Submission on TGA consultation: Proposed standards for human blood and blood components, human tissues and human cellular therapy products

Organisation: **Cell and Tissue Therapies WA (CTTWA)**

Thank you for providing your comments using the template below.

- Rows may be added or deleted as required. Tables may be left blank or deleted if no comments are to be made on other documents.
- 'Reference' indicates the specific section/ subsection/ paragraph where relevant, e.g. In the infectious disease Order, 8(1)(b) would be used to reference requirements for donor interview timeframe in Prt 3, Section 8, Subsection (1), paragraph (b).
- 'Issue' invites a short statement to summarise the comment.
- 'Comments' may include a position including justification or an alternative position.
- Additional general comments are also invited on the impact of these standards, as indicated below each table.

Submission on TGA consultation: Proposed standards for human blood and blood components, human tissues and human cellular therapy products

Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products

SUBMITTING ORGANISATION: Cell and Tissue Therapies WA (CTTWA)

Reference	Issue	Comment
Microbial definition, Page 4	Inclusion of mycoplasma and Rickettsia in the definition of "microbial"	It is unclear why these organisms are specifically identified in the "microbial" definition? The current validated and approved test methods (eg. BactAlert/BacTec) used to identify bioburden or microbial contaminations do not detect either of these organisms. In addition, there is only one laboratory in Australia licensed to test for mycoplasma and we are unaware of any testing laboratories whose licensed test methods detect Rickettsia. Therefore, criteria for acceptance and release of products cannot be based on microbial specifications if the definition of "microbial" includes mycoplasma and Rickettsia. (see Cardiovascular tissue TGO – 7. (2) (d) and 7. (4) (b) comments below).
6. (3) (b)	Exemptions	Clarification sought. Does this mean that all blood, blood components and HPC manufactured within hospitals are exempt from this order?
8. (2)	"and/or examination of the medical documentation…"	Does this mean that an examination of the medical documentation alone is sufficient even if an interview is possible? Suggested rewording: *An interview with the next-of-kin/guardian or other knowledgeable historian of a deceased donor and examination of the medical documentation to obtain and record the medical and social history of the donor must take place and be recorded at the time of, or no more than 7 days prior to or following collection. If an interview is not possible, examination of the medical documentation may be sufficient.*
Table 1; (h)	Donors who have received blood, organs cells or tissue	Does the statement *"not in accordance with the requirements of this order*" mean that product manufactured prior to this order which does not meet some of the criteria of this TGO (eg. NAT), will have to be discarded?
Table 1 (i)	recipients of blood, organs, cells, tissues….	'……. *recipient of allogenic organ(s) cells or tissue that are not in accordance with the requirements of this order'.* Does this mean recipients of these graft items outside of Australia are permanently ineligible as a donor ? Alternatively, does this mean that for a recipient of the listed items in Australia, there is no ineligibility as a donor?
Table 1. (q)		Is electrolysis no longer considered a risk of acquiring a blood borne transmissible infection?

Table 1. (s)	Exposure to particular epidemiological situation	Does this reference only apply where alerts have been issued for an epidemiological situation that is of concern?
8 (11) (b)	Validation of Donor age range	It will be difficult to impossible to "validate" a donor age range, particularly as scientific literature on this topic is minimal to non-existent. Suggested rewording: *The age range of donors from whom specific cells and tissues can be collected must be supported by data, industry standards or documented evidence which justify appropriateness for the intended therapeutic use*
9.(6) (a) and (b)	Requirements in relation to donor blood sampling	**(6)** *The test kits/methodologies used for the mandatory screening and confirmatory microbial and virological tests must:* ***(a)*** *be the most appropriate ……. for the sample being tested;* Who determines most appropriate? Who determines what test kit or methodology is "most appropriate. *and* **(b)** *be approved by the relevant authority in the country in which the testing is performed,* ***or****, performed in a facility approved by the same authority to perform such testing.* Does this mean we can have the tests done in a non-TGA licensed laboratory provided the kit is TGA licensed?
9. (9)	"Archived samples must be retested"	1. Archived samples are not always suitable for use in new screening test protocols (eg. NAT testing). Suggested modification of reference: *"Where practical, the donor's archived sample is to be retested with the new screening test protocol prior to release of the product ….*

10. (2) (a)	Physical assessment of a living donor at the time of donation.	Further clarification sought and definition. To what extent is physical examination required for blood and autologous donors.
11.(2)	"Human cells & tissues"	Does the term tissue include ocular tissue. If so, this is more restrictive than requirements in TGO
11. (3)	Transport temperature conditions	See comment for the Cardiovascular TGO, 7. (2) (a) below.

What is the perceived impact, if any, of implementing these requirements in your organisation?

Other general comments: Overall, this version is a significant improvement over the 2009 document. It is much easier to understand and, except where indicated above, the requirements appear to be much more reasonable, relevant and practical.

Standards for human cardiovascular tissue

SUBMITTING ORGANISATION: Cell and Tissue Therapies WA (CTTWA)

Reference	Issue	Comment
Microbial definition, Page 3	Inclusion of mycoplasma and Rickettsia in the definition of "microbial"	See comment for Infectious Diseases TGO See comment for 7. (2) (d) below
7. (2) (a) 7. (4) (a)	Transport temperature of heart/ cardiovascular tissue to manufacturing facility (2-8^{o}C) to restrictive.	Transport of the product starting material (i.e. cardiovascular tissue – heart or heart block*) at the temperature range indicated (i.e. 2-8^{o}C) is not critical to the safety or quality of the final product. Validated transport procedures, which consistently obtain heart valves that meet release criteria & demonstrate efficacy upon implantation, do not always maintain this temperature range throughout the duration of transport. The temperature of hearts retrieved from deceased or domino donors can be close to body temperature. Placing the heart into a temperature-conditioned & validated transport container even with the addition of a litre of refrigerated solution (eg. Hartmanns) to the primary heart container, can result in a temperature reading of >8^{o}C for a period of time during transport, depending upon the size/volume/starting temperature of the added heart. Transport temperatures of up to 10.2^{o}C for 15-55min have been recorded for a substantial number of hearts transported for processing. Valves processed from hearts transported at these temperatures do meet release criteria and demonstrate competency and efficacy when implanted into recipients. Restricting the transport temperature of the product starting material to the indicated temperature range will result in the un-necessary discard of generously donated and extremely limited tissue. Suggested modification of reference: Cardiovascular tissue that is subjected to a bioburden reduction process must be: (a) *transported to the manufacturing facility within a defined temperature and timeframe that maintains the safety and efficacy of the final product, ... (see 7. (2) (i) & (ii) below).* *Eastern State Banks retrieve and transport starting cardiovascular tissue as "heart blocks". Retrieval of heart blocks is not allowed in WA. Rather, the entire heart is retrieved from deceased donors with the remains of the heart returned to the body following valve retrieval at the manufacturing site. Whole hearts are also retrieved from domino donors and transported for processing to CTTWA.

7. (2) (i) & (ii)	Processing and treatment with antimicrobial agents must commence within 30 hrs. of asystole or within 30hr of collection from a living donor.	[Infectious Diseases TGO – 11 (2) (a) & (b)]. Hearts must be retrieved from cadaveric donors within 24hr of asystole if the body has been refrigerated within 12hr of asystole or within 15hr of asystole if the body has not been refrigerated. Depending upon when the heart is retrieved (up to 24hr of asystole) and worst-case scenarios for transport to the manufacturing facility (up to 10hr), it may not be possible for processing and treatment with antimicrobial agents to commence within 30hr of asystole or 30hr collection from a living donor. Outcomes have demonstrated that as long as cryopreservation is initiated within 48hr of death (asystole), the valves meet release criteria and demonstrate competency and efficacy upon implantation. Again, the proposed reference has the potential to result in the un-necessary discard of generously donated and extremely limited tissue. Suggested modification of reference: Cardiovascular tissue that is subjected to a bioburden reduction process must be: *(a) transported to the manufacturing facility …. where cryopreservation must commence:* *(i) within 48hr of asystole; or* *(ii) within 48hr of collection from a living donor; and* This proposed change is also required to allow 7. (5) (b) to be feasible.
7. (2) (d)	Assessed for microbial growth	This reference needs to be more clearly stated. Is "assessed for microbial growth" referring to bioburden determination? Does "must demonstrate no microbial growth when cultured" mean when "tested"? Lastly, does the "must demonstrate no microbial growth" only apply to samples tested POST incubation with antimicrobial agents or does it cover all samples taking for bioburden determination throughout processing? Pre-treatment samples may demonstrate microbial growth which are removed via anti-microbial treatment. The definition of microbial growth in terms of "no microbial growth" needs to be clarified. Suggested modification of reference: *"(d) assessed for microbial growth as defined in the product dossier. Post anti-microbial treated samples must demonstrate* no microbial growth when…… Again, the definition of "microbial" has to be changed. The tests currently validated and approved to test for microbial growth (bioburden) (BactAlert/BacTec), do not test for mycoplasma or Rickettisa both of which are specifically identified in the definition for "microbial". It is unclear

		why these two families of organisms have been specifically identified, particularly as the likelihood of them being present is extremely low and the likelihood of them being transmitted to a recipient via a tissue is also extremely low. We are not aware of any testing laboratories whose licensed test methods detect Rickettsia and there is only one laboratory in Australia licensed to test for mycoplasma. Suggested modification of "microbial" definition: Means microorganisms including, but not limited to, bacteria and fungi, but does not include viruses or prions.
Additional General Requirement	Specified microorganisms of clinical significance	To standardise requirements between product specific TGOs the following reference should be added to the cardiovascular TGO possibly as 7. (2) (e) so that other reference numbering does not have to be changed: *"Cardiovascular tissue subjected to a bioburden reduction process must be sampled for bioburden determination to exclude tissue contaminated with specified microorganisms of clinical significance".*
7. (4) (b)	"must demonstrate no microbial growth"	As for 7. (2) (d), current, approved bioburden testing methods do not test for mycoplasma or Rickettisa both of which are specifically identified in the definition for "microbial". Definition needs to be changed. See 7. (2) (d) above.

What is the perceived impact, if any, of implementing these requirements in your organisation? Implementation of the proposed temperature range (2-8^{o}C) for the transport of product starting material (i.e. whole heart) is likely to force CTTWA to cease heart valve processing as it will not be able to meet this TGO requirement. CTTWA's current, validated method of transport (temperature-conditioned, blood in motion eskies), which is an improvement over the use of "wet-ice", does not meet this temperature restriction throughout transport of the heart to the processing facility.
The TGA addressed this comment at the meeting held in Sydney – 27th Jan. 2011 and provided the requested change is made [7. (2) (a) and 7. (4) (a)], this perceived impact will be addressed.
The inclusion of mycoplasma or Rickettisa in the definition of "microbial" would also prevent Banks from meeting release criteria, as they would not be in a position to test for these organisms in their samples to be assessed for microbial contamination. There is currently only one site in Australia licensed to test for mycoplasma and there are no laboratories whose licensed test methods test for Rickettisa. As both organisms are of low incidence and of low risk of being transmitted by transplanted tissue, inclusion of these organisms in the definition of "microbial" when assessment for microbial growth is a release criteria, is not justified based on scientific risk assessment.
Provided the requested changes [7. (2) (d)] are made, this perceived impact will be addressed.

Other general comments:

General requirements for the labelling of biologicals

SUBMITTING ORGANISATION: Cell and Tissue Therapies WA (CTTWA)

Reference	Issue	Comment
6. (2)	General requirements	Do the requirements stated in 6. (2) apply to labels used on any sample collected for a product or just for the containers used for collection and/or release of the product?
6. (2) (c)	Restricting letter height to ≥ 1.5mm	Requiring the letter height to be ≥1.5mm is not an issue for product containers and primary pack labels used at collection and/or release. However, this letter height cannot be accommodated on cryovials used for product aliquots collected and stored for internal testing purposes. The intention is to label these vials with a 2D bar code containing the required product information. IF this requirement applies to all labels, an additional statement needs to be included after 6. (2) (d): "Product aliquots collected and stored in cryovials for internal testing purposes, which cannot meet these labelling requirements, alternative labels containing the required product information may be use e.g. 2D barcodes".
	Restricting letter height to ≥ 1.5m	Hospital labels which are often used on collection containers are not standardised and not all the information provided on these labels meets the letter height requirement (i.e. ≥1/5mm).

6. (3) 6 (3) (c)	General requirements Recording time and date of tissue collection on the primary container.	In general, Hospital labels are used on collection containers. These labels provide at least two identifiers including a unique identification number linked to the donor, but do not contain the information listed in b-e. These details are provided with the product as accompanying documentation. Suggested rewording: *(3) At collection, the following information must be included on the container containing the blood, cells and tissues:* *(a) unique identification number/alphanumeric linked to donor* *(b) type of starting material for the biological.* *(4) At collection, the following information must be included on the container containing the blood, cells and tissues or on documentation accompanying the product:* *(a) date and time of collection* *(b) identification of the collection facility* *(c) identification of the person collecting the starting material for the biological (if applicable).*
6. (5)	Requirement (a) & (d) combined in automated labelling system.	1. Some validated labelling systems (eg. Stemsoft) identify a product/donor by a unique identification number (5a), which incorporates the sponsor name and address (5d). The product type/name (5c) is also included, whereas the batch number (5b) is not applicable. The remaining information (5 e-r) will be included on the documentation accompanying the released product. Will this labelling system be acceptable?

What is the perceived impact, if any, of implementing these requirements in your organisation?

Other general comments: