DCGT Deputy Director Memo, October 2, 2012 - Ducord

From: Kimberly Benton, Ph.D., Deputy Director, Division of Cellular and Gene Therapies, OCTGT, CBER
Date: October 2, 2012

BLA/ STN#: 125407
Applicant Name: Duke University School of Medicine, Carolinas Cord Blood Bank
Date of Submission: September 9, 2011
Action Goal Date: October 8, 2012
Proprietary Name/ Established Name: DUCORD
Non-Proprietary name: HPC, Cord Blood
Indication: DUCORD is an allogeneic cord blood hematopoietic progenitor cell therapy 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, acquired, or result from myeloablative treatment**.** The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.
Product Reviewers: Denise Gavin, Ph.D, Mercy Quagraine, Ph.D., Safa Karandish, B.S., MT (ASCP) Cheng-Hong Wei. Ph.D., Joydeep Ghosh, Ph.D.
Branch Chief: Keith Wonnacott, Ph.D.
Recommended Action: Approval
Duke University School of Medicine submitted Biologics License Application (BLA) STN#125407 for DUCORD (HPC, Cord Blood). DUCORD is an allogeneic cord blood hematopoietic progenitor cell therapy indicated 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, acquired, or result from myeloablative treatment. The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.
The applicant followed the recommendations in FDA's 2009 Guidance and cited Docket 1997N-0497 for the efficacy data to support this application. The BLA includes the applicant's safety outcomes dataset to support the safety of the product.
The applicant requested that all DUCORD units processed since 2001 be approved in this BLA. The CMC review team recommended approval for DUCORD lots manufactured after the approval date, but there was disagreement among the reviewers

regarding whether DUCORD units processed from donor mothers who received intrapartum antibiotic prophylaxis should be included in the license.

The sterility test validation was not designed to assess the potential effect of the presence of residual antibiotics in the product. The review memo noted that DUCORD lots may contain residual antibiotics if they originate from donors on intrapartum antibiotic prophylaxis for Group B streptococcal sepsis in newborns. Literature was cited to support the conclusion that antibiotics administered to the mother will cross the placenta and be present in the fetal blood. The review assessed that the processing method used is not likely to significantly reduce levels of residual antibiotics. The applicant did not provide any data on quantitation of residual antibiotics in DUCORD.

The review memo discussed potential modifications to the sterility test method that the applicant might consider to address this issue. The review stated that results from the current sterility test may be unreliable for DUCORD products originating from donors on intrapartum prophylaxis, and therefore recommended that DUCORD products processed from donors undergoing intrapartum antibiotic prophylaxis be excluded from the licensed inventory.

The published recommendations of the CDC (MMWR 2010 59:RR-10) on antibiotic prophylactic regimens for Group B streptococcal (GBS)sepsis in newborns provide an algorithm for selection of either penicillin G, ampicillin, or cefazolin (all β-lactam antibiotics), or clindamycin or vancomycin for those with a history of allergic reactions to β-lactams. The review memo did not discuss the spectra of activity of these antibiotics. All 5 of these antibiotics are primarily active on Gram positive organisms, with limited activity against Gram negatives (Yao, J.D.C.and RC Moellering, Jr. (1999). Antibacterial Agents. In P.R. Murray (Ed), *Manual of Clinical Microbiology* (7, 1474-1504). Am. Soc. Microbiol, Washington, D.C.). Many of the typical fecal bacteria, which are expected product-related contaminants from cord blood collection, are Gram negative. The β-lactams have bactericidal activity, and so if present at bactericidal concentrations in cord blood these antibiotics may reduce the number of viable susceptible organisms to undetectable levels. Based on these considerations, the potential interference by residual antibiotics used for GBS prophylaxis with the proposed sterility test appears to be limited.

The review memo discussed that the sterility assay may be modified by addition of a β-lactamase to the culture media, to inhibit the activity of β-lactam antibiotics. This would be at best a partial solution because antibiotics other than β-lactams are used in GBS prophylaxis.

The review memo discussed that the applicant could switch to a membrane filtration method. The composition of the ----------(b)(4)---------- would need to be shown not to interfere with this method. The applicant selected the ---(b)(4)--- method based on its history of use for clinical specimens in the clinical microbiology labs at its affiliated medical institution. As the review memo states, the bottles for the ---(b)(4)--- system that contain neutralizing agents (----------(b)(4)----------)

have not been shown to remove therapeutic levels of antibiotics. Either of these changes would require a new assay validation.

A validation study would need to consider multiple variables including the types of antibiotics that may be used, quantities in the cord blood, data on the neutralization capacity for the culture media components, microorganism susceptibility to the antibiotics used, and the potential for bactericidal activity of antibiotics in organism spiking studies. Such a study would need a large number of cord blood samples to address all of the variables, which would require sacrifice of many potentially life-saving cord blood units.

Maternal antibiotic prophylaxis is not isolated to this application, but is also relevant to approved BLAs, future BLA applications, and INDs for HPC, Cord Blood products. Obtaining the most accurate information on the residual level of antibiotics from intrapartum prophylaxis would require a consolidated effort of all cord blood banks in the US and the agencies which make policy regarding cord blood banking and transplantation.

Recommendation

I recommend that units from mothers with intrapartum antibiotic prophalaxis be included in the BLA approval. The PI was revised to include information on the potential for residual antibiotics as a risk of allergic reaction, and the potential to transmit infectious bacteria or fungi.

I further recommend discussion of this issue with agencies involved in establishing policy for cord blood banking and transplantation.