

Product Quality Issues

Unrelated Donor Products

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Overview

- **URD product quality considerations and questions at collection, transport, processing and product release**
- **FHCRC/SCCA experience with URD processing and system improvements to become more “GTP/GMP” compliant**

Scope

- **URD products received from NMDP-affiliated (or other similar registries) collection facilities**
- **Products collected from and transported for patient infusion to facilities all over the world**
- **Products intended for “fresh” infusion**

FHCRC/SCCA 2005 URD Activity

- **164 transplants**
 - 32 Bone Marrow
 - 132 Peripheral Blood (174 products)
 - 1790 total since 1987
- **All products received and processed in the Cellular Therapy Laboratory**
- **30% of products received from outside U.S.**
- **140 products received after 1800 hours**
- **Products requiring additional processing**
 - 20 for RBC or plasma reduction
 - 139 had partial product cryopreserved for future DLI

Collection Facility – Equipment and Validation

- **Variety of collection devices in use**
- **Standardization of equipment, process and test method validation**
 - **Installation Qualification**
 - **Operational Qualification**
 - **Performance Qualification**

Collection Facility – Product Characterization

- **Product measurements (i.e. hematology, viability, flow analysis may or may not be performed at the collection facility)**
 - **Difficult to access results – testing may be performed after product in transit**
 - **Results not always comparable to testing performed at processing facility**
 - **We rely on our own testing results to make processing and product release decisions**
- **Qualification of laboratories used for product testing (CLIA or CAP is preferred in US)**

Collection Facility – Storage

- **Overnight storage of products**
 - 33% of PBSC transplants require 2 collections – therefore require storage at collection facility
- **Things to consider for proper storage**
 - Acceptable temperature range of storage devices
 - PM/calibration of storage devices
 - Appropriate cell concentration
 - Types of volume expanders, if required
 - Quarantine of products where donor is ineligible (per FDA regulations)

Collection Facility – Transport

- **Standardized procedures are needed:**
 - Temperature specifications
 - Qualification of transport containers
 - Temperature monitoring
 - Packaging requirements
- **Courier training and qualifications**
 - All are volunteers
 - Is this standardized?
- **Issues**
 - Not all containers arrive with temperature indicators
 - No continuous monitoring used – no information about warming or cooling during transit
 - A few products have arrived partially frozen or warm ($> 10^{\circ}\text{C}$)
 - Flights delayed or changed last minute – communication is critical between courier and transplant facility

Collection Facility – Other Considerations

- **Who qualifies collection facilities?**
- **What documentation should the processing/transplant facility receive to assure the product quality has been maintained by the collection facility?**
- **European products**
 - **Product labeling does not meet FACT standards**
 - **FDA donor eligibility forms sometimes do not accompany the product**
 - **All donors ineligible due to BSE**

Processing Facility – Storage

- **Same issues as collection facility regarding overnight storage**
 - **Clinical decision to infuse all products intended for transplant upon ASAP**
 - **Some concerns regarding product quality after storage therefore no overnight storage at this time for URD transplant products**
 - **If applicable, DLI portion stored and cryopreserved next day**

Product Expiration Dates

- **Appropriate expiration dating should be defined**
 - We use 48 hours after the end of collection for PBSC transported and stored at refrigerator temperature
 - 24 hours for BM stored at room temperature
 - 6 hour extension allowed
 - If viability < 70% physician must be notified and provide additional orders for infusion
 - 2 PBSC collections – first collection older, nearing or exceeding expiration date
- **Use an expiration date based on stability data for temperature and cell concentration using viability as a measurement?**

Product Characterization

- **Total nucleated cell (TNC) dose**
 - Perform WBC upon prior to release (if product requires further processing, second count performed)
 - 1×10^8 TNC/kg specification – if lower, physician notification required
- **Viability**
 - $\geq 70\%$ specification (based on what FDA requires for IND products)

Product Characterization (cont.)

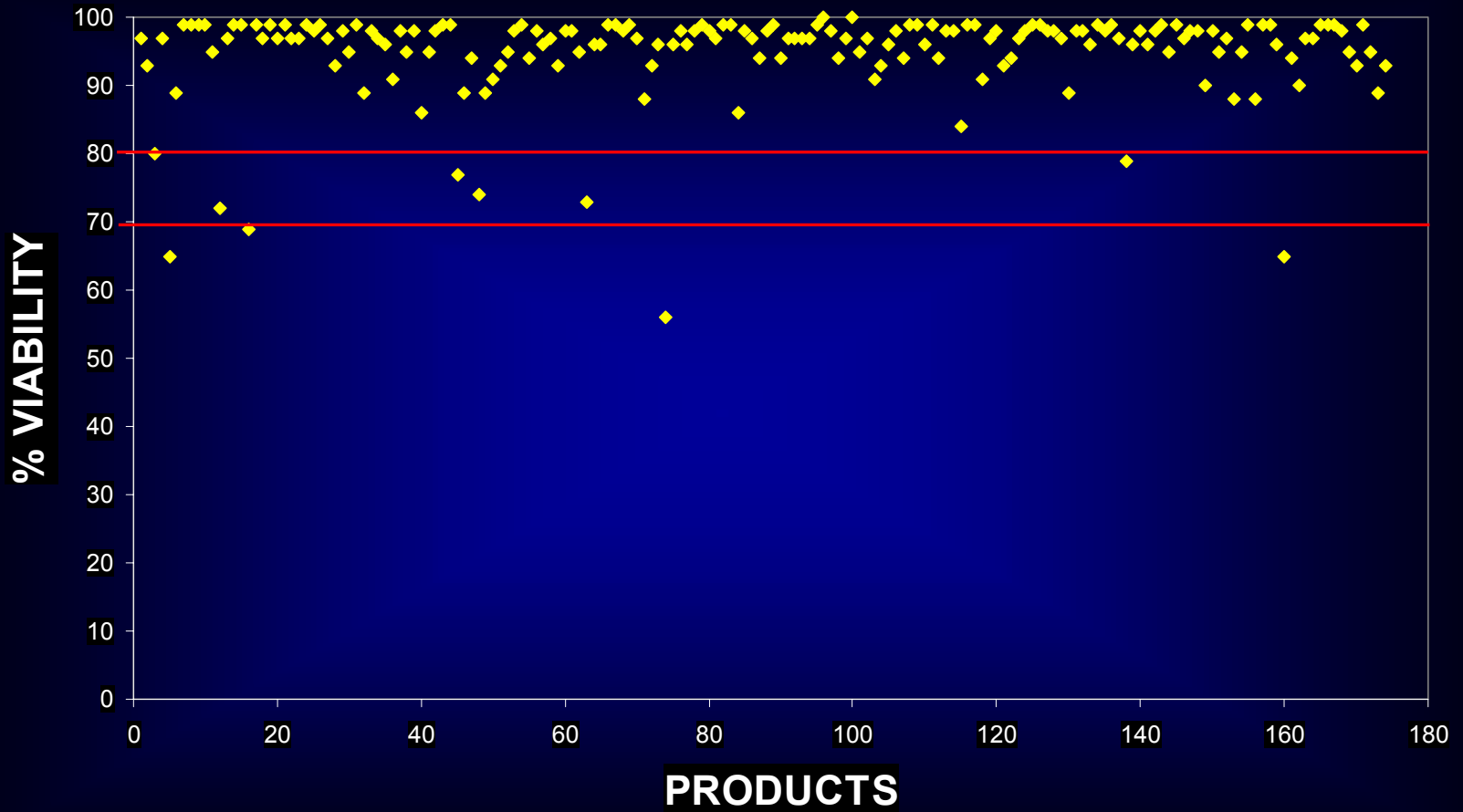
■ CD34/CD3

- Flow analysis done for all products but not required for release
- Products received “after hours” viability staining performed; full characterization performed next morning

■ Sterility testing

- Specimen for culture sent – results pending at the time of release
- No gram stains performed

2005 PBSC Viability Results



Viability Outliers

- All PBSC products (BM always > 90%)
- 9 products < 80%
- 7 products collected and transported from Europe
- 3 products (33%) arrived at > 10°C (2% for products with > 80%)
- 3 products were day 1 collections that were stored at collection facility
- 5 of 9 products (55%) > 2×10^8 /ml WBC (30% for products with > 80%)
- All patients engrafted (ANC > 500 μ l by day 28)
 - Avg. days 15.2 (< 80%)
 - Avg. days 15.9 (> 80%)

Product Release

- **FDA interpretation is for “independent review and release”**
- **“Real-time” product release in place for majority of PBSC products**
 - **Performed by QA**
- **For products received between the hours of 2100 – 700, 2 technicians present to review calculations and perform “interim” release**
 - **“Official” release performed by QA next morning**

Product Release (cont.)

▪ Requirements

- Sterility – specimen sent
- TNC/kg 1×10^8 TNC/kg
- Viability $\geq 70\%$
- ABO/Rh verified
- Product container integrity verified

▪ Physician notified if any result “Out of Specification”

- Additional orders required by physician
- Does not stop infusion of product

Processing Facility – Outcomes and Reporting

- **Review of engraftment data**
 - Investigation required for patients with delayed or no engraftment
- **Adverse reactions and positive sterilities**
 - Require investigation
 - PBSC might be reportable to FDA
 - Who should report – the registry, transplant facility, IND holder?
- **During investigations need information from collection facility – not easy to get**

Summary

- **Many questions and uncertainties**
 - **How are collection facilities qualified? What is the responsibility of the transplant facility as the final distributor in this process?**
 - **Qualification/validation of equipment, processes and test methods**
 - **Product handling concerns**
 - **Product characterization**
 - **FDA oversight**

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