Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Guide to consultation process

Consultation on proposed standards and Code of GMP for human blood and blood components, human tissues and human cellular therapies

December 2009

Contents

General information

Purpose of this guide

This guidance has been prepared to assist consultation on the proposed:

- Australian Code of Good Manufacturing Practice human blood and blood components, human tissues and human cellular therapies (Code of GMP);
- Therapeutic Goods Order (TGO) - Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies (infectious diseases standard);
- TGO – Standards for banked human cardiovascular tissue;
- TGO – Standards for banked human musculoskeletal tissue;
- TGO – Standards for banked human ocular tissue; and
- TGO – Standards for banked human skin.

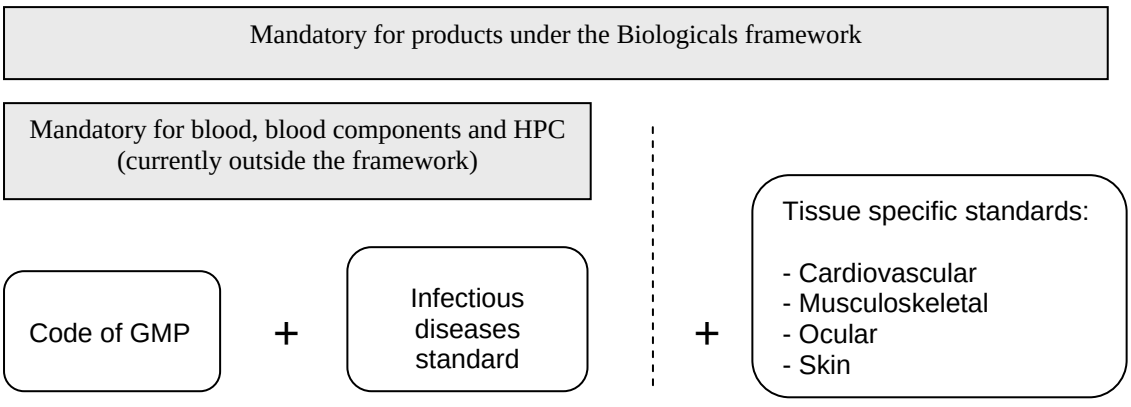
The infectious diseases standard and the four tissue specific standards outlined in this guide detail product safety and quality requirements and have been written to work in conjunction with the new Code of GMP.

It is recommended that this guide be read prior to or in conjunction with the draft Code of GMP, draft infectious diseases standard and the four draft tissue specific standards.

Scope of consultation documents

The Code of GMP and the infectious diseases standard will apply to all human blood and blood components, human tissues and human cellular therapy products. These will apply to products that are within the scope of the proposed Biologicals framework (for example cell and tissue products), as well as to products that are not within the scope of the framework (for example blood, blood components and haematopoietic progenitor cells (HPC)).

The four tissue specific standards will apply to biologicals that are within the scope of the framework, where relevant.



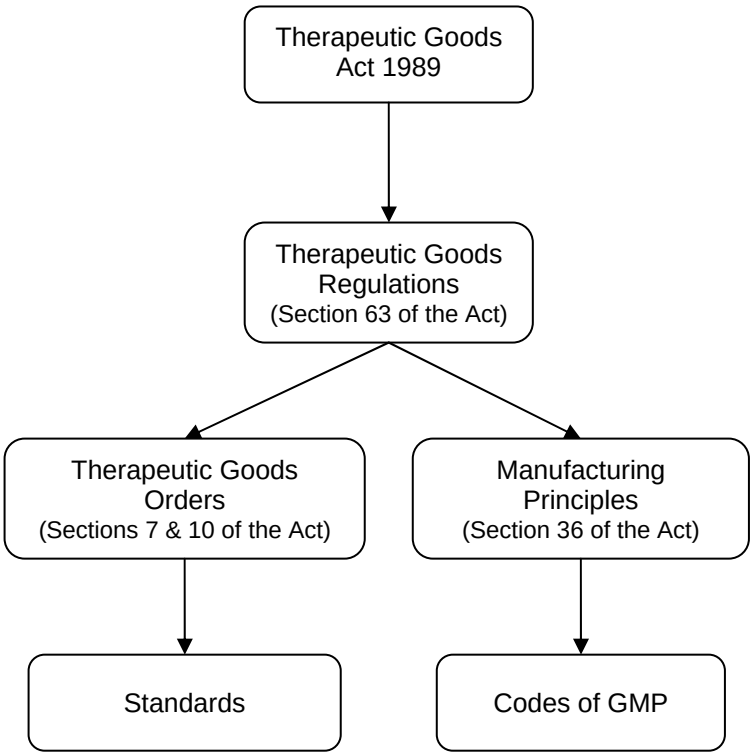
For more information on the Biologicals framework please see http://www.tga.gov.au/bt/hct.htm

Legislation

The *Therapeutic Goods Act 1989* (the Act) is the primary legislation. The object of the Act is to establish and maintain a system of controls for the quality, safety, efficacy, presentation and timely availability of therapeutic goods in Australia. Unless exempt, the Act requires that a therapeutic good must be registered, listed or included in the Australian Register of Therapeutic Goods (ARTG) before it can be lawfully imported into, manufactured in, supplied in, or exported from Australia. Many human blood, cellular and tissue products are currently exempt from ARTG entry. However, many of these exemptions are proposed to be removed for products regulated by the new Biologicals framework. The Act can be accessed via the TGA website http://www.tga.gov.au/legis/index.htm

Sponsors and manufacturers of therapeutic goods for supply in Australia are obliged to comply with the *Therapeutic Goods Act 1989* and the Therapeutic Goods Regulations and the relevant legislative instruments. Figure 1 below depicts the relationship between the different types of legislation governing therapeutic goods, including biological products.

Figure 1: Legislation governing therapeutic goods



TGA approach to the regulation of human blood and blood components, human tissues and human cellular therapies

With the development of the Biologicals framework, the TGA will apply a risk-based approach to the regulation of human blood and blood components, human tissues and human cellular therapies to ensure quality, safety and efficacy of therapeutic products.

The Code of GMP and the standards included in this consultation cover three major areas.

- The Code of GMP sets out principles for good manufacturing practice that will be used to audit manufacturers of human blood and blood components, human tissues and human cellular therapy products to ensure that products are safe, efficacious and have the quality that is expected.
- The infectious diseases standard sets out minimum requirements for limiting the risk of transmission of infectious diseases from donors to recipients of human blood and blood components, human tissues and human cellular therapies.
- The four tissue specific standards outline minimum requirements for specific human tissue products.

For a product to be included in the ARTG (and thus legally supplied) there must be a sponsor. The sponsor will be responsible for ensuring compliance with the Code of GMP, the infectious diseases standard and other applicable standards.

While compliance with the Code of GMP and standards is mandatory, it is proposed that a mechanism for 'Exceptional Release' will be developed as part of the Biologicals framework to enable the discretionary use of an approved tissue or cellular product which does not conform to manufacturing requirements, standards, or release specifications, to be used for an individual patient in unique and critical circumstances. These provisions will require a written notification to the TGA including documentation of a risk-benefit statement, rationale for use, and informed consent from the recipient/guardian, similar to the existing Special Access Scheme notification provisions for use of unapproved/unregistered products. Exceptional release provisions for the Biologicals framework are currently being developed and will be part of a separate consultation in 2010.

General background to the Biologicals framework

In July 2002 the Australian Health Ministers' Conference recommended that the Therapeutic Goods Administration develop a new regulatory framework for human cell and tissue therapies and other emerging biological therapies. A framework to regulate these products was proposed during the development of the now postponed joint Australia New Zealand Therapeutic Products Agency (ANZTPA). During this time significant consultation was undertaken on the development of standards.

Following the postponement of ANZTPA in 2007, the Government agreed in 2008 to move forward with a number of improvements identified during the development of ANZTPA in an Australia-only context. Detailed consultation on the overarching aspects of the Biologicals framework will continue to occur separately to this consultation on standards and Code of GMP.

Code of GMP

How the TGA developed the Code of GMP

The draft *Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapies* is a revision of the current Code of GMP for Human Blood

and Tissues 2000. The revision was undertaken by the TGA in consultation with Medsafe New Zealand and the Australian and New Zealand human blood and human tissue establishments.

The amended Code of GMP is principles based and identifies requirements that should be demonstrated by the manufacturer. Being principles based allows a manufacturer to apply alternative arrangements to demonstrate an equivalent level of quality assurance to meet the stated principles or objectives. In contrast to the current Code of GMP for Human Blood and Tissues 2000, all product specific requirements, including infectious disease standards, have been removed from the draft Code of GMP. The document has been restructured and sections re-written to provide clarity and substance to the clauses in the sections.

How the Code of GMP will be applied

A manufacturing licence will only be issued to Australian manufacturing facilities that are able to demonstrate compliance with the Code of GMP.

The TGA will audit manufacturers of human blood and blood components, human tissues and human cellular therapies against the requirements of the Code of GMP to ensure that therapeutic product(s) are safe, efficacious and have the quality that is expected and ensure compliance with Manufacturing Principles.

The TGA may also assess overseas manufacturers of human blood and blood components, human tissues and human cellular therapies against Australian manufacturing requirements set out in the Code of GMP to ensure that therapeutic product(s) are safe, efficacious and have the quality that is expected and ensure compliance with Manufacturing Principles.

How the Code of GMP is organised

There are ten Sections in the Code. The Sections cover Quality Management, Personnel and Training, Premises and Equipment, Documentation, Control of Material, Subcontracting, Complaints and Recalls, Collection and Processing, Quality Control and Computer Systems.

- Section 1 Quality Management - outlines quality management system requirements. This section includes the manufacturer's obligation to periodically review all manufactured products to verify process consistency, appropriateness of specifications, highlight trends and identify the need for product and process improvements. The review includes materials used for the product, critical in-process controls, deviations, changes, complaints, recalls, corrective actions, and equipment qualification and contractual agreement. The results of the review are assessed to identify the need for corrective and preventive action or revalidation.
- Section 2 Personnel and Training – prerequisites are outlined including general quality and production nominee responsibilities.
- Section 3 Premises and Equipment – outlines generic requirements. This section includes where applicable review of the premises environment which may be specific for manufacturing of a particular product.
- Section 4 Documentation – the documentation system requirements are outlined in this section.
- Section 5 Control of Material – generic requirements for all material which may affect product quality is contained within this section. A clause requirement for the management of returned products is included.

- Section 6 Subcontracting – requirements to ensure that product or services are defined and agreed to by the contractor and the manufacturer.
- Section 7 Complaints and Recalls – general requirements are outlined in this section.
- Section 8 Collection and Processing – outlines general and specific Biologicals requirements. This section includes a requirement for the prevention of contact or cross contamination from human tissue and human cellular therapies from other donors. There are requirements for specific processing steps in the manufacture of particular biologicals. Included in this section are validation requirements.
- Section 9 Quality Control – sampling, testing and product release are included in this section.
- Section 10 Computers – where a manufacturer has introduced computerised systems to control steps of manufacture, this section applies.

Infectious diseases standard

How the TGA developed the infectious diseases standard

The infectious diseases standard has been developed in consultation with clinical and technical experts (both internal and external to the TGA) to develop requirements for limiting the risk of transmission of infectious diseases from donors to recipients. A number of these requirements have been taken from the current Code of GMP for Human Blood and Tissues 2000.

How the infectious diseases standard will be applied

The infectious diseases standard contains the minimum requirements for donor selection, donor testing and cell and tissue management as related to infectious agents during the collection and processing for human blood and blood components, human tissues and human cellular therapies. The infectious diseases standard is applicable to human blood and blood components (including red cells, white cells, platelets and plasma), human tissues and human cellular therapies (including haematopoietic progenitor cells).

Manufacturers must comply with the infectious diseases standard as part of the sponsors evidence that a human blood and blood components, human tissues and human cellular therapy product complies with the TGA's regulatory requirements.

How the Infectious diseases standard is organised

- Sections 1- 3 provide an introduction and background to the standard
- Section 4 explains the use of the terms "must" and "should" and contains a glossary of terms and abbreviations
- Sections 5 & 6 describe the products to which the infectious diseases standard applies, and outlines those products exempt from the requirements of the standard
- Section 7 outlines the general requirements for all products and relates to the six schedules contained in the standard.

- Schedule 1 is a navigation tool to assist in the identification of the relevant provisions which will apply to a particular donor group in order to achieve full compliance with the infectious diseases standard.
- Schedule 2 describes the requirements for policies in relation to donor screening, donor consent, notification of test results and microbial specifications.
- Schedule 3 includes the requirements for the donor selection, donor interview and informed consent process
- Schedule 4 outlines the requirements in relation to donor blood sampling, test protocols, test kits, test validation and the documentation of testing and the test results.
- Schedule 5 includes the requirements for donor physical examination and donor testing. Table 4 of the schedule lists the infectious disease tests to be undertaken.
- Schedule 6 outlines the requirements in relation to the selection and evaluation of any critical materials employed during the manufacture (collection, processing, storage or transport) of blood and blood components, human tissues and human cellular therapies.

Tissue specific standards

How the TGA developed the tissue specific standards

The tissue specific standards for banked cardiovascular, musculoskeletal, ocular tissues and skin have been developed following consultation with the tissue sector between 2005 and 2007. Where applicable and relevant, these have been harmonised with a number of Australian and international standards and guidelines relevant to banked tissues.

How the tissue specific standards will be applied

Tissue specific standards describe the requirements for the collection, manufacture, processing, storage, packaging, labelling, and transport of human cardiovascular, musculoskeletal, ocular and skin products for clinical use.

Compliance with the relevant tissue specific standard will be required as part of the sponsors evidence that a human blood and blood components, human tissues and human cellular therapy product complies with the TGA's regulatory requirements.

Note that although product labelling requirements have been placed within Schedule 1 of all tissue specific standards, consideration is being given to establishing a separate labelling standard for biologicals. Stakeholders are invited to provide comment on the labelling requirements for each type of tissue during the current consultation.

How the tissue specific standards are organised

- Sections 1- 3 provide an introduction and background to the standard.
- Section 4 explains the use of the term "must" and contains a glossary of terms and abbreviations.

- Sections 5 and 6 describe products for which the tissue specific standard applies, and outlines those products exempt from the requirements of the standard
- Section 7 specifies the general requirements and relates to Schedule 1 of the standard. The general requirements include when a biological must not be manufactured in relation to donors having a disease or condition that could potentially compromise the quality and safety of the tissue, donor age requirements, collection of tissue, critical materials used in the manufacture of the tissue and the packaging of the tissue.
- Section 8 (for ocular tissue) specifies the requirements for the evaluation, examination and testing of ocular tissue.
- Schedule 1 specifies tissue specific labelling requirements.

The consultation process

Documents for consideration

The TGA is requesting comment from interested parties on the following documents:

- Australian Code of Good Manufacturing Practice human blood and blood components, human tissues and human cellular therapies
- Draft Therapeutic Goods Order: *Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies*
- Draft Therapeutic Goods Order: *Standards for banked human cardiovascular tissue*
- Draft Therapeutic Goods Order: *Standards for banked human musculoskeletal tissue*
- Draft Therapeutic Goods Order: *Standards for banked human ocular tissue*
- Draft Therapeutic Goods Order: *Standards for banked human skin*

Invitation to comment

Interested parties are invited to provide comment on the draft Code of GMP, the infectious diseases standard and the four tissue specific standards.

The TGA will be reviewing comments received as they relate to each consultation document. It would be helpful if you could please provide comments for each consultation document as separate documents and clearly indicate the specific standards/Code of GMP and section to which each comment relates. Where possible, relevant data and/or examples to support the views expressed should be provided.

Submissions

As the consultation period for the Code of GMP and the five proposed standards falls during the Christmas and New Year holiday, an extended period of 9 weeks for comment has been provided. Submissions must be received by close of business on **Friday 12 February 2010.**

Electronic submissions are preferred and should be emailed to biologicals_consultation@tga.gov.au

Please include 'Standards and Code of GMP' and your organisation in the subject line of the email.

As an alternative, hard copy submissions may be faxed to 02 6203 1291 or mailed to:

Blood and Tissues Unit
Standards and Code of GMP
Office of Devices Blood and Tissues
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Coversheet

Submissions should include the coversheets provided:

- Consultation submission coversheet form: Australian Code of Good Manufacturing Practice human blood and blood components, human tissues and human cellular therapies
- Consultation submission coversheet form: Draft Therapeutic Goods Order: *Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies*
- Consultation submission coversheet form: Draft Therapeutic Goods Order: *Standards for banked human cardiovascular tissue*
- Consultation submission coversheet form: Draft Therapeutic Goods Order: *Standards for banked human musculoskeletal tissue*
- Consultation submission coversheet form: Draft Therapeutic Goods Order: *Standards for banked human ocular tissue*
- Consultation submission coversheet form: Draft Therapeutic Goods Order: *Standards for banked human skin*

A coversheet is to be filled in for each separate document for which you are providing comments.

Enquiries

Enquiries should be directed via email to biologicals_consultation@tga.gov.au or by telephone to (02) 6232 8443.

What will happen to the submissions?

Submissions will be reviewed by the TGA and provided to the Therapeutic Goods Committee (TGC) for consideration. Recommendations made by the TGC following consideration of submissions from interested parties will be published on the TGA website as committee outcomes.

Notes on submissions

All submissions received will be placed on the TGA's website, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked 'IN CONFIDENCE'. Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet.

For submissions made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's website.

In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

This document is intended to be a resource document and should therefore not be relied upon for advice regarding the regulation of human blood and blood components, human tissues and human cellular therapies.