



American Association of Tissue Banks

07 March 2010

Blood and Tissues Unit, and  
Therapeutic Goods Committee  
Standards and Code of GMP  
Office of Devices, Blood and Tissues  
Therapeutic Goods Administration  
PO Box 100  
WODEN ACT 2606

**In Re: THERAPEUTIC GOODS ACT 1989, Section 10**

**THERAPEUTIC GOODS ORDER NO. XX - *Standards for banked human musculoskeletal tissue.***

Dear Madams and Sirs:

The American Association of Tissue Banks [hereinafter referred to as the "AATB" or the "Association"] submits these comments in response to the Therapeutic Goods Administration's (TGA) publication of the above-captioned document. These draft Standards were published online on December 7, 2009.

### **I. THE INTEREST OF THE AATB**

The AATB is a voluntary, professional, scientific and educational organization. The Association was founded in 1976 and is tax-exempt under Section 501(c)(3) of the Internal Revenue Code of the United States (U.S.). The AATB's mission is public health.

The Association is dedicated to ensuring that human tissues intended for transplantation are safe and free of infectious disease, of uniform high quality, and available in quantities sufficient to meet national needs. We also aim to harmonize cell and tissue regulations that are being developed by our international tissue banking colleagues.

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To further this mission, the Association has, since 1985, published the recognized authoritative source for the tissue banking profession, the AATB's *Standards for Tissue Banking*. Beginning in 1986, the AATB initiated a voluntary Accreditation Program to ensure that tissue-banking activities in the U.S. are being performed in a professional manner in compliance with these *Standards*. All of the AATB's institutional members must be accredited and re-inspected and re-accredited every three years. The Association's membership currently includes approximately 1,000 individual members and 111 accredited tissue banks in the U.S. and Canada that may be engaged in tissue donor screening and obtaining or verifying donation consent/authorization, as well as the recovery, processing, storage and/or distribution of human tissue.

The AATB has consistently and publicly supported balanced governmental regulation aimed at safeguarding human tissues from disease transmission. The Association has long advocated and continues to support balanced and reasonable regulation of tissue banking.

The AATB's *Standards* contain extensive requirements for donor screening and testing to ensure safety and to avoid disease transmission. With the exception of ocular tissue, AATB-accredited tissue banks provide most of the commonly used structural tissues for clinical use in the United States and many of these finished tissue allografts are distributed internationally. The Association is, therefore, interested in these draft Standards and its potential effects on the safety, effectiveness and supply of human tissue for transplantation.

Over the years, the AATB has provided useful information to assist regulatory authorities in addressing public health challenges, most notably disease transmission. The Association has worked with state, national, and international regulators to develop appropriate regulatory schemes in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit. The AATB also intends to continue to provide constructive criticism and recommendations for regulatory changes where it believes they are warranted.

The AATB agrees with a majority of what is contained in these draft Standards and we commend the TGA for its work to construct them.

These recommendations are submitted for consideration and they are aligned with the spirit of the TGA's new biological framework, which has been described as being in development "to address the following:

- the need to minimise infectious disease risk associated with the use of these products/therapies;
- the desirability of international harmonisation of regulatory requirements;
- the need for greater flexibility to respond to changes in technology; and

- the desirability of adopting a risk-based approach to regulation reflecting the differing risk profiles of each biological product.<sup>1</sup>

AATB's comments, recommendations, and rationale we offer in this document are in agreement, and often based upon, these four key points described above.

The need for international harmonization of regulatory requirements for tissue allografts is very important for patient safety everywhere. Today, any nation's citizens can experience environmental disasters that can require a need for massive amounts of medical supplies to treat victims and this can quickly exhaust the local inventory of allograft types available for transplantation. Brushfires, earthquakes, tsunamis, or hurricanes occur, and domestic factory explosions and fires erupt, plus acts of terrorism, can affect many. Situations can include an immediate as well as ongoing need for human tissues for transplantation to treat burns and other traumatic injuries such as bone fractures and soft tissue injuries from blasts, falls, or other accidents. As you now, the therapeutic use of allografts can alleviate pain, save limbs, and retain functionality and quality of life. Tissue allografts from deceased donors, such as skin for burn use and pediatric allograft heart valves, can be life saving for recipients in need. Synthetic materials alone may not be indicated for some repairs or they may be combined with allograft tissue for others. To be able to import safe and effective allografts in times of a national emergency can benefit your citizens or it can be made impossible or severely delayed by requirements of regulations. Regulatory authorities in each nation share a common goal to protect public health so risks associated with communicable diseases should match when possible.

Due to the ability and often ease of global travel from the island continent of Australia to anywhere in the world, risks related to endemic disease in some parts of the world should be considered when screening potential donors. Conversely, some transmissible risks exist within Australia's border much as they do elsewhere.<sup>2</sup>

<sup>1</sup> TGA Biologicals Framework Newsletter: Issue 1 – July 2009

<sup>2</sup> 2008 Report on the global AIDS epidemic, Joint United Nations Programme on HIV/AIDS (UNAIDS)

## II. COMMENTS

For purposes of clarity, our recommendations to add text to the draft Standards are underlined and italicized (e.g., *Example*), and recommendations to delete text utilize the strikethrough (e.g., ~~Example~~).

### **Comment #1**

Page 6 of 10

#### Provision:

*(relevant part only)*

#### **7. General Requirements**

(3) A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(b) all forms of malignancy except:

(i) basal cell carcinoma;

(ii) non-metastasising primary brain tumours;

(iii) *in situ* carcinoma of the uterine cervix; and

(iv) for surgical bone donors, squamous cell carcinoma of the skin which has been fully excised and not recurred for the last 5 years.

#### Recommendation:

#### **7. General Requirements**

(3) A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(b) ~~all forms~~ *donors with a current or prior diagnosis of malignancy except: unless the type of malignancy, clinical course, and treatment is evaluated by the Medical Director or licensed physician designee for suitability in accordance with the tissue bank's policies and procedures (quality system). The evaluation and reasons for acceptance shall be documented in the donor's record.*

~~(i) basal cell carcinoma;~~

- ~~(ii) non-metastasising primary brain tumours;~~
- ~~(iii) *in situ* carcinoma of the uterine cervix; and~~
- ~~(iv) for surgical bone donors, squamous cell carcinoma of the skin which has been fully excised and not recurred for the last 5 years.~~

Or,

## 7. General Requirements

- (3) A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(b) all forms *donors with a current or prior diagnosis* of malignancy except: *unless acceptance is justified on the basis of a documented risk assessment approved by the responsible person. Acceptance must be based on an analysis of scientific evidence and risk related to the application of the specific cells/tissues.*

- ~~(i) basal cell carcinoma;~~
- ~~(ii) non-metastasising primary brain tumours;~~
- ~~(iii) *in situ* carcinoma of the uterine cervix; and~~
- ~~(iv) for surgical bone donors, squamous cell carcinoma of the skin which has been fully excised and not recurred for the last 5 years.~~

### Rationale:

Malignancies are not designated in regulations or guidance issued by the U.S. Food and Drug Administration (FDA) as relevant communicable diseases when considering donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) for transplantation. Health Canada's regulations and guidance governing the safety of human tissues for transplantation do not list malignancy as a donor screening concern. Likewise, the Tissue for Transplantation Standards of the Canadian Standards Association does not identify a history of a malignancy as a donor exclusion criterion. The European Union's Commission Directive 2006/17/EC for tissues and cells for transplantation is in harmony with AATB's *Standards for Tissue Banking* where a current or past history of malignancy is individually evaluated for relevance using information about the specific type, including whether it is known to affect the tissue type being recovered or not, and the potential donor's clinical course and treatment

information. Included in a risk assessment analysis are considerations of how the tissue is processed and how the tissue will be used.

It is understood that characteristic features of cancer invasion and metastasis of malignant cells is that they require a blood supply to grow. The tissue types towards which this listing is directed do not provide a source of nutrition necessary to keep cancer cells alive so transmission potential is highly questionable. The malignant cells would have to survive the recovery process, handling steps such as freezing and long term storage, washes and soaks, plus chemical and other treatments to which ligaments, bone and cartilage allografts may be exposed.

These tissue allograft types are not large sized grafts but if small numbers of cancer cells would survive and be transplanted, a recipient's healthy immune system response would be to isolate these few cells and destroy them. The structural integrity of these grafts would also be adversely affected if invaded by the growth of cancerous cells and this would be noticeable either upon recovery or especially at processing where the tissue grafts are cleaned and closely evaluated for quality.

A report titled "Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study" (Edgren, G., et al., *Lancet* 2007; 369:1724-30) showed there was no evidence that blood transfusions from donors deemed to have sub-clinical cancer within 5 years of donating increased risk of cancer in recipients. Today, a cancer history is not an automatic deferral for blood donation and the blood establishment's medical director can consider the suitability of a donor with a malignancy history. See reference that follows.

Many malignancies can be cured today so a blanket criterion to rule most of them as an ineligible history for ligament, certain bone, and cartilage tissue donation is not supported by current knowledge. Please reconsider this requirement. If kept, the risk criterion would only appear in TGA's Standards and could restrict import potential for these allograft types.

References:

AABB's *Standards for Blood Banks and Transfusion Services*, 26<sup>th</sup> edition 2009

**Reference Standard 5.4.1A—Requirements for Allogeneic Donor Qualification**

7) Medical History and General Health

The prospective donor shall appear to be in good health and shall be free of major organ disease (eg, heart, liver, lungs), cancer, or abnormal bleeding tendency, unless determined suitable by the medical director.

AATB's *Standards for Tissue Banking*, 12<sup>th</sup> edition, 2008

**D4.340 Malignancies**

Donors with current or prior diagnosis of malignancy shall be evaluated by the Medical Director or licensed physician designee for suitability in accordance with the tissue bank's *SOPM*. The evaluation shall include: the type of malignancy, clinical course, and treatment prior to acceptance of a donor. The evaluation and reasons for acceptance shall be documented in the donor's record.

EU Commission Directive 2006-17-EC:

*"ANNEX I*

**SELECTION CRITERIA FOR DONORS OF TISSUES AND/OR CELLS  
(EXCEPT DONORS OF REPRODUCTIVE CELLS) AS REFERRED TO  
IN ARTICLE 3(a)**

Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells/tissues. Indicators of these risks must be identified by physical examination, review of the medical and behavioural history, biological testing, post-mortem examination (for deceased donors) and any other appropriate investigation. Unless justified on the basis of a documented risk assessment approved by the responsible person as defined in Article 17 of Directive 2004/23/EC, donors must be excluded from donation if any of the following criteria applies:

**1. Deceased Donors**

*1.1. General criteria for exclusion*

1.1.3. Presence, or previous history, of malignant disease, except for primary basal cell carcinoma, carcinoma *in situ* of the uterine cervix, and some primary tumours of the central nervous system that have to be evaluated according to scientific evidence. Donors with malignant diseases can be evaluated and considered for cornea donation, except for those with retinoblastoma, haematological neoplasm, and malignant tumours of the anterior segment of the eye.

**Comment #2**

Page 6 of 10

Provision:

*(relevant part only)*

**7. General Requirements**

(3) A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(f) history of chronic haemodialysis;

Recommendation:

**7. General Requirements**

(3) A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(f) history of chronic haemodialysis;

Rationale:

There are no references provided that support that ligaments, certain bone, and cartilage allografts would be adversely affected if a donor has a history of chronic dialysis. The relationship and the relevant risk is not clear. This is not an ineligibility criterion used by other regulatory authorities globally and it is not found in AATB's *Standards for Tissue Banking*.

**III. CONCLUSION**

The AATB thanks the TGA for the opportunity to comment on this draft document. The Association commends and supports the TGA's efforts to prevent the transmission of communicable disease agents and disease by cell and tissue transplants.

As was said at the outset, the AATB has a long and valued history of working with regulators to develop appropriate regulations in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit.

The AATB stands ready and willing to assist the TGA with this draft document in any way that the Administration deems appropriate.



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7 March 2010  
Page 9

Sincerely and respectfully,

*Scott A Brubaker*

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Chief Policy Officer