



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 minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies

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 is a confusing and complicated document which impairs the ability to correctly interpret and implement its requirements. This is due to its ambitious aim of including all blood and tissues under the one set of infectious disease standards but subsequently having to compromise the document because the same universal standards cannot apply to all of these tissue types. The result is a complicated list of exceptions and inclusions for specific tissue categories, many of which are inaccurate or out of date.

For clarity, accuracy, workability and responsiveness to a constantly changing operating environment and changing standards, this Therapeutic Goods Order should be discarded, and its standards incorporated appropriately into the Therapeutic Goods Order that is specific to the product group.

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

4. Interpretation

Page 3

- **critical material**

deletion to –“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 have a demonstrable affect as determined through risk assessment.*

Page3

- **domino donor**

“means a living person from whom a diseased organ is removed and replaced with a healthy organ, and healthy parts of the diseased organ are ~~salvaged retrieved~~ and processed to produce banked tissue e.g. in a heart transplant the heart valve from the diseased heart, if healthy and structurally sound, may be processed and banked for future use”

This provides a more appropriate description.

Page 4

- **physical examination**

physical ~~examination~~ **assessment** means a clinical based inspection of a living or deceased potential donor to determine suitability of the person to be a donor and includes at minimum the relevance of any abrasion/laceration, bruise/haematoma, fracture, tattoo, piercing, scars, skin lesion, surgical incision or other distinguishing external feature that may be indicative of a behaviour, lifestyle or disease **while taking into consideration a risk assessment for each individual donor.**

The EBAA / FDA provides the necessary interpretation:

*The purpose of the physical **assessment** of a cadaveric donor or the physical examination of a living donor is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease. For a cadaveric donor, the physical assessment means a limited autopsy, or a recent antemortem or postmortem physical examination (§ 1271.3(o)). You may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health care professionals.*

Such an interpretation makes for a workable and relevant approach which maintains respect for both the donor and the health professional. Without this interpretation, for example, conceivably a blood donor would be required to present for an anal examination.

Page 4

- **pre-mortem blood sample**

“means a blood sample collected ~~from a heart beating donor~~ prior to cardiac death”

This provides a more accurate, less ambiguous description.

Page 4

- **prion disease- risk of**

“means having been exposed to the putative causative agent(s) of any one of the family of pathogenic transmissible spongiform encephalopathies through genetic (familial), environmental* or iatrogenic** means. ~~i.e. lived in or consumed or undergone treatment with potentially contaminated product, e.g. beef products (e.g. bovine insulin), blood transfusion or tissue transplantation, in a high risk country.”~~

~~Criteria used in Australia that define “risk of prion disease” include donors who have~~
~~* a) lived in or visited England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period of six months or more, between 1st January 1980 and 31st December 1996 inclusive;~~

~~**b) received a transfusion or injection of blood or blood components while in England, Scotland, Wales, Northern Ireland or the Isle of Man from 1st January 1980 onwards.~~

The criteria applied that defines “risk of prion disease” does not represent Australian and New Zealand Eye Donation Standards. In addition, the definition provided for “risk of prion disease” is that of ‘risk of exposure to the putative causative agents’ (as prescribed by the Australian Blood Service NOT “risk of prion disease” per se).

Also see the reference by Hirst et.al.¹

The following changes are necessary to comply with the Australian and New Zealand Standards for Eye Donation and Eye Banking and internationally developed standards for Eye Banking

Page 6

Schedule 1

PRODUCT REQUIREMENTS

Table 1 column 1

Change – 2. Deceased ~~cornea~~ eye donor

Table 1 column 3

Change - Any tissue other than ~~cornea~~ eye or skin

Table 1 row 2

Change – delete the second sub-row (cornea preserved at >10°C) and alter Product or starting material to Eye. Delete any reference to how the cornea is stored (cornea preserved at <10°C and cornea preserved at >10°C. i.e. the second row is not split and becomes one row with the descriptors remaining the same as the original top sub-row as below.

Donor Groups	Intended use	Product	Compliance with Sch 2	Compliance with Sch 3	Compliance with Sch 4	Compliance with Sch 5	Compliance with Sch 6
Deceased eye donor	Allogenic	Eye Tissue	All except clause (4)	All except clause (2)	All except clause (2) and paragraph (4)(b)	All except subparagraph (1)(b)(ii) and clauses (2) to (5)	All

The distinction and variations in exemptions for different forms of corneal preservation are not valid. These relate to bioburden or microbiological surveillance. Bioburden testing is invalid for all corneas regardless of preservation method.

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.^{2,3,4}

Bioburden testing is done to determine the total number of viable microorganisms in or on a 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 particularly 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. Microbiological surveillance for normothermically stored corneas is covered within the Ocular Standards.

Table 1 row 2 column 8 (Schedule 6)
Add – All requirements except subparagraph (2)(a)
And see later comments regarding Schedule 6

It cannot be demonstrated that all solutions used in ocular processing satisfy sterility requirements (to do so may compromise the viability of the cornea). Many solutions used in normothermic methods are compounded to their final formulation at the time of the introduction of a non-sterile tissue.

Page 9
Schedule 2
POLICY

Page 9
Deletion

(1)(b) for manufacturers of allogeneic blood and blood components, human tissues and human cells required to be manufactured in a facility with an approved quality system, an informed risk/benefit analysis regarding donors who have resided/travelled outside Australia ~~and at minimum, be consistent with the policy applied to donors of blood for blood components:~~ (clause (i) and (ii) must also be deleted).

The vector of transmission and likelihood of transmission, degree of risk, product pooling or batching and donor populations all vary between blood, blood components, cells and tissues (including within tissue types). The requirement to be consistent with policies applied to donors of blood is inconsistent with the differences in risk of the different products and inconsistent with the differences in donor assessment between living and cadaveric donors. What applies to blood donation does not necessarily apply to other forms of donation. This is the basis of the original

TGA concept for these drafts i.e. to return to separate codes and rules for blood and for tissues.

Page 9

Exemption

(4) *all eyes, regardless of resting method must be exempt (as stated in Schedule 1) -* The manufacturer must have policies in place for the acceptance and release of each human blood and blood component, human tissue or human cellular therapy product based on the microbial specifications.

The distinction and variations in exemptions for different forms of corneal preservation are not valid. Most of these relate to bioburden or microbiological surveillance. Bioburden testing is invalid for all corneas regardless of preservation method (see notes above). Microbiological surveillance for normothermically stored corneas is covered within the Ocular Standards.

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Schedule 3

MEDICAL AND SOCIAL HISTORY

Page 10

Change

(3) An interview, where possible, with a person most capable of providing information regarding ~~the next of kin/guardian of~~ a deceased donor (this may be a next-of-kin or a friend) and/or examination of the medical record to obtain and document the medical and social history of the donor must take place and be documented ~~at the time of, or~~ no more than 7 days prior to the donation.

A more accurate assessment of risk factors may be provided by a friend or person that knew the deceased better in this regard than a next-of-kin. The requirement to perform and document this interview at the time of donation seems inflexible (especially for recently bereaved relatives) and does not take into account access issues to people with these associations. Instead it should be a requirement, where possible, to have this interview conducted prior to release of tissue for transplantation.

Page 11

Table 2

(m)

Add Exemption - (m) Physical evidence of sepsis such as unexplained generalised rash/generalised petechiae (For corneas to be stored normothermically donation is acceptable)

Septicaemia is not a contraindication to donation of corneas if the corneas are stored by normothermic means. This is a well-established and validated practice world-wide^{5,6,7,8,9}.

Page 12

Table 2

(s)

Add Exemption - (s) Being a recipient of allogeneic organ(s) or cells, or deceased donor tissue allograft (**ocular tissue donation is acceptable**)

The immunological status or general systemic effects of having received donor tissue does not affect the quality of ocular tissue and therefore donation for this purpose is acceptable. Any possibility of septicaemia can be assessed independently of the status of organ or tissue recipient and is covered under section (m). The risk of infectious disease in the donor (those covered under this schedule) is no greater than that of any other deceased donor.

Page 12

Table 2

(u)

Delete – Being a recipient of live vaccine(s) ~~or Hepatitis B vaccine~~

Hepatitis B vaccine should be deleted as this contradicts section 5c (vi) page 13

Page 15

Schedule 4

SAMPLING, TEST KITS, TEST PROTOCOLS AND TEST MANAGEMENT

Page 15

(8)

Add- (8) Screening and confirmatory microbiological and virological tests **that are required for the release of product** must be performed in laboratories using appropriately validated testing techniques as regulatory requirements specify.

It is unclear whether this extends to ANY testing or only testing required for the release of product – it would appear to be unnecessarily restrictive to require this for tests that are not required for release of tissue.

Page 15

(9)

Add - (9) **When possible** samples of donor serum/plasma must be archived under optimal conditions to ensure sample availability for retesting or additional testing up to, at minimum, the time of transfusion or implantation of human blood and blood components, human tissues or human cellular therapies.

After mandatory testing there is often not enough sample remaining to archive (especially in relation to cadaveric donors).

Page 15

(10)

Add - (10) **When possible** dedicated samples of the serum from deceased or living donors taken at time of donation, and also the samples taken from live donors at 180 days post-donation, must be archived at or below minus 25°C unless the conditions of archive are validated at a different temperature (or as recommended by the test kit manufacturers) for the period from sample collection to a minimum of 2 years after the expiry date of the human blood and blood components, human tissues or human cellular therapies.

After mandatory testing there is often not enough sample remaining to archive (especially in relation to cadaveric donors).

Page 15

(12)

Delete all

This clause is relevant to service level agreements (and thus should be in the cGMP document) and not to each individual donation. To append these details to each donor record is both impractical and duplicitous and serves no useful purpose

Schedule 5

DONOR TESTING AND EXAMINATION

(1) (c)

Add and delete - (c) A physical ~~examination-evaluation~~ must be conducted by a competent person to ascertain the suitability of a donor to donate cells or tissues and must take place,

- (i) on the day of blood, cell or tissue collection; or
- (ii) if not possible for cells and tissue, as close as practicable prior to the time of cell or tissue collection, i.e. generally within 5 days and no more than 7 days; or
- (iii) for a deceased donor, prior to cell or tissue collection and no later than 24 hours after death;

*The purpose of the physical **assessment** of a cadaveric donor or the physical examination of a living donor is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease. For a cadaveric donor, the physical assessment means a limited autopsy, or a recent antemortem or postmortem physical examination. Examination should extend to only those parts of the body that are necessary to evaluate for Schedule 2 risk factors based upon the relevant donor history that has been obtained during the interview and review of available records. Records of a recent report of a physical examination by other health care professionals for a deceased donor are likely to be more accurate than a postmortem examination on a deceased body in rigor mortis. (See also notes in relation to Interpretation – page 4 physical examination).*

(1)(d)

Change - The cells and tissues of a deceased donor whose cause of death is unknown must be deemed unacceptable, unless ~~autopsy~~ **a pathologist** provides sufficient information to conclude that death has not been caused by a transmissible disease or any other condition that would be a contraindication or preclude transplantation of the cells or tissue from that donor.

It is not the autopsy that makes this decision but the Pathologist

(4) and (5)

Exemption for ocular tissue

For the reasons stated under comments regarding Schedule 1 and 2 microbiology issues, ocular tissue should be exempt from the type of microbiology tests described in clauses (4) and (5) regardless of storage method.

Table 4: Donor Testing Requirements.

Change – Cornea-only donors needs to be changed to Eye Donors or Eye Donation.

Schedule 6

Relocate to cGMP document and change the wording “must” to “should”.

Schedule 6 has nothing to do with risk reduction of infectious disease transmission from donor to recipient. Rather it addresses Materials used in Production and is better suited to be incorporated within the cGMP document.

*In addition, it cannot be demonstrated that all solutions used in ocular processing satisfy sterility requirements (to do so may compromise the viability of the cornea). Many solutions used in normothermic methods are compounded to their final formulation at the time of the introduction of a non-sterile tissue. However, monitoring processes are in place to reduce the risk of contamination with pathogenic bacteria or other infectious agents. To ensure the continuing viability of the normothermic storage system for corneas the wording **has to** be changed from “must” to “should” i.e. an alternative approach may be used if the aim is satisfied.*

References

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