Facility and Operational Issues for Cord Blood Banks: FDA Draft Guidance

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ISCT 7th Annual Somatic Cell Therapy Symposium, September 26-28, 2007

Summary

- Establishment Description section
  - General Information
  - Specific Systems
  - Contamination/Cross-Contamination Issues
- Guidance on Applicable Regulations
  - Current Good Manufacturing Practice (CGMP)

Establishment Description: General Information

- For each manufacturing location (collection sites not included) provide floor diagram with general layout.
- On diagram or separate narrative provide:
  - What takes place where; room numbers; location of major equipment
  - General description of processing room surfaces
  - Activities in areas adjacent to processing
  - Product, personnel, equipment and waste flows

Establishment Description: Specific Systems

- Water used for processing and/or cleaning
  - If purchased, description of water quality for use in manufacturing and rinsing of product contact surfaces
  - If manufactured on site, general system description, validation summary and routine monitoring program

Establishment Description: Specific Systems (cont…)

- Heating, Ventilation and Air Conditioning (HVAC):
  - Description of controls used to prevent contamination/cross contamination including air handling units, pressure differentials, whether air is once through or re-circulated and air changes per hour
  - Description of environmental quality of each room and laminar flow units
  - Validation summary for the system

Establishment Description: Specific Systems (cont…)

- Facility Controls – Description of:
  - Facility cleaning/sanitization procedures
  - Personnel gowning practices
  - Measures used to prevent unauthorized access
  - Brief description of the environmental monitoring program – airborne viable and nonviable and surface sampling, frequency, and alert and action levels

Establishment Description: Specific Systems (cont…)

- Computer Systems that control critical manufacturing processes:
  - Identity of developer of system
  - Brief description of procedures for making changes to the system
  - A list of the manufacturing steps that each of the systems controls
  - Validation/verification summary for each system – further specified in draft guidance

Establishment Description:
Contamination/Cross Contamination

- Equipment cleaning procedures and cleaning validation
- Containment features – description of segregation and containment procedures and:
  - Air handling (where appropriate)
  - Decontamination and equipment cleaning when there is a breach in container integrity and product leakage

Current Good Manufacturing Practice (CGMP)?

- Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FDCA) states that a drug shall be deemed adulterated if “the methods used in, or the facilities and controls used for, its manufacturing, processing, packing, or holding do not conform to or are not operated or administered in conformity with….

CGMP?

..**current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets quality and purity characteristics, which it purports or is represented to possess."

CGMP?

- FDA considers umbilical cord blood collected for further processing into HPC-C to be an intermediate product. While there are no specific regulations governing the manufacture of intermediates, drug substances or what are termed active pharmaceutical ingredients, compliance with section 501(a)(2)(B) of the FDCA is required.
- Accordingly, for collection of cord blood for further processing into HPC-C, section 501(a)(2)(B) or statutory CGMP would be applied

CGMP?

- Regulations at 21 CFR Parts 210 and 211
- Applicable to preparation of drug products, in this case HPC-C, for administration to humans and animals, including clinical trials
- GMPs cover manufacturing, controls, testing and documentation
- CGMP - the “C” means current – CGMP regulations are minimum standards.

Status of CGMP Regulations

- 21 CFR 210.1(a)
- …..the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

CGMP?

- **What other biological drug products are required to be manufactured in accordance with parts 210 and 211? Examples:**
  - Blood and blood components – in addition to part 606 CGMP and other applicable requirements in parts 600-680.
  - Vaccines, plasma derivatives, allergenics, somatic cell therapies – in addition to other applicable requirements in parts 600-680 and elsewhere.

Public Health Service Act

- Section 351(a)(2)(B)
- Biologics license application shall be approved on the basis of a demonstration that-
- The biological product ..subject to the application is safe, pure and potent.
- The facility in which the biological product is manufactured, processed, packed or held meets the standards designed to assure that the biological product continues to be safe, pure and potent.

Applicable Licensing Regulations

- 21 CFR 601.2(d)
- Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in **parts 210, 211**, **600**, 606, and 820 of this chapter.

Applicable Licensing Regulations

- 21 CFR 601.20(a)
- Examination--compliance with requirements. A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in **parts 210, 211, 600**, 606, and 820 of this chapter.

CGMP vs. CGTP?

- From a facility, environmental control and cleaning perspective, the requirements are very similar; as freedom from contamination is the objective for these requirements in both cases.
- Tenet of CGMP is prevention – reliance on product failures as process control would not be considered compliance with CGMP.
- Tenet of CGTP is prevention – reliance on product failures as process control would not be considered compliance with CGTP.

Facility Considerations:

- Open exposure of product during processing; should be in controlled environment
- Use and validation/verification of “closed” systems –Is it really closed??
- CGMP regulations do not specifically require “clean rooms” or certain room classifications
- “When appropriate” used in the CGMP regulations, **there is flexibility!**

Facility Considerations

- Elimination of practices that would be considered unacceptable, regardless of facility classification
  - Example: Open processing of multiple donor units at the same time – potential for cross-contamination.
  - Example: Inadequate personnel practices: gowning, glove sanitization and/or use of aseptic technique

Environmental Monitoring

- Commensurate with criticality of operations and exposure of product to the environment
- Important qualification, validation (e.g. cleaning) and maintenance “tool”
- Regulations do not specify type or frequency – **there is flexibility!**

Documentation

- Procedures and Records: Examples:
  - 21 CFR 211.100(a) and (b) require that there be written procedures for production and process control. These procedures and changes to them reviewed and approved by the quality control unit. The procedures will be followed and documented at the time of performance. Deviations will be recorded and justified.
  - 21 CFR 211.186 and 211.188 –require that Master and Batch production and control records be prepared for each drug product and drug product batch, respectively

Quality Control Unit
21 CFR 211.22

- Responsibility and authority to approve/reject all components, in-process materials, packaging, labeling and drug products and authority to review records to assure no errors have occurred and if occur; fully investigated; including contract operations.
- Responsibility to approve/reject procedures/specifications impacting on identity, strength, quality, and purity of the drug product
- Adequate laboratory facilities for testing
- Responsibilities and procedures in writing

Additionally

- 21 CFR 211.100
  - Production and process controls procedures (process validation), including changes ..reviewed and approved by the QCU.
- 21 CFR 211.160
  - Establishment of specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including changes to any…reviewed and approved by the QCU

Additionally

- 21 CFR 211.192 – Production Record Review
  - All drug product production and control records…shall be reviewed by the QCU to determine compliance with all established, approved, written procedures before a batch is released or distributed. Any discrepancies must be thoroughly investigated .

Additionally

- 21 CFR 211.198 - Complaint Files
  - Written procedures established and followed, including provisions for review by the QCU of any complaint related to drug product failures; need for investigation; need to evaluate whether represents and adverse drug experience and, if so, reported properly

Summary

- CGMP ≠ “one size fits all”
- Flexibility exists for application of CGMP
- We appreciate your comments on the draft guidance; your comments are important to us
- We expect the final guidance to have changes but it would be premature for us to say what those changes are

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