

	WMDA Guidelines for validation of transport containers			
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**WMDA guidelines
for validation of transport containers used for the distribution of
Haematopoietic Stem Cell (HSC) products**

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Executive Summary: WMDA recommends that registries and cord blood banks use only validated containers when transporting fresh Haematopoietic Stem Cell (HSC) products. Furthermore; WMDA advocates a prospective modified version of the WHO Cold Life and Warm Life Test protocol as a 'gold standard' methodology to validate fresh transport containers before they enter courier service.

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1. INTRODUCTION/GENERAL INFORMATION

WMDA has published recommendations for product transport¹. These guidelines are to provide guidance to registries and cord blood banks subject to specific distribution/transport of haematopoietic stem cell products.

In addition, there are regulatory requirements; for example, the European Directive 2006/17/EC (Second technical directive)² section D. DISTRIBUTION AND RECALL stipulates:

1. *Critical transport conditions, such as temperature and time limit must be defined to maintain the required tissue and cell properties.*
2. *The container/package must be secure and ensure that the tissue and cells are maintained in the specified conditions. All containers and packages need to be validated as fit for purpose.*

Validation of transport containers for transportation of fresh non-cryopreserved haematopoietic stem cell products is an activity concerned with collecting data and conducting scientific studies aimed at generating evidence proving or disproving that these items of equipment consistently meet predetermined specifications / criteria. These evaluations must be documented to record the performance of these pieces of equipment regarding their effectiveness based on intended use.

These guidelines describe existing validation strategies / protocols and provides a methodology for validating transport containers to be used in the transport of fresh HSC products. The guidance is deemed the minimal requirement to meet safety standards in regard to validation of transport containers. Although it is the entity providing the courier that is responsible for ensuring that the transport takes place per WMDA guidance¹, it is the registry or cord blood bank's responsibility ultimately to assure itself that the transport container(s) used in fresh product transport have been validated appropriately per requirements. A further responsibility for these entities is to ascertain whether by adhering to these specific guidelines; that local governmental laws and regulations are met.

Some governments may specify certain validation protocols must be followed for an entity to achieve national compliance. If this is the case, WMDA recommends a registry or cord blood bank perform a gap analysis of mandated validation protocols against these guidelines (and any other standards applicable to the entity for example AABB, FACT-NetCord), to ensure all requirements are met or exceeded.

Validation activity begins at the start of a transport container procurement process. The product selection / user requirements specification (URS) or tender process should be limited to container solutions that are designed for shipping use with medical or pharmaceutical payloads under temperature-controlled conditions. It is advisable that entity 'quality assurance representative(s)' are involved during all stages of any solution selection, validation and implementation into use.

The procurement / selection process will need to ensure that the chosen transport container solution is:

- An isothermal transport container capable of supporting maintenance of the criteria stipulated in section 4;
NOTE: It is possible that entities will need to procure two different transport container solutions to successfully achieve these requirements; one designed for cooled transport and one designed for room temperature transport (see section 6).
- Constructed of strong rigid material to protect the bags of HPC from damage arising from shock or impact;
- Compliant to all applicable laws and regulation regarding the mode of transportation;
- has sufficient internal dimensions to accommodate the maximum load size and number of bags used for collection of HPC at collection centre(s);

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- Compatible with airline cabin baggage restrictions pertaining to size and weight and amenable to being comfortably carried by a courier on long journeys;
- Amiable to the external affixing of labels as per other WMDA guidelines, regulatory or accreditation specific requirements;

Currently, WMDA does not recommend the use of any ‘active’ based cooling systems, for example externally or on-board powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation. These systems have the potential to cause additional difficulties with airport security or cabin crews, if couriers were to attempt to board flights carrying them.

Manufacturer, supplier and available published literature and temperature performance data should be obtained and reviewed to inform any purchase decision. Ideally, the selected container should have been previously tested or ‘pre-qualified’ by a third party to hold a particular temperature range (typically refrigerated or room temperature) for a certain amount of payload capacity for a specified period of time for example 24, 72 or even 96 hours. Preferably, the pre-qualification testing will have been performed to the International Safe Transport Association- ISTA 7D, ISTA 7E procedure or other named protocol as listed in section 5 and allow a certain amount of extrapolation in regard to intended use within our field. Additional shock, vibration and / or compression study information may be available from the manufacturer and will provide evidence that the containers are physically robust enough for intended use. Entities should perform their own validation studies after purchase, despite the availability of this data.

2. **DEFINITIONS / ABBREVIATIONS**

- CAPA (Corrective Action Preventive Action): consists of improvement to an organisation’s processes taken to eliminate causes of non-conformities or other undesirable situations.
- EDLM (Electronic Data Logging Monitor): portable devices that measure and stores temperature at pre-determined time intervals by means of an electronic sensor. Features and functions vary by manufacturer. They can include: programmable alarm capabilities, integrated displays, integrated USB and ability to create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases. Includes any continuous temperature recording devices and thermocouples.
- GM-CFC (Granulocyte-macrophage colony-forming cells): a monomeric glycoprotein that functions as a cytokine (it is a white blood cell growth factor).
- GMP (Good Manufacturing Practice): the practices required in order to conform to the guidelines recommended by agencies that control authorisation and licensing for manufacture and sale of food, drug products, and active pharmaceutical products. GMP provides minimum requirements that a pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public.
- HPC (Haematopoietic Progenitor Cell): are the cells, which give rise to blood and immune system cells. These cells are found in bone marrow, growth factor stimulated peripheral blood, and umbilical cord blood. The source of stem cells can be abbreviated as follow: HPC(M) – Marrow, HPC(A) – Apheresis, HPC(CB) - Cord Blood.
- ISTA (International Safe Transport Association): a global alliance of shippers, carriers, suppliers, testing laboratories, and educational and research institutions focused on the specific concerns of transport packaging. ISTA publish standardised validation procedures e.g. Test Procedure 7D, Test Procedure 7E. 7D covers the thermal performance testing of packaged products to evaluate the effects of external

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temperature exposure while Test Procedure 7E is aimed at evaluating temperature-controlled product packaging for the transport of temperature sensitive medicinal products.

- Metrological traceability: property of a measurement (temperature in regard to these guidelines) result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.
- NIST (National Institute Standards and Technology): US institute promoting standardisation in science.
- Passive items: items which contribute to maintaining a temperature-controlled environment. For example, cooler / coolant packs, extenders, shells, frames, TIC® (Thermal Isolation Chamber) panels or other advanced phase change materials. Includes any insulating / cushioning material.
- Prequalification / Prequalified: a preliminary study, which is generally the initial test(s) taken to ensure that a solution will meet generic objectives such as an ability to maintain a standard shipment temperature range over a standard timeframe (Prequalified equates to a solution successfully completing the initial tests).
- QA (Quality Assurance): actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected individually and collectively. Entities usually achieve this by implementing a quality management system and employing or contracting an individual(s) with expertise in quality management – the ‘quality representative(s)’ (for example quality specialist, quality officer, quality supervisor, quality manager etc.).
- SOP (Standard Operating Procedure): A compilation of written detailed instructions describing the steps in the process, including materials and methods to be used and the expected end product.
- Transport system: all components / containers constituting a completed package including: the outer transport container, all internal ancillary packaging.
- Thermal test chamber: an incubator or refrigerator capable of maintain a constant temperature such as +35°C (± 2°C) or +4°C (± 2°C), of sufficient dimensions to comfortably allow the safe placement of a transport container inside for testing. N.B. The chamber should be exclusively available for use by staff performing the validation for the 72-hour test period described in these guidelines.
- Validation: establishing documented evidence that a process will consistently produce predetermined specifications. Evaluation and written documentation of the performance of equipment, a reagent, a process or a system with regard to its effectiveness based on its intended use.
- WHO (World Health Organization): WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

3. EQUIPMENT REQUIREMENTS

- A. Isothermal transport container selected during the procurement process that meets all selection criteria in section 1.
- B. EDLMs ideally capable of producing a permanent record of temperature and elapsed time such as a printout and / or download. These items should have sufficient memory (where applicable) to record for >72 hours of continuous use. Devices should be metrological traceable to the ISO/IEC 17025³ or a national standard (for example NIST in the Unites States), and within calibration date. These will be used to accurately record the temperature inside the container under test, as well as the temperature outside the container during validation studies.

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- C. Collection kits, representative of those used at collection centres / sites within the registry or cord blood banks network.
- D. Stock of 10% glycerol or saline, to be added to the collection kits to simulate full loads during the performance of the validation studies (for example: dummy or placebo product bags).
- E. Timer or stop watch capable of alarming and running continuously for >72 hours.
- F. Internal packaging (as stipulated by the manufacturer):
 - Cushioning and insulating material;
 - Passive items which contribute to maintaining a temperature-controlled environment e.g. cooler / coolant packs, extenders, shells, frames, TIC® (Thermal Isolation Chamber) panels or other advanced phase change materials;
 - Primary collection bags shall be placed in a secondary securely sealed container such as a resealable plastic bag (ideally sterile) which can withstand leakage of contents;

4. **ACCEPTANCE CRITERIA**

4.1. **TRANSPORT DURATION**

4.1.1 72 hours

As per WMDA standard 8.08; “Cells must be transported in a timely and reliable fashion to meet transplant centre requirements for the quality and quantity of the cell product upon arrival at the transplant centre. Packaging must comply with national and international regulations.”⁴

A historical review of the WMDA S(P)EAR database for transport / distribution of adult derived product related adverse events (for example where delays in transport were experienced) supported the minimum time required for transport containers to be used for international distribution of adult derived products would need to maintain the temperature criteria listed in section 4.2 for up to 72 hours. For this reason, **72 hours** was chosen as a sufficiently challenging length of time on which to base a recommended validation protocol (see section 6).

Registry / cord blood bank quality management systems should consider the possibility of severe product distribution delays, which might result in an exceeding of the time the transport container system was validated to achieve, thus threatening the potency and viability of the product being transported. For adult derived products; business continuity strategies to militate against such eventualities should be formulated in accordance with previously published WMDA guidance⁵.

Examples of possible risk mitigations include agreements with appropriate centres within your network (or external specialist biobanking or blood transfusion entities) for temporary refrigerated storage and/or emergency cryopreservation of products.

4.2. **TEMPERATURE PROFILES**

4.2.1. +1°C to +10°C

4.2.2. Room Temperature range: +15°C to +25°C

Note: An alternative range may be selected if mandated by a national regulatory body or stipulated by the entity providing the courier. Alternate ranges should be based on the scientific literature and / or on the entities own more detailed experimental and validation data

4.2.3. If opened (for example by airport security staff) the temperature within the container should return to range within 60 minutes of re-closure.

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5. VALIDATION STRATEGIES

The globalised supply chain delivery of pharmaceutical products and GMP has shaped temperature profiling, validation of transport containers and the safe controlled transit of perishable products destined for therapeutic use in humans. Over time there has been an evolution and dichotomy in validation strategy between the constant temperature profiles to the so-called cycling temperature profiles⁶.

Examples of constant temperature validation test profiles include:

- WHO Cold Life and Warm Life Test, for use when validating shipments of vaccines⁷

In this strategy, a vaccine must be packed to ensure that the warmest storage temperature of the vaccine does not rise above +8°C in continuous outside ambient temperatures of +43°C, for a period of at least 48 hours. The cold profile is used to determine how long the vaccine can be safely stored inside a box at temperatures above 0°C in an extremely cold outside environment (ambient temperature -5°C).

- DIN 55545⁸

The test methods specified with the German DIN 55545 are intended for use in the evaluation of temperature retention capacity in different insulation containers, regardless of how the box is configured. Based on such an evaluation the performance of different boxes can be compared. The test is performed at +30°C for a period of 72 hrs. 35% of the internal net volume is filled with frozen cooling elements with these elements being placed on the bottom of the box.

Examples of cycling temperature validation profiles include:

- ISTA 7D Procedures⁹

This protocol requires climatic chambers and an entity wishing to apply an ISTA validation of its transport containers would most likely require 3rd party expertise to perform it effectively. Winter and summer profiles are established, resulting in different configurations of the passive cooling box throughout the year. Containers are subjected to different temperatures over the test time. For example, a 48-hour summer challenge might see a container held at 22°C for 4 hours, 35°C for 2 hours, 30°C for 36 hours and then again at 35°C for 12 hours. The aim is to validate a container under 'real world' ambient shipping of cargo temperatures. ISTA procedures are commonly used by manufacturers / suppliers when performing prequalification studies and can provide good evidence to guide product selection during procurement of a transport container solution.

- Association Française de Normalisation (AFNOR)¹⁰

This is a detailed protocol for qualification of insulated containers and is published by the French association of standards. The temperature profiles vary from destination to destination (Mediterranean – Continental - Northern) and from summer to winter seasons. In the summer profile, the temperatures range during testing cycles between +22°C up to +40°C for Mediterranean and continental destinations and from +20°C up to +32°C for northern destinations. In the winter profile, a minimum temperature of +8°C (Mediterranean destination) and -2°C (northern destination) respectively is assumed⁶.

These constant or cycling testing strategies attempt to either simulate a worst-case scenario or assume the payload is effectively shipped as an unattended cargo with episodes of unattended warehouse / cargo hold storage. During transit in our field of healthcare, only fresh cord blood may be shipped as a

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cargo in a similar way¹¹. However, for adult derived fresh HSC and for many cord blood banks during the initial pre-processing fresh transport, distribution must be couriered by hand via car, airplane or train for most if not all of the time on a direct route to the transplant centre or cord bank. This means the distribution is mainly via closed indoor surrounding at room temperature with the exposure to open air being restricted to occasions such as when a courier boards an aircraft.

Published studies have shown how temperature and time can potentially adversely affect HSC product potency and viability¹²⁻¹⁷. There is therefore, a risk that failure to validate transport containers adequately could lead to inappropriate transport conditions which in turn could adversely affect the quality of product. Considering how precious fresh HSC products are, coupled with best risk management practices; WMDA advocates a prospective modified version of the WHO Cold Life and Warm Life Test strategy as a 'gold standard' to achieve validation of transport containers as described below in section 6. Inappropriate product transport temperature not only increased the risk of patient harm but also increases the chances that a donor may be asked to donate again to replace a product that has lost its viability and potency during inappropriate transport.

Few transport containers are currently available that can meet the extreme validation protocol described below in section 6 however, and so other protocols derived from the strategies listed in section 5 or protocols as defined by the responsible entity are permissible, as long as the protocol sufficiently challenges the transport container in terms of intended use.

Drop, impact or shock testing of the container during validation are not recommended unless the container is to be used in a cord programme for fresh cord blood 'shipping' as cargo (i.e. not carried by hand by a courier), or unless these types of validation tests are required to ensure compliance with an accreditation programme, local governmental laws or regulations. This is because such testing is usually performed by manufacturers / suppliers during prequalification before the transport solutions are marketed with data available to entities on request. Running these types of tests also poses a risk of damaging containers destined for active service use. Likewise, actual viability or potency testing of any representative samples of actual HPC(A) or HPC(M) product is not required as part of any validation as the published evidence base has sufficiently established how HSC products can be adversely affected by temperature, cell concentration and fresh transport time using tests such as Flow viable CD34 counts and GM-CFC¹²⁻¹⁷.

Cord blood programmes do have ready access to excess cellular material however and so viability and potency testing should be incorporated into validation studies of transport containers destined for use in fresh cord blood transport, as per Netcord-FACT guidance¹¹.

The evidence base supports the use of the temperature profiles listed in section 4.2, and the necessity to dilute HPC-Apheresis products to a cell concentration of less than 200 10⁹/L if transport is to be over a long distance / transit time.

6. VALIDATION PROTOCOL

Different transport containers are available that are specifically designed to maintain a cooled or a room temperature range of temperatures. It is advisable to first procure and attempt to validate a transport container designed to maintain a cool range as defined in 4.2.1. If the validation is successful, an attempt could be made to validate the same transport container (without its cooler / coolant packs, extenders, shells, frames, TIC® or alternatively these items could be thermally conditioned to room temperature rather than the cooled temperature) to ascertain whether the system can also maintain

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the range specified in 4.2.2. If this second validation is successful, one design solution will suffice for both temperature profiles.

If this second validation fails however; a second container solution designed for room temperature transport use will need to be procured to meet Transplant Centre requirements.

If the intention is to perform a validation to place numerous transport containers into service at the same time; it is permissible to select a sample of the containers at random to validate and extrapolate the findings to the other containers procured at the same time.

The suggested prospective validation protocol guidance is as follows:

- 6.1. Use manufacturer instructions and these guidelines to write a draft SOP(s) with internal stakeholder involvement. The SOP(s) need to cover: conditioning, packaging of the transport container(s) and use of EDLMs. This new draft SOP(s) will need to be approved by a Quality Representative(s), at a minimum. Deliver any staff training as required but limited to individuals involved in performing the validation only at this stage (this training could be facilitated by the SOP draft author / owner, quality assurance representatives or transport solution suppliers).
- 6.2. Next, begin the validation study; as per the newly written draft SOP(s); ensure the adequate preconditioning of items which contribute to the maintenance of the temperature-controlled environment within the transport container including passive items. This will likely involve their placement within a refrigerator, a freezer, incubator or left at room temperature for a minimum length of time.
- 6.3. Prepare sufficient collection bags by adding 10% glycerol or saline to create a simulated / dummy maximum transport load of 1500mls and place them within individual resealable plastic bags. These should then be stored as they would at the collection centre within the registry or cord blood collection site for a length of time comparable to the time real products would be stored awaiting courier collection.

It is important to remember that transport container efficacy regarding temperature regulation will be impaired if products payloads are not conditioned for a minimum length of time as stated within transport container manufacturer's instructions for use. Additional data gathering / studies may need to be performed to determine minimum adequate product conditioning time but as a rule if a product is to be transported cooled; it should be placed in a medical refrigerator at the collection centre as soon as possible after collection to facilitate transport within the desired temperature range.

- 6.4. As per draft SOP(s); pack the transport container being validated including careful placing of passive items. Add the conditioned dummy collection bags representing a simulated payload of 1,500 mls.
- 6.5. As per the draft SOP(s); set EDLMS to take readings at 5-minute intervals (minimum) throughout the duration of the test.
- 6.6. While attempting to minimise the time the container is open; place a minimum of one interior payload EDLM. The payload EDLM(s) should be positioned to capture temperature variation or temperature stratification within the payload space. Multiple devices will be needed to achieve this however, but this is considered best practice. Interior placed probes or EDLMs should be taped in place so that they remain in contact with the dummy bags. Close lid.
- 6.7. Affix or rest one external ambient EDLM to the exterior/top of the transport container.

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- 6.8. Transfer the test transport container into the thermal test chamber set at +35°C, or +4°C, depending on which temperature profile is under test.
- 6.9. Set the timer to alarm in 36 hours (sensible scheduling of the validation is needed to ensure a staff member is available to perform the next step).
- 6.10. At 36 hours remove the test container from the thermal test chamber, to simulate the container being opened by airport security mid journey i.e. place the container on a table well away from the incubator or refrigerator and open the container fully for 2 minutes (use timer).
- 6.11. Return the test container to the thermal test chamber and set timer for 36 hours.
- 6.12. After the full 72 hours, remove the container and empty the contents.
- 6.13. Compile and interrogate the data from all EDLMs. Prepare a validation report in the scientific style. This report should summarise the test data and performance characteristics established during validation testing and provide conclusions based upon these data and an overall statement as to whether the transportation container under test has passed or failed the validation. The report should include a copy of the draft SOP(s) with signature log, complete equipment list, and material specifications. In addition, include test graphs, complete test worksheets, all testing data, equipment calibration certificates, and any applicable deviation reports in respect to section 4.2 criteria.
- 6.14. There will be few acceptable deviations. One example of an acceptable deviation that will need to be explained in the validation report will be the fact the externally affixed device will show temperature transiently to be out of test range (the devices will record room temperature on removal) when the container is taken out from the refrigerator/incubator in step 6.10. Another deviation might be if temperature conditioning of the simulated / dummy payload has not occurred during step 6.3. In these cases, there will be a probable time lag before the interior temperature of the transport container enters the ideal temperature ranges listed in 4.2. Lack of conditioning will also likely result in the transport container failing to hold listed temperature ranges for the full 72 hours. Under these circumstances an entity should consider devising their own temperature and time ranges based on how they intend to use the transport containers, Transplant Centre requirements, the scientific literature and / or more detailed experimental and validation data.
- 6.15. If the criteria described in 4.2 are not met; the transport container has failed to be validated and cannot be used for the intended purpose. A root cause investigation should rule out the possibility that the failure is attributable to poor execution of the validation test protocol; for example, because the container was not assembled properly, that the dummy load or that the passive items were not preconditioned properly etc. If the criteria described in 4.2 are met; the transport container has successfully passed validation and can be put into routine service as intended, subject to SOP(s) being finalised and delivery of further training as required.

Final SOP(s) will need to include regular cleaning of all items and periodic inspection for damage. The transport containers are assets that will need to be fully integrated into the Quality Management System. Certain items that constitute the solution may even have an expiry date that will require staff to be alerted when these dates approach, with systems in place to ensure timely reordering and replacement.

After validation and regardless of infectious disease testing; products shall still be considered potentially infectious.

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Infection control needs to be considered and enshrined within the final version of SOP(s) e.g. Regular cleaning and inspection (for damage) of items that constitute the entire transport container solutions. For example; passive items could be placed in resealable plastic bags if while they are being preconditioned / stored in shared laboratory refrigerators or freezers (i.e. where cross contamination is a possibility).

After validation, and during routine use it is highly recommended that EDLMs are used to monitor all transport of HPC products with temperature excursions (temperatures recorded that are outside those defined in section 4.2) being reported to transplant centres on an exception basis only.

Formal revalidation of transport containers is deemed not necessary if continuous temperature monitoring remains within range during trips and satisfactory routine transport container and ancillary packaging item integrity checks are carried out periodically, during the service life of the transport containers.

7. QUALITY ASSURANCE (QA)

A Quality Assurance (QA) representative(s) should be involved early in the procurement and validation process as they are usually responsible for managing overall compliance with regulatory, qualification and accreditation standards and for approving the overall safety, scientific validity and effectiveness of the validation.

A QA representative from the entity providing the courier **and** a representative(s) from the registry / cord blood bank (if not the entity providing the courier) should at a minimum; review pre-qualification / published data / manufacturer's instructions concerning transport container solutions (pre-procurement), the validation protocol / draft SOP(s) pre-execution, and the documentation and results post validation study completion. The review and applicable approvals should address the following:

- If the validation protocol was adequately planned, scientifically valid and followed (if different from these guidelines);
- If the acceptance criteria were met;
- That any deviation from the test protocol were supported with proper investigation, corrective action and documentation;
- If any true instances of failure or temperature excursion exist; and that the equipment involved fail validation as appropriate;
- That all raw data is complete, that all tests were documented, and that all raw data is compiled and authorised within a validation report and retained appropriately;
- That rework /retesting / initiation of a different solution selection process, is performed as required;

A QA representative is responsible for the review and approval of the validation protocol / draft SOP(s) prior to the performing of the protocol itself. The following elements should be taken into consideration:

- That the scope of the draft validation SOP(s) are well defined and meet applicable manufacturers' instructions, scientific / medical literature, guidelines, qualification, accreditation and / or regulatory requirements;
- That roles and responsibilities of the professionals conducting the validation are well defined and documented, and that appropriate training is delivered and documented

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- That the protocol and equipment used during the validation are covered by an approved draft procedure(s);
- That sampling of equipment selected for validation is acceptable and statistically sound
- That the equipment to be used is properly conditioned, calibrated, monitored and pre-qualified (as appropriate);

A QA representative(s) will review the validation report which includes the raw data, test results and conclusion etc. as described in 6.13. The review will consist of identifying and addressing:

- If the validation protocol / SOP were followed as indicated;
- That any deviation from the test procedure are supported with proper documentation;
- If any instances of failure exist;
- That all raw data is complete and that each step of the validation procedure is well documented and authorised;
- If the proper method and equipment were used;
- If the documentation associated with the validation report is complete and acceptable: raw data sheets, test results, preventive maintenance schedules, test incidence reports and equipment calibration certifications etc.;
- If expected results are achieved and the acceptance criteria were met;
- Ensure the final report addresses any revalidation requirement;

8. REFERENCES

1. World Marrow Donor Association (WMDA) Transport Guidelines (<https://share.wmda.info/x/EgA0Ew>)
2. European Directive 2006-86-EC (Second technical directive)
[https://www.hta.gov.uk/sites/default/files/European_Directive_2006-86-EC_\(Second_technical_directive\).pdf](https://www.hta.gov.uk/sites/default/files/European_Directive_2006-86-EC_(Second_technical_directive).pdf)
3. ISO/IEC 17025: 2005: General requirements for the competence of testing and calibration laboratories
4. World Marrow Donor Association International Standards for Unrelated Haematopoietic Stem Cell Donor Registries (2017) (<https://www.wmda.info/professionals/quality-and-accreditation/wmda-standards/>)
5. World Marrow Donor Association Crisis Response, Business Continuity, and Disaster Recovery Guidelines
6. Pingel, Julia *et al.* *Biology of Blood and Marrow Transplantation*, Volume 18, Issue 1, 1785 – 1789
7. Spiggelkötter, N. Temperature Profiles, GMP Publishing LOGFILE No. 14. 2011
8. WHO/V&B/01.05, Guidelines on the International Packaging and Shipping of Vaccines. World Health Organisation 2002
9. DIN 55545-1 Prüfverfahren für Verpackungen mit isolierenden Eigenschaften Teil 1: Erstbewertungsprüfung, Beuth Verlag 2005
10. 7D: Temperature Test for Transport Packaging. International Safe Transit Association. 2007
11. NF S99-700: Emballages isothermes et emballages réfrigérants pour produits de santé - Méthode de qualification des performances thermiques. AFNOR 2007
12. NETCORD-FACT. International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release for Administration Accreditation Manual, 6th edn. 2016. FACT: Omaha, Nebraska, USA
13. Jansen, J., Hanks, S.G., Akard, L.P., Morgan, J.A., Nolan, P.L., Dugan, M.J., Reeves, M.I. & Thompson, J.M. (2009) Slow platelet recovery after PBPC transplantation from unrelated donors. *Bone Marrow Transplantation*, 43, 499–505.

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14. Jansen, J., Nolan, P.L., Reeves, M.I., Akard, L.P., Thompson, J.M., Dugan, M.J. & Hanks, S.G. (2009) Transportation of peripheral blood progenitor cell products: effects of time, temperature and cell concentration. *Cytotherapy*, 11, 79–85.
15. Jansen, J., Nolan, P.L., Reeves, M.I., Morgan, J.A., Akard, L.P., Thompson, J.M., Dugan, M.J. & Hanks, S.G. (2010) Transportation of peripheral blood progenitor cell products: effect of ambient temperature. *Cytotherapy*, 12, 919–923.
16. Kao, G.S., Kim, H.T., Daley, H., Ritz, J., Burger, S.R., Kelley, L., Vierra-Green, C., Flesch, S., Spellman, S., Miller, J. & Confer, D. (2011) Validation of short-term handling and storage conditions for marrow and peripheral blood stem cell products. *Transfusion*, 51, 137–147.
17. Fry, L.J., Giner, S.Q., Gomez, S.G., Green, M., Anderson, S., Horder, J., McArdle, S., Rees, R. & Madrigal, J.A. (2013) Avoiding room temperature storage and delayed cryopreservation provide better post thaw potency in hematopoietic progenitor cell grafts. *Transfusion*, 53, 1834–1842.
18. Hahn, S., Sireis, W., Hourfar, K., Karpova, D., Dauber, K., Kempf, V.A.J., Seifried, E., Schmidt, M. and Bönig, H., 2014. Effects of storage temperature on hematopoietic stability and microbial safety of BM aspirates. *Bone Marrow Transplantation*, 49(3), pp.338-348.