Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

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Change Orders

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TITLE: POLICY FOR MANAGEMENT OF TEMPERATURE EXCURSIONS DURING THE TRANSPORTATION OF BLOOD PRODUCTS AND MEDICINAL PRODUCTS

Change Description:
1) Page 11 – For products placed in Quarantine: Add to 4th and 6th bullet points the following: For any decisions made to release products from quarantine, the documented justification will be included in the IR or QC file and a risk assessment included where applicable.

Reason for Change:
1) Corrective Action from HPRA GDP inspection 34437 & 34438.

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Referenced Documents

IBTS/EXT/DOC/0002	IBTS/EXT/DOC/0004	IBTS/EXT/DOC/0005	IBTS/EXT/DOC/0006
IBTS/EXT/DOC/0012	IBTS/EXT/DOC/0027		

SmartSolve Roles

DSP THOD MRTC	MED CON MSD IBTS	MED CON DON NBC	SSCD THOD NBC
DSP CSS NBC	QA SPVR MRTC	MED SMO MRTC	TDOQ
MM SS NBC	QA SQBP NBC	MED SMO NBC	QC MGR IBTS
PHS DIR IBTS IBTS	QA THOD IBTS	QC RAM IBTS	SC MGR IBTS

Training Type

All Roles	Read and Understand

SmartSolve Document Category

Category	Mobile	Cryobiology	Website	GDP
Yes / No	No	No	Yes	Yes

TITLE: POLICY FOR MANAGEMENT OF TEMPERATURE EXCURSIONS DURING THE TRANSPORTATION OF BLOOD PRODUCTS AND MEDICINAL PRODUCTS

1 INTRODUCTION

The Irish Blood Transfusion Service, as a Blood Establishment, must comply with the requirements of Directive 2002/98/EC (Ref.1) of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

Further regulatory requirements for the storage and transportation of blood products and medicinal products are outlined in Directives 2005/61/EC (Ref.2), 2005/62/EC (Ref.3) and 2004/33/EC (Ref.4) and the principles of Good Manufacturing Practice in Directive 2017/1572 of 15th September 2017. (Ref. 5)

The requirements in the Guidelines of 5 November 2013 on Good Distribution Practice for Medicinal Products (2013 / C 343/01) also apply. In particular, Chapter 7.0 (Outsourced Activities) and Chapter 9.0 (Transport) (Ref. 6)

Further guidance is available from the Council of Europe Guide to the preparation, use and quality assurance of blood components, (Ref. 7) the HPRA Guides (Ref. 8, 9 and 10) and the PIC/S Guide for Blood Establishments.(Ref. 11).

2 OBJECTIVE

This Policy is used to provide IBTS QA, IBTS Medical, HSE, contracted couriers and Hospital personnel with specifications and guidance on categorising the extent of a temperature excursion occurring during transport. For minor temperature excursions (refer to Tables 1, 2 & 3.), quarantining is not necessary.

For major temperature excursions, the consequence may be to quarantine or to discard the products.

Any decision to release the products from quarantine by IBTS Medical concessionary release needs to be based on a risk assessment documented in accordance with Quality Risk Management Principles.

3 SCOPE

This policy specifically covers transportation of Blood Products and Medicinal Products carried out by the IBTS and its contracted couriers.

Transport of Medicinal products into the IBTS by manufacturers and wholesalers are specifically covered by separate procedures and by Service Level Agreements with the IBTS.

4 ROLES AND RESPONSIBILITIES

The following are the general Roles and Responsibilities within the organisation associated with the implementation and operation of this Policy.

Role	Definition	Responsibilities
QA Staff	QA Staff managing the NC documentation processes.	Shall refer to this policy where temperature excursions occur during transport.
National Quality Assurance Manager	The NQA Manager oversees all aspects of Quality Assurance activities	Shall ensure that this QA Policy is implemented in their areas of responsibility & shall identify where formal risk assessment is required.
Quality, Compliance & Regulatory Affairs Manager	The QCRA Manager oversees compliance and regulatory affairs	Shall ensure that this QA Policy is updated with the most recent changes in regulatory requirements. Audit for compliance to this policy.
Director of Quality & Compliance	The Director of Quality / Compliance ensures that the required standards of quality are achieved	Shall ensure that the Quality Management System is implemented across the organisation and that regulatory requirements are met & will identify where formal risk assessment is required. Shall make decisions on release from quarantine in conjunction with Medical as required.
Medical & Scientific Director / designee	The Medical & Scientific Director is responsible for authorisation of exceptional release of product	Shall authorise Exceptional Product Release with reference to IBTS/QA/SOP/0059. This is carried out in conjunction with the Director of Quality & Compliance (Responsible Person)
Executive Management Team	The IBTS Executive Management Team oversees all organisational processes	Shall ensure that this QA Policy is fully implemented through procedures and Service Level Agreements in their relevant area of responsibility.
Health Service Executive	HSE representative for the distribution of products to the hospitals	Shall ensure that this QA Policy is fully implemented through procedures and Service Level Agreements for contracted couriers / outsourced activities.
Contracted Couriers	All couriers contracted for the distribution of IBTS products.	Notify the HSE and IBTS of all significant temperature excursions potentially impacting the integrity of products. Will review non conformances and identify suspected Serious Adverse Events and will manage reporting of SAEs & SAR's to the HPRA

5 POLICY

5.1 Transport Temperature Requirements

Blood products and medicinal products should be transported under conditions which ensure that their quality is maintained.

Blood products and medicinal products usually require transportation within a specified temperature range where there is an upper and lower limit. For some medicinal products there may be a single upper temperature limit specified. These conditions must be maintained throughout the distribution chain, often referred to as the 'cold chain'.

The controlled temperature transport system in use should take account of the following:

- volumes and quantities to be stored
- capability of the temperature control unit
- back up power for all elements of the control system
- Internal layout and loading pattern maintains cooling capability.
- Type and suitability of temperature monitoring probes
- Location of recording probes
- Functionality checks
- Temperature records
- Calibration of probes
- Maintenance requirements of the system
- Alarm/alert system installed and procedure to respond to these.

It is important to note, in the case of small volume operations, the implications of storing products in a location which is affected by repeatedly opening and closing the door.

The internal air temperature distribution should be mapped on installation in the empty and full states. External conditions should also be taken into consideration during the mapping exercise, as seasonal extremes of temperature may adversely affect the performance of the temperature control unit.

It is important that blood products and medicinal products are transported within their required temperature ranges because elevated temperatures can adversely affect the stability and physical properties of these products. Equally, transportation of some products at sub-zero temperatures for even brief periods may irreversibly denature protein and lead to a loss of efficacy.

Conditions within the distribution chain can vary markedly at different times of the year. The environment also changes significantly according to the season

and all of these variables have an influence on cold-chain distribution. Validation needs to provide an adequate level of assurance for normal transport conditions as well as the worst-case conditions.
Distribution requirements for blood components are outlined in EU Directive 2005/62/EC. This details requirements for GMP, validation, separation, records, packaging and returns.

Annex IV of 2004/33/EC sets out transport and distribution conditions for blood and blood components. It also states that "Transport and distribution of blood and blood components at all stages of the transfusion chain must be under conditions that maintain the integrity of the product''.

Further guidance on the transportation of blood components can be found in the Good Practice Guidelines Section 6.0 (Blood Collections), Section 7.0 (Storage & Distribution), Section 8.0 (Outsourced activities) and Chapter 4.0 (Storage & Distribution) in the Council of Europe Guide to the preparation, use and quality assurance of blood components.

The requirements for medicinal products are outlined in the Guidelines of 5th November 2013 on Good Distribution Practice of Medicinal Products for Human Use.

Contracted couriers are expected to meet the transportation requirements for blood, blood components and medicinal products at all times.

The IBTS Product Master file also specifies storage and transportation conditions for each of the products. These requirements are also included on the product labels.

5.2 Equipment Failure during the delivery of Blood Products and Medicinal Products:

The contracted courier has the following backups in place:

1. In the event of the malfunction of a thermal unit or the continuous temperature monitoring system the driver will initiate the manual backup procedure. This includes recording the digital temperature display. The driver will present this documentation on arrival at the hospital, in place of the ticket printout.

2. In the event of printer failure i.e. ticket printout, a backup report is also available from the TK tracking system. A copy will be sent to the hospital. This data is transmitted from the thermal unit monitoring probe via the van GPS. The TK tracking logs every 15 mins to one place of decimals.

3. In the event of a thermal unit failing whilst product is on board, a backup vehicle will be sent to assist where this is considered necessary.
   The driver has been instructed in the event of any of the above that no products should be removed from the van before the matter is discussed with hospital blood bank personnel, contracted courier and the IBTS.

5.3 Quarantine

A **Minor temperature excursion** is defined as one where the extent of the excursion and the total length of time it occurred for will not adversely affect Blood or Medicinal Product Quality. Quarantining of product is not required. Ref.Table 1.

A **Major temperature excursion** is defined as one where the extent of the excursion and the total length of time it occurred for has the potential to adversely affect Blood or Medicinal Product Quality. Quarantining of product is necessary until a review has been completed. Ref. Tables 1, 2 & 3.

Occasional minor temperature excursions will occur with loading and unloading which will not require the quarantining of product. However, in the event of a more significant or major temperature excursion, the products will need to be quarantined until such time as a decision can be made whether it is suitable or not suitable for use. (Refer to Tables 1.0, 2.0 & 3.0)

When reviewing the temperature printout at delivery the following points should be considered:

- The effect on the temperature of the thermal unit as a result of loading and unloading. Temperatures will increase/decrease when the door is opened but under normal operating conditions will recover within the alarm settings.
- The number of deliveries the driver makes prior to arriving at the hospital. Each delivery and unloading will have a temporary impact on the temperature.
- The weather conditions. All thermal units are influenced by the ambient temperature outside.
- Wind conditions, high winds and gales can influence data logging within the vehicle

The specifications and guidance in **Tables 1, 2 & 3** were determined by the IBTS in conjunction with the HSE and the contracted courier. They are designed to assist the hospital in deciding on when to quarantine a blood/blood product or medicinal product delivery. If there is a minor temperature excursion meeting the criteria below, then quarantining is not necessary. If there is a major excursion as defined below, then the product should be quarantined until a decision is made by the IBTS. In most cases quarantining will be undertaken at the hospital.

Table 1- Information for Hospitals (Red Cells & Platelets)

Product	Storage Temperature Requirements	Transport Temperature Requirements	Guidance for acceptance of Minor excursions where there is no consequence for product. (Quarantining not necessary)	Guidance for Major excursions where there is a discard consequence subject to medical approval. (Quarantine pending review)
Red Cells	2 -6 ^{0}C	2-6 ^{0}C (core) 2-8 ^{0}C (air)	-Temperature excursion reached a level of >/= 1.0^{0}C and < 2^{0}C (air). Duration of excursion(s) is up to 60 mins combined. -Temperature excursion reaches a level of >8^{0}C and </= 10^{0}C (air) Duration of excursion(s) is up to 60 mins combined.	- Temperature excursion <1^0 C. (air) - Temperature excursion reached a level of >/= 1.0^{0}C and < 2^{0}C (air). Duration of excursion(s) exceeds 60 mins combined. - Temperature excursion reaches a level of >8^{0}C and </= 10^{0}C (air). Duration of excursion(s) exceeds 60 mins combined. - Temperature excursion >10^0 C
Platelets	20-24 ^{0} C	As close as possible to 20-24 ^{0}C.	-Temperature excursion reaches a level of >/=18^{0}C and <20^{0}C or >24^{0}C and </=26^{0}C (air). Duration of excursion(s) is up to 2 hours combined.	-Temperature excursion reaches a level of <18^{0}C (air) -Temperature excursion reaches a level of >/=18^{0}C and <20^{0}C or >24^{0}C and </=26^{0}C (air). Duration of excursion(s) exceeds 2 hours combined. -Temperature excursion reaches a level of >26^{0}C (air).

Table -2 Routine Journey Times for platelets [Within temperature Specification]

Product and Transport System	Journey Time	Guidance for acceptance of Minor Deviations where there is no consequence for product. (Quarantining not necessary)	Guidance for Major Deviations excursions where there is a discard consequence subject to medical approval. (Quarantine pending review)
Routine delivery of platelets by transport box (3- 4 platelets per box)	journey time of </= 6 hours 40 minutes	Length of journey > 6hours 40 minutes and </= 7 hours 40 minutes	#Journey time > 7 hours 40 minutes
Routine delivery of platelets by transport box (1- 2 platelets per box)	journey time of </= 8 hours 35 minutes	Length of journey > 8 hours 35 minutes </= 9 hours 35 minutes	#Journey time > 9 hours 35 minutes

Platelet Transport box

In the event that transport delays may lead to transport times exceeding these limits, the platelet box validation data and ambient temperatures will be taken into consideration in order to determine the platelet disposition.

Platelet transport by temperature controlled vehicle

For routine deliveries of platelets by temperature controlled vehicles there is no journey time limit applied. However, in the event of roadside breakdown the limit is 8 hours from time of breakdown which is the length of time temperature control can be maintained (length of back up battery power). For example if journey time to point of breakdown was 5 hours then total limit is 13 hours. Otherwise where temperature can be maintained, the maximum transport time is limited to </= 24 hours from start of journey which is the limit for platelets without agitation. This is only applicable where the temperature requirements in Table 1 have also been met.

Table 3 - Medicinal Products

Product	Storage Temperature Requirements	Transport Temperature Requirements	Guidance for acceptance of Minor excursions where there is no consequence for product. (Quarantining not necessary)	Guidance where there is a discard consequence subject to medical approval. (Quarantine pending review)
Octaplas	</= -18 ^{0}C	</= - 18^0 C Guideline </= -22 C at loading	Temperature must recover within 30 mins of loading/unloading	Temperature has not recovered within 30 mins of loading/unloading
Medicinal Products (Octaplex Fibrygia)	Do not freeze. Store at 2-8 ^{0}C. Protect from light.	2-8^0 C (air)	Not applicable	Octaplex not to exceed 25 ^{0}C or to freeze in accordance with product insert Fibrygia not to exceed 25^{0}C or freeze. Protect from light.

- **Non–conformances need to be raised by the contracted courier for adverse temperature trends, temperature excursions and equipment failures where they have the potential to or have actually compromised product quality.**
- **All deviations (minor and major) are presented by the contracted courier to the IBTS and HSE for review at the quarterly meeting.**

For products placed in quarantine:

- When a product is quarantined, FDM (First Direct Medical) will immediately determine if the Hospital requires replacement product and FDM will immediately inform the IBTS of this.
- FDM will provide a report to the IBTS of the events surrounding the excursion and a copy of the available records of the temperature excursion as soon as possible. (Ref. FD GEN 0035). These will be sent to the IBTS Medical Officer.
- FDM will supply the hospital with any additional temperature data.
- The IBTS Medical Officer will review the temperature excursion and make a decision on the quarantined products. For any decisions made to release products from quarantine, the documented justification will be included in the IR or QC file and a risk assessment included where applicable.
- Sufficient time should be allowed for all of the necessary investigations to be carried out.
- If there is a difference of opinion on the status of products in quarantine the matter should be referred to the Director of Quality & Compliance (Responsible Person) who in conjunction with the Medical and Scientific Director (or Deputy) at IBTS, will make the final decision. For any decisions made to release products from quarantine, the documented justification will be included in the IR or QC file and a risk assessment included where applicable.
- The disposal of products deemed not suitable for clinical use must be discussed with FDM.
- In accordance with a statement issued by Octapharma, the licensed storage conditions of LG-Octaplas are to remain at or below -18 ^{0}C . Products which have not been stored at this temperature are used at the discretion of the hospital and distributor (IBTS).
- In the event that any of the MAH's advise us of an adverse impact on the stability and integrity of a medicinal product the IBTS will contact the Quality Defects and recall section in the HPRA.
- In the case of temperature excursions affecting Medicinal Products the manufacturer may need to be consulted to determine the potential impact of the excursion on the product.

Note:

FDM cannot lift quarantine restrictions. This decision can only be taken by the hospital in consultation with a medically qualified member of IBTS staff.

6 REFERENCES

(1) Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. Articles 22, 29 (e) (IBTS/EXT/DOC/0012)

(2) Directive 2005/61/EC implementing Directive 2002/98/EC as regards traceability requirements and notification of serious adverse reactions and events. (IBTS/EXT/DOC/0012)

(3) Directive 2005/62/EC implementing Directive 2002/98/EC as regards community standards and specifications relating to a quality system for blood establishments. Annex 7.1-7.6, 9.1 (IBTS/EXT/DOC/0012)

(4) Directive 2004/33/EC implementing Directive 2002/98/EC as regards certain technical requirements for blood and blood components. Article 5 and Annex IV. (IBTS/EXT/DOC/0012)

(5) Commission Directive (EU) 2017 / 1572 of 15th September 2017 - Principles and Guidelines of Good Manufacturing Practice for medicinal products for Human Use. (IBTS/EXT/DOC/0006)

(6) Guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use. (2013/C 343/01) (IBTS/EXT/DOC/0004)

(7) Council of Europe Guide to the preparation, use and quality assurance of blood components - Recommendation No. R (95) 15. (Current Edition) Good Practice Guidelines 6.0, 7.0 and 8.0. Chapters 4.0 and 5.0. (IBTS/EXT/DOC/0002)

(8) HPRA Guide to Control and Monitoring of Storage and Transportation Temperature conditions for Medicinal Products and Active Substances. (IBTS/EXT/DOC/0027)

(9) HPRA Guide to Good Distribution Practice of Medicinal Products for Human Use. (IBTS/EXT/DOC/0027)

(10) Guide to a Quality System for general Sale Wholesale Distributors. (IBTS/EXT/DOC/0027)

(11) PIC/S GMP Guide for Blood Establishments AND Hospital Blood Banks (June 2021) – Sections 3.5.5, 6.2.11- 6.2.15, 7.1 - 7.12. (IBTS/EXT/DOC/0005)

7 ATTACHMENTS

N/A