Thank you for providing opportunity to make comments on the new draft code of Manufacturing Practice and Standards. There has been a very long gestation period for this draft code and, unfortunately, I cannot help but feel somewhat let down now that it has finally arrived. However, we hope that the combined response of the eye, tissue, cellular therapy and blood sectors are able to provide sufficient accepted input to improve the Code and Standards.

There is general agreement that the current Code requires updating. The difficultly in doing this is, in part, due to the requirement to have so much overlap in the documents for sectors that vary so greatly. We had been lead to believe that the blood sector would once again be placed under a separate structure, but this has not occurred. We commend the authors for their effort in bringing together all the sectors, but the difficulties of accommodating small eye and tissue banks along with the large blood sector is evident in the complications that have arisen in the documents.

When the original code of GMP was being derived I was one of the few that supported it, saying it makes me do today what I had planned to do tomorrow. Over the years however my views have changed. I have found TGA auditing to be inconsistent, some sites appearing to have to meet higher demands than others. My view is that the almost exclusive use of the word “should” rather than “must” will give even more latitude for auditors to be inconsistent with their audit. Using “should” questions whether any particular clause is actually required, particularly if it is also used with “where appropriate”. I appreciate that “must” should not be overly restrictive, but this can be achieved. I had never envisaged requiring a tighter code, but I do not feel in its current form it can be best used for the stated purpose of auditing.

Because so many sectors are involved there will be advances in treatment and methods that will mean the Code and its documents will need to change. The TGA does not appear to have a facility such as the FDA federal register where amendments can be efficiently circulated, or is the Commonwealth of Australia Gazette the method? How will the TGA make amendments to any of the documents? An annual review would also seem to be appropriate with such large sectors. I think that the TGA should address these issues.

In the Code currently in force the TGA is charged with deciding, in consultation with industry, which test methods are to be used to test for infectious disease. In practice they have in the past been unable to provide a list of acceptable tests. It is with concern therefore that I see in Schedule 4, 6, a, of the infectious disease Standard, that tests must be current technology etc. There is no indication who and how current technology will be decided. I suggest that the TGA is required to provide an approved list of tests available at any time to supplement the Code. The TGA should say what is acceptable and what is not. Not to do this will result in inequity. When a test will be superseded then the TGA should say the latest time when the superseded test will be permissible.

Comments on TGO for Minimising infectious disease transmission **dated December 2009**

Definitions

pre-mortem blood sample means a blood sample collected ~~from a heart beating donor~~ prior to cardiac death;

prion disease- risk of means having been exposed to the putative causative agent(s) of any one of he family of pathogenic transmissible spongiform encephalopathies through genetic (familial), evironmental* 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 issue 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.*

Comment [A1]: *It is important that such a change is made, as someone can be dead, but still have a beating heart.*

Comment [A2]: This needs section needs to be rewritten whether or not you believe the UK exclusion rule should be applied to eye or other donors. It now reads that any beef product eaten in a high risk country would be high risk and the donor contraindicated. The limit on when and how long the donor has lived in a high risk country is not taken into account in the wording.
If you believe that the UK exclusion rule should not be applied then only the genetic and iatrogenic should be left in place.

Schedule 1

PRODUCT REQUIREMENTS

Table 1: Schedule 2 to 6 requirements for products manufactured from a particular donor group

1. Deceased donor - Allogeneic - Any tissue other than eye or skin

2. Deceased Cornea Donor – Allogeneic use – Cornea preserved at ≤10°C/ Cornea preserved at >10°C 3

Comment [A3]: My apologies for the text not being aligned. The issue is that cornea be changed to eye in table 1 column 1 otherwise a whole eye it more restricted than a cornea. This should occur throughout all the documents. Furthermore I would prefer ocular to be replaced with eye to aid consistency throughout the documents.

Deleted: cornea

Comment [A4]: In column 3 rather than have cornea preserved at 10C or above etc I would substitute "Cornea preserved at ≤10C to Whole eye, cornea or sclera preserved at ≤10C" or "Cornea preserved at ≤10C to Whole eye, cornea or sclera preserved at ≤10C" as otherwise only cornea are captured and for example a whole eye would be treated in a more restrictive way.

Schedule 2

POLICY

(1) The manufacturer must demonstrate that steps are taken to mitigate the risk of infectious disease transmission either during collection, manufacture or via the finished product. The policy (or policies) must address the process for selection of suitable donors and include:

(a) eligibility requirements for donors who have resided/travelled outside Australia; and

(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~~:

(i) must not be manufactured from donors who have lived in or visited England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period

Deleted:

Comment [A5]: There is a different risk associated with use of eye tissue compared with that of blood.

(4) 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. Eyes are exempt as noted in Schedule 1.

Comment [A6]: You cannot expect normal bioburden testing for eye tissue.

Schedule 3

MEDICAL & SOCIAL HISTORY

(3) An interview, where possible, with the next-of-kin/guardian or person most capable of providing information of a deceased donor 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.

Comment [A7]: On some occasions a legal next of kin may not be the person most able to give medical information.

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Schedule 3; Table 2: Minimum medical and social criteria required to define a donor's risk of recent exposure to infectious disease

Donor medical and social history criteria	Period of ineligibility prior to donation for Allogeneic use	autologous use
(m) Physical evidence of sepsis such as unexplained generalised rash/generalised petechiae	Ineligible until a disease free state can be established	Nil
(s) Being a recipient of allogeneic organ(s) or cells, or deceased donor tissue allograft	Permanent	Nil
(t) Being a recipient of allogeneic blood, blood components or blood products that do not meet the requirements of this Order	12 months unless (q) or (r) apply, then permanent	Nil
(u) Being a recipient of live vaccine(s) ~~or Hepatitis B vaccine~~	Ineligible for the periods specified in (5)	Nil

Schedule 4

SAMPLING, TEST KITS, TEST PROTOCOLS AND TEST MANAGEMENT

(3) Blood sampling of a deceased donor must take place prior to cell or tissue collection and no later than 24 hours after death, if a pre-mortem blood sample is not ~~available~~.used

(8) Screening and confirmatory microbiological and virological tests must be performed in laboratories using appropriately validated testing techniques as regulatory requirements specify.

(9) Any available 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.

(10) 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.

(11) Where screening protocols change during the life of a product in storage, where possible and practicable the donor's archived serum/plasma must be retested with the new screening test protocol prior to release of human blood and blood components, human tissue or human cellular therapy products.

(12) Documentation is to be maintained of the tests performed, test modifications, analyses and any anomalies ~~required to be appended to the donor record in addition to the test results~~.

Comment [A8]: We need an exception here as corneas stored normothermically are acceptable for use.

Comment [A9]: There may need to be exceptions here. Previous corneal transplants do not significantly affect immunology. Bone that has been cleaned to remove antigenicity and has been terminally sterilised would appear to also require an exception.

Comment [A10]: Do the authors appreciate that there will be a need for a grandfather period stated for this new order, otherwise when the order comes into force anyone who has received allogenic blood etc will be unsuitable to donate until after 12 months.

Comment [A11]: Unless this is removed t would seem to contradict section 5 c vi

Comment [A12]: There may not always be sample available for archive. It would appear difficult to expect a n archive sample otherwise the donor could not be used. I would think such a demand is excessive but if the TGA requires it this should be more clearly stated.

Comment [A13]: As previous comment.

Comment [A14]: I do not agree that this is only relevant to service level agreements as the tests could be performed in house. The issue here is the way it is written by the TGA which says tests and modifications and analyses have to be attached to the donor notes – all of us would disagree with this I think.

Deleted: S

Comment [A15]: As above

Comment [A16]: I do not agree that this is only relevant to service level agreements as the tests could be performed in house. The issue here is the way it is written by the TGA which says tests and modifications and analyses have to be attached to the donor notes – all of us would disagree with this I think.

Comment [A17]: I do not agree that this is only relevant to service level agreements as the tests could be performed in house. The issue here is the way it is written by the TGA which says tests and modifications and analyses have to be attached to the donor notes – all of us would disagree with this I think.

Schedule 5

DONOR TESTING AND EXAMINATION

This Schedule sets out the requirements in relation to donor testing and examination.

(1) Each donor of human blood and blood components, human tissues or human cellular therapies must be tested and examined for evidence of infectious diseases in accordance with the relevant and applicable donor groups. Assessment of donor blood samples and the physical ~~examination~~ assessment of the donor are key determinants of donor acceptability or rejection. Donors of human blood and blood components, human tissues and human cellular therapies must be evaluated as follows:

(d) 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.

Table 4: Donor testing requirements

ID testing	**Deceased**	**Cornea**

A HBcAb reactive sample is acceptable only if HBsAb when tested is =100 IU/L, or a specified recipient is known to be immune to HBV. 2

~~Non specific (reaginic) syphilis tests are prone to false positive results. Therefore specific syphilis testing must be conducted on tissue donors, where it is required~~. 3

Schedule 6

CRITICAL MATERIALS~~SUBSTANCES~~ USED IN PRODUCTION

This Schedule sets out the requirements in relation to the selection and evaluation of any critical materials employed during the manufacture (collection, processing, storage or transport) of human blood and blood components, human tissues or human cellular therapies.

(2) Where blood, cells and tissues are required to be manufactured in a facility with an approved quality system, critical materials used in manufacture that are

(a) solutions, other than the disinfectant/antiseptic solutions used in a validated tissue 4cleaning process, which contact the human cells or tissue during collection, processing, storage or transport must be

(i) manufactured under an approved quality management system and be supplied as a sterile solution; or

(ii) tested for and satisfy sterility requirements in accordance with an approved pharmacopoeial test for sterility; or

(iii) if required by the Act, approved for an equivalent purpose and entered on the ARTG.

Comment [A18]: The extent of the assessment will vary from case to case based on risk assessment.

Comment [A19]: An autopsy comes too late for tissue use whereas a pathologist who is to do the autopsy can provide earlier indication.

Comment [A20]: This change acknowledges that not all sectors will require microbial treatment

Comment [A21]: Cornea needs to be changed to Eye donors, otherwise whole eyes would have more restrictions than corneas.

Comment [A22]: The foot note regarding specific syphilis testing states that specific tests must be used, where they are required. This is too restrictive. If a facility wishes to use a non-specific screening test then if it is negative the order should not prevent use of the tissue

Comment [A23]: This whole schedule seems out of place here. It should be moved to the code of GMP.

Comment [A24]: This section concerns "critical materials" and so why use "substances" which is not defined. Suggest rename to "Critical materials used in production".

Comment [A25]: This section should be deleted or substantially changed.
As it is written there would be onus on the eye or tissue bank to have a record of an approved quality management system, but how is approved assessed and by whom? Plus it stated "supplied as a sterile solution", but (ii) indicates "or" and "approved pharmacopoeial test for sterility". How then in "i" is sterility measured if it is not against an pharmacopoeial standard?
Also in "ii" "with an approved pharmacopoeial", should be changed to "with a TGA approved pharmacopoeia", or some other source stated.