Autologous Supply Chain

INSIGHTS INTO THE REGULATORY CONSIDERATIONS FOR SHIPPING VALIDATION SUPPORTING NOVEL PRODUCTS - CELLULAR PRODUCTS
Federal Food, Drug, & Cosmetic Act (FDCA)

Under Sec 501(a)(2)(B) A drug may be deemed to be adulterated: if “the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices...”
How are Autologous Cell Therapy Products Regulated?

- Autologous cell therapy products are human cells, tissues and cellular and tissue based products (HCT/Ps). If cellular HCT/Ps do not meet all the criteria in 21 CFR 1271.10(a), they are regulated as biological products that are also drugs. As such, these products are held to section 501(a)(2)(B) of the FDCA (statutory CGMP) and 21 CFR parts 210-211, as well as the additional biological product standards in parts 600-610 and relevant 1271s.

- Autologous cell therapy products combined with a device are regulated as combination products.
Relevant Regulations Packaging, Storage, and Distribution

§211.142  Warehousing procedures.
   (b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

§211.150  Distribution procedures.
   Written procedures shall be established, and followed, describing the distribution of drug products.

§211.166  Stability testing
   (a)(2) Written program shall include storage conditions for samples retained for testing.
Examples of temperature requirements in the CFR

§600.15 Temperatures during shipment.

(a) Products

Cryoprecipitated AHF \(-18^\circ\text{C}\) or colder

Whole Blood ...shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours.

Source Plasma Liquid 10 °C or colder

Red Blood Cells Frozen \(-65^\circ\text{C}\) or colder

Liquid Plasma 1 to 10 °C.

§610.53 Dating periods for Whole Blood and blood components.

(b) Table of dating periods

Source Leukocytes Temperature appropriate for final product
Examples of temperature requirements in the CFR

§640.2 General requirements.
   (c) (3) The blood has been stored continuously at 1 to 6 °C and shipped between 1 and 10 °C

§640.34 Processing
   (b) Fresh Frozen Plasma. Fresh frozen plasma shall be prepared from blood collected by a single uninterrupted venipuncture... The plasma must be separated from the red blood cells or collected by an apheresis procedure, and placed in a freezer within 8 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system, and stored at −18 °C or colder.
Additional References

• USP <1079> Good Storage and Distribution Practices for Drug Products
• USP <797> Pharmaceutical Compounding – Sterile Preparations – Packaging, Handling, and Transportation
• USP <659> Packaging and Storage Requirements
• WHO Good Distribution Practice of Pharmaceutical Products
• ICH Q1A Stability Testing of New Drug Substances and Products
• ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry Distribution Procedures
• American Society for Testing and Materials (ASTM) Standard Practice for Performance Testing of Shipping Containers and Systems
• International Safe Transit Association (ISTA)
Traceability is CRITICAL

Maintenance of patient material traceability through the entire process from collection to administration of product is essential.
Elements of USP <1079>

• Labeling environmental requirements on container (Frozen, 2-8°C, 20-25°C)

• Maintenance of QMS Systems
  – Storage location management
  – Distribution management
  – Environmental management
    • Real time monitoring of shipments
Shipping Logistics

• Shipping contents
  – Final product container(s) (i.e. bag, cryovial)
  – Supporting documentation/procedures

• Shipping container
  – Cooler/box
  – LN$_2$ shipper
Elements of Shipping Validation

• Understanding of shipment logistics
  – Length of trip/down time
    • Down the hall or cross country/globe
  – Environmental conditions of product and external surroundings
Elements of Shipping Validation - 2

- Passive vs active temperature control
- Qualification of external container system
Elements of Shipping Validation -3

- Stability Chamber Challenge vs Real Time Study
- Effects of packaging and load configurations
Elements of Shipping Validation - 4

• Other simulated/real testing for shipping validation – effect on CCI
  – Vibration testing
  – Drop testing
Quality
Systems Involved with Shipping

- Approved written procedures and specifications
- Training Program
- Calibration Program
- Preventive Maintenance Program
- Qualification Program
- Change Control Program
- Deviation & Investigation Program
- Corrective/Preventive Action Program
- Audit Program
- Monitoring of Transportation Data (Trending)
- Stability Program

*Look at the package as a whole*
Issues with Shipping Studies

Unacceptable explanations of temperature excursions during shipping

Excursions (from USP<1079>— The mapping process will help determine when excursions occur....alarms should be used to reveal environmental excursions during operations.....Temperature excursions for brief periods outside of respective storage label conditions may be acceptable provided stability data and scientific/technical justification exists....

Temperature recorder flying lead in incorrect location

Validated time of shipper in specification not directly compared to total elapsed shipping time

Lack of shipping studies assessing seasonal variation

Poor performance of shipper materials due to value cost of shipping material
Examples of Observations for Biological Products

• Shipment of lot 09066P200 and lot 09066P202 took place over 32 hours between 15 June 2004 and 16 June 2004. The temperature probe recorded temperatures over the 2-8°C limit for up to 720 and 270 minutes, respectively. There were no deviations or investigations for these temperature excursions.

• With respect to shipping validation studies:
  A. The study performed from May 2001 - June 2001 showed that locations #7 and #8 were the worst-case locations, however location #6 is used to monitor product during shipments.
  B. The study did not address potential worst-case shipping conditions with respect to the temperature outside the shipping carton.
  C. The new validation study for the OQ protocol for <product> export packaging (Document # 266 30) had not been designed to monitor the temperature of the seven 2 liter bottles in the shipping container.

• Equipment used in the [collection] [processing] [compatibility testing] [storage and distribution] of blood and blood components is not observed, standardized and calibrated with at least the frequency required. Specifically, *** (7)
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