cGMP Challenges for Cord Blood Banks

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Cord Blood Bank processing facility challenges

What does cGMP mean for these facilities?
Regulation of HCT/P

- DN 97N-0068, A Proposed Approach to the Regulation of Cellular and Tissue-Based Products, Feb 28 1997
- Reinventing the Regulation of Human Tissue, DHHS, Feb 28 1997
- Section 361 of the Public Health Services Act [PHSA], 21 CFR Part 1271), Jan 21 2003
Regulation of Cord Blood

- Section 351 of the PHSA (21 CFR Part 1270)
- Investigational New Drug (IND) regulations (21 CFR Part 312)
- Licensing and general biological products standards (21 CFR Parts 600, 601, 610)
- Current Good Manufacturing Practice (cGMP) (21 CFR Part 211)
Good Manufacturing Practice

- GMP = control and management of manufacturing & quality control testing of pharmaceutical products.

- GMP takes the holistic approach of regulating the manufacturing and laboratory testing environment.
GMP requires:

- **documentation** of every aspect of the process, activities, and operations involved with manufacture
- **traceability** for recall if the product does not meet the required specification
- **qualification** of manufacturing & testing equipment as suitable for use
- **validation** of operational methodologies and procedures utilized in the manufacturing process to demonstrate that they can perform their purported function(s).
Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

VII. Guidance Section, Part B., Current Good Manufacturing Practice and Current Good Tissue Practice
Objectives & Format

- Present the guidance
- Identify the challenge
- Propose a solution
- Summarize the survey question
Informal, six question survey

Distributed to 17 domestic, public banks

9 responses returned

The survey was not conducted solely for this presentation
designed & maintained to

- provide adequate environmental conditions for manufacture
- adequate segregation of operations to prevent mix-ups
- adequate sanitation SOPs to prevent contamination and cross contamination.
General Air Handling Systems

- Adequate ventilation must be provided.
- Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature must be provided, when appropriate.
- Air filtration systems must be used, when appropriate, on air supplies to manufacturing areas.
Buildings used in the manufacture of HPC-C must be maintained in a clean and sanitary condition. There should be SOPs for facility sanitation designed to prevent the contamination of equipment, components, product containers, closures, packaging, labeling materials, or products.
Challenge - Adequacy

- The level of environmental control for facilities performing minimal manipulation of products should be commensurate to the risks associated with the system.
How much is adequate?

- Determine vulnerabilities within system
  - Open vs closed
- Blood Banks vs pharmaceutical mfrs
  - benchtop vs BSC vs clean room
- Monitoring
  - At what level
  - Correlation of environment to product
  - Product disposition
Challenge – Safety / Availability

- Mandating strict compliance with the CGMP required for manufacture of pharmaceuticals, vaccines, and other extensively manipulated products: improve safety of these UCB products?
- Add unnecessary cost burdens to programs that strive to increasing availability of therapeutic cells?
Challenge - Comparability

- Compliance with cGMP may be compounded for products that are stored long term.
  - cGMP not currently standardized
  - Concepts continue to evolve
- Considerable challenge to demonstrate comparability of existing inventories
Questions to Consider

- Have you always had complete SOPs?
- Have you always performed?
- Have you always documented?
  - work area & instrument cleaning practice between products?
  - facility cleaning?
- Issues in demonstrating comparability
Question 1

How do you achieve a clean environment?

<table>
<thead>
<tr>
<th>Clean room</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic safety cabinet</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Anti-contamination sticky mats at lab entrances</td>
<td></td>
</tr>
<tr>
<td>Closed system</td>
<td></td>
</tr>
</tbody>
</table>


**Question 2**

How do you accomplish environmental monitoring?

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-viable particles</td>
<td>1</td>
</tr>
<tr>
<td>Viable particles</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>1 - Quarterly microbial spot plate testing</td>
</tr>
<tr>
<td>No special monitoring</td>
<td>3</td>
</tr>
</tbody>
</table>
**Question 3**

What level of PPE is used?

<table>
<thead>
<tr>
<th>PPE Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gowns (lab coats) &amp; gloves</td>
<td>8</td>
</tr>
<tr>
<td>Masks &amp;/or slippers</td>
<td>2</td>
</tr>
<tr>
<td>Ante room</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>- Eye / face shields</td>
<td></td>
</tr>
<tr>
<td>- Closed system</td>
<td></td>
</tr>
</tbody>
</table>
Batch production and control records must be prepared for each HPC-C and must include complete information relating to the manufacture and control of each HPC-C.
Challenge - Terminology

- CB products are distinct
  - Batch?
  - Lot?

- Batch production
  - Each product?
  - Production where processes are shared?
Prevention of Mix-ups, Contamination and Cross-Contamination

- Separate or defined areas or other control systems must be in place for the operations as necessary to prevent contamination or mix-ups, including:
  - manufacturing and processing operations;
  - quarantine storage before release of products;
  - control and laboratory operations; and
  - aseptic processing, including, when appropriate, an environmental monitoring system, a room and equipment cleaning/disinfecting system, and a maintenance system for equipment used to maintain aseptic conditions.
Summary

- In the interest of being an ‘industry’
  - Harmonize and avoid individual bank interpretation of cGMP
  - CBBs must transition current concepts into ‘industry’ language
- Continue constructive dialogue with the FDA, industry professionals, and each other
Conclusion

- Cord blood is a limited resource
- Keep focused on reasonable means to balance patient safety with product availability
Acknowledgement

- FDA
- ISCT, AABB
- Participating labs