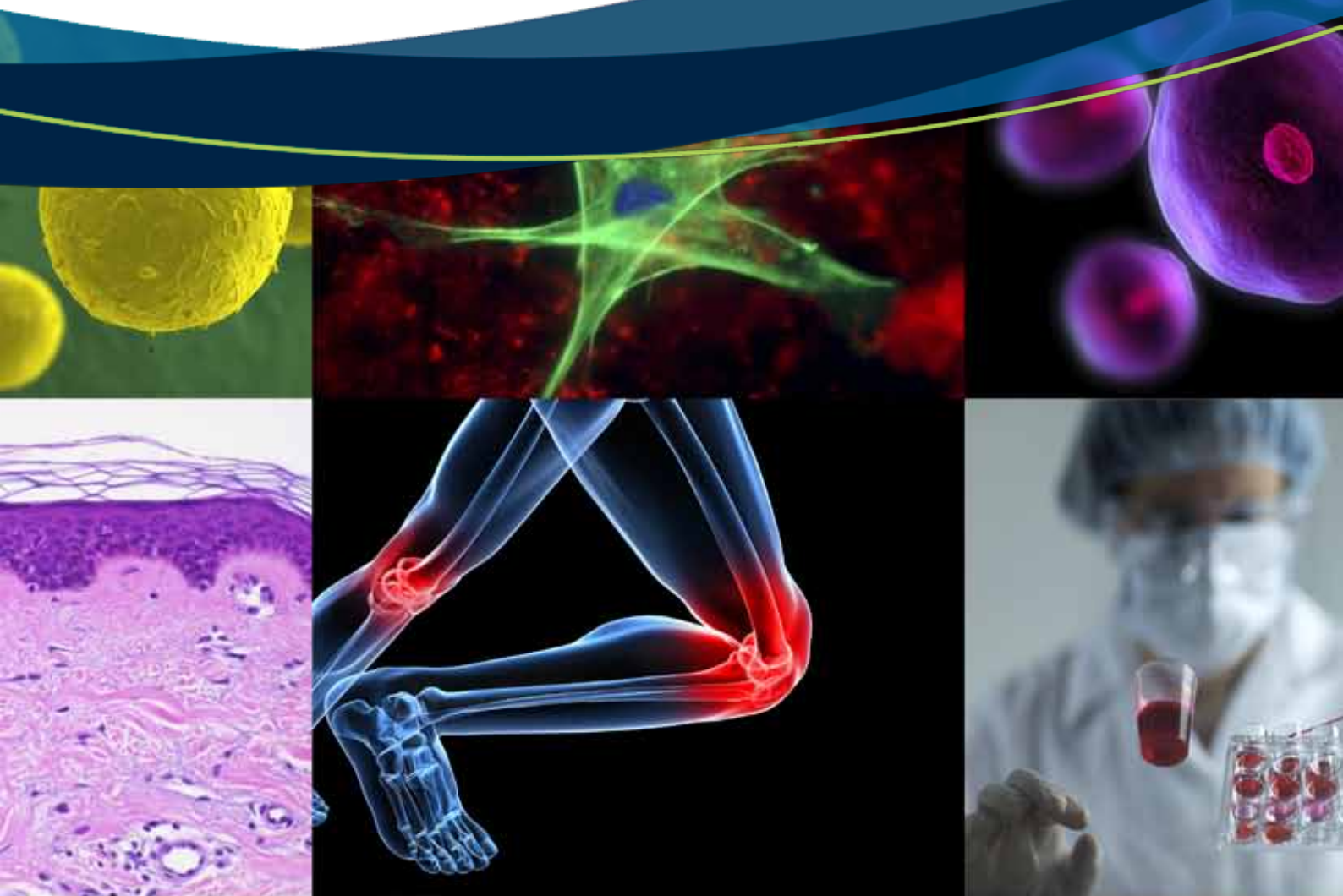
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Appendix 5 – Guidance on TGO 85 (Standards for human ocular 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

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Introduction

Therapeutic goods order (TGO) 85 (Standards for human ocular tissue) applies to human ocular tissue, including the eye globe, cornea or sclera, when collected from living human donors for allogeneic use, or deceased human donors for allogeneic use. TGO 85 does not apply to human ocular tissue that is exempt from compliance according to section 14 and 14A of the Act, human ocular cells and tissue samples that are biopsied for the purpose of an *in vitro* diagnosis, ocular tissue processed beyond 'minimal manipulation' and amniotic membrane used for therapeutic ocular procedures. If you are unsure if the Ocular 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 85, 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 85 commences on the 31st May 2012. This will allow for a transition period for manufacturers to achieve compliance with the standards. All human ocular tissue collected prior to 31st May 2012 will be exempt from this order.

TGO 85 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 85 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)

The requirements for the collection of ocular tissue from a deceased donor in the ocular order take precedence over those detailed in the Appendix 4, Annex 1.

Subsection 7(3)

Where ocular tissue is removed from the stated storage conditions to allow quality determination, e.g. warmed to room temperature to optimise microscopic evaluation and/or endothelial cell counting, the process must be strictly defined and sound scientific justification provided as to why the quality and safety is not compromised.

Subsection 7(5)

This section only applies to 7(4)c – excised cornea maintained in storage medium at 28°C to 37°C for no more than 30 days.

All storage and transport solutions used in processing ocular tissue should be sterile.

If the storage medium is intended to be sterile, then it should be tested and pass the harmonised test for sterility by the filtration method specified in the default standard pharmacopoeias. Validation of the test method is described as the "suitability of test" and involves a demonstration of neutralisation of antimicrobial agents that might interfere with the growth of contaminants. Alternatively, the filtration method as described in the microbial contamination chapters of the pharmacopoeias should be validated to demonstrate the absence of growth in solutions not required to be sterile.

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 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.

Subsection 7(6)

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(7)

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.

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

Location of requirements in dossier

Table 1 Summary table comparing TGO 85 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 85 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 ocular tissue	4.1.4 (Collection) 4.2.3 (Control of critical materials)		
7 (2)	Collection of ocular tissue	4.1.4 (Collection)		
7 (3)	Evaluation of ocular tissue	4.1.4 (Collection) 4.4.1 (Release specifications)		
7 (4) all parts	Ocular tissue storage	4.2.4 (Critical steps and intermediates) 4.5 (Stability & Storage)		
7 (5)(a)	Ocular tissue (excised cornea maintained in storage media for ≤30days) - exposure to transport medium	4.5 (Storage & Stability) 4.7 (Transportation)		
7 (5)(b)	Ocular tissue (excised cornea maintained in storage media for ≤30days) – testing of storage medium	4.2.3 (Control of critical materials) 4.7 (Transportation)		

7 (5)(c)	Ocular tissue (excised cornea maintained in storage media for ≤30days) – rejection if storage medium contaminated	4.4.1 (Release specifications)		
7 (5)(d)	Ocular tissue (excised cornea maintained in storage media for ≤30days) – reporting of contamination if post-release	4.6 (Labelling and release documentation)		
7 (6)	Ocular tissue packaging	4.4.6 (Containers)		
7 (7)	Ocular tissue terminal sterilisation	4.2.5 (Validation of manufacturing process)		
8(1)	Examination and evaluation	4.4.1 (Release specifications) 4.4.5 (Justification of specifications)		

* 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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