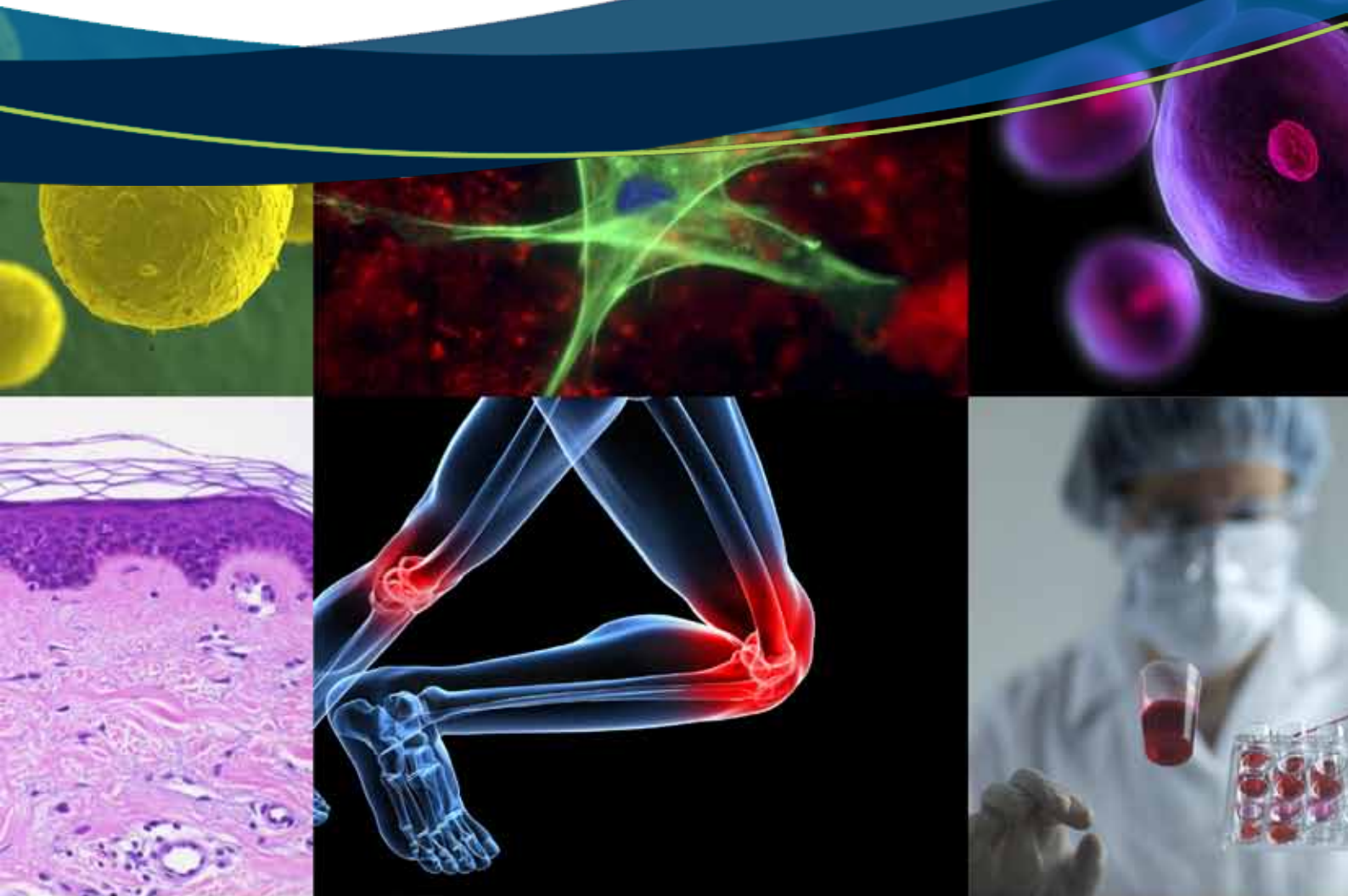
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Appendix 8 – Guidance on TGO 86 (Standards for human skin)

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) 86 (Standards for human skin) applies to biologicals that are human skin collected from living human donors for autologous or allogeneic use, or deceased human donors for allogeneic use. TGO 86 does not apply to human skin cells and tissue biopsied for the purpose of an *in vitro* diagnosis and human skin processed beyond minimal manipulation. If you are unsure if the TGO 86 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 86, 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 86 commences on the 31st May 2012. This will allow for a transition period for manufacturers to achieve compliance with the standards. All human skin tissue collected prior to 31st May 2012 will be exempt from this order.

TGO 86 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 86 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)

This subsection specifies the bioburden sampling and packaging requirements for collected skin. Both of these processes will require validation to demonstrate compliance with the Standard.

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.

Subsection 7(3)

The defined and documented microbial contamination reduction procedure should be validated to ensure its effectiveness, and be detailed in the appropriate dossier section.

The following guidance applies to validation of the bioburden test methods in the presence of the tissue sample when determining the initial bioburden and again following exposure to any bioburden reduction process:

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 and Annex A.5.3 of ISO 14160 provides guidance on performing bioburden tests on animal tissues.

Method validation 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.

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

** 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.

Note: Although details of bioburden reduction processes using antimicrobial rinses or washes should be provided in the dossier, these processes will be examined during a GMP audit.

Subsection 7(4)

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.

Subsection 7(5)

When microbial growth is detected following culture, the physician treating the recipient of the human skin must be informed that growth has been detected, including the identity of the microbes and required outcome based on subsection 7(4). Normal skin micro flora is to be expected in donor skin, therefore, the treating physician should be informed if this is the case and alerted to the presence of any significant isolates. These isolates are not those named on the list of specified microorganisms, preventing use of the tissue, but their identification allows the treating physician to make informed decisions regarding suitable antibiotic coverage for the recipient. The incubation and identification timeframes and the reporting procedure should be detailed in the appropriate dossier section.

Subsection 7(6)

If skin tissue is to be terminally sterilised then qualification and routine control of sterilisation processes should be in accordance with the relevant parts of international (ISO) sterilisation standards. For example**:** ISO 11135 (ethylene oxide), ISO 14937 (general methods), ISO 17665 (moist heat), ISO 11137 (radiation), ISO 14160 (chemical sterilisation), ISO 20857 (dry heat).

Some of these standards are relevant to the sterilisation of containers and ancillary materials used during tissue processing.

All containers should be sterile and any of the ISO standards listed above provide guidance for validating the relevant sterilisation process for containers, or the containers could be purchased sterile.

If human skin is harvested and processed aseptically the ISO 13408* series of standards provide useful guidance.

*ISO 13408 Aseptic processing of health care products (Note that Part 8 is being developed for the aseptic processing of cell and tissue products)

Subsection 7(7)

The sterile packaging should be compatible with product and if terminally sterilised, 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 novel sterilisation method validation can be found in ISO 14937).

If the tissue is aseptically manufactured, then it should be transferred into a sterile container and validated as an aseptic process (refer to ISO 13408).

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

Subsection 7(8)

The specific post-processing skin storage and transport conditions detailed in this subsection take precedence over those recommended in ARGB 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 skin tissue. If further clarification is required then please contact the TGA.

Location of requirements in dossier

Table 1 Summary table comparing TGO 86 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 86 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 skin tissue	4.1.4 (Collection) 4.2.3 (Control of critical materials)		
7(2)	Collected skin bioburden sampling and packaging requirements	4.1.4 (Collection)		
7(3)	Defined and documented microbial contamination reduction procedure	4.2.2 (Description of manufacturing process) 4.2.5 (Validation of the manufacturing process)		
7(4)	List of microorganisms that indicate rejection for therapeutic use	4.2.4 (Critical steps and intermediates) 4.4.1 (Release specifications)		
7(5)	Microbial growth must be reported to the medical practitioner treating the recipient	4.6 (Labelling and Release)		
7(6)	Skin tissue terminal sterilisation	4.2.5 (Validation of		

		manufacturing process) 4.4.1 (Release specifications)		
7(7)	Skin tissue packaging	4.4.6 (Containers)		
7(8)a	Storage of skin tissue	4.5 (Storage & Stability)		
7(8)b	Transport of skin tissue	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

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