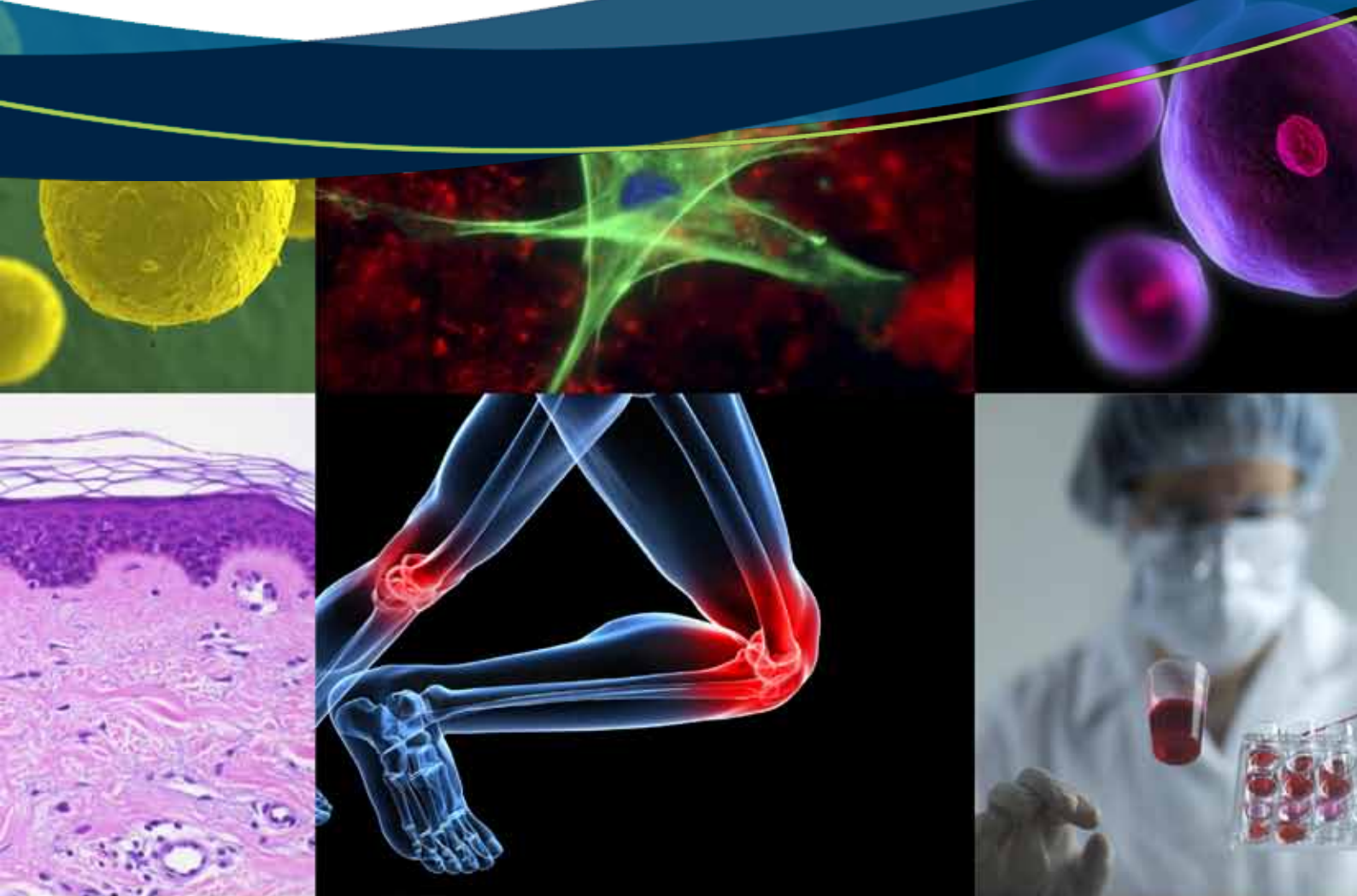
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Appendix 6 – Guidance on TGO 83 (Standards for human musculoskeletal tissue)

Version 1.0, June 2011

TGA Health Safety Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating biologicals, medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of biologicals, medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with biologicals, medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a biological, medicine or medical device, please see the information on the TGA website.

Version history

Version	Description of change	Author	Effective date
V1.0	Original	BSS	June 2011

Contents

Introduction

Therapeutic goods order (TGO) 83 (Standards for human musculoskeletal tissue) applies to human musculoskeletal tissue, such as muscle, ligament, bone or cartilage collected from living human donor for autologous or allogeneic use, or from deceased human donors for allogeneic use only. TGO 83 (Standards for human musculoskeletal tissue) does not apply to human musculoskeletal cells and tissue biopsied for the purpose of an *in vitro* diagnosis only and human musculoskeletal tissue processed beyond minimal manipulation. If you are unsure if the musculoskeletal order applies to a specific biological, the TGA should be contacted for clarification prior to the preparation of a dossier.

This guidance comprises notes on the interpretation of the various requirements of TGO 83, and a table (Table 1) aligning the requirements of the TGO with the dossier preparation guidance. Table 1 is designed to provide both guidance on where information may be placed in the dossier and evidence that the various requirements of the TGO have been addressed. The requirement in question should be discussed in the indicated sections of the Dossier, and that information should be summarized as evidence the requirement has been met. Please note that the TGA will evaluate the entire dossier, so only a brief summary is required. The completed table should be included with the submitted dossier as Appendix 1.

Commencement and updates

TGO 83 commences on the 31st May 2012. This will allow for a transition period for manufacturers to achieve compliance with the standards. All human musculoskeletal tissue collected prior to 31st May 2012 will be exempt from this order.

TGO 83 will be subject to review on a regular basis, or as changes in technology, policy, or best practice requires. Ongoing stakeholder feedback in relation to any changes in practices or evolving technologies which may impact upon the Orders is desirable.

TGO 83 Section 7 guidance

Subsection 7(1)

The definition of 'critical materials' is provided in ARGB Appendix 14 – Glossary.

In order to minimise extrinsic contamination of the starting material tissue, any container or packaging material in direct contact with the tissue material should be sterile, and collection/processing staff should wear appropriate clothing.

Subsection 7(2)

Collection should commence as soon as possible after asystole with the maximum allowable time for completion of the collection being 36 hours. In addition, the time post-asystole in which the collection of tissue must commence is dependent on the temperature the body has been stored at: if it has been refrigerated below 10°C within 12 hours of asystole then collection must commence within 24 hours, otherwise collection must commence within 15 hours. This takes precedent over subsection 8(2) of Appendix 4, Annex 1.

Subsection 7(3)

This clause takes precedence over the recommendations of ARGB Appendix 4 Annex 1, to allow for pre-operative physical assessment of musculoskeletal donors to be performed up to 30 days prior to donation. Physical assessment, as defined in the order, refers to clinical inspection to determine suitability of the person to be a donor and does not mandate full physical examination. Inspection can be limited, provided it is appropriate to the tissue to be collected, and should be informed by a risk assessment with justification in the dossier of information. Physical assessment must be performed by a trained assessor affiliated with the tissue bank, but there is no requirement that this is done only by a medical practitioner.

Subsection 7(4)

This clause details the packaging requirements for collected musculoskeletal tissue. In order to minimise extrinsic contamination of the starting material tissue, any container or packaging material in direct contact with the tissue material should be sterile, and collection /processing staff should wear appropriate clothing.

Subsection 7(5)

This subsection applies to musculoskeletal tissue that is not to be processed after collection. In this case, the tissue must be sampled for bioburden at the time of collection and subsequently shown to be free of microbial growth. Both the sampling method and the bioburden test method must be validated, the details of which should be included in the relevant section of the dossier. The flowchart in Annex 1 (Figure 1) shows how the requirements identified in this subsection (and subsection 7(6) to 7(8)) establish the suitability of the collected musculoskeletal tissue for therapeutic use.

Unless the entire tissue product is subject to bioburden testing, it is necessary to validate that a sample or portion is representative of the entire tissue. During sampling validation studies it is necessary to sample from a variety of areas across the tissue and to compare the bioburden test

results. Routine bioburden samples should subsequently be taken from any area which represents the 'worst case' in terms of bioburden.

The microbial contamination sections of the pharmacopoeial default standards*, as well as ISO 11737-1**, and ISO 14160*** provide useful guidance on suitable bioburden test methods and their validation to demonstrate neutralisation/inactivation of antimicrobial substances. ISO 11737-1 specifically describes steps to establish the recovery efficiency and correction factor(s) to be applied when testing bioburden on or within solid and semi-solid starting materials (e.g. bone, tendon, etc) and Annex A.5.3 of ISO 14160 provides guidance on performing bioburden tests on animal tissues.

* British Pharmacopoiea, European Pharmacopoeia, United States Pharmacopeia (also see TGO 77 for medicines for section references)

** ISO 11737-1 Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products

***ISO 14160 Sterilization of health care products –Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives – Requirements for characterization, development, validation and routine control of a sterilization process for medical devices

Subsection 7(6)

There are two possible outcomes for musculoskeletal tissue, collected and sampled as per subsection 7(5), which demonstrates microbial growth. Either the tissue must be deemed unsuitable for therapeutic use, or provided that specified microbes are excluded (see subsection 7(9)) the tissue can be subject to further processing to render the tissue free from microbial contamination (as detailed in subsection 7(7)).

Subsection 7(7)

Tissue should be sampled at the time of collection for bioburden, and when contaminated with specified microorganisms (see subsection 7(9)) the tissue excluded from therapeutic use. If not contaminated with specified microorganisms, the tissue should either (a) be sampled post-bioburden reduction and demonstrate no microbial growth, or (b) be subjected to a bioburden reduction process that has been validated to render the tissue free from microbial growth. See guidance on validation of bioburden sampling method and validation of bioburden test method proposed under subsection 7(5) above.

When a bioburden reduction treatment renders a tissue 'free from microbial growth', then that tissue is not regarded as sterile unless the process was validated as a sterilisation process and the product passes a pharmacopoeial sterility test.

Pharmacopoieal and ISO standards for bioburden test methods include a requirement to validate the methods. This involves challenging the method used for the material or product with low numbers (< 100 cfu) of reference challenge microorganisms and recovering these organisms within the shortest test incubation time. Given that antimicrobial agents could be present in the starting materials and/or the end product, it is necessary to attempt to neutralise these agents to optimise the recovery of the challenge microorganisms, and ultimately, any product contaminants. Pharmacopoeial and ISO methods mandate this step under "suitability of test method" or "method validation". Antimicrobial activity can often be removed by filtration, dilution and/or chemical inactivation by use of a suitable neutralising agent. Tissue banks should attempt to identify antimicrobial agents used to treat donors and those agents used during processing to assist them to identify suitable neutralising agents. If, after exhaustive attempts, antimicrobial properties cannot be neutralised, then pharmacopoeias permit the product to be tested under the set of conditions

established as optimal for recovery. This approach must be justified and details provided for assessment and/or audit by the TGA.

Subsection 7(8)

If any musculoskeletal tissue that demonstrates growth of specified microorganisms post-collection then this tissue must not be used for therapeutic use. In addition, where any microbial growth is detected post-processing the tissue must not be used for therapeutic use.

Subsection 7(9)

The manufacturer should use a risk assessment process to develop the list of specified microorganisms of clinical significance for ocular tissue, which if isolated require rejection of the tissue for clinical use. This process should include consideration of the category of tissue, the method of processing, and the nature and type of microorganisms which might be present. The list of microorganisms should be detailed in the appropriate dossier section.

In addition, the validation of any terminal sterilization process used must also be detailed in the relevant dossier section.

Subsection 7(10)

The packaging should be compatible with the method of sterilisation e.g. the packaging should allow the ingress of ethylene oxide sterilant gas and allow for desorption of the gas during aeration. If this is the case, then the container is not sterile to begin with but it is sterilised along with the tissue, which is permissible. The use of new technology (e.g. critical CO_2) would be considered on a case-by-case basis based on evidence of validation to demonstrate an SAL of 10^{-6} for a terminal sterilisation process. (Guidance on other sterilisation methods validation not covered by a specific ISO standard can be found in ISO 14937*).

*ISO 14937 Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices

If the tissue is aseptically manufactured, then it should be transferred into a sterile container and validated as an aseptic process according to the ISO 13408 (Aseptic processing of health care products).

“Other than for a gas sterilant if applicable” includes air and/or incubation gases.

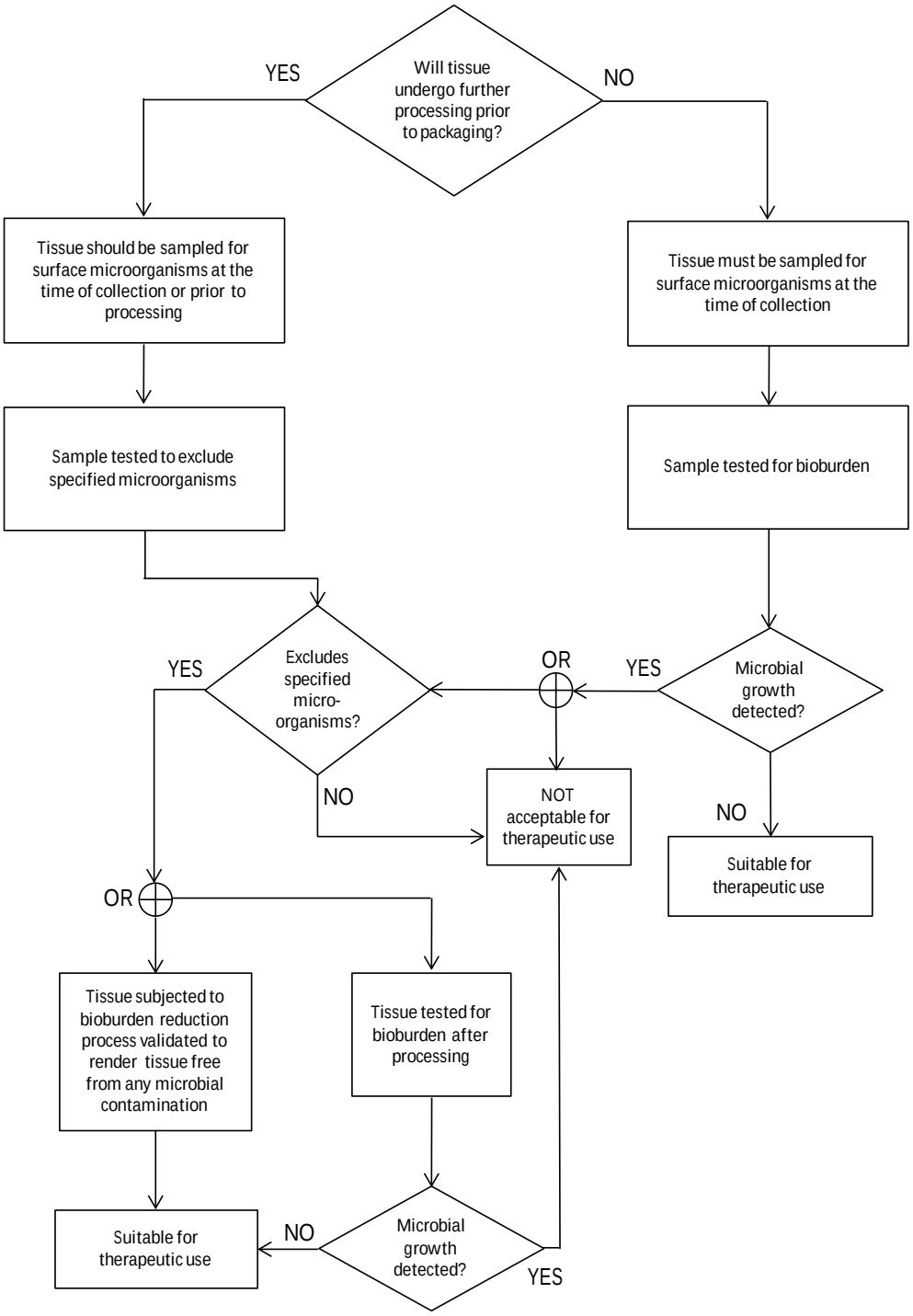
Subsection 7(11)

The specific post-processing storage and transport conditions detailed in this clause take precedence over those detailed in subsection 7(4) of Appendix 4, Annex 1. If alternative storage conditions are specified by the manufacturer then validation will be required.

Please note that in addition, all relevant requirements of TGO 87 (Labelling) apply to Musculoskeletal tissue. If further clarification is required then please contact the TGA.

Annex 1 Flow chart

Figure 1 Flow chart summarizing decision points and subsequent outcomes of TGO 83 Subsection 7(5) to 7(8)



Location of requirements in dossier

Table 1 Summary table comparing TGO 83 requirements with the dossier sections in which it is suggested they are addressed

Please submit the completed table as Appendix 1 to the dossier.

Subsection	Summary of TGO 83 requirement	Relevant dossier section/s*	Summary of how requirement is met**	Reference documents (SOPs etc)
7(1)	Critical materials employed in the collection and manufacture of musculoskeletal tissue	4.1.4 (Collection) 4.2.3 (Control of critical materials)		
7(2)	Collection of musculoskeletal tissue from a deceased donor	4.1.4 (Collection)		
7(3)	Physical assessment of the donor	4.1.3 (Donor evaluation and management)		
7(4)	Collected musculoskeletal tissue packaging requirements	4.1.4 (Collection)		
7(5)	Unprocessed musculoskeletal tissue bioburden testing	4.1.4 (Collection) 4.2.4 (Critical steps and intermediates)		
7(6)	Outcome of the detection of microbial contamination in unprocessed musculoskeletal tissue	4.4.1 (Release specifications) 4.2.4 (Critical steps and intermediates)		

7(7)	Requirements for musculoskeletal tissue subjected to processing	4.1.4 (Collection) 4.2.2 (Description of Manufacturing process) 4.2.4 (Critical steps and intermediates) 4.4.1 (Release specifications)		
7(8)	Outcome of the detection of microbial growth	4.2.4 (Critical steps and intermediates) 4.4.1 (Release specifications)		
7(9)	Requirements for rejection and sterilisation	4.4.1 (Release specifications) 4.2.5 (Validation of manufacturing process)		
7(10)	Musculoskeletal tissue packaging	4.4.6 (Containers)		
7(11)	Musculoskeletal tissue storage	4.5 (Storage & Stability) 4.7 (Transport)		

* Suggested dossier location; actual location of information may vary depending on the nature of the product, but must be defined under this heading.

** Only a very brief summary is required, the entire dossier will be evaluated.

References

Resource	URL
TGA website	http://www.tga.gov.au
ISO (International Organisation for Standardization)	http://www.iso.org/iso/home.html

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au