HRSA Advisory Council on Blood Stem Cell Transplantation
May 29, 2014

Impact of FDA Licensure on Cord Blood Banking & Transplantation

Challenges When Applying cGMP to Cellular Therapies

- Biological variation of starting product
  - Cells vs. chemicals
- Lot sizes
  - Single patient lots vs. thousands of tablets
- Manufacturing Process Controls
  - Many drugs can be terminally sterilized
  - CT rely on aseptic processing
- Mechanism of action known…
  - TNC, CD34, CFU or other?

Cost of Licensure Questionnaire

- Sponsored by the NMDP as part of their responsibility as the contractor for the Cord Blood Coordinating Center (CBCC) under the C.W. Bill Young Transplantation Program
- Assess financial impact of achieving and maintaining a biologics license application (BLA) for the purposes of operating an FDA licensed cord blood bank
- Issued March 26 for submission by April 25

Capital Costs

- Establishment of microbiology laboratory
- Renovation to classified manufacturing space
- Build out of locker type receiving area
- > $400,000

Preparation

- Microbiology lab
  - validate rapid microbial method
  - perform microbial surveillance on products and environmental monitoring
- Performed disinfection effectiveness studies
  - created rigid cleaning policy
  - implemented rotation schedule of disinfection agents
- Implemented more robust monitoring of aseptic processing (including media fill)
- Comprehensive environmental monitoring plan to provide benchmark data
- Hired an independent housekeeping contractor to clean to cGMP level

Preparation, cont'd

- Established QC section (separate from Quality Unit) to perform
  - equipment qualification
  - facility maintenance
  - reagent conformance
- Increased equipment preventive maintenance and qualification frequency (including thermometers, data loggers and timers)
- Renewed validations, including
  - collection (with more robust temp tracking and inclusion of FDA cleared collection bag)
  - processing (with tighter documentation and timing controls)
  - characterization (demonstrating accuracy with cord blood as sample matrix)
- Reagent conformance testing beyond Certificate of Analysis
  - lot specific and parallel physical and performance qualification
  - referral of testing to external labs per USP requirements

Preparation, cont'd

- Identified and validated secondary reagent systems and vendors
- Replaced collection bag with FDA cleared product (3.7-fold increase in price)

Prep Costs

- Rapid microbial method validation
- Disinfection studies
- EM (including viable and air particle counters)
- Housekeeping contract
- QCS = 2 technical staff, 1 resource coordinator
- Validations and qualifications (collection, characterization, processing)
- Reagent conformance and reference testing
- FDA cleared collection bag

- total > $1,100,000

Ongoing Regulatory Compliance – Staffing

- Quality Manager – ultimate authority for approval and/or rejection of drug product
- Information Systems Specialist – upgrade IT systems
- Resource Coordinator – equipment qualification, facility maintenance, vendor relationships
- Microbiology Tech – microbial surveillance of product and environmental monitoring, media fill studies, associated media qualification
- Quality Control Section Techs – quality control and conformance testing, other GMP related tasks

Ongoing Regulatory Compliance – Other

- Microbiology
  - microbial media qualification and conformance studies (growth promotion)
  - Incorporated antibiotic neutralization bottle into testing platform – increased cost of bottles by 17.3%
  - Associated proficiency testing program
- Disinfection agents and disposables/supplies to maintain current cleaning practices
- Maintenance of housekeeping contract, EM activities, conformance testing

Summary of Costs

- Pre-licensure total: $1,600,000
- Ongoing costs of compliance: $600K
- Of note, distribution has dropped 15% during this same time period, raising additional challenges for sustainability of public banking, particularly for licensed banks

Cost to Bank a Unit

- $2000 in 2010 to $3000 in 2013
- 50% increase is attributable to
  - higher TNC acceptability criteria imposed during transition – costs spread across fewer products
  - annual inflation factors
  - increasing operational costs due to licensure

Price on Sale of an Unit

- $22,800 in 2010
- Oct 2013 to $35,000
- 50% increase is comparable to production cost increases

Clinical Data

- Rely on data submitted to the docket for this guidance and data in docket number FDA-1997-N-0010 (Legacy Docket number 1997N-0497)
- Clinical safety data
  - Summary of safety experience
  - Narrative of adverse events
  - Details of clinical outcome analyses

Inventories

- Stability data to support expiration date
  - Containers
  - Storage conditions
  - Source and number of samples
  - Over history
- Processing method specific
- Though legacy inventory contributed to the body of knowledge by which safety, efficacy, stability and expiration were assessed, legacy inventory was not licensed
- IND for release of legacy units and new indications

Closing Remarks

- Increased quality?
- Served industry goals of accelerating growth of high quality product inventory and providing greater access to life saving treatment?
- The expectation has been created…