Closed System Development for On-Site Preparation of ProHema™-CB

(Ex Vivo CXCR4-Upregulated CD34-Positive Hematopoietic Progenitor Cells from Cord Blood)

Elizabeth Read, MD
Head of Product Development
Fate Therapeutics, Inc
San Diego, CA, USA
FT1050

- Small molecule: synthetic analog of prostaglandin E2
- Potent regulator of hematopoiesis in all vertebrate species (Zon lab, Harvard)
- When used *ex vivo* to modulate hematopoietic progenitor cells, enhances their homing, engraftment & proliferation in rodent and non-human primate models
- Currently used as the key ancillary reagent for manufacture of ProHema™-CB, in phase 1 clinical trials
Kinetics of FT1050 effect on upregulation of CXCR4 in hematopoietic stem cells

22-fold CXCR4 transcripts

Vehicle vs. FT1050
6% vs. 28%

2 hour incubation
*Ex vivo*

First 4 hours
*In vivo*
• Product shelf life is limited primarily by progressive loss of viable CD34+ HSCs in thawed cord blood unit
ProHema™-CB Manufacturing Model

- Product must be released rapidly for infusion, after limited release testing
- Product must be prepared in close proximity to patient
- Manufacturing is done at clinical cell processing facilities that are qualified and trained, but have a range of facility specifications and practices
- Development of closed system with standardized disposables is a practical solution to many issues associated with this model
How does one begin to develop a closed system?
How to begin? (1)

- Perform a survey of open steps
  - Cell source
  - Reagent preparation
  - Transfer of cells during processing steps
  - Transfer of reagents during processing steps
  - Sampling of intermediate & final products

- Prioritize by risk
  - Are some steps more open than others?
  - Are some steps more prone to contamination because of technical skill required to work with a particular container size or configuration?
How to begin? (2)

- Consider the tools already used in blood banks, transfusion services and cell therapy labs, and look for new tools
Challenge: Reagents may not be readily available in with closures that can be sterile-connected.
Challenge: Cryopreserved CBUs are typically packaged with closures that cannot be sterile-connected

Source: Package Insert for HemaCord (New York Blood Center)
When should closed system development begin?
Incremental cGMP During Product (CMC) Development

**CMC SAFETY INFORMATION**
- Source characterization
- Component qualification
- DS/DP characterization
- Impurities & contaminants
- Control of safety processes

**CMC DEVELOPMENT ACTIVITIES**
- DS/DP characterization
- Formulation development
- Component characterization
- Assay development/validation
- Specification development
- Stability
- Manufacturing process control

**cGMP**
- Personnel
- Quality Control
- Facilities & Equipment
- Laboratory Control
- Component Control
- Production Control
- Distribution & Records
- Labeling

**Stage-Specific cGMP**
- **Phase 1**
- **Phase 2**
- **Phase 3**
- BLA or NDA

*Fate Therapeutics*
When to begin?

• For most cell therapy products: as soon as possible
  – Especially for product intended for commercialization (before phase 2)
  – Especially if you want to reduce need for more extensive facility cleaning & environmental monitoring

• Caveats
  – Substituting closed system elements (e.g., bags for flasks) may have unintended consequences for some cellular products
    • Cell recovery and/or function may change
  – Locking down the closed system design too early may restrict development options
    • Requirements for container size/configuration and sampling at one or more steps may change
Plan and Develop Closed Systems In Context of Overall CMC Development from Phase 1 to 3

Closed System Development & Progressive cGMP

- Risk Assessment
- Selection & qualification of containers, closures, sampling devices in context of overall manufacturing process qualification
- Progressive development of specifications for final system design

Stage-Specific cGMP
Incremental Approach to Closed System Development

Off the shelf disposables selected by processing facilities
- Readily available and relatively modest cost
- Multiple sterile connections
- Not standardized

Off the shelf disposables specified by sponsor
- Readily available and relatively modest cost
- Multiple sterile connections
- Improved standardization

Custom disposable parts specified and provided by sponsor
- More cost & time to develop & qualify
- May reduce number of parts and number of sterile connections
- Standardized but still allows some development flexibility

Fully customized disposable set
- More cost & time to develop & qualify
- May eliminate other disposables and further reduce or eliminate sterile connections
- Most standardized, but requires greater commitment to specific design
Summary

• Closed systems should be used whenever possible for cell-based therapies
• Development of closed systems should be considered as early in development, and in relationship to the overall manufacturing process
• An incremental approach may be useful to allow flexibility in design and development of the manufacturing process
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