



Australian Government
Department of Health and Ageing

THERAPEUTIC GOODS ACT 1989
Section 10

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

I, Rohan Hammett, delegate of the Minister for Health and Ageing for the purposes of section 10 of the *Therapeutic Goods Act 1989* and acting under that section, having consulted with the Therapeutic Goods Committee in accordance with subsection 10(4) of that Act, HEREBY:

DETERMINE that the matters specified in this Order shall constitute a standard for human cardiovascular tissue.

Dated this day of 2011

Rohan Hammett
Delegate of the Minister for Health and Ageing

1. Name of Order

This Order may be cited as *Therapeutic Goods Order No. XX Standards for 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. Purpose of the Order

The purpose of this Order is to specify the minimum technical requirements for the safety and quality assurance for a biological that is a human cardiovascular tissue.

4. Interpretation

(1) For the purpose of this Order, the presence of the term “must” in relation to a particular requirement in a provision set out in this Order means that the requirement is to be complied with at all times.

(2) In this Order:

allogeneic use means the use of a biological that is removed from one person and applied to another.

antimicrobial means the ability of a substance to kill or inhibit growth of microorganisms.

asystole means the reference time for cardiac death. A documented pronounced time of death is used as asystole when life-saving procedures have been attempted and there were signs of, or documentation of, recent life (e.g. agonal respirations, pulseless electrical activity). If death was not witnessed, ‘asystole’ must be determined by the last time known alive. Asystole will be ‘cross clamp time’ if the tissue donor was also a solid organ donor.

bioburden has the same meaning as in “bioburden” in subsection 3(1) of the *Therapeutic Goods Act 1989*, as amended from time to time.

biological has the same meaning as “biological” in subsection 3(1) of the Act as amended from time to time.

Note that “biological” under the Act 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;

cell(s) means individual cells or a collection of cells when not bound by any form of connective tissue.

collection means the process of removing a biological or a source of a biological from a donor.

competent valve means a dissected valve that is capable of functioning in a defined effective manner.

container has the same meaning as in “container” in subsection 3(1) of the *Therapeutic Goods Act 1989*, as amended from time to time.

critical material means all components, materials or supplies which could have a direct impact on the quality, safety and function 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.

domino donor means a person who by receiving an organ transplant donates the removed organ or tissue for allogeneic use.

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

manufacture has the same meaning as in ‘manufacture’ in subsection 3(1) of the *Therapeutic Goods Act 1989*, as amended from time to time.

microbial means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia but does not include viruses or prions.

minimal manipulation means a process involving any of the following actions:

- (a) centrifugation;
- (b) trimming, cutting or milling;
- (c) flushing or washing;
- (d) refrigeration;
- (e) freezing;
- (f) any similar thing to a thing mentioned in paragraph (a), (b), (c), (d) or (e).

processing means any operation involved in the preparation, manipulation, preservation for storage and packaging of a biological.

recipient means a person who receives blood, blood components, cells or tissues by infusion or implantation.

storage means the process of maintaining a substance, material or product under appropriate controlled conditions.

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

transport means transfer within or between premises of a substance, material or product under appropriate controlled conditions.

5. Application of this Order

- (1) The requirements of this Order apply to a biological that is a human cardiovascular tissue collected from
 - (a) living human donors, including domino donors, intended for allogeneic use; or
 - (b) deceased human donors intended for allogeneic use, including
 - (i) a heart valve: aortic, pulmonary, mitral and tricuspid valve or any part of these valves;
 - (ii) a vascular tissue: conduit or greater vessel graft;
 - (iii) a peripheral vascular tissue graft;
 - (iv) a pericardial graft.
- (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).

6. Exemptions

- (1) Biologicals exempt from the requirements set out under this Order are the following:
 - (a) human cardiovascular tissue that is a biological and to which an exemption from compliance with this Order in relation to the supply of the human cardiovascular tissue has been granted by the Secretary in accordance with section 14 and 14A of the Act; and
 - (b) 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; and
 - (c) human cardiovascular tissue that is processed beyond minimal manipulation.

7. General Requirements

- (1) Critical materials employed in the collection and manufacture of cardiovascular tissue must be of a design, composition, quality and safety to protect the quality and safety of the cardiovascular tissue.
- (2) Cardiovascular tissue that is subjected to a bioburden reduction process must be:
 - (a) transported at 2°C to 8°C to the manufacturing facility where processing and treatment with antimicrobial agents must commence:
 - (i) within 30 hours of asystole; or
 - (ii) within 30 hours of collection from a living donor; and

- (b) 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
- (c) sampled for bioburden determination from representative samples of tissue prior to addition of cryopreservative and/or freezing and tested to exclude presence of microorganisms.
- (d) assessed for microbial growth. Samples must demonstrate no microbial growth when cultured. If the samples selected demonstrate growth when cultured, the product must be discarded.
- (3) Where antimicrobial agents have been used in the bioburden reduction process on the cardiovascular tissue, validation of bioburden determination must include neutralisation of the antimicrobial agents present in the sample.
- (4) Cardiovascular tissue that will not be subjected to a bioburden reduction process must be:
 - (a) collected, manufactured, sampled for bioburden determination, packaged in an operating theatre and maintained at 2°C to 8°C during transport to the manufacturing facility and frozen
 - (i) within 30 hours of death; or
 - (ii) within 30 hours of collection from a living donor; and
 - (b) sampled for bioburden determination and when tested must demonstrate no microbial growth.
- (5) Further to the requirement under paragraph 7(4)(b), if the samples for bioburden determination demonstrate microbial growth, then the cardiovascular tissue must be:
 - (a) discarded; or
 - (b) undergo further manufacture including treatment with antimicrobial agents in accordance with subsection 7(2).
- (6) A heart valve must be determined to be a competent valve prior to freezing.
- (7) Cardiovascular tissue must be sealed within a sterile container and at least double packaged so as to
 - (a) prevent ingress/egress of material other than gas sterilant (if applicable);
 - (b) ensure breach of integrity will be evident
- (8) If terminal sterilisation is performed on the cardiovascular tissue, the manufacturing process must comply with the requirements of Annex 1 of the Code of GMP for Sterile Medicinal Products, available on the TGA website <http://www.tga.gov.au/industry/manuf-pics-gmp-medicines.htm#technical>
- (9) Storage conditions for cryopreserved cardiovascular tissue must be at or below minus 100° C for no more than 5 years.
- (10) Cryopreserved cardiovascular tissue must be transported at or below minus 100°C in a validated container system.