CRYOSTORAGE AND DISCARD OF CELL PRODUCTS:
SCIENTIFIC, ETHICAL AND LEGAL ASPECTS

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CELLULAR PRODUCTS INVOLVED

Autologous
- HPC A
- HPC M

Allogeneic
- HPC A
- HPC M
- TC A
- HPC CB?
Other tissues and cells

- Lawmakers have foreseen defined storage durations for non-hematopoietic cells
- Assisted Reproductive Technology
  - 10 years for gametes
  - 5 years for embryos
- How about HPC?

Today’s point

- Primary goal
  issue of discard related to long term storage
- Hoping to gather information and experiences for future consensus?
- Other causes of discard not ignored, but out of focus

Contents

- Applicable laws
- Current standards and guidelines
- (Short) bibliography
- Examples in real life
- Proposals for practical and rational guidelines
APPLICABLE LAWS

Law of Dec 2008 (MLM-MCH)
Royal Decree 28 Sept 2009
• Maximum storage duration must be defined

CURRENT STANDARDS AND GUIDELINES
HGR-CSS Quality Standards

CHAPTER 2.1

2.1.1 Objectifs portant sur la structure

La division de données, la vérification de la qualité, l’acquisition du système de données, le traitement de données, l’analyse et l’utilisation des données sont des éléments essentiels dans le processus de production de données.

2.1.2 Objectifs portant sur la qualité

La qualité des données est garantie par le processus de production de données. Les données sont vérifiées à plusieurs étapes, y compris lors de la collecte, de la transformation et de l’analyse. Les erreurs de données sont identifiées et corrigées au fur et à mesure qu’elles sont détectées.

2.1.3 Objectifs portant sur le système de données

Le système de données est un ensemble de composants qui sont conçus pour travailler ensemble pour collecter, stocker et analyser des données. Le système de données est conçu pour être flexible et évolué, permettant d’ajouter ou de supprimer des composants selon les besoins. Les données sont stockées de manière sécurisée, et les accès sont contrôlés par des autorisations d’accès.

JACIE 5th edition

2.1.6 Cryopreservation and thawing.

2.1.7 Labeling (including labeling of processed forms and samples).

2.1.8 Product expiration dates.

2.1.9 Product storage to include alternative storage if the primary storage method fails.

2.2 STORAGE

2.2.1 Storage facilities shall ensure storage areas are to prevent exposure to detergents, temperature, freeze-thaw, and improper distribution of washed therapy products.

2.2.2 Thawing facilities, in consultation with the Clinical Programs, shall establish policies for the duration and conditions of storage and thawing of the product to be used in the Clinical Programs.

ED.2.2.1.1 Patients, donors, and associated Clinical Programs should be informed prior to these policies, before the therapeutic product is released.

ED.2.2.2 Processing facilities processing, storing, and/or releasing cellular therapy products, be administered at the date of expiration of and date for which appropriate, for non-cryopreserved products and for products thawed after cryopreservation.

JACIE 5th Edition

Accreditation manual

STANDARDS:

The Processing Facility should define what constitutes storage. Storage may occur prior to processing, either in the Processing Facility or at the Collection Facility as well as after processing is complete. Storage temperature and duration shall be defined by the facility. The facility should define appropriate procedures for handling, testing, and releasing these products. Products that have been processed and are awaiting the results of release testing should be stored at a temperature lower than the release temperature at the end of the process.

Procedures that may not be suitable for cryopreservation or high temperature storage are not to be used. Products that have been stored at a temperature lower than the release temperature at the end of the process shall be released.

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Since the duration limits for storage of cryopreserved products has not been determined experimentally. Frozen products are not required to include a specific expiration date. However, once thawed, an expiration date and time must be assigned.
### CB standards 5th Edition and Accreditation manual

#### D11.1 Disposal of cellular therapy products shall include the following requirements:

- **D11.1.1** A pre-collection written agreement between the storage facility and the designated recipient or the donor, defining the length of storage and the circumstances for disposal of cellular therapy products.
- **D11.1.2** The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.
- **D11.1.3** Documentation of designated recipient's death or no further need for the cellular therapy product before any product is discarded.
- **D11.1.4** Approval by the Processing Facility Medical Director or the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.
- **D11.1.5** A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.

#### D11.2 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the patient is lost to follow-up, the storage facility shall:

- **D11.2.1** Communicate with the designated recipient's physician about continuing need for storage of the cellular therapy product.
- **D11.2.2** Make a documented effort to notify the donor or designated recipient about product disposition, including disposal or transfer.

#### D11.3 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

### Written SOPs are required that detail the conditions under which product disposal may occur and the process to be followed for the disposal of products. The limits for storage and reasons for disposal must be defined prior to the collection of the product, and is usually contained in the consent for the collection of products.

### The most common reasons for disposal are the following:

- **Death of the recipient**: death of the recipient, identification of cellular therapy products, and notification of the recipient's responsible physician must be documented before the product can be discarded.
- **No further need for the cellular therapy product**: in certain circumstances, the physician responsible for the recipient may determine there is no further need for the product. If the recipient is alive at the time the facility must offer the recipient an opportunity to move the product to another facility. This situation has potential legal liability to the institution, and many institutions may decide to store products for the life of the intended recipient rather than expose themselves legally to disposal of potentially life-saving products.
- **Discard to comply with written agreements with donor registries**: donor registries may have their own specific standards for product cryopreservation and disposal that will be agreed upon between the processing/storing facility and the registry. The processing/storing facility must adhere to these standards and/or to the FACT-JACIE Standards, whichever is more stringent.
Processing Facilities are not required to directly contact the recipient; however, they must require that the transplant physician obtain an agreement on the length of storage and circumstances for disposal of cellular therapy products.

Two of the biggest problems faced by older cellular therapy programs are the disposition of cellular therapy products collected.

- When there was no pre-existing agreement describing conditions for product storage and/or disposal
- When patients were lost to follow-up and their survival could not be confirmed.

Each institution must establish its own policy on discarding such products. The definition of a good faith effort to contact the recipient or family likewise is a decision left to the individual center. The rights of the donor (whether related or unrelated) should be protected according to local laws and the standards of donor registries.

- Common reasons for product disposal
  - Death of the intended recipient
  - No further need for product
  - Compliance with registry agreements
  - Poor quality product / contaminated
  - Patient lost to follow-up (survival cannot be confirmed or death verified)

- Common product disposition
  - Offer to patient to relocate product
  - Discard according to applicable laws and regulations
  - Release to research
  - Used in laboratory quality control or process development
  - Indefinite storage

Scientific considerations

- Viability
  - Maximum storage time unknown
  - Literature review
- Contamination
  - Positive infectious disease marker tests
  - Microbial contamination

Ethical considerations

- Respect to donor / recipient
- Importance of informed consent
- Ownership of the product - usually considered to belong to the recipient


### Bibliography


### High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years

- NAs 2003
- UCB @ 10 years & 9 @ 15 years
- CFU and NOD/SCID repopulation assay
- MNCs cryopreserved in cryotubes
- Demonstrate that HPC with extensive proliferative, self-renewal and in vitro expansion capabilities, and HSC with NOD/SCID repopulating ability can be effectively recovered after 15-yr storage in a frozen state
- Confirms previous observations
Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood

- **Blood** 2011
  - UCB (n=23)
  - CFU, NOD/SCID secondary repopulation assay and IPS cells generation
  - CD34+ selected cells cryopreserved in cryotubes

- **Bmt** 2013
  - 18 BM and 13 PBSC
  - Flow cytometry and CFU
  - Controlled-rate freezing, vapour phase of LN, 10% DMSO in autologous plasma

- PB and BM harvest do deteriorate with long-term storage: recovery of TNC, CD34+ cell count and cell viability decreased with time but CFU-GM did not

**Limitations**
- Most of the older stored stem cells were from BM and the more recently stored cells were from PB harvests
- Methodologies used for determining CD34 cells, TNC and CFU-GM have changed over the period of sample storage

- Storage conditions have significant effects, particularly "TRANSIENT WARMING EVENTS" (TWE) associated with the removal and/or placement of stem cell units in the dewars: it is possible that the deterioration over time observed in this study may reflect, in part, the cumulative exposure to transient warming events rather than an intrinsic loss in the viability of frozen stem cells over time
<table>
<thead>
<tr>
<th>Center</th>
<th>Duration</th>
<th>Procedure</th>
<th>Information to Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>UZ Brussels</td>
<td>10 years or death</td>
<td>Longer on request</td>
<td>3 months notice before destruction (old IC)</td>
</tr>
<tr>
<td>UCL St Luc</td>
<td>Death</td>
<td>Signed permission of Tx physician</td>
<td>Until useful</td>
</tr>
<tr>
<td>Roeselaere</td>
<td>Death Duration depends on disease (detailed list)</td>
<td>Agreed by Tx physician and patient</td>
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<tr>
<td>Liège</td>
<td>Death 23 years by SOP</td>
<td>Yearly review of Rijkregister/Registre national</td>
<td>Up to 20 years Option to shorten when necessary</td>
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<tr>
<td></td>
<td></td>
<td>Agreed by Tx physician</td>
<td></td>
</tr>
<tr>
<td>Brugge</td>
<td>20 years</td>
<td>1 month notice then destroy</td>
<td>Special release if product &gt; 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agreed by Tx physician and Cell bank director</td>
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**PROPOSALS FOR PRACTICAL AND RATIONAL GUIDELINES**

*recommandations SFGM-TC
à définir lors de l’atelier*
critères de destruction des produits cellulaires autologues

1. patient décédé ou perdu de vue
   - date du patient : justificatifs minimum : courrier médical ou enregistrement dans le dossier médical
   - date de la décision : 5 ans ou le retrait du produit cellulaire autologue

2. non conformité du produit cryopréréervé
   - absence de l'étiquetage de la poche
   - absence de nom du receveur
   - absence de la date de production
   - absence de la date de stockage

3. limite d'âge
   - 70 ans, 75 ans pour les lymphomes et myélomes

4. perte de l'indication d'autogreffe ou poches résiduelles après intensification(s) thérapeutique(s)
   - décision de RCP (peut inclure CI médicale, changement de programme thérapeutique, refus du patient, etc.)

critères de destruction des produits cellulaires allogéniques

1. receveur décédé ou perdu de vue
   - date du patient : justificatifs minimum : courrier médical ou enregistrement dans le dossier médical

2. non conformité du produit cryopréréervé
   - absence de l'étiquetage de la poche
   - absence de nom du receveur
   - absence de la date de production

3. perte de l'indication d'autogreffe ou poches résiduelles après intensification(s) thérapeutique(s)
   - décision de RCP (peut inclure CI médicale, changement de programme thérapeutique, refus du patient, etc.)
Recommendations SFGM-TC

Criteria for destruction of allogeneic cellular products
It is accepted that allogeneic products are dedicated to the initially intended recipient. (nominative prescription, labeling, current recommendations)
1. Recipient deceased or lost from FU
   - idem autologous products
2. Non-conformity of stored product
   - idem autologous products
3. Loss of indication of residual products
   - Upon decision of MDC (second allo HSCT, GvHD, etc)

proposition de mentions relatives à la conservation et à la destruction à insérer dans les consentements donneur familial et patient

allogreffe / donneur familial
  - J’ai été informé qu’il peut arriver que tout ou partie des cellules qui m’ont été prélevées puissent être conservées. Dans le cas où ces prélevements ne seraient pas utilisés, j’ai compris qu’ils sont exclusivement destinés au receveur désigné, et ne seront pas conservés si l’état de santé du receveur désigné ne le justifie plus.
  - En cochant la case ci-après, j’accepte que ces prélevements puissent être utilisés à des fins de recherche scientifique ou médicale avant leur destruction.

autogreffe / patient
  - J’ai été informé que les cellules qui m’ont été prélevées seront conservées congélées afin de m’être restituées, sous réserve de leur conformité, soit en totalité soit en partie lors de l’autogreffe.
  - Si, à l’issue d’une période de 5 ans, elles n’ont pas été utilisées pour tout ou partie, la poursuite de leur conservation sera réévaluée par l’équipe médicale qui m’a pris en charge. Il pourra alors être décidé, en fonction de l’évolution de mon parcours thérapeutique et/ou de l’état des cellules congélées, de ne pas les conserver.
  - En cochant la case ci-après, j’accepte que ces prélevements puissent être utilisés à des fins de recherche scientifique ou médicale avant leur destruction.

Proposal of mentions related to storage and destruction (of cellular products) to be included in IC (related/autologous donor)

Related donor
  - I have been informed that some part or all of my collected cells may be stored. In the case such collections are not used, I understand that they are exclusively reserved for the intended recipient, and will not be kept if the recipient’s condition does not require it anymore.
  - If, after checking the box hereafter, I accept that the cells are used for research or medical purposes before destruction.

Autologous donor
  - I have been informed that some of my collected cells will be cryopreserved and stored in order to be infused to me (if confirming) either in part or in total as an autologous transplantation.
  - If, after a 5 year period, the cells have not been used, the continuation of storage will be evaluated by the medical staff in charge of my treatment. It could be decided, depending on the evolution of my treatment plan, or on the condition of the cells in stock, not to keep the cells in stock anymore.
  - If, after checking the box hereafter, I accept that the cells are used for research or medical purposes before destruction.
Conclusions

The facts
- Assigning expiry dates or maximum duration of storage ➔ mandatory/strongly recommended
- Conformity criteria have evolved over time ➔ liability/safety
- Accumulation of products ➔ burden of costs
- Storage conditions ➔ impact on biological properties (difficult to evaluate precisely)
- No uniform solution so far

Constraints
- Keep in mind best interests of patients ➔ potentially divergent aspects
- Make rational policies based on most recent data and standards
- Try to find solutions from consensus before others find them for us

Documents
- Batch record
- Policies and SOPs
- Literature
- Standards
- Legislation

Storage
Temperature
Time
Costs

Product
Contents
Packaging
Labeling

État du stock produits cryopréservés
CHU Liège