



Australia and New Zealand Corneal Society  
*The Royal Australian and New Zealand College of  
Ophthalmologists.*

11 February 2010

**Joint Submission to Therapeutic Goods Administration Consultation on Proposed standards and Code of GMP for human blood and blood components, human tissues and human cellular therapies**

Please find attached a joint submission from The Eye Bank Association of Australian and New Zealand and the Australian and New Zealand Corneal Society (the special interest group on cornea and eye banking of the Royal Australian and New Zealand College of Ophthalmologists) regarding the draft Code of GMP for Blood and Tissues, the infectious diseases standard and the specific product standard for Ocular Tissue.

Both associations represent the highest level of professional expertise in relation to eye donation, eye banking and corneal transplantation in Australia and New Zealand.

The high standards that have been developed and applied by these organisations are based on many years of accumulated experience, research, risk assessment and the application of world's-best practice. The result is an enviable record of quality, safety, efficiency and transplantation success that is unmatched in any other field of human donation or transplantation. Our two Associations are uniquely placed to comment and advise on codes of practice and infectious disease risk in relation to ocular tissue, and have also published internationally recognised Medical and Quality Standards for Eye Donation and Eye Tissue Banking.

We believe that eye donation, eye banking and corneal transplantation should be regarded in a separate category from blood and other products. This recognises the unique properties of the cornea and the specific risks to the patient of transplantation. Specifically the cornea has a surface exposed to the outside environment, as well as having several layers of cells that must remain viable if the transplant is to succeed. This has the consequence that the tissue can never be rendered completely sterile.

The attached comments on each of the relevant TGA draft documents embodies advice that allows for a workable, rational, and efficient set of codes and standards while still retaining the highest standards and principles of safety and quality that are clinically significant to ocular tissue transplantation. We believe all these comments need to be incorporated into any future documents to ensure that Australia develops a practical and responsible regulatory approach to ocular tissue donation and transplantation.

Yours sincerely,

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**Therapeutic Goods Order**  
**- Standards for banked human ocular tissue.**

**COMMENT AND JOINT SUBMISSION FROM:**

**EYE BANK ASSOCIATION OF AUSTRALIA AND NEW ZEALAND and  
AUSTRALIAN AND NEW ZEALAND CORNEAL SOCIETY OF  
ROYAL COLLEGE OF AUSTRALIAN AND NEW ZEALAND OPHTHALMOLOGISTS**

**General Comments**

This Therapeutic Goods Order relates to standards that must embody current, recognised and acceptable best-practice for ocular tissue, and standards that should also be achievable in practice. Many of the standards listed within this draft are based on those approved by the Eye Banking Association of Australia and New Zealand (EBAANZ) and verified by its associated Societies and Colleges. However, many standards listed here are *already* out-of-date. Importantly, many standards have been altered from the original EBAANZ wording giving the standard a different meaning from that originally intended. In addition, standards have been introduced into this document that originate from blood banking and tissue banking standards: many of these standards are inappropriate for eye donation and eye banking and are not achievable in practice.

The document also needs to incorporate the elements of the draft ‘Therapeutic Goods Order - Standards for minimising infectious disease transmission’ that would apply to ocular tissue. In attempting to cover all blood and tissues (cadaveric and non-cadaveric) this Order contains many exemptions and conditions. For clarity, accuracy, workability and responsiveness to a constantly changing operating environment and changing standards, the standards for minimising infectious disease transmission that relate to ocular tissue should be appropriately incorporated into the Therapeutic Goods Order for banked human ocular tissue.

A most important issue is that the standards remain up-to-date and that they are directly responsive to a continually changing environment. This will be difficult for the TGA to achieve - at a bare minimum the standards will require an annual revision in consultation with the relevant professional body.

We suggest that the most efficient way to ensure that these Standards truly represent world’s best practice and that they are based on risk assessment principles that apply to ocular tissue banking, is to more fully and more accurately adopt or incorporate the prevailing editions and revisions of EBAANZ Medical and Quality Standards for Eye Donation and Eye Tissue Banking<sup>1</sup>.

Notwithstanding these comments and suggestions, the following are specific comments and corrections necessary to allow this document to accurately represent those standards that apply to ocular tissue.

Page 2

## 2. Commencement

### Addition -

#### 2. Commencement and Review

This Order commences on the day after the day it is registered on the Federal Register of Legislative Instruments. **This document will be reviewed on an annual basis.**

Page 2

## 4. Interpretation

Page 2

- **aseptic technique –**

**addition and change** to “**Ocular tissue is not sterile. Asepsis is not possible. In this sense aseptic technique means ~~the measures used to prevent contamination by microorganisms~~ minimisation of cross-contamination.**”

*This needs to be explicit, clarified and prominent as it forms the basis for all standards relating to the microbiology of ocular tissue and subsequent handling and processing.*

Page 3

- **clean collection environment**

### **change and deletions –**

“clean ~~collection-retrieval~~ environment

means an area or facility, ~~such as a mortuary or equivalent facility~~ with the following conditions:

- (a) ~~air-conditioning to regulate temperature, humidity and particulates required for maintenance of tissue quality; and~~
- ~~(b)~~ (a) control measures to limit access ~~to qualified and operational persons~~ during retrieval; and
- ~~(e)~~ (b) sufficient space to perform the tissue recovery and avoid cross contamination; and
- ~~(d)~~ (c) work surfaces able to be adequately cleaned prior to commencing retrieval. ~~and~~
- ~~(e) records confirming current pest control measures.~~”

*There are two components to the changes –*

1. *Ocular tissue retrieval takes place in many different environments and circumstances eg. Mortuary, bedside hospital ward, operating theatre, funeral directors, residence.*
  - a. *The characteristics of humidity, particulates and temperature that are encountered in the example environments (and are not controlled) do not impact on the maintenance of tissue quality as the eyes in situ are normally exposed to these environments. Common sense suggests that if the environment is noxious to the operator then it is unsuitable.*
  - b. *Other persons not deemed to be “qualified to retrieve” are often present (eg. Nursing staff in an operating theatre) or are valuable in assisting during the procedure (eg. Mortuary technician acting as a runner for aseptic procedures). To do otherwise is akin to suggesting that nursing staff or students should not be present during surgical procedures.*

2. *The manufacturing facility (in this case the Eye Banks) are not in control of the retrieval site and nor can they predict beforehand where that site may be (a specific hospital room, ward, operating theatre, level, mortuary etc.). Therefore it is both impractical (impossible?) and overly onerous to demonstrate current pest control measures at collection sites. In addition, it cannot be demonstrated that the absence or presence of pest control documentation for retrieval places any additional risk to the quality of ocular material.*
3. *The word “collection” is that used within the blood banking area. A more appropriate term that relates to the surgery required to remove cadaveric ocular tissue is “retrieval”.*

*We suggest as reference the “Facilities Requirements – Ocular Tissue Retrieval Areas” and the accompanying risk assessment produced by the TGA’s Blood and Tissues Technical Expert Reference Group (attached).*

Page 3

- **critical material**

**deletion** –“critical material means all components, materials or supplies which **could** have a direct impact on the quality of the end product”.

*The inclusion of the word “could” implies that conceivably **anything** could affect tissue quality. Critical material should be defined as those materials or supplies that could have a demonstrable affect as determined through risk assessment.*

Page 4

## **7. General Requirements**

Page 4

### **7 (1)**

**deletion and addition to** - “(1) Each manufacturer releasing banked tissue for supply in Australia must have a formally established **comprehensive** quality system that **is fully documented and** meets the requirements of the **~~Therapeutic Goods Act 1989~~ Australian Code of Good Manufacturing Practice Human Blood and Blood Components, Human Tissue and Human Cellular Therapies.**

*“Comprehensive” is an ill-defined descriptor. In addition the quality system should meet the requirements of the relevant cGMP – the Act itself doesn’t refer to or describe a quality system.*

Page 4

### **7 (2)**

**Delete entire clause**

*With infectious disease standards incorporated into the Ocular Standards there is no need to reference this draft document.*

Page 5

7(4)

**Delete and revise**

(4) ~~The minimum donor age to donate ocular tissue for a banked biological for allogeneic use is two (2) years old.~~ Each tissue establishment must have a documented policy regarding the ~~upper~~ age limits for donation.

*The upper and lower age limits for donation are not clearly defined, and new technologies incorporating endothelial keratoplasty place further doubt on the ability to define absolute parameters. The relevant clause within the EBAANZ standards will be reviewed in March and highlights the need for continual review of standards.*

Page 5

7(5)

**Deletion and addition to** – “(5) ~~Collection~~ **Retrieval** of ocular tissues from a deceased donor ~~must~~ **should** take place in, at minimum, a clean ~~collection~~ **retrieval** environment such as a mortuary ~~or equivalent facility, using aseptic technique.~~ For a living donor the ocular tissue must be retrieved in an operating theatre.”

*For the same reasons as stated above under “Interpretation - clean collection environment”.*

Page 5

7(6)

**deletion to** - (6) ~~The collection of tissue from a deceased person must occur as soon as possible and no more than 24 hours after death.~~ Time intervals between death and enucleation and preservation and/or corneal excision must be recorded.

*Acceptable time intervals from death to enucleation or excision, or from excision to preservation may vary according to the circumstances of death, interim means of storage of the body and/or method of corneal preservation. For example, periods of death to surgical retrieval of eyes are often extended well beyond 48 hours if normothermic storage is undertaken without any adverse effects because the corneas are assessed at the **end** of the storage period<sup>2,3,4,5</sup>. Similarly, if tissue is collected for anterior lamellar keratoplasty the death to enucleation time may also be extended. It is generally **recommended** that corneal preservation occur as soon as **practicable** after death<sup>1,3</sup>.*

Page 5

(9)(b)

**Addition to** – “(b) described in subsection 7(9)(a)(i),(ii), or (iii) may be banked for an extended period of time under the specified conditions, but that period must be less than the ~~maximum documented storage period respective to expiry date of~~ the medium used and only if authorised by the Medical Director (~~or authorised delegate~~) of the facility and with the agreement of the transplanting surgeon”

Page 5

(9)(c)

**deletion to-** (c) that is excised corneas, preserved according to subsections 7(9)(a)(iii), then a subsequent exposure to transport medium at ~~28°C to 37°C~~ **must should** not exceed 5 days.

*Exposure to transport medium may be at any temperature from 0°C to 37°C.*

Page 6

(10)

**deletion to-** (10) Ocular tissue must be sealed within a ~~sterile~~-container and packaged and sealed so as to

- (a) prevent ingress/egress of material other than for a gas sterilant (if applicable);
- (b) ensure any breach of integrity will be evident.

*The tissue is not sterile and therefore the container cannot be considered sterile.*

Page 8

## **8. Evaluation and testing of ocular tissue**

Part (1) and (2)

**Replace with a paraphrased Section 10 of EBAANZ Medical and Quality Standards Edition 2, 2009<sup>1</sup>.**

*The current evaluation of ocular tissue standards as written in the draft are out of date and no longer current.*

*The suitability of any individual cornea may depend on the intended surgical use of the cornea. Therefore the ultimate responsibility for accepting any individual cornea for surgery rests with the transplanting surgeon. e.g. a cornea that does not meet normal endothelial quality criteria for penetrating keratoplasty may be used for tectonic or anterior lamellar keratoplasty. The EBAANZ Standards recognise these important distinctions and 1) are written to allow for these variables and 2) are written to recognise the newer and emerging procedures of posterior lamellar keratoplasty and laser-assisted preparation of tissue.*

(1) General

The suitability of any individual cornea may depend on the intended surgical use of the cornea. "Examination" refers to the method of inspection; and "evaluation" refers to an assessment of quality; either qualitative, quantitative, or both.

(2) Gross Examination & Evaluation at Retrieval

- (a) The corneal-scleral segment shall be initially examined grossly for clarity, epithelial defects, foreign objects, contamination and scleral colour e.g. jaundice. This examination may be aided by use of a penlight or portable slit-lamp.

(3) Laboratory Slit-lamp Examination & Evaluation

- (a) Prior to storage the cornea should be examined by slit-lamp for epithelial, stromal and endothelial pathology, for example: scars, oedema, significant arcus, striae, epithelial defects, endothelial guttae or disease, polymegethism, pleomorphism, infiltrates or foreign bodies. Slit-lamp examination and evaluation shall be documented.

- (b) Eye Banks should perform slit-lamp evaluation after lamellar or laser-assisted preparation of tissue to detect any damage to the corneal endothelium, or surgical detachment of Descemet's membrane that may have occurred during preparation.
- (4) Endothelial Cell Examination & Evaluation
- (a) The endothelium of the excised cornea shall be examined by specular microscopy or light microscopy. Evaluation should include an assessment of cell morphology and determination of cell density.
- (b) When it is not possible to obtain an endothelial cell density or endothelial image, this requirement may be waived on a case-by-case basis by the Medical Director or authorised designate.
- (c) Eye Banks may choose to perform pachymetry and/or endothelial evaluation after lamellar or laser assisted preparation of tissue.
- (d) Endothelial cell examination and evaluation is not required for those corneas intended to be used only for anterior lamellar procedures.
- (5) Examination of Sclera
- (a) Although there are no absolute criteria for evaluation of scleral quality, scleral shells should be visually examined for gross defects before storage and distribution.

Pages 6 and 7

**Section 8 Part (3) & (4)**

**Re-write section –**

- (3) ~~Bioburden on~~ For ocular tissue that is preserved according to subsection 7(9)(a)(iii) ~~and/or~~ its storage medium ~~must~~ should be tested for the presence of microbial growth using a validated testing method. This test shall be performed several days into the storage period, and/or at the time of terminal evaluation and transfer of the cornea into ~~determined prior to release or transfer to~~ transport medium.
- (a) ~~Unless the visual~~ Visual evidence of growth or confirmed evidence of growth using the testing methodology results in discard of the biological. ~~a report of positive microbial culture must include an estimate of the total viable count and the organism(s) identified to at least the genus level;~~ and
- (b) results of the microbial tests must be reported to the transplanting surgeon, and any growth of organisms detected after release of the tissue must be reported to the transplanting surgeon (identified to at least the genus level).

~~(4) Bioburden on ocular tissue that is preserved in accordance with subsection 7(9)(a)(iv) and (v) must be determined and meet specification documented for the clinical application of the tissue prior to its release by the manufacturer.~~

*Bioburden testing of any ocular tissue is not required.*

*The unique nature of ocular tissue (i.e. exposed to the external environment and therefore never sterile or completely decontaminated) renders the results and significance of bioburden testing invalid, and any subsequent decisions based on the results such testing are unsound<sup>6,7,8</sup>.*

*Bioburden testing is done to determine the total number of viable microorganisms in or on a medical device, container, component or tissue after completion of all in-process steps before and after sterilisation or decontamination. Its purpose is 1) to evaluate the quality of aseptic recovery and 2) to make decisions on the likely*

*efficiency of the sterilisation or decontamination process. Even if post-processing cultures are 100% negative for growth a decision may be made to discard tissue based on the pre-processing bioburden results (for example if an organism is considered particular pathogenic for the transplant to be performed or if an organism is considered to be resistant to the sterilisation or decontamination process).*

- 1. Total estimated bioburden of incoming tissue measured by filtration and culture of tissue transport fluid reflects primarily surface contamination. It is used to evaluate and monitor quality of aseptic recovery and handling. For ocular tissue retrieval this evaluation is invalid because it is not possible to determine the relative contributions of pre-existing organisms and contamination due to recovery.*
- 2. Pre-process estimated bioburden of ocular tissue is not possible because necessary testing renders it unsuitable for transplantation.*
- 3. Ocular tissue is transplanted non-sterile, into a non-sterile host bed and environment. Post-transplant infection rates are no higher than for other ophthalmic procedures.*
- 4. The results of a complete and valid bioburden test are not available until well after (a least one week) transplant. This still holds true for normothermically stored corneas. Normothermically stored corneas do not complete their processing until transfer into transport/thinning media, and once transferred they must be transplanted within 5 days. Therefore the results of any post-processing bioburden testing (integral to the process) are not available until well after transplant.*

*For all these reasons ocular tissue is not subject to bioburden testing. The method of storage makes no difference. The purpose of microbiological surveillance during normothermic storage is to monitor the growth of microorganisms within a system which may promote microbiological growth – not to assess bioburden.*

Page 8

### **Schedule 1 Labelling**

Page 8

**(2)(d)**

**Change** - (d) storage conditions and ~~expiry-procedure~~ date

Page 8

**(2)(f)**

**Change** –(f) ~~biohazard label and~~ a statement - ~~including that the biological could transmit infectious agents~~ “Infectious disease transmission cannot be excluded”.

*This tissue is intended for transplant and therefore does not knowingly contain any biohazardous material. To label a transport container otherwise is both exceedingly alarmist and inaccurate.*

*To suggest that the material could transmit infectious agents can be interpreted that this is a likely occurrence. A more responsible and less alarmist phrasing suggests that it is highly unlikely but cannot be excluded.*



**Delete clause**

*The reporting of results of microbiological tests is not necessary because the results will always be “no growth”. Corneas are not released when any microbiology testing demonstrates growth.*

**References**

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<sup>1</sup> Eye Bank Association of Australia and New Zealand. EBAANZ Medical and Quality Standards for Eye Donation and Eye Tissue Banking. Edition 2, April 2009.

<sup>2</sup> Pels E, Houdijn Beekhuis W, Volker-Dieben HJ. Long-term tissue storage for keratoplasty. Ch 106 In Brightbill FS, Editor: *Corneal Surgery, Theory, Technique and Tissue*. 2<sup>nd</sup> Edn St Louis, Mosby, 1993.

<sup>3</sup> European Eye Bank Association. Members Directory 17<sup>th</sup> Edition, 2009.

<http://www.europeaneyebanks.org/files/directory2009.pdf> accessed 12/1/2010.

<sup>4</sup> European Eye bank Association. Technical Guidelines for Ocular Tissue, 2009.

[http://www.europeaneyebanks.org/downloads/Technical%20Guidelines%202009\\_revision3%20final.pdf](http://www.europeaneyebanks.org/downloads/Technical%20Guidelines%202009_revision3%20final.pdf) accessed 12/1/2010.

<sup>5</sup> European Eye Bank Association. Agreements on Medical Standards, 2009.

[http://www.europeaneyebanks.org/downloads/Technical%20Guidelines%202009\\_revision3%20final.pdf](http://www.europeaneyebanks.org/downloads/Technical%20Guidelines%202009_revision3%20final.pdf) accessed 12/1/2010.

<sup>6</sup> Rehany U, Balut G, Lefler, E, Rumelt S. The Prevalence and Risk Factors for Donor Corneal Button Contamination and Its Association With Ocular Infection After Transplantation. *Cornea*. 23(7):649-654, 2004.

<sup>7</sup> Fontana L, Errani PG, Zerbinati A, Musacchi Y, Pede BD, Tassinari G. Frequency of Positive Donor Rim Cultures After Penetrating Keratoplasty Using Hypothermic and Organ-Cultured Donor Corneas. *Cornea*. 26(5):552-556, June 2007.

<sup>8</sup> Everts RJ, Fowler WC, Chang DH, Reller LB. Corneoscleral Rim Cultures: Lack of Utility and Implications for Clinical Decision-making and Infection Prevention in the Care of Patients Undergoing Corneal Transplantation. *Cornea*. 20(6):586-589, August 2001.