1997.[1,2] Consumers and private cord blood banks insisted that federal regulation should not interfere with their once-in-a-lifetime opportunity to collect the newborn's placental cord blood for autologous or family-member use. Physicians experienced with cord blood transplantation were convinced that cord blood was a safe and effective alternative to bone marrow for unrelated allogeneic pediatric transplantation. After extensive public comment, numerous scientific workshops and public meetings, FDA developed and implemented the US federal regulations for human cells, tissues, and cellular and tissue-based products and requested data from the scientific community to develop product standards for minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications.[3–6] Several public cord blood banks voluntarily submitted Investigational New Drug (IND) applications to FDA and provided their cord blood product information and transplantation outcome data to a public docket to help FDA develop product standards.[5] The product standards were developed to assist public cord blood banks in meeting the minimum product acceptance criteria to obtain a Biologics License Application (BLA) for minimally manipulated, unrelated allogeneic cord blood intended for hematopoietic reconstitution (summarized in Table 1).[6]

The FDA defines minimal manipulation of cells as processing that does not alter the relevant biological characteristics of cells or tissues.[4] If cord blood cells are manipulated by processes such as gene transfer or *ex vivo* expansion, they are regulated by FDA as a somatic cell therapy and subject to IND regulations.[7] If the cord blood cells are minimally manipulated but used for a clinical purpose other than their normal function of hematopoietic reconstitution, such as repair of nonhematopoietic organs or tissues, they are also subject to IND regulations.[2] The IND regulations apply when clinical studies are necessary to evaluate the

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Table 1 US FDA-recommended minimum acceptance criteria for cord blood units to qualify as licensed products[6]

Product characteristics	Testing	Results
Safety	Infectious disease testing of maternal peripheral blood obtained within 7 days of cord blood collection is required according to 21 Code of Federal Regulations (CFR) 1271.45 through 1271.90[4]	All tests must be negative except non-treponemal test for syphilis when confirmatory test is negative Cytomegalovirus results are recorded
	Sterility—bacterial and fungal cultures are required according to 21 CFR 211.165(b) and 21 CFR 610.12)[6]	Cultures must show no growth
	Hemoglobin analysis of cord blood	No homozygous hemoglobinopathy
Purity and Potency	Total nucleated cells before cryopreservation	$\geq 5.0 \times 10^8$ total nucleated cells per cord blood unit
	Viable nucleated cells before cryopreservation	≥85% viable nucleated cells
	Viable $CD34^+$ cells determined by flow cytometry	$\geq 1.25 \times 10^6$ viable $CD34^+$ cells per cord blood unit
Identity	Human leukocyte antigen (HLA) typing	Must be reported
	Confirmatory HLA typing	Must confirm initial typing
	Blood Group and Rh Type of cord blood	Must be reported

safety and efficacy of an investigational product before it is marketed.[8]

1.1. US regulations for human cells, tissues, and cellular and tissue-based products (tissue rules)

The US tissue rules consist of three major subparts covering procedures for establishment registration and listing, donor eligibility, and current good tissue practice.[4] US private cord blood banks are required to register and list their products with the FDA and follow current good tissue practice defined as manufacturing to ensure that the cord blood products do not contain communicable disease agents, are not contaminated, and do not become contaminated during manufacturing. If the cord blood units are intended for potential allogeneic use in a first-degree (parent, sibling, or child) or second-degree (aunt, uncle, nephew, niece, grandparent, or half-sibling) blood relative, donor eligibility determination is required. If the cord blood units are intended for autologous use only, the donor eligibility determination is recommended but not required. Donor eligibility includes screening and testing the mother of the cord blood donor for relevant communicable diseases which include the following: human immunodeficiency virus type1 and type 2, hepatitis B virus, hepatitis C virus, human T-lymphotropic virus type I and type II, cytomegalovirus, *Treponema pallidum*, and West Nile virus. Testing must be performed with FDA-licensed tests.[9] Tests are performed on maternal samples within 7 days of cord blood collection rather than the cord blood units because none of the donor screening tests are FDA-licensed or approved for cord blood samples.

If the mother of the cord blood donor has a positive result for a communicable disease, the cord blood can be stored for potential use in a first-degree or second-degree blood relative with the requirement that the physician using the cord blood unit is informed of the test results, and a Biohazard label is provided with the cord blood unit warning that the patient should be advised about the communicable disease risk associated with the product. Cord blood units associated with communicable disease risk may also be used for an urgent medical need which FDA defines as a situation in which no comparable human cell, tissue, cellular, or tissue-based product is available, and the recipient is likely to suffer death or serious morbidity without the product. The FDA recognizes the potential need for transplantation of otherwise ineligible cord blood units in first-degree and second-degree relatives and in urgent medical need situations.

1.2. BLA and IND requirements for public cord blood banks

An FDA-approved BLA allows a public cord blood bank to distribute cord blood units in the United States that are manufactured according to the license specifications on or after the date the BLA is approved. The Guidance for Industry that FDA released in October 2009 details the regulatory requirements for a BLA which include all of the subparts of tissue rules, current good manufacturing practice regulations, general biological products, and biological products standards.[6] Effective October 2011, public cord blood banks in the United States and non-US banks shipping unlicensed cord blood units to the United States for unrelated allogeneic transplantation are required to obtain an FDA-accepted IND or participate with a sponsor of an FDA-accepted IND application before the cord blood units are distributed for clinical use.[10] The IND sponsors may be a public cord blood bank (also referred to as the manufacturer), a transplant center, or a national or international cord blood registry involved in coordinating the search for and distribution of cord blood units from participating cord blood banks.

The IND regulations allow for the use of cord blood units that do not meet the product standards required for licensed cord blood units.[10] Some cord blood units may have a lower cell dose than the minimal standard (Table 1); however, the unit may provide a sufficient cell dose for small pediatric patients. It is possible that some cord blood units were stored with incomplete donor screening or a donor had a reactive or positive test result. For example, FDA requires two tests for hepatitis B virus: antibody to hepatitis B core antigen (anti-HBc) and a test for hepatitis surface antigen (HBsAg).[9] Some cord blood banks also include hepatitis B virus nucleic acid testing (HBV NAT) for screening the maternal samples. In November 2011, FDA released draft guidance for blood establishments that collect whole blood and blood components for transfusion or for further manufacturing stating that FDA considers the use of an FDA-licensed HBV NAT to be necessary to reduce the risk of transmission of HBV.[11] Since the screening of US cord blood donors is consistent with the screening and testing requirements of US blood donors, it is likely that HBV NAT will be required for maternal samples associated with the cord blood donors. Cord blood units from individuals who are HBV NAT-negative, anti-HBc-reactive, and HBsAg-negative can be used for unrelated transplantation for urgent medical need under an FDA-accepted IND, when test results are shared with the physician and transplant recipient. Cord blood units associated with positive infectious disease markers are required to be quarantined during storage. Since placental cord blood was collected, banked, and distributed by public cord blood banks for 20 years before the first FDA BLA was approved in November 2011, the vast majority of public bank cord blood units are currently distributed in the United Sates under FDA IND regulations.

2. Challenges

A major challenge for public cord blood banks is transitioning from good laboratory and good tissue practices to the rigorous good manufacturing practices required for an FDA-approved BLA. Public cord blood banks are also challenged with increasing the availability of ethnically diverse cord blood units with human leukocyte antigens that adequately match minority populations while