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

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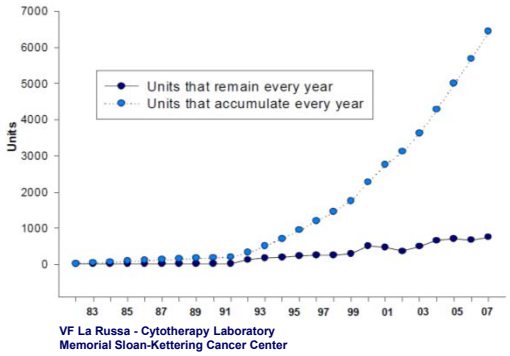


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## CELLULAR PRODUCTS INVOLVED

**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

F. 2009 — 3602 [C − 2009/18414]

28 SEPTEMBRE 2009. — Arrêté royal fixant les normes de qualité et de sécurité pour le don, le prélèvement, l'obtention, le contrôle, le traitement, le stockage et la distribution de matériel corporel humain, auxquelles les banques de matériel corporel humain, les structures intermédiaires de matériel corporel humain et les établissements de production doivent répondre

Lorsque les opérations pour lesquelles un agrément est demandé impliquent le stockage et la libération de matériel corporel humain, les procédures autorisées suivies par l'établissement doivent satisfaire aux critères énoncés ci-après.

1. Le temps de stockage maximal doit être défini pour chaque type de condition de stockage. La période choisie doit être liée, entre autres, à la détérioration possible des propriétés requises pour le matériel corporel humain. Pendant le stockage, ce temps de stockage maximal peut être adapté en fonction de l'état de la science ou aux propres données de validation. Dans le cas où l'état de la science ou de données propres de validation indiquent un temps de conservation plus court, celui-ci est également adapté dans ce sens.

2. Il y a lieu de mettre en place un système pour bloquer le matériel corporel humain, afin de s'assurer qu'ils ne puisse être libéré avant que toutes les exigences de la loi et du présent arrêté soient satisfaites. Il doit exister un mode opératoire normalisé décrivant de façon détaillée les conditions, les responsabilités et les procédures pour la libération du matériel corporel humain en vue de sa distribution.

N. 2009 — 3602 [C − 2009/18414]

28 SEPTEMBER 2009. — Koninklijk besluit tot vaststelling van de kwaliteits- en veiligheidsnormen voor het doneren, wegnemen, verkrijgen, testen, bewerken, bewaren en distribueren van menselijk lichaamsmateriaal, waaraan de banken voor menselijk lichaamsmateriaal, de intermediaire structuren voor menselijk lichaamsmateriaal en de productie-instellingen moeten voldoen

Indien de handelingen waarvoor de erkenning wordt gevraagd de bewaring en vrijgave van menselijk lichaamsmateriaal omvatten, voldoen de goedgekeurde procedures van de instelling aan de onderstaande criteria.

1. Voor elk soort bewaarconditie wordt een maximale bewaartijd bepaald. Hierbij wordt onder andere rekening gehouden met eventuele achteruitgang van de vereiste eigenschappen van het menselijk lichaamsmateriaal. Tijdens de bewaring kan deze maximale bewaartijd worden aangepast in functie van de stand van de wetenschap of of op eigen validatiegegevens. In het geval de stand van de wetenschap of eigen validatiegegevens op een kortere bewaartijd wijzen, wordt deze ook in deze zin aangepast.

2. Er is een systeem om menselijk lichaamsmateriaal te blokkeren, zodat zij pas kunnen worden vrijgegeven als aan alle voorschriften van de wet en dit besluit is voldaan. Er is een standaardpraktijkvoorschrift waarin de omstandigheden, verantwoordelijkheden en procedures voor het vrijgeven van menselijk lichaamsmateriaal voor distributie wordt beschreven.

## CURRENT STANDARDS AND GUIDELINES

## HGR-CSS Quality Standards

**C.2.1 Exigences portant sur le contenu**

Le dossier du donneur, conservé à la banque de tissus, comprend au moins les informations suivantes, qui sont pertinentes pour le type de matériel (les points mentionnés en gras sont valables pour tous les tissus):

Numéro d'identification
Identité, sexe et âge du donneur (de la mère)
Identité du centre de prélèvement et du médecin qui l'effectue
Absence de contre-indications médicales
Consentement éclairé de la mère
Date et heure du prélèvement
Description qualitative et quantitative du greffon (quantité prélevée, nombre et type de conditionnements préparés)
Date et heure de la prise en charge par le laboratoire
Type et volume du milieu cryoprotecteur utilisé
Type et volume du milieu de conservation utilisé
Données de cryopréservation (tracé de la courbe de refroidissement - congélation)

**Date et heure de la conservation**
**Méthode de conservation**
**Température de conservation**
**Date de péremption: la date de péremption peut être remplacée par un avertissement mentionnant l'absence ou les limites de données scientifiquement disponibles sur la durabilité de ces types de produits cellulaires cryopréservés ainsi que la possibilité d'obtenir toutes informations et/ou références utiles à ce sujet par consultation du site web de la banque ou sur demande auprès du responsable médical de la banque.**

Groupe ABO
Facteur Rhésus

## JACIE 5th edition

D5.1.6 Cryopreservation and thawing.

D5.1.7 Labeling (including labeling of associated forms and samples).

D5.1.8 Product expiration dates.

D5.1.9 Product storage to include alternative storage if the primary storage device fails.

D9 STORAGE

D9.1 Processing Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.

D9.2 STORAGE DURATION

D9.2.1 Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.

D9.2.1.1 Patients, donors, and associated Clinical Programs should be informed about these policies before the cellular therapy product collection.

D9.2.2 Processing Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time, as appropriate, for non-cryopreserved products and for products thawed after cryopreservation.

## JACIE 5th Edition Accreditation manual

**STANDARD:**
*D9 STORAGE*

The Processing Facility should define what constitutes storage. Storage may occur prior to processing, either within the Processing Facility or at the Collection Facility as well as after processing is complete. Storage temperature and duration shall be defined by the storing facility and shall include conditions for non-cryopreserved, cryopreserved, and thawed cellular therapy products. Products that have been processed and are awaiting the results of release testing (i.e., CD34 cell assessment by flow cytometry or the completion of allogeneic donor eligibility determination) may be held in quarantine at one temperature (i.e., up to 4 hours at room temperature) but stored for longer periods at another temperature (i.e., 1-8°C). Temperature ranges and duration must be determined for each type of product and should be based on the medical literature and/or on the facility's own experimental data. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time must be established to ensure adequate viability and to decrease the risk of contamination. Processing procedures should specify the temperatures at which products are handled and processed prior to storage. Likewise, transport and shipping temperature both from the Collection Facility to the Processing Facility and at distribution from the Processing Facility must be defined.

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

**STANDARD:**

*B2.15.2 Both individual CB unit data and aggregate data shall be evaluated.*

*B2.15.3 There shall be a written stability program that annually evaluates a minimum of three CB units per manufacturing method.*

*B2.15.3.1 There shall be a plan for defining an expiration date.*

**Explanation:**
Because the length of CB unit storage is unknown, confidence needs to be demonstrated that the unit stored can provide acceptable hematopoietic reconstitution. Since units cannot easily be tested prior to release, the CBB must develop a stability program that annually tests units of various storage duration for viability and potency. Applicable Law may specify what testing and the frequency of testing that needs to be performed.

Processing methods change over time and may affect the expiration date. The stability program must test a reference sample from a CB unit from each method of processing used. When an expiration date has not been assigned, the CB unit should be assessed against available stability data prior to release for administration.

**Evidence:**
The inspector will review the stability program and the associated policies and procedures for identifying CB units to be tested and the acceptable end point parameters.

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- **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**

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- **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**: under 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 in disposing of potentially life-saving products.
  - **Discard to comply with written agreements with donor registries**: donor registries may have their own specific standards on 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 are lost to follow-up and their survival cannot 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 can not 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

# LITTERATURE



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

Hal E. Broxmeyer*†‡§¶, Edward F. Srour*‖**, Giao Hangoc*§¶, Scott Cooper*§¶, Stacie A. Anderson††, and David M. Bodine††

- **PNAS 2003**
- **UCB (8 @ 10 years & 9 @ 15 years)**
- **CFU and NOD/SCID repopulation assay**
- **MNCs cryopreserved in cryotubes**
- **Demonstrate that HPC with extensive proliferative, self-renewal and *ex vivo* expansion capabilities, and HSC with NOD/SCID repopulating ability can be effectively recovered after 15-yr storage in a frozen state**

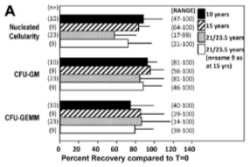
| Parameter, yr | Mean ± 1 SD | Range | No. |
|---|---|---|---|
| Nucleated cells | | | |
| 15 | 83 ± 12 | 64–100 | 9 |
| 10 | 88 ± 20 | 47–100 | 10 |
| CFU-GM | | | |
| 15 | 95 ± 15 | 56–100 | 9 |
| 10 | 92 ± 11 | 81–100 | 10 |
| BFU-E | | | |
| 15 | 84 ± 25 | 29–100 | 9 |
| 10 | 91 ± 17 | 55–100 | 8 |
| CFU-GEMM | | | |
| 15 | 85 ± 25 | 29–100 | 9 |
| 10 | 74 ± 25 | 40–100 | 8 |

- **Confirms previous observations**
  - Mugishima H, et al. Effects of long-term cryopreservation on hematopoietic progenitor cells in umbilical cord blood. Bone marrow transplant. **1999** feb;23(4):395-6.
  - Kobylka p, et al. Preservation of immunological and colony-forming capacities of long-term (15 years) cryopreserved cord blood cells. Transplantation. **1998** may 15;65(9):1275-8.
  - Broxmeyer he, et al. High-efficiency recovery of immature haematopoietic progenitor cells with extensive proliferative capacity from human cord blood cryopreserved for 10 years. Clin exp immunol. **1997** jan;107 suppl 1:45-53.

## Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood

Hal E. Broxmeyer,[1] Man-Ryul Lee,[1] Giao Hangoc,[1] Scott Cooper,[1] Nutan Prasain,[2] Young-June Kim,[1] Coleen Mallett,[2] Zhaohui Ye,[3] Scott Witting,[4] Kenneth Cornetta,[4] Linzhao Cheng,[3] and Mervin C. Yoder[2]

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



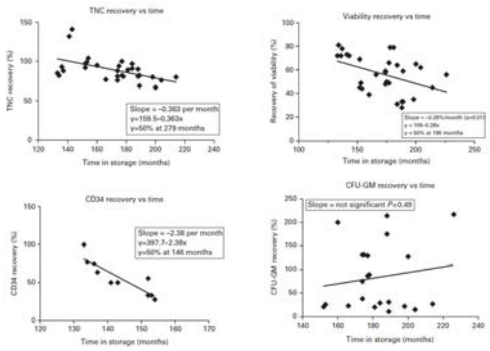

## Relative recovery of haematopoietic stem cell products after cryogenic storage of up to 19 years

LJ Fernyhough[1,2,3], VA Buchan[2], LT McArthur[2] and BD Hock[3]

- **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**

## Relative recovery of haematopoietic stem cell products after cryogenic storage of up to 19 years

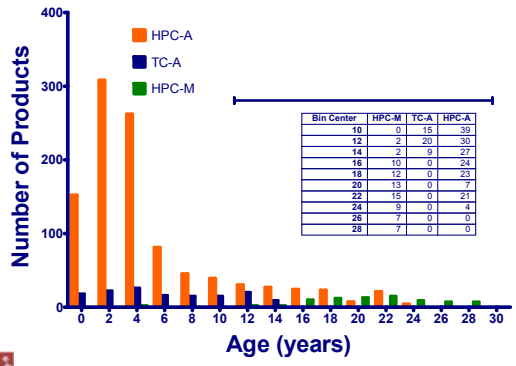
LJ Fernyhough[1,2,3], VA Buchan[2], LT McArthur[2] and BD Hock[3]



## REAL LIFE

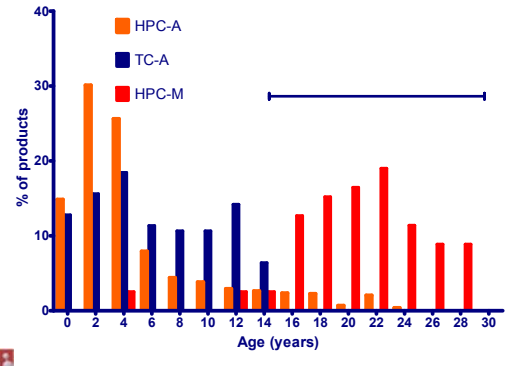


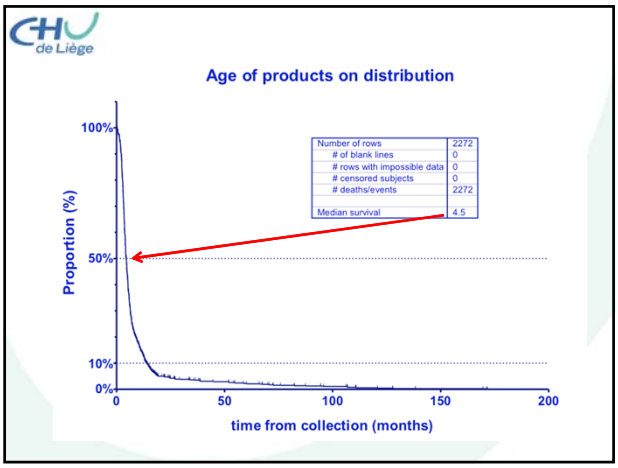
## Products in stock

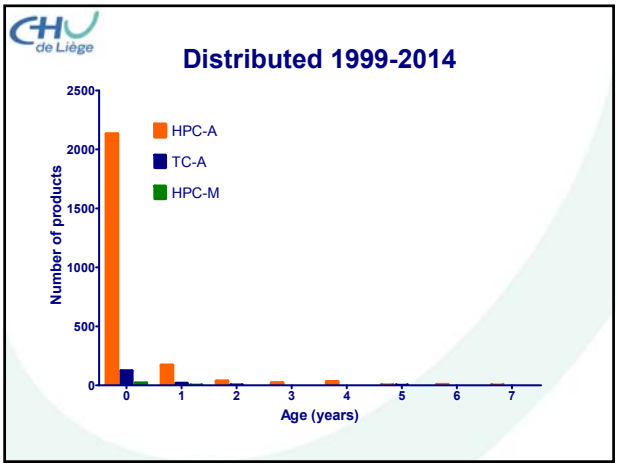


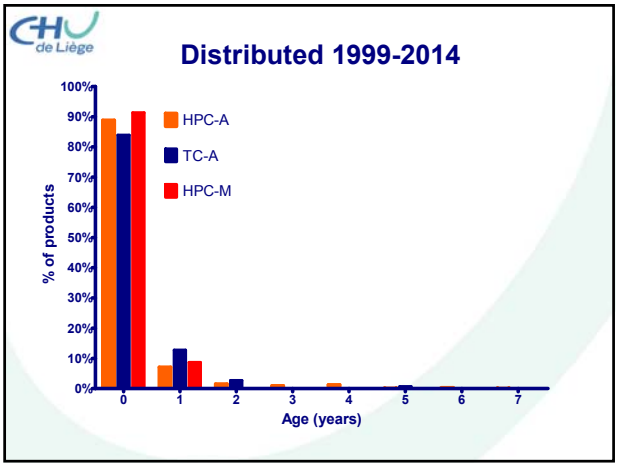

| Bin Center | HPC-M | TC-A | HPC-A |
|---|---|---|---|
| 10 | 0 | 15 | 39 |
| 12 | 2 | 20 | 30 |
| 14 | 2 | 9 | 27 |
| 16 | 10 | 0 | 24 |
| 18 | 12 | 0 | 23 |
| 20 | 13 | 0 | 7 |
| 22 | 15 | 0 | 21 |
| 24 | 9 | 0 | 4 |
| 26 | 7 | 0 | 0 |
| 28 | 7 | 0 | 0 |

## Products in stock (%)




Age of products on distribution
Number of rows 2272
# of blank lines 0
# rows with impossible data 0
# censored subjects 0
# deaths/events 2272
Median survival 4.5
Proportion (%)
100%
50%
10%
0%
0
50
100
150
200
time from collection (months)


Distributed 1999-2014
HPC-A
TC-A
HPC-M
Number of products
2500
2000
1500
1000
500
0
0
1
2
3
4
5
6
7
Age (years)


Distributed 1999-2014
HPC-A
TC-A
HPC-M
% of products
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
Age (years)

| Center | Duration | Procedure | Information to Pt |
|---|---|---|---|
| UZ Brussels | 10 years or death<br>Longer on request | | 3 months notice before destruction (old IC) |
| UCL St Luc | Death | Signed permission of Tx physician | Until useful |
| Roeselaere | Death<br>Duration depends on disease (detailed list) | Agreed by Tx physician and patient | |
| Liège | Death<br>23 years by SOP | Yearly review of Rijksregister/Registre national<br>Agreed by Tx physician | Up to 20 years<br>Option to shorten when necessary |
| Brugge | 20 years | 1 month notice then destroy<br>Agreed by Tx physician and Cell bank director | Special release if product > 5 years |

## PROPOSALS FOR PRACTICAL AND RATIONAL GUIDELINES



**recommandations SFGM-TC**
*à définir lors de l'atelier*

## recommandations SFGM-TC

- **critères de destruction des produits cellulaires autologues**
  1. **patient décédé ou perdu de vue**
     - décès du patient : justificatifs minimum : courrier médical ou enregistrement dans le dossier médical commun informatisé (informations requises : nom, prénom, ddn et nip), interrogation du RNIPP, idéalement certificat de décès
     - patient perdu de vue : date des dernières nouvelles > 5 ans et recherche du statut vital infructueuse (courriers aux mairies et/ou interrogation du RNIPP), décision validée en RCP
  2. **non conformité du produit cryopréservé**
     - perte d'intégrité de la poche (infiltration d'azote, rupture des soudures)
     - identification incomplète de la poche : absence de numéro ou de code produit, identification incomplète du receveur, dossier de lot incomplet ou inexistant
     - contrôle de qualité ou processus de production non conforme : absence de CD34 pour des cssp ou de CNT pour des mo, absence de contrôle microbiologique, non atteinte des critères de libération
     - greffon < $2.10^6$/kg CD34+ avec au minimum un échec de collecte documenté dans les deux années suivantes, décision validée en RCP
     - contamination microbiologique : discussion en RCP avec avis du CLIN, en prenant en compte le rapport bénéfice/risque
     - durée de stockage > 20 ans (ref biblio 2013)
  3. **limite d'âge**
     - seuil à 70 ans, étendu à 75 ans pour les lymphomes et myélomes
  4. **perte de l'indication d'autogreffe ou poches résiduelles après intensification(s) thérapeutique(s)**
     - sur décision de RCP (peut inclure CI médicale, changement de programme thérapeutique, refus du patient, etc)

## Recommendations SFGM-TC

- **Criteria for destruction of autologous products**
  - **Patient deceased or lost from FU**
    - Deceased: minimal documentation: medical letter, medical records, RR, death certificate?
    - Lost from FU: date of last FU >5 years AND failure to track live status, validated by multidisciplinary committee (MDC)
  1. **NON conformity of cryopreserved product**
     - Loss of bag integrity (N2 infiltration, leaks)
     - Incomplete bag identification: absence of product ID, incomplete identification of recipient, incomplete or non existing batch record
     - Non conforming QC or production process: absence of CD34 pour for HPC-A or of TNC count for HPC M, absence of microbiological culture, release criteria not reached
     - Product with < $2.10^6$/kg CD34+ with minimum 2 failures to collect documented in the 2 following years, to be validated by MDC
     - Positive bacterial culture to be discussed by MDC, opinion of physician in charge, risk benefit analysis
     - Storage duration of > 20y (literature 2013)
  2. **Age limit**
     - 70, extended to 75 for lymphoma and MM
  3. **Autologous Tx no longer indicated, residual products after finalization of intensification therapy**
     - Decision of MDC (may include medical CI, change in therapeutic plan, patient withdrawal, etc.)

## Recommendations SFGM-TC

- **critères de destruction des produits cellulaires allogéniques**
  - Il est considéré que les prélèvements allogéniques sont exclusivement destinés au receveur(prescription médicale nominative, étiquetage du produit et recommandations JACIE et ISCT)
  1. **receveur décédé ou perdu de vue**
     - idem produits cellulaires autologues
  2. **non conformité du produit cryopréservé**
     - idem produits cellulaires autologues
  3. **perte d'indication des produits résiduels**
     - sur décision de RCP (seconde allogreffe, GvHD, 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)

## recommandations SFGM-TC

- **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 puisse être conservé. Dans le cas où ces prélèvements 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 prélèvements 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 congelées 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 congelées, de ne pas les conserver.
  - En cochant la case ci-après, j'accepte que ces prélèvements puissent être utilisés à des fins de recherche scientifique ou médicale avant leur destruction.

## recommendations SFGM-TC

- **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.
  - By checking the box hereafter, I accept that the cells arte 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 conforming) 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 with 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.
  - By checking the box hereafter, I accept that the cells arte 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