Australian Government

Department of Health and Ageing

THERAPEUTIC GOODS ACT 1989
Section 10

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

I, Rohan Hammett, delegate of the Minister for Health and Ageing for the purposes of the exercise of the Minister's powers under 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 banked musculoskeletal tissue.

Dated this ….. day of ……. 2010

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 banked human musculoskeletal 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 musculoskeletal tissue.

4. Interpretation

(1) For the purpose of this Order, the term "must" means that the Standard 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;

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;

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
(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.;

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.;

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;

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

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;

Grade D means a condition of air quality designed to have a maximum permitted number of particles/cubic meter equal to or no more than 3500000 for particles of ≥ 0.5µm diameter and 20000 particles that ≥ 5µm diameter when the system is at rest; when the system is in operation the maximum permitted number of particles/cubic meter are not defined: recommended microbial limit in operation 200 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.;

SAL means Sterility Assurance Level;

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

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

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

5. Application

(1) This Order applies to a banked biological that is a human musculoskeletal tissue, such as muscle, ligament, bone or cartilage, retrieved from

(a) living human donor(s) intended for autologous or allogeneic use; or

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

(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) human musculoskeletal tissue that is processed so that its physical (disregarding shape or size) or biological characteristics are altered; or

(b) freeze-dried and demineralised musculoskeletal tissue; or

(c) chondrocytes or other musculoskeletal cell or tissue types that are cultured or otherwise highly manipulated.

6. Exemptions

Biologicals exempt from this Order:

(1) banked human musculoskeletal 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) Musculoskeletal 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 musculoskeletal 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 musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including:

(a) autoimmune diseases where the disease or its treatment may have affected the quality of the musculoskeletal tissue;

(b) all forms of malignancy except:

(i) basal cell carcinoma;
(ii) non-metastasising primary brain tumours;
(iii) *in situ* carcinoma of the uterine cervix; and
(iv) for surgical bone donors, squamous cell carcinoma of the skin which has been fully excised and not recurred for the last 5 years.

(c) metabolic bone disease;

(d) Paget's disease;

(e) osteomyelitis (except 2 years after being declared cured)

(f) history of chronic haemodialysis;

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

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

(4) Donor age requirements for musculoskeletal tissue:

(a) The manufacturer must have a documented policy to specify age selection criteria for donors from whom musculoskeletal tissue can be retrieved.

(b) Deceased donors of osteochondral grafts and soft musculoskeletal tissue grafts must be between the ages of 15 to 55 years.

(5) A biological manufactured from musculoskeletal 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 and no more than 24 hours after death, provided the body has been refrigerated (1°C to 10°C) within 12 hours of death; or

(c) a deceased donor, who has not been refrigerated, within 15 hours of death.

(6) A musculoskeletal tissue that is to be transported to the manufacturing facility must be

(a) sampled using a representative and validated sampling technique to collect surface micro-organisms for bioburden determination, prior to packaging;

(b) packaged using aseptic technique with at least one moisture impermeable barrier and maintained at or below 10°C prior to and during transportation.

(7) Critical materials, containers and closures employed in the manufacture of banked musculoskeletal 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 transport.

(8) Final formulations and concentrations of active substances, e.g. antibiotics[1], applied in the preparation of the biological must be documented and justified.

(9) A biological that is non-irradiated (or any similar bioburden reduction process) banked musculoskeletal tissue must demonstrate no microbial growth when the representative samples or specimens for bioburden from tissues that were collected and processed in accordance with subsection 7(9)(a) and (b) or when additionally processed and sampled in accordance with subsection 7(9)(c), are tested.

(a) collected, processed and sampled for bioburden in a operating theatre of an accredited hospital; and

(b) maintained at 1°C to 10°C for less than 72 hours prior to freezing;

(c) thawed under specified conditions, and further processed in an environment that is at minimum equivalent to Grade B with a background environment which is equivalent to Grade C using aseptic technique, sampled for bioburden using a validated method and refrozen within 24 hours.

(10) A biological that is irradiated (or subject to a similar bioburden reduction process) banked musculoskeletal tissue must be collected in an operating theatre or mortuary and manufactured so that

(a) representative musculoskeletal tissue samples, referred to in subsection 7(10)(b) and (c), sampled prior to a bioburden reduction process, must be tested for bioburden to determine the total viable count to exclude tissue contaminated with specified microorganisms of clinical significance. Specifications for the tissue must include microorganisms that will result in rejection of the tissue.

(b) the tissue must be sampled for bioburden, packaged and maintained at 1°C to 10°C for less than 72 hours prior to processing. Processing and re-sampling for bioburden must be undertaken in an environment that is at minimum equivalent to Grade C with a background environment which is equivalent to Grade D, followed by freezing; or

[1] Where antimicrobial substances are used in the processing, neutralisation of the antimicrobial substance must be demonstrated prior to sampling tissue for bioburden testing.

(c) the tissue must be sampled for bioburden, packaged, maintained on wet ice at 1°C to 10°C for less than 72 hours prior to freezing, and subsequently thawed, processed and re-sampled for bioburden in an environment that is at minimum equivalent to Grade C with a background environment which is equivalent to Grade D and refrozen within 24 hours; and

(d) representative samples of musculoskeletal tissue subject to a terminal bioburden reduction process such as irradiation must demonstrate no microbial growth when tested;

(e) if terminal sterilisation is performed, a Sterility Assurance Level (SAL) of at least 10^{-6} must be achieved.

(11) Musculoskeletal 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 for a gas sterilant (if applicable);

(b) ensure any breach of integrity will be evident.

(12) Storage conditions for each type of musculoskeletal tissue must be established based on validation data or scientific literature. Conditions for storage of musculoskeletal tissues include:

(a) temporary storage at minus 20°C to minus 40°C for no more than 6 months.

(b) frozen and cryopreserved at below minus 40°C for no more than 60 months.

(13) Frozen or cryopreserved musculoskeletal tissue must be transported at a temperature below minus 20°C.

(14) Labelling of musculoskeletal tissue must comply with Schedule 1.

Schedule 1 Labelling

Human musculoskeletal tissue collected from a donor for a banked biological must be labelled and traceable to that donor through each step of manufacture (1) and the released biological (2).

(1) At retrieval the minimum information to be included:

(a) on the outer packaging of the musculoskeletal tissue
- (i) unique identification number/name linked to the donor;
- (ii) type of tissue;
- (iii) date of collection

(b) within the accompanying documentation:
- (i) unique identification number/name linked to the donor;
- (ii) type of tissue;
- (iii) identification of the retrieval site;
- (iv) name of person retrieving the tissue;
- (v) date and time of collection

(2) At release the final product label on the container and primary pack must include the following minimum information:

(a) unique identifying number/alphanumeric linked to donor number;

(b) type of tissue;

(c) tissue size in metric units for critical measurements e.g. struts, quantity of milled bone;

(d) name and address of the supplying tissue establishment;

(e) single patient use – symbol;

(f) instruction for opening to sterile field;

(g) expiry date;

(h) storage conditions;

(i) sterile (if applicable);

(j) antibiotics, if applicable;

(k) autologous use only, if applicable;

(l) "See package insert"

(3) Additional information must be supplied on issue with the released musculoskeletal tissue:

(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), volumetric (cc), where relevant;

(c) biohazard label and a statement including a warning that the biological could transmit infectious agents;

(d) indication of cleared for use status;

(e) return instructions where relevant;

(f) sterilisation method or 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.