

## Joint UKBTS / NIBSC Professional Advisory Committee <sup>(1)</sup> Summary Sheet

<b>1. Paper for the JPAC meeting on:</b>	8 <sup>th</sup> July 2010
<b>2. Date submitted:</b>	25 <sup>th</sup> June 2010
<b>3. Title (including version no.):</b>	Long term storage of tissue products v1
<b>4. Author(s):</b>	Helen Gillan, Kyle Bennett, Philip Yates
<b>5. Brief summary:</b>	<p>The SAC-T have reviewed the current shelf life of tissue products and propose the following changes:</p> <ol style="list-style-type: none"> <li>1. To extend the expiry date of frozen products (stored at -40°C or lower) from 3 years to 5 years.</li> <li>2. To extend the expiry date of all freeze dried products from 3 years to 5 years.</li> <li>3. To extend the expiry date of cryopreserved tissues from 3 years to 5 years. For tissues (e.g. heart valves) where there needs to be a wide range of sizes available this will remain at 10 years.</li> <li>4. To perform a Risk Assessment following a substantial change to the JPAC Donor Selection Guidelines as to the impact on current stock and whether a change to expiry or other actions were required to be carried out</li> </ol>
<b>6. Action required by the Joint Professional Advisory Committee:</b> (What do you want JPAC to do in response to this paper?) e.g. <ul style="list-style-type: none"> <li>• endorse a specific recommendation</li> <li>• advise where there is a choice of possible actions</li> <li>• advise on priorities within the work plan</li> <li>• provide a steer on policy</li> </ul>	To endorse the proposed changes
<b>7. Any other relevant information:</b>	See attached paper

<sup>(1)</sup> Joint United Kingdom Blood Transfusion Services and National Institute for Biological Standards and Control Professional Advisory Committee



# Blood and Transplant

## Review of Long-Term Storage of Tissue Products

**INTRODUCTION**..... 3  
**PROPOSAL**..... 3  
**RATIONALE FOR PROPOSAL** ..... 3  
**REFERENCES**.....6  
**APPENDIX A**.....Change Notifications.....7  
**APPENDIX B**.....extracts from standards.....8

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## Introduction

Prior to the 5<sup>th</sup> Edition of the Red Book in 2001 tissues could routinely be stored for up to 5 years by UKBTS tissue banks. This was in line with other major tissue banks throughout the world. In 2001 UKBTS reduced the expiry date for most tissues from 5 years to 3 years. It is understood that the reason for the reduction was purely related to ongoing changes to the tissue donor selection guidelines and possible future changes to the virology testing protocols. It was not related to any reported adverse effects of long term storage on tissue viability.

The current guidelines for the long term storage of tissue products are provided in the 'Guidelines for the Blood Transfusion Services in the United Kingdom 7<sup>th</sup> Edition 2005, Addendum 2007 and are as follows,

### *Frozen Tissue may be stored*

1. At -20°C or lower for up to **six months**
2. At -40°C or lower for up to **three years**. Temporary storage of frozen musculoskeletal tissue between -20°C and -40°C is limited to six months in total. Grafts stored at this temperature must then be transferred to -40°C or colder to give an expiry of up to a maximum of three years from donation.

### *Cryopreserved tissue should be stored*

1. At -135°C or lower to claim a **10 year** expiry for all grafts to maintain a reasonable inventory of size matched grafts (e.g. heart valves and menisci). Other cryopreserved tissue should have a **three year** expiry.
2. At higher temperatures up to -80°C; the same expiry pertains providing it has been validated.

### *Glycerol preserved tissue*

1. Skin preserved in high concentration (>90%) glycerol may be stored at 0-10°C for up to **two years**.
2. Amnion preserved in low concentration (50%) glycerol may be stored below -40°C for up to **two years**.

### *Freeze-drying*

Where tissues are freeze-dried, a sample of each type of tissue from each freeze-drying run must be analysed for residual moisture content which must be less than 5% (weight/weight) of the dry weight of the graft to allow a **three year** expiry at ambient temperature

## Proposal

1. *Frozen Tissue*  
To extend the expiry date of frozen products (stored at -40°C or lower) from 3 years to **5 years**.
2. *Cryopreserved tissue*  
To extend the expiry date of cryopreserved tissues from 3 years to **5 years**. For tissues (eg heart valves and menisci) where there needs to be a wide range of sizes available this will remain at 10 years.
3. *Freeze-drying*  
To extend the expiry date of all freeze dried products from 3 years to **5 years**.
4. To perform a Risk Assessment following a substantial change to the JPAC Donor Selection Guidelines as to the impact on current stock and whether a change to expiry or other actions were required to be carried out.

## Rationale for Proposal

There are two points which should to be considered when recommending the expiry dates of tissue products.

1. The Donor Selection Guidelines
2. The biology of long term storage.

### Donor Selection Guidelines

As detailed in the 'Guidelines for the Blood Transfusion Services in the United Kingdom 7th Edition 2005, Addendum 2007',

'Decisions on donor assessment should be consistent with JPAC *Donor Selection Guidelines*<sup>(1)</sup>'

The JPAC Donor Selection Guidelines are continually assessed and reviewed. Since 2005 'Change Notifications' have been issued when the guidelines required amending or updating. Prior to 2005 'Concessionary Letters' were issued.

Currently a risk assessment is only carried out when changes to serological testing are introduced, not when there are changes to the donor selection guidelines. Due to this it had previously been agreed that a 'cut off' was required for when the number of changes to donor guidelines were deemed to have reached a level whereby existing stock no longer conforms to current JPAC requirements and in theory an inferior or less safe product may be issued. Currently this 'cut off' is three years which is why the current expiry date for the majority of UKBTS tissue products is three years from the date of donation. The exception

to this being tissues where a reasonable inventory of size matched grafts were required (heart valves and menisci) which have a ten year expiry. If the same three year criteria were to be used for these specific tissues it would result in an inadequacy of supply due to the scarcity of some sizes of these tissues.

Based on the current assumption that over a three year period the number of Change Notifications issued by JPAC would render existing stock as non-conforming, a study into the JPAC Change Notifications was carried out. This showed that between January 2005 and June 2010 there were a total of 93 Change Notifications issued by JPAC. Of these only 34 had implications for the Tissue Donor Selection Guidelines for living and/or deceased donors (see Appendix A). Of these changes 18 produced either no change or a relaxation of guidelines and only 16 produced a tightening of the guidelines. Nineteen of the 34 change notifications related to West Nile Virus, malaria or chikungunya virus with amendments to acceptable destinations for the travel history of donors. A change to travel destinations within the guidelines would not necessarily have a negative influence on existing stock as these products would have been assessed against the travel guidelines and risk, relevant at the time of their donation. Other minor changes such as decrease in deferral period due to improved testing regimes, or changes to donor age do not have any impact on tissue grafts in stock. There has only been one Change Notification (transfusion history) that would have had a possible impact on stock in the last five years.

The reduction to a three year expiry date for most tissues on the basis of possible changes to donor guidelines can therefore no longer be justified. This is not mandated by any statutory body responsible for tissue banks nor recommended in any other tissue organization's guidelines. Instead it is proposed that a risk assessment be performed following any substantial change to the JPAC Donor Selection Guidelines to assess the impact on current stock and determine whether a change to expiry or other actions are required. A similar risk assessment is currently performed when a new serology test is mandated to assess whether retrospective testing of archive samples should be performed.

### The biology of long term storage

Effects of long term storage on the biological function and structure of tissues requires consideration when setting an expiry date. Blood for example, has a known shelf life past which its biological function reduces with the donation/sample being unsuitable for use. Early evidence suggested that tissue could be stored at -80°C for a number of years and an arbitrary storage period of 5 years was adopted. This standard has been followed by most tissue banking organizations and tissue banks for over 40 years with no adverse effects reported or changes made to the recommended storage period. A literature search shows there have been no reports of additional loss of biological function due to storage at five years compared to three.

There are no regulatory requirements regarding the storage period for tissues. The EC Directive 2006/86/EC Annex II Section C para 1 states only "The maximum storage period must be specified for each type of storage condition".

In the absence of any regulatory requirements the UKBTS guidelines should be compared to those of other tissue organization's guidelines or standards. The American Association of Tissue Banks (AATB) produces and updates its standards<sup>(2)</sup> for tissue banking on a very regular basis. The European Association of Tissue Banks (EATB) and European Association of Musculo-Skeletal Transplantation produced common standards<sup>(3)</sup> for musculo-skeletal tissue banking although these have not been updated for some time. The British Association of Tissue Banks (BATB) also used to publish guidelines<sup>(4,5,6)</sup> but these were discontinued once the EC Tissue Directives were published. A summary of their storage periods is given in the table below with the periods proposed for change highlighted.

Tissue	Storage conditions	UKBTS	AATB	EATB/EAMST	BATB
Musculoskeletal tissue	Refrigerated +1°C to +10°C	-	5 days	-	-
	Frozen -20°C to -40°C	6 months	6 months	-	1 year
	Frozen below -40 °C	3 years	5 years	5 years	5 years
	Cryopreserved -80°C to -130°C	3 years	5 years	-	5 years
	Cryopreserved below -130°C	3 years**	5 years	-	10 years
	Lyophilised (stored at room temperature)	3 years	5 years	5 years	5 years
Skin	Refrigerated + 1°C to +10°C		14 days	N/A	-
	Frozen below -40°C,		5 years	N/A	-
	Cryopreserved below -40°C,		5 years	N/A	-
	Glycerolised +1°C to +10°C	2 years (0°C to +10°C)	-	N/A	2 years (+2°C to +8°C)
	Cryopreserved -60°C to -100°C		-	N/A	2 years
	Cryopreserved below -135°C		-	N/A	10 years
	Lyophilised (stored at room temperature)		5 years	N/A	5 years
Cardiovascular	Cryopreserved	10 years (below -130°C)	5 years (below -100°C)	N/A	Each bank to determine
	Cryopreserved -60°C to -100°C	-	-	-	3 months
	Refrigerated +2°C to +8°C	-	-	-	4 weeks

\*\*10 years for menisci where a reasonable inventory of size matched grafts is required

Prior to 2001 UKBTS tissue banks used the 5 year expiry date for frozen and freeze-dried tissues and ten years for cryopreserved tissues. The 5<sup>th</sup> Edition of the Red Book in 2001 reduced the expiry date for most tissues to 3 years. The expiry date for cryopreserved cardiovascular tissue was kept at 10 years. In 2007 an amendment to the expiry of certain cryopreserved tissues was made permitting an expiry of ten years for products where availability of sizes was an issue and certain sizes were in short supply. In order to extend the expiry date it was accepted that there is no greater loss of biological properties and function in cryopreserved tissues stored for ten years than those stored for three years. Providing tissue is stored below the glass transition point, no recrystallisation occurs which enables the graft to remain stable.

Following the rationale used for extending size specific tissues to a ten year expiry, there is no biological reason why any other cryopreserved tissue could not have at least a five year expiry. With regards to frozen and freeze dried allografts there is no biological reason why

the storage period could not be increased to five years in line with the AATB, EATB and other recognized standards.

## **References**

1. Joint UKBTS / NIBSC Professional Advisory Committee's (JPAC) Donor Selection Guidelines available at [www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk)
2. Standards for Tissue Banking 11<sup>th</sup> Edition (2007), American Association of Tissue Banks, [www.aatb.org](http://www.aatb.org).
3. Common Standards for Musculo-Skeletal Tissue Banking (1997, revised 1999) European Association of Tissue Banks (EATB) and European Association of Musculo-Skeletal Transplantation
4. BATB Technical Guidelines for Musculoskeletal Tissue Banking BATB/MSK/GDE/001 ver 3 Effective 01/11/2003
5. BATB Technical Guidelines for Skin Banking BATB/GUI/SKN/1 Effective 29/09/1999
6. BATB Technical Guidelines for Cardiovascular Tissue Banking BATB/GUI/ CVS1/1 Effective 29/09/1999

Change Notifications affecting tissue donors live (LT) or deceased (DT) JPAC 10-59

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CN	topic	change	effect	LT	DT
2007-9	WNV (general)	no change to risk period, wording revised following publication of GDRI	no change	x	x
2007-8	WNV - USA & Canada	no change to risk period, wording revised following publication of GDRI	no change	x	x
2007-2	replacement of travel index of donor selection guidelines	replacement by GDRI	no change	x	x
2007-15	malaria -airs top overs: clarification	clarification	no change	x	x
2006-3	WNV	following revised JPAC statement	no change	x	x
2006-2	multiple sclerosis	reinstatement of missing entry	no change/tightening	x	x
2010-4	inoculation injury	shortening of deferral period	relaxation	x	x
2010-3	endoscopy	shortening of deferral period	relaxation	x	
2010-2	body piercing	shortening of deferral period	relaxation	x	x
2009-8	age limit for pulmonary valve donors	extension of age limits	relaxation		x
2009-35	complementary therapy	shortening of deferral period	relaxation	x	x
2009-33	acupuncture	shortening of deferral period	relaxation	x	x
2009-11	CHIKV Italy	removal of area covered	relaxation	x	x
2008-3	endoscopy	exclusion criteria removed	relaxation		x
2007-18	bleeding disorder -sexual partner & family members	shortening of deferral period	relaxation	x	
2006-4	age	increase of upper age limit for tendon donors	relaxation		x
2006-17	malaria -Great Exuma	removal of area covered	relaxation	x	x
2005-3	malaria (withdrawal of 2005-1)	removal of area covered	relaxation	x	x
2009-29	relenza	new entry	tightening	x	x
2009-28	tamiflu	new entry	tightening	x	x
2009-27	CHIKV Maldives	extension of area covered	tightening	x	x
2009-26	WNV USA & Canada	extension of relevant time period	tightening	x	x
2009-25	WNV Italy	extension of relevant time period	tightening	x	x
2009-24	WNV Italy	extension of area covered	tightening	x	x
2007-7	malaria -Great Exuma	extension of area covered	tightening	x	x
2007-6	CHIKV (general)	new entry in GRDI	tightening	x	x
2007-5	CHIKV - Italy	extension of area covered	tightening	x	x
2006-8	infection -acute	2 week recovery from acute infection	tightening	x	x
2006-20	malaria -Jamaica	extension of area covered	tightening	x	x
2006-15	CHIKV	new entry via SACTTI	tightening	x	x
2006-14	malaria -Great Exuma	extension of area covered	tightening	x	x
2005-4	blood transfusion recipients	major revision re-vCJD	tightening	x	
2005-2	WNV	extension of deferral period	tightening	x	x
2005-1	malaria (post tsunami)	extension of area covered	tightening	x	x



## Extracts from standards relating to the storage period for tissues

The **AATB Standards for Tissue Banking** state the following<sup>(2)</sup>,

- E4.120 Temporary storage of processed frozen or cryopreserved musculoskeletal tissue between -20°C and -40°C is limited to six months total and grafts stored at this temperature range must then be transferred to -40°C or colder, used or discarded.
- E4.310 The expiration time of refrigerated musculoskeletal cells and/or tissues shall be 5 days from the date of recovery, or established in the *SOPM* using a validated method for determining the expiration dating.  
Skin shall be stored refrigerated for no longer than 14 days.
- E4.320 Frozen and Frozen Cryopreserved Tissue (-40°C or colder)  
  
Expiration of frozen and frozen cryopreserved cells and / or tissue shall not exceed five years from the date of processing unless a longer expiration date has been validated.
- E4.330 Lyophilised / Dehydrated Tissue  
  
Expiration of lyophilised or dehydrated tissue shall not exceed five years from the date of initial processing unless a longer expiration date has been validated.

The **EATB/EAMST Common Standards for Musculo-skeletal Tissue Banking**<sup>(3)</sup> state the following:

- D 2.300 Frozen tissues, frozen at - 40°C or colder, may be stored for up to 5 years.
- D2.400 Freeze dried tissues packaged under vacuum have an indefinite shelf life. However, the practice to date is to not store tissues longer than five years, unless there is data to support a longer period.

The **BATB technical guidelines for skeletal tissue banking**<sup>(4)</sup> state the following

- 4.1.2 Lyophilised bone may be stored for up to 5 years at room temperature.
- 4.1.2 The maximum storage period for frozen bone may depend on the degree of prior processing and the storage temperature. Recommended time/temperature relationships for bone are given below:

Temperature	Storage period
-20°C to -40°C	1 year
-40°C to -80°C	5 years

- 5.4.3 Cryopreserved articular cartilage shall be stored in accordance with the limits detailed below:

Temperature	Storage period
-80 °C to -130°C	5 years
below -130 °C	10 years

6.1 Costal cartilage may be stored frozen using temperatures and storage periods previously specified for bone. Freeze dried lyophilised costal cartilage may be stored at room temperature for up to 5 years.

The **BATB technical guidelines for skin banking**<sup>(5)</sup> state the following:

4.5 Cryopreserved skin may be stored for up to 2 years at -60°C to -100°C; or for up to 10 years at -135°C or colder.

5.4 Freeze dried skin may be stored between +15°C and +30°C for up to 5 years

5.5 Glycerolised skin may be stored between +2°C and +8°C for up to 2 years

6. The **BATB Technical Guidelines for Cardiovascular Tissue Banking**<sup>(6)</sup> state the following

4.7.a Each tissue bank shall determine a maximum storage period allowable for cardiovascular tissue.

4.7.b Long term storage of cryopreserved cardiovascular tissue should be at a temperature lower than -135°C.

4.7.c Storage of cryopreserved tissue at -60 °C to -100°C is permissible. It is suggested that storage at -60 °C to -100°C should not exceed 3 months.

4.7.d Storage between +2°C and +8°C in a suitable storage solution is permissible provided that the storage period does not exceed 4 weeks. *Tissue stored in this way must not be frozen subsequently for long term storage.*