THERAPEUTIC GOODS ORDER NO. XX - *Standards for banked human cardiovascular tissue*

Reviewer: CTTWA RPH Heart Valve Bank	Date 02/02/2010

Clause Ref.	Page Ref.	Comment
4. Interpretation	Page 2	***allogeneic*** means material for administration to an individual that is obtained, or derived, from a genetically different individual; Does not include provisions for identical twin. **Recommend wording**: derived "from an individual other than the recipient"
4. Interpretation	Page 3	***banked*** means maintenance, under appropriate controlled conditions, in an inventory, of a finished product that has been determined suitable for supply; Current wording does not include cells/tissues "banked" prior to release. **Recommend wording**: "in an inventory, of any tissue/cellular in-process material through to a finished product that has been determined suitable for supply".
4. Interpretation	Page 3	***clean collection environment*** means an area or facility, such as a mortuary or equivalent facility with the following conditions: (a)air-conditioning to regulate temperature, humidity and particulates required for maintenance of tissue quality; and Mortuaries, theatres or other designated areas within Hospitals, funeral homes or hospices would not have formal systems in place for the regulation of humidity or particulates nor would they keep procedures or records of these conditions and their maintenance. **Recommend wording**: (a) environment controls required for maintenance of tissue quality (eg air-conditioning).
4. Interpretation	Page 3	***competent valve*** means a dissected valve that following manufacture, banking and thawing is capable of functioning in a defined effective manner; The manufacturer may not be in theatre to determine competency of a valve after thawing. **Clarification**: "in a defined effective manner as determined by the theatre operating team prior to implantation".
4. Interpretation	Page 4	***cryopreserved*** means suspended in a validated medium containing a suitable cryoprotectant and cooled according to a validated method that allows maintenance for long periods; Based on risk assessment, retrospective validation of medium and/or freezing method used in an established procedure would

		not be required as the risk to product safety or suitability is acceptable based on recipient outcomes. Verification of outcomes should be sufficient (Clause 835) **Recommend wording**: "suspended in a suitable solution containing a cryoprotectant and cooled according to a validated method that allows maintenance for long periods".
4. Interpretation	Page 4	***donor*** means every source, whether living or deceased, of blood, cells or tissues; Should clarify that the source is "human". **Recommend wording**: means every "human" source…
4. Interpretation		**Clarification/definition: "retrieval site".**
4. Interpretation		**Clarification/definition: "sterile"**
4. Interpretation	Page 4	***tissue*** means all constituent parts of the body formed by cells. should state exclusion of organs, hair, nails etc as these are also defined as tissue under this order. **Recommend wording** …formed by cells "excluding organs, hair, nails etc.."
7. General Requirements – (3b) footnote	Page 6	1. Include test for elevated serum beta human chorionic gonadotropin in female of child bearing age dying from unexplained intracerebral haemorrhage Donors dying in Hospital from an unexplained intracerebral haemorrhage would be investigated for a tumour or pregnancy. Similarly, cadaveric donors dying from an unexplained intracerebral haemorrhage would be subjected to autopsy. **Clarification/definition:** Requirement for inclusion, consideration of the "real risk" , and inclusion only for cardiovascular tissue and banked skin
7. General Requirements – (7)	Page7	(7) Critical materials, containers, & closures employed in the manufacture of banked tissue must be of a design, composition, quality & safety to protect the quality and safety of the biological at the various stages during manufacture and transport **Clarification/definition:** Do the requirements set out in Schedule 6 of the Infectious Diseases TGO (Substances Used in Production) cover this statement?
7. General Requirements – (8b)	Page7	(8) Banked cardiovascular tissue must have been Currently, this statement covers all CV tissue including domino donor tissue which is not subjected to antimicrobial treatment. **Recommend wording:** Banked cardiovascular tissue which will be subjected to antimicrobial treatment prior to release must have been…. (b) transported on wet ice to the laboratory…. Wet ice is too prescriptive; other transport systems meet this temperature requirement without the use of wet ice. **Recommend wording:** (b) transported under suitable temperature controlled conditions.

		(b) ….where processing and antimicrobial treatment must commence within 30 hours of death or collection from a living donor, in a critical processing zone equivalent to Grade B with a background environment equivalent to Grade C, and **Clarification/definition:** **"critical processing"** – is valve dissection considered to be "critical processing" which requires a Grade B zone or "pre-processing/dissection of the tissue from its surrounding tissue" which can be conducted in a clean environment of a lower Grade (eg. operating theatre; mortuary)? Clause (9) allows for valves which are not subjected to antimicrobial treatment to be retrieved in an operating theatre which would not be a critical processing zone equivalent to Grade B.
7. General Requirements – (8d) (i & ii)	Page7	(d). sampled [2] for bioburden determination from representative samples/specimens of tissue prior to addition of cryopreservative and/or freezing and tested to determine total viable count and exclude presence of specified microorganisms of clinical significance. Some bioburden testing systems (eg. Bactec bottles) do not provide a total viable count result – rather the results are reported as "growth/no growth" with subculturing conducted to identify organisms if growth occurs. **Recommend wording:** … tested to determine microbial growth and/or total viable count, and to exclude presence of specified microorganisms of clinical significance. (i) Samples selected in accordance with subsection 7(8)(d) must demonstrate no microbial growth when cultured. (ii) If the samples selected in accordance with subsection 7(8)(d) demonstrate growth when cultured then the cardiovascular tissue collected and manufactured in accordance with subsection 7(8)(a) to (c) must be discarded. **Clarification/definition:** Does this mean that ALL representative samples tested for bioburden (including initial samples which are not used for product release) MUST demonstrate no microbial growth when cultured OR MUST demonstrate no microbial growth of "specified microorganisms of clinical significance"? It is not uncommon for initial samples (eg. heart transport solution) to grow skin or other "normal" flora microbes. **Recommend wording:** "(i) All samples selected in accordance with subsection 7(8)(d) must demonstrate no microbial growth of specified microorganisms of clinical significance when cultured. Samples used for product release must demonstrate no microbial growth when cultured". (ii) If the samples selected in accordance with subsection 7(8)(d) demonstrate growth as indicated in (i) when cultured, then the cardiovascular tissue collected and manufactured in accordance with subsection 7(8)(a) to (c) must be discarded.

7. General Requirements – (9)	Page7	(9) If a biological that is cardiovascular tissue is banked for release without antimicrobial treatment it must have been This statement should clearly state that it applies only to tissue from live domino donors. **Recommend wording:** If a biological that is cardiovascular tissue from a domino donor is banked for release without antimicrobial treatment it must have been…
7. General Requirements – (8d) footnote	Page7	[2] Where antibiotics have been used, antibiotic neutralisation must be demonstrated prior to sampling the tissue for bioburden testing. Currently, antibiotic neutralisation is achieved prior to testing NOT prior to sampling. **Recommend wording:** "Where antibiotics have been used, antibiotic neutralisation must be demonstrated prior to microcontamination testing.
7. General Requirements – (11 & 12)	Page 8	(11) Cryopreserved cardiovascular tissue must be transported at or below minus 100° C in a validated container system. If tissue is to be transported at ~100°C (11); it is recommended that the transport time be kept to a minimum before thawing and implantation. In addition, if tissue transported at temperatures above the glass transition temperature (minus 123°C) is returned to storage, the potential for ice crystal formation and tissue cracking upon thawing for implantation should be assessed. See (12) below. (12) Cryopreserved cardiovascular tissue must be banked at or below minus 100° C for no more than 60 months. For tissue which has been rate-controlled frozen to minus ~150°C, storage at temperatures higher than the "glass transition" temperature (i.e. minus 123°C) has the potential to allow ice crystal formation which may contribute to tissue cracking when thawed thereby reducing tissue quality. To minimise this risk to tissue quality, storage temperatures should be maintained at or below minus 135°C. **Recommend wording:**: .must be banked at or below minus 135°C for no more than 60 months (5yrs).
7. General Requirements (13 & 14)	Page 8	(13) Labelling of cardiovascular tissue must comply with Schedule 1. **Recommend inclusion:** (14) Cardiovascular tissue specifications should be confirmed in the operating theatre prior to implantation. (14) A heart valve must be determined to be a competent valve after thawing in the operating theatre prior to implantation. Manufacturing staff will not always be in the theatre when the valve is thawed and therefore cannot be responsible for determining competency prior to implantation – that should be the responsibility of the surgeon.

		Recommend wording: (15) A heart valve must be confirmed as competent by the theatre operating team prior to implantation.
Schedule 1 - Labelling	Page 9	(1) At retrieval the minimum information to be included: (i) on the container of the cardiovascular starting tissue at the time of its collection: (i) unique identification number/name or date of birth linked to the donor; (ii) type of tissue; (iii) date of collection. (ii) within the accompanying documentation: (i) unique identification number/name or date of birth linked to the donor; (ii) type of tissue; (iii) name of person retrieving the tissue; (iv) date and time of collection. **Recommend inclusion:** (v) collection facility (eg. mortuary, Hospital). (2) The container and primary pack in which each unit of cardiovascular tissue is packaged for release for transplant must be labelled with, at a minimum, the following: (i) a unique identification number/alphanumeric linked to donor number; (ii) see "Product Insert" (if feasible); and **Recommend wording:** The container and primary pack in which each unit of cardiovascular tissue is packaged for release for transplant must be labelled with a unique identification number/alphanumeric linked to donor number; **(a)** The primary pack must also be labelled with, at a minimum, "see Product Insert" or (b) (i) type of tissue; (ii) tissue size in metric units for critical measurements, e.g. diameter (cm); (iii) name and address of the supplying tissue establishment; (iv) single patient use – symbol; (v) expiry date/manufacture date; (3) A package insert is to be supplied to the transplant unit with a released biological that is banked cardiovascular tissue detailing at least the following information: (a) instructions for storage, thawing and graft use including specification of which layers of packaging are acceptable to be exposed to the sterile field; (b) tissue size(s) in metric units: millimetres (mm), centimetres (cm), or grams (gm), where relevant;

		(c) biohazard label and a statement including a warning that the biological could transmit infectious agents; Is a biohazard label appropriate given it suggests something that should not be transplanted? ISBT: no requirement for biohazard label if serology negative just disclaimer. **Recommend wording:**: A statement including a warning that the biological could transmit infectious agents. (d) indication of cleared for use status; (e) return of biological policy/instructions; (f) sterilisation/bioburden reduction method (if applicable); (g) name and address of the supplying facility; the name of a contact person, a contact phone number. Email and web addresses may also be included. **General Comment:** In the interest of "global harmonisation", incorporation of ISBT128 labelling requirements is recommended.