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

Organisation: Australasian Tissue and Biotherapeutics Forum

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 Part 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

Introductory Statement

The members of the Australasian Tissue and Biotherapeutics Forum (ATBF) are pleased to have the opportunity to submit our comments in this current round of consultation on the Proposed Standards for human blood, blood components, human tissues and human cellular therapy products.

Although there is widespread agreement on the majority of issues raised, this submission consists of a compilation of the questions, concerns and issues raised by the membership across the sector. In the interest of wishing to express the views of all ATBF members, this submission is not intended to represent a consensus view of the ATBF.

The ATBF would like to express it's gratitude to the representatives of the Therapeutic Goods Administration, namely Glenn Smith, Ian Prosser, Alyce Maksoud and Loretta Huckstep, who met with members last week to discuss the issues contained in this submission. We appreciate the opportunity to consult personally at this level and thank the individuals for the open, informative and cooperative manner in which the discussions were conducted.

As an outcome of this meeting, the ATBF has chosen to include a summary of our interpretation of the TGA's response to each of the issues raised, as well as any suggested amendments for the wording of the standard. To highlight these items in the comments section, our interpretation of the TGA representative's comments have been included in red print and suggested amendments to the wording of the proposed standards are in blue print within the document.

Although this round of consultation does not strictly include the draft code of GMP Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products, members have made some important comments on the current draft, which were also shared with the TGA representatives last week. These comments have been included for consideration at the end of this submission.

Thank-you for the opportunity to express the views of the ATBF membership in this consultation. Any correspondence regarding this document can be directed via myself.

Representing the ATBF membership,

Gavin Van Der Meer
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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: Australasian Tissue and Biotherapeutics Forum (ATBF)

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 contamination do not detect either of these organisms. In addition, there is only one laboratory in Australia licensed to test for mycoplasma and I am not aware 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).
	TGA Response	The TGA clarified that this was a standard definition approved by the TGA Microbiology Section. Application of the definition will be product specific. As part of product dossiers, Banks will be required to submit a list of specified microorganisms of clinical significance, which, if tested and found to be present, will require rejection and discard of the tissue. Acceptance of the list and list justifications will be determined by a panel of experts. **COMMENT ADDRESSED**
6. (3) (b)	Exemptions	1. Clarification sought. Does this mean that all blood, blood components and HPC manufactured within hospitals are exempt from this order? 2. Autologous Skull Flaps are not identified as exempt. Our understanding is that this will be in the Excluded Goods Order.
	TGA Response	Exemptions are taken directly from Schedule 7 of the Act. Clarifications of exemptions are still being developed by TGA. Intended for minimally manipulated product prepared for use in a single procedure (autologous or directed; eg skull flaps; granulocytes prepared for use between Hospitals even if under more than one clinical governance/practitioner). Agreed that skull flaps can be stored by a Bank, with inventory controlled by the Bank's Quality System, but must be segregated from licensed products. These items will not be subject to audit. **EXEMPTION STATEMENTS STILL BEING DEVELOPED – SPECIFIC EXAMPLES CLARIFIED.**

8. (1) (b)	Interview timeframes TGA Response	1. What is the rational to limit the interview to 7 days prior or 30 days post collection. Should at statement exist that provides an option for a manufacturer to assess this requirement and determine the period of time and the suitability of the information provided within the user defined range on the risk to the manufacturing process (and operator), preparation and assembly of the final product and donor (recipient). The period of time stated in the TGO should represent the default time period if the manufacturer did not wish to assess the risk. 2. 'The interview must occur no more than 7 days prior to or 30 days after collection……..' For Live Donor femoral head collection where most collections are attended at off site Health Care facilities, the donor interview is conducted in the pre operative clinic. This is usually 4 weeks prior to surgery. Allowing 30 days both before and after surgery would allow current processes in place in many hospitals to continue. This is only the interview for Medical History. Most Musculoskeletal Tissue Banks collect blood for screening on the day of donation. The Musculoskeletal Tissue specific TGO could identify the expanded 30 day prior to and 30 days after collection timeframe for these donors for the donor interview. Timeframe was developed by TG Subcommittee – attempt to harmonise with international standards (eg. cord blood). Agreed that blood to be collected as close to donation as possible. TGA agreed to review interview timeframe and possibly change to: *(b) The interview must occur no more than 30 days prior to or 30 days after collection.*
8. (2)	"and/or examination of the medical documentation…" TGA Response	Does this mean that an examination of the medical documentation alone is sufficient even if an interview is possible? This statement was written to provide an option for donor acceptance in the event an interview with a NOK or other knowledgeable historian was not available. It was not intended for examination of medical documentation to replace an interview if available. <u>Suggested rewording:</u> *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) & (i)	Donors who have received blood, cells or tissue TGA Response	1. A deceased donor who has been a recipient of allogeneic organ(s), cells, or tissues and a recipient (*presumed although not stated to be a living person*) of allogeneic blood, blood components or blood products, organs, cells or tissues that are not in accordance with the requirements of this Order are ineligible permanently or for 12 months. This is interpreted to mean that recipients are accepted only if tissues received are banked after the date that the Order comes into effect. Could the TGA please clarify if this is the correct interpretation – i.e. if a person is a recipient of tissue from a TGA licensed tissue bank prior to the date this Order comes into effect, would this render the person ineligible? 2. As this TGO has introduced criteria not previously required, can *" ..... that are not in accordance with the requirements of this Order"* but replaced with "..... *that are not obtained from a TGA approved Tissue Bank"?* (generally donors who received **tissues** from TGA licensed banks prior to June 2011 will be excluded e.g. NAT testing was not required prior to Jan 2009 so a potential donor who had cadaveric bone in 2006, would be excluded). TGA agreed to reword so that stored products (for example) would not have to be discarded. Eg. *"that are not in accordance with the requirements of this TGO or previous regulatory documents or with legislation at the time of donation".*
Table 1 (i) P7	Donor eligibility **Requires TGA clarification**	'..... 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 ineligible as donors? '..... recipient of allogenic blood, blood components or blood products, organs, cells or tissues that are not in accordance with the requirements of this order': Can this be translated to if the recipient was a recipient of the listed items in Australia, there is no ineligibility as a donor? These comments were not discussed with the TGA but raise interesting questions. Would the TGA please clarify whether these donors are permanently ineligible, ineligible for 12 months unless (f) or (g) apply or have no ineligibility as a donor?
Table 1. (q)	TGA Response	Is electrolysis no longer considered a risk of acquiring a blood borne transmissible infection? Electrolysis not considered to be a risk of acquiring a blood borne transmissible infection. **COMMENT ADDRESSED**

		1. **"***A donor with exposure to risk of acquiring a blood borne transmissible"* is *"ineligible for 6 months from the time of exposure, or for 4 months provided NAT test for HCV is negative"* As the period of ineligibility does not acknowledge the 6 months retest period for a living donor, can this be amended to *"ineligible for 6 months from the time of exposure, to collecting blood for screening for HIV, HCV, HBV, or for 4 months provided NAT test for HCV is negative"*? 2. States ineligible for 6 months from the time of exposure. If patient is a live donor, can this be the 6 months that the tissue is in quarantine prior to 180 day testing, as is the case often at present? TGA agreed to consider rewording to take into account 180day retesting of live donors. (Individual banks may provide suggested rewording in their individual submissions). Can (iii) and (iv) be given the same 'escape clause' as (v) in relation to the use of sterile single use needles? The exemption for acupuncture "unless performed using sterile single use needles" was only allowed because acupuncturists are required to be registered. This exemption could not be extended to tattoos or body piercing because the same level of control cannot be established for these activities. **COMMENT ADDRESSED**
Table 1. (s)	TGA Response TGA Response	*"A donor with exposure to particular epidemiological situations"* This is very open ended to auditor interpretation can it be 1. Deleted, or 2. only apply where alerts have been issued for an epidemiological situation that is of concern. The reference is intended to apply only to alert situations (eg. Hep A). It will be the responsibility of the Banks to be aware of alert situations and to establish deferral parameters consistent with the situation. **COMMENT ADDRESSED**

8 (11) (b)	Validation of Donor age range TGA Response	The intent of this clause is understood – i.e. to prevent tissues being collected from an obviously unsuitable age group. The age range of donors of certain tissues can be determined from historical experience, physical assessment of the tissue or user specifications. This information however cannot necessarily be "validated" (i.e. confirmed that it consistently fulfils the requirements for a specific use) other than in the absence of adverse event reports. Suggest alteration of the wording to: *The age range of donors from whom specific cells and tissues can be collected must be supported by data, industry standards or documented evidence from the scientific literature which justify appropriateness for the intended therapeutic use* In this instance, the TGA agreed that the term "validated" means to "justify" the age range chosen. For clarity, particularly given scientific literature on this topic is minimal to non-existent, the following rewording is suggested for TGA consideration: *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 (1)	Aseptic blood collection TGA Response	It is understood that, particularly in the case of nucleic acid testing, aseptic blood collection is important to minimise the risk of contamination (interfering substances) which may lead to a false positive result (not a false negative result). Therefore query the role of aseptic blood collection in minimising transmission of infectious diseases. Is this out of scope in this TGO? This query was raised to address instances where blood collected prior to autopsy was not of sufficient volume to perform both serology and NAT. In these instances, blood may be collected directly from the heart post-autopsy for serology testing. Aseptic collection of these samples cannot be proven with the risk being a false positive not a false negative result. Banks are to include and justify this comment in their individual submissions to the TGA. TGA agreed to consider including this point in the relevant tissue specific TGOs based on the justifications provided by individual Banks.

9.(2) (a)		1. What objective evidence or rational supports limiting the window period to 7 days post donation and what is the management strategy of material being collected beyond this time period i.e. what is the difference between 7 days versus 8 days post donation? Again, the blood sampling range would be better served to represent the default range applied to manufacturer if they did not wish to undertake an assessment to determine an appropriate blood sampling range for the manufacturing process (and operator), preparation and assembly of the final product and donor (recipient). 2. If blood sampling of a living donor must occur no more than 7 days prior to or 7 days after collection of the tissue, it does not allow for recollection if a sample is then identified as haemolysed or insufficient for testing purposes. The graft would have to be discarded. A longer time frame would be beneficial. TGA Response The timeframe was based on the FACT standard for purposes of harmonisation. This timeframe was acceptable to most ATBF members, but examples were provided where this might result in discard of product. Eg. blood sample provided within timeframe not suitable for testing. Ability to obtain a repeat sample within 7d logistically impossible (eg. overseas or fly-in/fly-out client). TGA Response The recommendation from the TGA was for banks to submit documentation and objective evidence to justify an exemption from this requirement. Option for product specific Orders to address this issue is provided in 9. (2) (b) and may be included in the product specific Order if sufficient justification is provided. (Order for cellular therapies may need to be developed).
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? Request TGA clarification *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.* Where the tests are TGA approved is it possible that we can now use a non-TGA licensed lab for the mandatory screening, and confirmatory micro and virological provided the lab meets

		cGMP requirements 905 and 909? cGMP 905 requires a competent laboratory unless legislation requires otherwise. We have not found this requirement in the Act. Is this TGO the only relevant legislation for this requirement? (b) is not an "or" statement. The TGA will require the test kits/methodologies to be approved by the relevant authority in the country in which the testing is performed, AND performed in a facility approved by the same authority to perform such testing. (b) the "or" should be changed to "and" given this is the requirement.
9. (9)	"Archived samples must be retested" TGA Response	1. Archived samples are not always suitable for use in new screening test protocols (eg. NAT testing). Suggested modification of reference: "Where possible, the donor's archived sample is to be retested with the new screening test protocol prior to release of the product …." 2. Can where practicable be included re the testing of archived samples in the event of a screening protocols change? "Where practicable" is the intention of this statement with discussions between the sponsor and the TGA a requirement. Suggested rewording: *Where screening protocols change during the life of the product in storage, where practicable, the donor's archived sample must be retested with the new screening test protocol prior to release of the product. The requirement to retest is to be determined by the manufacturer based on risk, in consultation with the regulator.*

10. (2) (a)	Physical assessment of a living donor at the time of donation. TGA Response	1. Further clarification sought and definition. To what extent is physical examination required for blood and autologous donors. 2. May we seek clarification around the intent and meaning of this clause? 3. As it is written, this clause requires a physical assessment of the donor to be conducted during the operation (i.e. "at the time of donation" for a live femoral head donor) so this would have to be undertaken by a medical officer or nurse in the Operating Theatre. It then follows that tissue bank staff would have to train these health professionals in assessing their patients (i.e. the assessment must be conducted by a "trained assessor"). 4. This would appear to be inappropriate imposition on the Operating Theatre staff. *A physical assessment of the donor must be conducted ….. for a living donor …….* What does this mean and what is the intent? An escape clause (*unless specified in the product specific Order*) is included, but the MS TGO does not address living donors). 5. A physical assessment of a living donor at the time of donation is difficult as the Donor Consent/Medical History is frequently conducted in a Pre Operative clinic prior to the donation day. This should read that the assessment *may be conducted* when the interview is completed. The TGA clarified that the requirement was for a physical "assessment" not a physical "examination". This term allows the banks to justify the extent of assessment required based on a risk assessment specific for the tissue. **COMMENT ADDRESSED**
10 (3) (a) i		*… the test must demonstrate that the samples tested are non-reactive.* Why must we fail for results other than non-reactive that are assessed as being clinically negative? e.g. living donors retested at 180 days, where the donation results are assessed as being clinically negative and the retest results are negative? NRL comment – if initial sample is reactive but duplicate repeat samples are negative – the result is reported as negative. Not all laboratories report in this manner, which can result in donors being failed even though they are assessed as being clinically negative.

	TGA Response	TGA suggested banks develop a matrix of risk similar to that used by cord blood banks and controls used to identify acceptable reactive samples (eg duplicate repeat samples negative; results assessed as clinical negative and confirmed as negative by 180d re-test). As currently worded, use of the word "must" does not allow for an assessment as clinically negative. This clause should be reworded to allow for such an assessment
10 (4) (b)	Donor testing TGA Response	NB NAT testing should be renamed to "NAT" or "NA Testing". These clauses requires serological and nucleic acid testing to be performed at the time of collection to exclude a window period infection however this is not consistent with 9 (2) (a) which states that blood sampling of a living donor must take place no more than 7 days prior to or 7 days after collection. TGA agreed to make this statement consistent with 9 (2) (a). **COMMENT ADDRESSED** Do (a) and (b) therefore refer only to deceased tissue donors? This is not clear as (c) then goes on to refer to living donors. (a) refers to all donors (Table 3) (b) NAT is a must for deceased, non-ocular tissue donors and living, allogeneic, plasma donors for fractionation (Table 3). Clarity of wording sought.
Table 3	Donor resting requirements TGA Response	*Syphilis and HTLV-1/2 testing at donation* As both Syphilis and HTLV-1/2 both have window periods can banks be allowed the alternative to perform these tests at 180 days where relevant? This request is particularly relevant for HTLV1/2 due to its low prevalence. TGA agreed to consider this comment (would require a change to Table 3).
11.(2)	"Human cells & tissues" TGA Response	Does the term tissue include ocular tissue. If so, this clause is more restrictive than the requirements in the ocular TGO. TGA agreed to include statement: Unless specified in the tissue specific Order, human cells and tissues from a deceased donor must be collected…. **COMMENT ADDRESSED**

11 (2) (a) and (b)	Tissue collection within 24 hours of death TGA Response	It is not clear from this clause whether collection of tissue from a deceased donor must commence within 24 hours of death or be completed within 24 hours of death. Please note that should tissue retrieval have to be 'completed' within 24 hours of death, there is genuine concern that this will severely limit the number of tissue donors in many jurisdictions. Currently, the TGA interpret this statement to mean "completed" within 24hr of death. TGA recommended that banks justify, in their individual submissions, reasons why the statement should be changed (eg. (a) and "commence within 24hr of death" and be completed within 36hr). Any change will require a validated/justified time of completion. The TGA will consider the information provided. A justified timeframe for (b) would also have to be provided (eg. commence within 15hr of asystole death and be completed within 24hr) to be consistent.
11. (3)	Transport temperature conditions Storage conditions TGA Response	1. For bone, the industry follows a maximum of 72 hours of refrigerated temperature before freezing occurs. The draft TGO does not need a 72 hour limit if freezing of bone has already occurred. This comment was not presented for discussion with the TGA. However the 2 ℃ - 8 ℃ range for refrigerated tissues was discussed. *The identification of a lower limit was queried. The TGA indicated agreement that since 2 ℃ is stated, banks will have to demonstrate that bone does not get colder despite a lower temperature having no negative impact.* Suggest the refrigerated range be changed to *less than 10 ℃*, or if this is critical for other tissue groups, then identify the storage ranges in the MS TGO. 2. See comment also 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:

Standards for human cardiovascular tissue

SUBMITTING ORGANISATION: Australasian Tissue and Biotherapeutics Forum

Reference	Issue	Comment
Microbial definition, Page 3	Inclusion of mycoplasma and Rickettsia in the definition of "microbial"	See comment for Infectious Diseases TGO above
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. <u>Suggested modification of reference:</u> 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.

	TGA Response	TGA agreed to make the transport temperature requirement consistent with the Infectious Diseases TGO (11. (3). Suggested rewording: (see (a) above). Same will apply to 7. (4) (a). **COMMENT ADDRESSED**
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. TGA Response	[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* TGA agreed to consider proposed reference modification i.e. cryopreservation must commence within 48hr of asystole…. Rather than processing and treatment with antimicrobial agents must commence within 30hr of asystole….. 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 that is removed via anti-microbial treatment.

	TGA Response	Suggested modification of reference: "(d) assessed for microbial growth. *Post anti-microbial treated samples must demonstrate* no microbial growth when…… TGA agreed to clarify that (d) refers only to post-antimicrobial treated samples (see above). **COMMENT ADDRESSED** 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 Rickettsia 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. I am 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. **COMMENT ADDRESSED** in the Infectious Diseases TGO.
7. (4) (b)	"must demonstrate no microbial growth"	As for 7. (2) (d), current, approved bioburden testing methods do not test for mycoplasma or Rickettsia both of which are specifically identified in the definition for "microbial". Definition needs to be changed. See 7. (2) (d) above. **COMMENT ADDRESSED** in the Infectious Diseases TGO.

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

Other general comments:

Standards for human musculoskeletal tissue

SUBMITTING ORGANISATION: Australasian Tissue and Biotherapeutics Forum

Reference	Issue	Comment
7 (2) (a) p4	Transport	Identify more clearly that this refers to transport of musculoskeletal tissue that has been collected, and is in transit from the collection facility to the Bone Bank. Possible rewording: *Musculoskeletal tissue that is to be transported from a collection facility to the manufacturing facility must be:*
7 (2) (b)	Tissue sampling TGA Response TGA Response	If the tissue is subjected to processing then a sample using a validated technique is taken at the **end** of processing (not the beginning) and this test is the release test. There should not be a requirement for a pre-processing test to occur unless perhaps antibiotics are used during processing. Strongly request that this requirement is removed or re-worded. TGA clarified that the requirement to sample prior to processing using a representative and validated sampling technique and test method was to ensure that both the swabbing procedure and the test method were appropriate to detect micro-organisms identified by the Bank as being of clinical significance and requiring discard of the tissue. It was agreed that given the pre-processing sample was the release test for unprocessed tissue, the sampling technique & test method had to be validated. The TGA stated that even for processed tissues, the Bank would need to know if a specified organism was present on the tissue prior to processing which is why a validated sampling technique & test method were required for processed tissues. The Banks were invited to provide objective evidence to justify why a validated pre-processing sampling technique and test method should NOT be a requirement for processed tissue. These comments are to be provided by the individual Banks for consideration by the TGA.
7 (4)	 TGA Response	Will the auditors accept each bank's determination of the *specified microorganisms of clinical significance?* This information is to be provided in the product dossier with acceptance determined by experts in the area. Banks will be audited to dossier specifications.

		It was suggested that the ATBF undertake to prepare a list of specified microorganisms of clinical significance for each tissue, including justifications, for submission to the TGA for approval. These standardised lists could then be made available to ATBF members for inclusion in their product dossier. This proposal will be discussed at the next ATBF Executive meeting and presented to ATBF members. **COMMENT ADDRESSED**
7 (6) (c)	 TGA Response	Does this clause make post irradiation sampling mandatory where the irradiation process has been validated? Is the intent of this clause to allow tissue with a positive micro test result to be released provided a sample tested post terminal bioburden reduction is negative? Assuming post irradiation sampling is not mandatory for tissue with a negative pre bioburden reduction test result, can *'These samples may be representative of pre and / or post bioburden reduced tissue'* be added to avoid auditors interpreting that testing is required both pre and post terminal bioburden reduction for these tissues. The TGA accepted this comment and agreed to reword the reference to allow the "representative samples" to include negative, pre-bioburden reduction samples, provided the terminal, bioburden reduction process (eg. irradiation) was validated. **COMMENT ADDRESSED**
8.	 TGA Response	Why must we establish storage condition if we meet the stated storage conditions? The 'must be established' should apply where implementing conditions other than those stated. TGA agreed that the requirement to establish storage conditions was irrelevant given the reference stated the conditions of storage that must be met. Deletion of the first sentence should be considered.
8. (b)	 TGA Response	Clause (b) should include a commencing date. Is this about the final packaging or life of tissue from date of retrieval? TGA clarified that the 5 year timeframe was from final packaging not from date of retrieval. Suggested clarification (b): frozen and cryopreserved at less than minus 40^{o}C for no more than 5 years from final packaging; unless... **COMMENT ADDRESSED**

	Donor Interview TGA Response	Identify in this Tissue specific TGO that the timeframe for donor interview can be 30 days prior and 30 days after bone collection. This is not the consent to collect the bone. The consent must be done prior to collection. The blood collection for serology testing is usually done on the day of collection. I am asking for the 30 day timeframe prior and after collection for the Donor Interview and physical assessment only, as this is what occurs for Live Donors now and allows the use of authorised people in the Pre Operative clinics to conduct questioning while the patient is in the hospital for the surgery workup. This comment was not specifically presented for discussion but was addressed during discussion of the Infectious Diseases TGO [8. (1) (b)]. The TGA agreed to consider this comment and provided it is changed in the Infectious Disease TGO, would not have to be included in this Tissue specific TGO.

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

Other general comments:

Standards for human ocular tissue

SUBMITTING ORGANISATION: Australasian Tissue and Biotherapeutics Forum

Reference	Issue	Comment
		No comments issued on this standard

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

Other general comments:

Standards for human skin

SUBMITTING ORGANISATION: Australasian Tissue and Biotherapeutics Forum

Reference	Issue	Comment
7 (2) and 7 (10) (b) and definition of storage	Storage TGA Response	May we seek some clarity around the intent of 7 (2) and 7 (10) (b) please. 7 (2) appear refers to storage prior to processing or banking which infers temporary "storage" during transport however storage in (10) (2) appears to refer to a period after the tissue has been banked? TGA clarified that 7 (2) were the storage and transport conditions required prior to processing whereas 7 (10) indicated the storage requirements after processing. **COMMENT ADDRESSED**
7 (10)	Requirement to establish storage conditions of processed tissue	Again, as with the musculoskeletal TGO, given the storage conditions stated are a "must be", there is no reason why the conditions "must be established". Suggest deleting the first sentence, with 7 (10) to read: *Conditions for storage of processed skin must be….*

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

Other general comments:

General requirements for the labelling of biologicals

SUBMITTING ORGANISATION: Australasian Tissue and Biotherapeutics Forum

Reference	Issue	Comment
6. (2)		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 an issue for the labels on containers used for collection of femoral heads in operating theatres as theatre staff use hospital generated labels with printing that is often <1.5mm. 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".
	TGA Response	The TGA clarified that this requirement was only for product containers. **COMMENT ADDRESSED**
		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).
	TGA Response	The TGA agreed to review this requirement.

6 (3) (c) and 6 (4)	Recording time and date of tissue collection on the container. TGA Response	1. In relation to musculoskeletal tissue collection – deceased donor: The time of musculoskeletal tissue collection would be an estimate given that the procedure can span a number of hours, therefore this is not meaningful information nor critical. This information is recorded on the documentation. 2. In relation to musculoskeletal tissue collection – living donor: For starting materials collected in theatre (surgical residues) e.g. femoral heads, why is it critical that the date and time of collection and the person collecting the FH be written on the jar in which the FH is contained or indeed the type of tissue i.e. *FH*? Femoral head collection kits are manufactured by a third party as a sterile item and there is no provision to determine the date and time of tissue collection at the time of kit manufacture. This information is recorded on the accompanying documentation, which is linked by a unique identification number to the tissue. 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. Whilst having to write femoral head on a jar containing a femoral head is a case of stating the obvious we can instruct these jars to be labelled femoral head by the third party manufacturer. The jar will then have two labels. The ATBF requested that information required to be included on the container containing the blood, cells & tissues be limited to (a) and (b) with the rest of the information (c-e) allowed to be provided on the accompanying documentation. The TGA agreed to consider this request. 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 should 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?
	TGA Response	Acceptable.
	Information …. On the label on the container and primary pack	2. As *container* is the *cover that immediately covers the goods,* this requirement will have a significant negative impact for unprocessed products. E.g. the packaging supplied to hospitals for FH collection is obtained sterile (ARTG listed) from a third party, having the third party put these details onto the container (a plastic bag or jar) is not practical (e.g. donor I.D. is unknown). This requirement would prohibit the provision of non-irradiated and whole FHs and put an end to the non-processing FH collection banks.
	TGA Response	TGA accepted comments presented and agreed to consider allowing this information to be provided on the outer or secondary packaging rather than on the container.
6 (5) (d)	Address	3. Query the need to have address on the inner tissue container. This text takes up considerable space on a label and query its relevance in the Operating Theatre at the point of surgery. Suggest leaving name but remove address from the inner tissue container label, but have address on the primary pack label. For MS tissues that are wrapped in a number of sterile layers (to facilitate unwrapping and handing across the sterile field in theatre) the relevance and wisdom of putting a label on the final sterile layer was questioned. Suggest labelling be restricted to the wrap covering the sterile layers Addressed by TGA response to #2 above.

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

Other general comments:

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

Draft Australian Code of Good Manufacturing Practice Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products

SUBMITTING ORGANISATION: **Australasian Tissue and Biotherapeutics Forum (ATBF)**

Although the code is not in the scope of this current consultation, members have raised the following issues with the current draft, as published as a reference for this consultation. The following comments were discussed with representatives of the TGA last week and have been included with this submission for consideration.

Reference	Issue	Comment
104 dot point 1	GLP TGA Response	What is the rationale of including GLP in this statement? i.e. What aspects of GLP are not covered by meeting GMP requirements? Reference to GLP to be removed from Code.
104. dot point 7	"authorised person" TGA Response	Please provide a definition for authorised person Banks are to define authorised person.
203	 TGA Response	Will the persons responsible for quality and production still be specified on the manufacturing licence? No. The TGA will be reviewing international requirements, but the intention is that the nominees for quality and production not to be specified on the manufacturing licence so that licences will not have to be re-issued when there are changes to personnel. These staff will be identified on the TGA network. Intention is for licences to be electronic.
206 vs 207 dot point 1		Should the Production nominee also have the responsibility to "approve or reject, as appropriate, material and therapeutic products"? This comment was not addressed
300	Premises TGA Response	Definition of "premises" required. For facilities located within Hospitals or Institutions, "premises" may include areas beyond the control of the licensed facility. Premises refers to those areas, which may not be in the licensed facility, but which the primary manufacturer needs to have over-site/control of for the purposes of product manufacture (eg collection areas).

300	Pyrogenic contamination Applicable code clauses in Annex 1. TGA Response	This statement indicates that clean rooms & BSCs are to be tested for pyrogenic contamination as well as microbiological and particulate contamination. How does one test for pyrogens in the environment and how can one test that a negative result is a true negative without introducing pyrogens into the test system? Does this statement only apply to the manufacture of sterile products. If not, what code clauses are applicable to products required to have a low bioburden? References to pyrogenic contamination and Annex 1 only apply to sterile products.
328 dot point 2	 TGA Response	Eskies, dry shippers, blood in motion containers are temperature monitored, but are not alarmed. TGA accepts this is the case and these items will not need to be alarmed. However, the containers and processes will have to be validated and included in the product dossiers.
Section 5	Control of material TGA Response	Do the materials covered by this section refer to ALL materials or only critical materials? Refers only to critical materials. A specific reference to critical materials would be advantageous to prevent misinterpretation of the intent.
810	1st sentence is incomplete TGA Response	Should read: Where State/Federal requirements require consent for the collection **of** tissue or cells, the consent should be obtained **at the time of collection.** To be corrected.
834	 TGA Response	How is a manufacturer to maintain and control the storage of products during their shelf life for products that are distributed and stored at other sites/banks and are no longer under their control? Should read: There should be a system in place to maintain and control the storage of products during their shelf life, including any transportation that may be required. Site/banks storing products for another Bank will be responsible for controlling storage of products at their site. Banks will be responsible for the products only to the point of release. Distribution requirements and responsibilities will be covered by GDP (Good Distribution Practice) to be developed.
General	Glossary TGA Response	Other definitions required. Is a glossary for the code in development? Yes

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