The Regulatory Requirements

**Federal Register / Vol. 72, No. 10 / Wednesday, January 17, 2007**

“For use in unrelated allogeneic recipients. These HCT/Ps are regulated as **biological products** under section 351 of the PHS Act (21 CFR 1271.20). ”

**Guidance for Industry; October 2009**

Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications

**Guidance for Industry; March 2014**

Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System
The Regulatory Requirements

- FDA Guidance for License: October 2009; March 2014
- FDA Guidance for IND: June 2011; March 2014

**HPC, Cord Blood:** Hematopoietic Progenitor Cells, Cord Blood: minimally manipulated CB product

**Manufacturing:** all steps from collection to release of product to search

**Licensed product:** “prescription” drug with specific indications

**IND product:** “investigational”; requires IRB approved consent for use
Biologics License Application

Process Validation
Stability Studies, Product Expiration
Media Fill Validation
Laboratory Assays Validations
IT Systems Validations
Equipment Qualifications
Facility, Environmental Monitoring, Supplies
Packaging, Labeling
Product Batch Record
Quality Unit for Product Review and Release
.....and many others.....
## The work

### Example: Stability Evaluation - Label

Apply Criteria Annually

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
<th>Stability-Indicating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Inspection after thawing</td>
<td>Determine Integrity of container / closures and Identity Label</td>
<td>Integrity, Identity</td>
</tr>
<tr>
<td>Total nucleated cell (TNC) count</td>
<td>Measure TNC content</td>
<td>Potency</td>
</tr>
<tr>
<td>Viable CD34+ cell content</td>
<td>Measure CD34+ cell number and viability</td>
<td>Potency</td>
</tr>
<tr>
<td>Colony-Forming Units (CFU)</td>
<td>Count CFU - functional progenitor cells</td>
<td>Potency</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Detect microbial contamination</td>
<td>Integrity, Purity, Safety</td>
</tr>
</tbody>
</table>

### Example Label

**HEMOPHILIC PROGENITOR CELLS, CORD BLOOD**

**HEMACORD**

Injectable Suspension

- **HEMACORD ID:** 123456P
- **NDC:** 76489-001-01
- **Recipient:** Last, First
- **Search ID:** 11111
- **TNC/kg:** $2.3 \times 10^7$
- **HLA match with recipient:** one B locus mismatch

For Intravenous Administration Only

Do Not Irradiate

Rx only

- **Cryopreservation (concentration):** DMSO (10%) / Dextran 40 (1%)
- **Volume:** Approx. 25 mL
- **Storage:** $<-150^\circ$C

**Expiration Date:** 10/11/2020
The work

Example: Environmental Monitoring of the Facility

Air Viable Counts at Static Condition 2013

Panel variable: Room

Air Viable Counts at Dynamic Condition 2013

Panel variable: Room

Annual cost appx. $35,000
The Time:  Biologics License Timeline - NCBP

Pre-BLA Meeting(s), New Facility, validations, preparation of BLA submission

2009

2010

- Amendments Completed; Package Insert
- Advisory Committee Briefing Book Submission

8500 Pages of Documents
2.02 GB of Electronic Submission

Nov. 10, 2011
The aim

Biologics License

The goal is for ALL banked CB units to be of consistent high Quality, and to have reliable Identity, Safety, Purity and Potency, so that there will be maximum Safety and Efficacy at Transplant.
The challenges

CB Licensure: benefits

Cord Blood Banks

Regulatory oversight and guidance
Quality Systems in Manufacturing and Testing
Consistently safer, high quality products
Close Monitoring of Adverse Events

Transplant Community

Experience with and easier/faster access to high quality HPC-C products
Enhanced safety of transplant procedures
More patients can benefit from the treatment

NCBP presentation: Cellular, Tissue and Gene Therapies Advisory Committee Meeting, Sep. 22, 2011
The challenges

CB Licensure: challenges

Cord Blood Banks

Substantially Increased Costs of:
Documentation - Facilities - Operations - Personnel - Testing - Equipment

Licensure will be beneficial for the transplant community if it contributes to broader utilization of the higher quality HPC, Cord Blood products

*NCBP presentation: Cellular, Tissue and Gene Therapies Advisory Committee Meeting, Sep. 22, 2011*
The Time: Events after License - NCBP

- Amendments
- License-related Reports (PAER, Distribution, Annual, Events)
- Post-License FDA inspection
- Package Insert and Label submissions/revisions

Maintaining the License is an ongoing process.
The current NCBP Search Inventory

Investigational and Licensed CB products

Number of Cord Blood Units

Unlicensed CBU (IND)  Licensed CBU (HEMACORD)
The current situation

- CB Banks are using all (limited) resources to meet FDA Requirements – increased cost of Banking – higher cost of CB products
  
  NCBP CBU price (2008): $35,000  
  NCBP IND CBU (2012): $42,500  
  HEMACORD CBU: $45,000

- As a result of changes related to cost and higher TNC at collection, the CB Inventory is growing at a lower rate – the decreased growth affects primarily the licensed products

- Overall, utilization of CB products for transplantation is decreasing, at the same time when the clinical results are improving
FDA-licensed CB products

Will we be using them to their full potential?

HRSA subsidy covers part of the cost of the NCBI CBU – still, provides important revenue for the CB Banks

Increases in HRSA subsidy will impact significantly the future inventory and the sustainability of the CB Banks

Increased funding is needed