ATBF Comment to

THERAPEUTIC GOODS ORDER NO. XX - Standards for banked human skin

February 2010

1. Name of Order

This Order may be cited as Therapeutic Goods Order No. XX Standards for banked human skin.

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 minimum technical requirements for the safety and quality assurance for a biological that is banked human skin.

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:

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

Suggest addition of "other than the recipient" for clarification.

aseptic technique means the measures used to prevent contamination by microorganisms;

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;

Should be defined in consistent form to preceding text – i.e. as in General Standards

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.;

Should be changed to reflect already suggested changes as in General Standards

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.;

Should be changed to reflect already suggested changes as in General Standards

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

Should read - "means every human source,

glycerolised means treated with and stored in the presence of glycerol;

Should read – "means treated with and stored in the presence of glycerol in a concentration > 75%."

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.;

Primary pack – suggested to use terminology consistent with other international standards: should indicate the first packaging that is in contact with the products.

SAL means Sterility Assurance Level;

skin is the outer integument or covering of the body, consisting of the dermis and the epidermis and resting upon the subcutaneous tissues;

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.

Tissue – suggested: "means all constituent parts of the body formed by cells and extracellular matrix***"***

5. Application

(1) This Order applies to banked biologicals that are human skin grafts collected as skin from

Suggested to remove that are human skin grafts

(a) living human donors and intended for autologous or allogeneic use; or

(b) deceased human donors and intended for allogeneic use;

and are

(i) unprocessed; or

(ii) cryopreserved; or

(iii) glycerolised.

(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 skin that is processed so that its physical (disregarding shape or size) or biological characteristics are altered or is otherwise highly manipulated; or

(b) a human skin graft collected from one surface on a person and grafted to another surface on the same person during a single surgical procedure, as this is considered to be within the clinical supervision of the surgeon.

6. Exemptions

Biologicals exempt from this Order:

(1) banked human skin 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) skin 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 skin 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 skin obtained from a donor who is known to have a disease or condition compromising the quality and safety of the skin to be collected, including:

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

(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) Acceptability criteria for minimum and maximum age of a donor, the body surface area and quality of the skin to be donated to produce a biological must be defined and documented by each manufacturer of skin.

[1] Include test for elevated serum beta human chorionic gonadotropin in female of child bearing age dying from an unexplained intracerebral haemorrhage

Note 1: this seems to be an illogical demand that would require testing levels of human chorionic gonadotrophin in 95% if not more of all female donors (living and cadaveric!!!) – suggested a better risk benefit analysis to maintain demand and consider the issues with results from testing post mortem blood samples and existence of validated platforms

(5) Banked human skin must be collected from

(a) a donor in, at minimum, a clean collection environment such as a mortuary or equivalent facility, using aseptic technique;

Definition of environment should be changed to reflect the same conditions for tissue collection in General Standards!

(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 12 hours of death;

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

should read: "… within 12 hours of death"

(6) The collected tissue must be sampled for bioburden determination, using a validated sampling technique, prior to being packaged within at least one moisture impermeable barrier using aseptic technique, maintained and transported at 1°C to 10°C. The maximum time that the skin remains at 1°C to 10°C before either processing or freezing must be no more than 72 hours.

Should read: "The collected tissue must be sampled for microbiological assessment, using…."

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

(8) If skin, collected according to subsection 7(5) and sampled for bioburden according to subsection 7(6), is to be subjected to further processing, such as trimming, examining for integrity, final sampling for bioburden and packaging prior to freezing, the critical processing zone must be equivalent to at least Grade B with surrounds Grade C.

(9) Each tissue establishment must define and document its microbiological contamination reduction policy for skin and specify those microorganisms that, if detected on the sampled[2] tissue specimens when tested for bioburden, will result in rejection of the skin for freezing or cryopreservation. Microbial growth detected when the sample/specimens are cultured must be reported. If sterilisation is performed it must be validated to achieve a SAL of at least 10^{-6}.

(10) A biological that is a skin graft 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); and

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

(11) A biological that is a skin graft must be banked at

(a) minus 40°C or colder for a maximum period 5 years when cryopreserved. These skin grafts must be transported in a validated container system at no more than minus 40°C; or

(b) 1°C to 10°C for no more than 14 days when refrigerated. This temperature must be maintained during transport; or

(c) 1°C to 10°C for no more than 2 years if banked in greater than 75% glycerol. This temperature must be maintained during transport.

(12) Labelling of skin and skin grafts must comply with Schedule 1.

---

[2] Where antibiotics have been used, antibiotic neutralisation must be demonstrated prior to sampling the tissue for bioburden testing.

Suggested modification of note 2:"Where applicable, the sampling methodology should include neutralization of the disinfecting agents"

Schedule 1 Labelling

Human skin 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:

(a) on the container of the skin at the time of its collection:

(i) unique identification number linked to the donor;
(ii) type of tissue;
(iii) date of collection.

(b) within the accompanying documentation:

(i) unique identification number linked to the donor;
(ii) type of tissue;
(iii) identification of the collection site
(iv) name of person collecting the tissue;
(v) date and time of collection.

(2) The container and primary pack in which each unit of skin is packaged for release for transplant must be labelled with, at minimum, the following:

Labels should not be required to be on the primary pack – i.e. sterile – as sterile labels are difficult to be prepared. Option could be offered for labels to be placed on a secondary layer when this still protected by a third and outermost pack.

(a)

(i) unique identification number linked to donor number;
(ii) see “Product Insert” (if feasible); and

(b)

(i) type of tissue;
(ii) tissue size in metric units for critical measurements, e.g. cm^2;

(iii) name and address of the supplying tissue establishment;
(iv) single patient use – symbol;
(v) expiry date/manufacture date;

suggested to exclude “manufacture date”

(vi) storage conditions;
(vii) sterile (if applicable);

Please define “Sterile”

(viii) antibiotics/additives (if applicable);
(ix) autologous use only (if applicable);
(x) see “Package Insert”; or

(c) For small packaging 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 skin 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) relevant to the dimensions;

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

"Biohazard" label may be not appropriate (although the statement may be) as such label would indicate something that should not be transplanted, providing a misleading message.

(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 suppling facility; the name of a contact person, a contact phone number. Email and web addresses may also be included.