ATBF Comment to

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

February 2010

This response only includes those items wherein the ATBF wishes to submit comments at this time.

1. Name of Order

This Order may be cited as *Therapeutic Goods Order No. XX Standards for banked human cardiovascular tissue.*

2. Commencement

This Order commences on the day after the day it is registered on the Federal Register of Legislative Instruments.

3. Introduction

This Order specifies the minimum technical requirements for the safety and quality assurance for a biological that is a banked human cardiovascular tissue.

4. Interpretation

(1) For the purpose of this Order, the term "must" means that the Order is to be complied with at all times.

(2) In this Order:

accredited hospital means a clinical institution that has been assessed and approved under a national, state, or territory law to perform surgical and clinical procedures on humans under an aseptic controlled environment;

allogeneic means material for administration to an individual that is obtained, or derived, from a genetically different individual;

Allogeneic – does not include provisions for identical twin,
Suggested rewording: derived "from an individual other than the recipient"

antiseptic has the same meaning as "antiseptic" in Part 1, Regulation 2 of the Therapeutic Goods Regulations 1990, as amended from time to time. Antiseptic means
a substance:
(a) that is recommended by its manufacturer for:
(i) dermal application; or
(ii) application to the mucous membranes of a person or an animal:
(A) to kill microorganisms; or
(B) to prevent the growth of microorganisms to a level that causes or may cause clinical infection; and
(b) that is not represented to be suitable for internal use.

aseptic technique means the measures used to prevent contamination by micro-organisms;

autologous means material that is obtained, or derived from, an

individual for administration to the same individual;

banked means maintenance, under appropriate controlled conditions, in an inventory, of a finished product that has been determined suitable for supply;

banked – current wording does not include cells/tissues "banked" prior to release..
Suggested rewording: "in an inventory, of any tissue/cellular in-process material through to a finished product that has been determined suitable for supply".

biological means

(1) Subject to subsection (3), a biological is a thing that:
  (a) either:
    (i) comprises, contains or is derived from human cells or human tissues; or
    (ii) is specified under subsection (2); and
  (b) is represented in any way to be, or that is, whether because of the way in which it is presented or for any other reason, likely to be taken to be:
    (i) for use in the treatment or prevention of a disease, ailment, defect or injury affecting persons; or
    (ii) for use in making a medical diagnosis of the condition of persons; or
    (iii) For use in influencing, inhibiting or modifying a physiological process in persons; or
    (iv) For use in testing the susceptibility of persons to a disease or ailment; or
    (v) For use in the replacement or modification of parts of the anatomy in persons.

(2) The Secretary may, by legislative instrument, specify things for the purposes of subparagraph (1)(a)(ii).

(3) the Secretary may, by legislative instrument, determine that a specified thing is not a biological for the purposes of the Act.;

cfu means colony forming units;
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

Not practical or achievable for off-site facilities (eg. mortuary & most Hospitals) which do not regulate particles nor would they have documented procedures or maintain records of these conditions.
Suggested rewording: (a) environment controls appropriate for maintenance of tissue quality (eg air-conditioning).

(b) control measures to limit access to qualified and operational persons; and
(c) sufficient space to perform the tissue recovery and avoid cross contamination; and
(d) work surfaces able to be adequately cleaned prior to commencing retrieval; and
(e) records confirming current pest control measures.;

Please provide definition for "**collection site**".

competent valve means a dissected valve that following manufacture, banking and thawing is capable of functioning in a defined effective manner;

Suggested clarification: "in a defined effective manner as determined by the theatre team prior to implantation".

container has the same meaning as in "container" in subsection 3(1) of the *Therapeutic Goods Act 1989* (the Act), as amended from time to time. Container, in relation to therapeutic goods, means the vessel, bottle, tube, ampoule, syringe, vial, sachet, strip pack, blister pack, wrapper, cover or other similar article that immediately covers the goods, but does not include an article intended for ingestion. ;

Terminology should be consistent with other standards where "primary pack/container" indicates the inner packaging in contact with the tissue and "container" indicates the packaging system or the final outer layer. Request standardisation of terminology.

critical material means all components, materials or supplies which could have a direct impact on the quality of the end product;

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 (Code – 835)
Suggested rewording: "suspended in a sterile medium containing a suitable cryoprotectant and cooled according to a validated method that allows maintenance for long periods".

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

donor means every source, whether living or deceased, of blood, cells or tissues;

Should clarify that the source is "human".
Suggested rewording: means every "human" source…

Grade B means a condition of air quality designed to have a maximum permitted number of particles/cubic meter equal to or no more than 3500 for particles of ≥ 0.5µm diameter and 0 particles that ≥ 5µm diameter when the system is at rest; when the system is in operation the maximum permitted number of particles/cubic meter is 350000 for particles of ≥ 0.5µm diameter and 2000 particles of ≥ 5µm diameter: recommended microbial limit in operation 10 cfu/cubic metre;

Grade C means a condition of air quality designed to have a maximum permitted number of particles/cubic meter equal to or no more than 350000 for particles of ≥ 0.5µm diameter and 2000 particles that ≥ 5µm diameter when the system is at rest; when the system is in operation the maximum permitted number of particles/cubic meter is 350000 for particles of ≥ 0.5µm diameter and 20000 particles of ≥ 5µm diameter: recommended microbial limit in operation 100 cfu/cubic metre;

primary pack has the same meaning as in "primary pack" in subsection 3(1) of the Act, as amended from time to time. Primary pack, in relation to therapeutic goods, means the complete pack in which the goods, or the goods and their container, are to be supplied to consumers;

See comment for "container" above. Request standardisation of terminology

Please provide definition of **"retrieval site"**.

specified microorganism means a microorganism which, if isolated from the tissue, necessitates discard of the tissue;

Please provide definition for **"sterile"**

storage means maintaining a substance, material or product under appropriate controlled conditions until supply;

suspending solution means a fluid supporting medium used to store/transport tissue to provide a moist and protective environment;

tissue means all constituent parts of the body formed by cells.

Tissue – should state exclusion of organs, hair, nails etc as these are also defined as tissue under this order.
Suggested rewording: …formed by cells "excluding organs, hair, nails etc.."

5. Application

(1) This Order applies to a biological that is a banked human cardiovascular tissue, such as

(a) a heart valve: aortic, pulmonary, mitral and tricuspid valve or any part of these valves;

(b) a vascular tissue: conduit or greater vessel graft;

(c) a peripheral vascular tissue graft;

(d) a pericardial graft,

retrieved from

(i) living human donors, including domino donors, intended for allogeneic use; or

(ii) deceased human donor(s) intended for allogeneic use.

Suggested clarification: deceased human donor(s) (eg. cadaveric, multi-organ, DCD)…

(2) This Order specifies requirements for biological and other therapeutic goods that are critical materials used in the manufacture of biologicals in subsection 5(1).

(3) This order does not apply to

(a) a biological that is not banked and is fresh viable cardiovascular tissue for organ transplantation; or

(b) human cardiovascular tissue that is processed so that its physical (disregarding shape or size) or biological characteristics are altered or is otherwise highly processed.

6. Exemptions

Biologicals exempt from this Order:

(1) banked human cardiovascular tissue that is a biological and to which an exemption from compliance with this Order has been granted by the Secretary in accordance with section 14 and 14A of the Act.

(2) cardiovascular cells and tissue biopsied for the purpose of an *in vitro* diagnosis and not for manufacture and/or reintroduction or transplant to a recipient.

7. General Requirements

(1) Each manufacturer releasing banked tissue for supply in Australia must have a formally established comprehensive quality system that is fully documented and meets the requirements of the *Therapeutic Goods Act 1989*.

(2) Banked human cardiovascular tissue must comply with Therapeutic Goods Order No. XX *Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies.*

(3) A biological must not be manufactured from cardiovascular tissue obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cardiovascular tissue to be collected, including:

(a) autoimmune disease where the disease or its treatment may have affected

the quality of the cardiovascular tissue;

(b) all forms of malignancy [1] except:
  (i) basal cell carcinoma;
  (ii) non-metastasising primary brain tumours;
  (iii) *in situ* carcinoma of the uterine cervix;

(c) previous radiotherapy/high dose radiation to the tissue to be retrieved;

(d) exposure to toxic substances (e.g. paraquat, heavy metals) affecting the tissue to be retrieved or present in toxic amounts;

(e) structural collagen diseases.

(4) The maximum age for a donor to be eligible to donate cardiovascular tissue for manufacture of a banked biological for allogeneic use is 65 years old. Donors that exceed 65 years of age may be considered for donation of cardiovascular tissue when

(a) special or particular circumstances exist, e.g. size or shape of tissue or extraordinary fitness of the donor; and

(b) a rationale and authority for release of this tissue is individually documented and appended to the donor record.

(5) Each tissue establishment must have a documented policy regarding the lower age limit for donation.

(6) A biological manufactured from cardiovascular tissue must be collected from

(a) a donor in, at minimum, a clean collection environment, using aseptic technique to minimise the risk of microbial contamination from other tissues, the environment or the operator; and

(b) a deceased donor as soon as possible after death and take place within 24 hours of death provided the body has been refrigerated (1°C to 10°C) within 15 hours of death; or

(c) a deceased donor, whose body has not been refrigerated, within 20 hours of death

2 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 haemorrhage would be subjected to autopsy.
Please clarify: Why has this requirement been included in this TGO, and why only for cardiovascular tissue and banked skin.

(7) Critical materials, media, containers and closures employed in the manufacture of banked cardiovascular tissue must be of a design, composition, quality and safety to protect the quality and safety of the biological at the various stages during manufacture and in transport.

Please clarify: Do the requirements set out in Schedule 6 of the Infectious Diseases TGO (Substances Used in Production) cover this statement?

(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.
Suggested clarification: Banked cardiovascular tissue which will be subjected to antimicrobial treatment prior to release must have been….

(a) collected in an operating theatre in an accredited hospital or a mortuary or equivalent facility, and
(b) transported on wet ice

Wet ice is too prescriptive; blood in motion eskies meet this temperature requirement without the use of wet ice.
Suggested rewording: (b) transported under suitable temperature controlled conditions.

to the laboratory 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

Please define "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? (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.

(c) exposed, between dissection of the tissue from its surrounding tissue and the time of its freezing, to conditions of antimicrobial treatment at:
    (i) 34°C to 39°C for 6 to 12 hours; or
    (ii) 2°C to 8°C for 18 to 24 hours; and
(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.
    (i) Samples selected in accordance with subsection 7(8)(d) must demonstrate no microbial growth when cultured.

Please clarify: Does this mean that ALL representative samples tested for bioburden (including initial samples used for internal QC only; not 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.
Suggested rewording: "(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 when cultured then the cardiovascular tissue collected and manufactured in accordance with subsection 7(8)(a) to (c) must be discarded.

As above (i).

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.
Suggested rewording: "Where antibiotics have been used, antibiotic neutralisation must be demonstrated prior to bioburden testing.

(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 domino donors.
Suggested wording: If a biological that is cardiovascular tissue is banked for release without antimicrobial treatment (eg. tissue from a domino donor) it must have been…

(a) collected, manufactured, sampled for bioburden, packaged in an operating theatre and maintained on wet ice during transport to the tissue establishment and frozen within 30 hours of death or collection from a living donor and samples tested for bioburden must demonstrate no microbial growth; or

(b) if the samples tested for bioburden demonstrate microbial growth, then the cardiovascular tissue collected and manufactured in accordance with subsection 7(9)(a) must be

(i) discarded; or

(ii) undergo further manufacture including antimicrobial treatment in accordance with subsection 7(8).

(10) Cardiovascular tissue must be sealed within a sterile container and at least double packaged and sealed so as to

(a) prevent ingress/egress of material other than gas sterilant (if applicable);
(b) ensure breach of integrity will be evident

(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^{o}C, storage at temperatures higher than the "glass transition" temperature (i.e. minus 123^{o}C) has the potential to allow ice crystal formation which may contribute to tissue cracking upon thawing thereby reducing tissue quality. To minimise this risk to tissue quality, the Banks suggest that storage temperatures be maintained at or below minus 135^{o}C.
Suggested rewording: .. must be banked at or below minus 135^{o}C for no more than 60 months (5yrs).

(13) Labelling of cardiovascular tissue must comply with Schedule 1.

Suggested 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.

Suggested rewording: (15) A heart valve must be confirmed as competent by the theatre operating team prior to implantation.

Schedule 1 Labelling

Human cardiovascular tissue collected from a donor as starting material for a banked biological must be labelled and traceable to that donor through each step of manufacture and the released biological.

(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.

Suggested 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

(iii)

Suggested rewording: 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;

Please clarify the relevance of the 'manufacture date.

(vi) storage conditions;
(vii) sterile (if applicable);
(viii) antibiotics/additives (if applicable);
(ix) suspending solution; or

(c) For small packages or where packing/conditions of storage cannot support all the information on the unit package label, the information required by Schedule 1(2)(b) must be provided with the product, as a Product Insert, at dispatch.

(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.
Suggested rewording: 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.

Please clarify: Would it be acceptable for the information required on the Product Insert and the Package Insert to be combined into one Insert which is provided with the product at dispatch??