



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Regulation impact statement for revision of manufacturing and technical standard requirements for human blood, human blood components, human tissues and human cell therapy products

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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 medicines, biologicals 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 medicines, biologicals and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines, biologicals and or medical devices. TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a medicine, biological or medical device, please see the information on the TGA website <www.tga.gov.au>.

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Introduction

This regulatory impact statement (RIS) has been prepared by the Therapeutic Goods Administration (TGA). The purpose is to assist Australian Government decision making on how to address concerns that the current manufacturing and technical standard requirements for human blood, blood components, tissues and human cell therapy products do not adequately address the evolution of technology in this area.

The current Code of Good Manufacturing Practice for Blood and Tissues (2000) (the Code) encompasses human blood and blood components, human tissues, human cellular therapy products, and early precursors to blood cells (haematopoietic progenitor cells). For the purposes of this RIS these products will be collectively referred to as human cellular and tissue therapies (HCTs).

To ensure government regulation remains relevant and credible for HCTs it is important that the Code and the associated standards are regularly reviewed and updated. Most countries revise and update their GMPs about every five years to keep up with changes in the industry and changes to manufacturing and testing technology. The market place for HCTs has undergone great change during the past decade with advances in technology in manufacturing practices, as well as changes to the type and nature of HCTs produced.

In light of this, concerns have been raised that the existing Code is outdated and insufficient for the contemporary regulatory environment. Since 2007 the TGA has been working with industry to develop an updated Code, with a corresponding new standard for infectious disease minimisation. Public consultation on the revised documents was undertaken in 2009 and 2010, which resulted in refined requirements and general support for the new Code and standard.

Four options to address the problem are examined in this RIS including their anticipated impact on HCT consumers and healthcare professionals, industry and government agencies.

The RIS details the problems associated with the existing Code and summarises the consultation process that was undertaken with stakeholders to determine the best way forward. The RIS concludes with a recommendation, including an outline of proposed implementation, for Government consideration.

Background

Current regulatory requirements for HCTs

The TGA administers the following legislation and requirements to regulate HCTs:

- *Therapeutic Goods Act 1989* (the Act)
- *Therapeutic Goods Regulations 1990* (the Regulations)
- Therapeutic Goods Orders (details technical requirements for specific products)
- *Australian Code of Good Manufacturing for Blood and Tissues 2000* (the Code).

To ensure product safety and quality, all therapeutic goods are required to be manufactured in a consistent and reproducible manner. This is achieved through manufacturers complying with the relevant legislation (the Act and the Regulations) and therapeutic manufacturing principles (the Code). In addition, there may also be requirements specific to a particular product detailed in a Therapeutic Goods Order (TGO). For example, for human blood and blood components, it may be specified that a blood donor needs to be tested for particular infectious diseases prior to that blood being used for transfusion.

In order for the TGA to maintain public confidence in the quality and safety of HCTs supplied in Australia, it is important that the regulatory requirements for these products remain current and contemporary to accommodate the emerging technology and products in this industry.

Additionally, Australian manufacturers must hold a manufacturing licence issued by the TGA. A licence to manufacture will only be issued if compliance with relevant manufacturing principles can be demonstrated; for HCTs this is the existing Code. Overseas manufacturers of HCTs supplied in Australia must also obtain a clearance by demonstrating compliance with manufacturing principles.

Application for inclusion of a therapeutic good in the Australian Register of Therapeutic Goods (ARTG) requires sponsors to submit a dossier that includes detailed scientific and clinical information about the product. The extent of the information required is dependent on the level of risk associated with the product. The dossier is assessed by TGA evaluators against relevant standards and guidelines.

Once approved for use in the Australian market, maintenance of an ARTG entry and TGA manufacturing license involves post-market regulation, including surveillance and monitoring. These activities may involve manufacturing facility inspections, collection and assessment of adverse event reports, and laboratory testing of product samples. The TGA also works with international regulators to detect signals that may indicate a safety issue associated with a therapeutic good. In the event of signal detection, the TGA will take appropriate regulatory action, which may include product recalls, addition of warning statements to labels or additional conditions to the continued supply of the therapeutic good.

Some HCTs are exempt from entry in the ARTG. Approval for use of human blood, human blood components and haematopoietic progenitor cells (HPCs) (early precursors to blood cells used for bone marrow reconstitution) is primarily dependent on the issuance of a TGA manufacturing licence, subject to compliance with the existing Code and any applicable technical standards. The existing Code and applicable technical requirements have been the principal tools for TGA regulation of human blood, human blood components and HPCs.

Risk management approach for regulation of HCTs

The TGA considers HCTs to be higher risk therapeutic products. TGA evaluators and inspectors use a range of tools to identify, analyse and mitigate risks associated with HCTs. These tools include the existing Code and additional technical standards.

The risks associated with the manufacture and production of HCTs includes:

- the human starting material (donated or laboratory-cultured cells and tissues) for the HCT may contain harmful viruses, bacteria or prions;
- the intended use of the product may not be supported by clinical evidence;
- the way the HCT is manufactured, if appropriate processes are not adhered to, can mean the product does not contain the materials or ingredients it should, or it contains contaminant, or is altered to produce undesirable characteristics and/or render the product non-efficacious or non-viable.

It is due to the higher risk profile of these products that a specific manufacturing Code and technical standards are required for regulating HCTs.

Licensing of HCT manufacturers

The Act requires that an Australian manufacturer must obtain a licence and also stipulates that there can be manufacturing principles (Part 3-3 section 36(1)) and that; if they exist they must be followed as a condition of licensing (Part 3-3 section 40(4) (a) (ii)). The *Therapeutic Goods Determination No. 1 of 2007* sets out the manufacturing principles to be observed in the manufacture of HCTs. The manufacturing principles for HCTs are the *Australian Code of Good Manufacturing Practice for Blood and Tissues (2000)* (the Code).

What requirements are in the Code

Good manufacturing practice (GMP) is part of a quality system required for the manufacture and testing of therapeutic goods. GMP outlines the aspects of production and testing that can affect the quality of a product, and are a series of general principles and objectives that must be observed during manufacturing. Many countries have legislated that manufacturers of pharmaceuticals, human blood and blood components, early precursors to human blood cells (including HPCs), human tissues, human cellular therapy products and medical device companies must follow GMP procedures and have developed corresponding GMP guidelines. The underlying objective of all these guidelines is to safeguard the health of patients through the production of good quality therapeutic products. Noted below are the basic principles of all GMP guidelines.

The manufacturer must:

- have a quality system that includes document control, change management, monitoring systems including internal audits, corrective action and management review;
- control manufacturing processes and evaluate any changes to the process. They must 'validate' any changes that affect the quality of the therapeutic product to ensure consistency of manufacture and compliance with specifications;
- train personnel in all aspects of manufacturing and associated activities that affect the quality of the therapeutic products, including general training, as well as training specific to their role;
- have premises and equipment to undertake ancillary procedures, storage and production, including quality control and dispatch areas, and equipment looking at qualification, calibration, performance verification, maintenance and the monitoring of use;

- have documentation setting out policies, manufacturing procedures, quality control procedures, ancillary procedures and records of outcomes for all areas;
- where applicable, have procedures for contract production and contract testing that include the contract giver, contract acceptor and the contracts;
- establish a complaints and recalls system for recalling therapeutic products prior to transplantation, implantation, transfusion and/or infusion, where indicated;
- have a system for managing critical material, including starting materials, packaging, intermediate, bulk and finished products, reagents, culture media and reference standards. The management of critical material must review rejected, recovered, reprocessed and reworked materials;
- ensure that the collection and processing of therapeutic products are undertaken in such a way to prevent cross contamination, mix-ups and bacterial contamination during production, processing operations, and packaging and release for supply. All critical processes should be either verified and/ or validated;
- have quality control practices that include the control of starting materials, intermediates, bulk and finished therapeutic products, the test requirements, batch records review and stability studies;
- where computer systems are required in connection with a step in the manufacture of the product, ensure the computer system meets the same quality system requirements for those manual functions that it replaces. There should be documentation from the time of the written protocol for initial verification and the prospective validation of the computer system, including the confirmation of accuracy and reliability of the data collected directly from the equipment, back-up of the system and contingency plans if the system fails.

The Code sets out all the requirements for GMP that collectively ensures that therapeutic products consistently meet specifications, and while it sets the benchmark for practices that should be followed, alternative approaches may be permitted provided it can be demonstrated that the intent of the Code is met in a timely and effective manner in order to meet quality objectives. It is the manufacturer's responsibility to determine the most effective and efficient quality process. Furthermore, it is important to note that the requirements of the Code are *minimum* requirements. Many manufacturers have already implemented comprehensive, modern quality systems and risk management approaches that may well exceed the minimum standards.

Consistent with the basic principles outlined above, the existing Code provides for systems that are consistent in monitoring and control of manufacturing processes and facilities to some extent.

Compliance with the Code and HCTs

The patient or treating physician usually cannot detect (through smell, touch, or sight) that a HCT product is safe or if it will work. While the Code requires testing to ensure quality of these complex products, it is difficult to ensure through testing alone. There is considerable reliance on a controlled manufacturing process.

In many instances, a single HCT product constitutes a 'batch' in manufacturing terminology, so that the entire product is required for the patient. The quality control tests that are required are performed on a representative sample of the 'batch'. If the full batch

is to be tested, destructive testing may result in the loss of the entire product. For some HCT, there may be a relative inability to characterise the product fully to ensure product quality and safety because of limitations to existing analytical technologies/bioassays or our fundamental knowledge of newly emerging cell therapy products. To allow for these circumstances and timely access to the latest therapeutic advances, there has to be a strong emphasis during HCT development on the concept that the '*manufacturing process defines product*'. There has to be an assurance that the production process is reliable and reproducible, and transferrable to anyone familiar with the specific techniques. Quality control of processes emphasises the testing of the product to ensure a level of safety assurance prior to the release of the therapeutic product.

In addition to GMP for HCTs, measures are taken to minimise the risk of transmission of harmful infectious diseases from donated starting material. The current Code contains the minimum national requirements relating to donor selection and testing, together with requirements for infectious disease minimisation to minimise the risk associated with starting materials for these products.

Examples of how Code requirements help to ensure the safety and efficacy of HCTs include:

- ensuring facilities are in good condition
- requiring equipment to be properly maintained and calibrated
- requiring all personnel to be fully trained and qualified
- ensuring all processes are reliable and reproducible.

The problem

The existing Code is not suited to the current manufacturing or regulatory environments.

At the time the Code was implemented in August 2000, it was considered adequate and relevant for the types of HCT used in clinical settings at the time, such as blood, tissues, and haematopoietic progenitor cells. These products have a well established clinical and manufacturing history spanning decades and as such, the risk profile in terms of manufacture is relatively low. Since 2000 there have been significant developments in manufacturing methods and types of HCTs used in clinical settings, however a revision of the Code has not occurred to keep pace with these developments.

Furthermore, the existing Code was developed to provide a regulatory model for human blood and human tissues, as well as for early precursors to blood cells (haematopoietic progenitor cells) for the purposes of bone marrow reconstitution in 2000, prior to the introduction of the Biologicals Framework¹.

As part of ongoing maintenance of manufacturing requirements and product standards, the TGA has reviewed the manufacturing principles and standards for HCTs. The review considered feedback received from industry on major difficulties manufacturers experienced in complying with existing Code requirements. It was concluded that the existing Code was no longer adequate and revision was required to reflect the current regulatory situation and the needs of the sector.

¹ For more information regarding the Biologicals Framework see <http://www.tga.gov.au/industry/biologicals-framework.htm>

Three main areas of concern were highlighted in the review including clarification of scope and requirements, inflexible requirements, and regulatory basis for requirements. These are expanded upon below.

There are currently 134 Australian manufacturers licensed to the existing Code. The degree to which these manufacturers are affected by the problems varies depending on the type of product manufactured and the scope of the licence. The numbers of manufacturers based on the type of HCT are as follows:

- 21 human tissues
- 86 human blood and blood components
- 2 cellular therapy
- 9 haematopoietic progenitor cell
- 16 testing laboratories

There are 9 laboratories that test for HCTs for overseas manufacturers that either hold a current GMP certificate or are undergoing GMP certification.

Scope clarification

The existing Code was introduced in 2000 in order to address requirements for blood and tissues. Since this time therapeutic and manufacturing advances have led to advanced tissue and cellular therapy products becoming available for clinical use. The scope of products and manufacturing procedures to which the Code applies requires expansion to specify inclusion of emerging tissue and cellular therapy products.

The manufacture of such advanced cell therapy products often requires complex procedures, for example, expansion and activation of cells outside the body, cell sorting and selection steps and cryopreservation for the storage of these cells, genetic modifications of cells and the lyophilisation (freeze drying) of processed HCTs. Many of these complex manufacturing procedures are captured in the scope of the existing Code in a generic fashion; however, there is a need for inclusion of specific requirements to provide regulatory clarity for these manufacturers.

The lack of clarity in the existing Code, specifically relating to new and emerging technologies for HCTs, can lead to misinterpretation and potential non compliance with GMP that may include sub-standard product quality that poses risks to human health and safety. The number of manufacturers that are involved in the manufacture of new or emerging therapies and potentially affected by this issue is approximately 18..

A modern Code needs to provide clarification of scientific principles and objectives that apply to emerging cellular and tissue technologies. It also needs to provide manufacturers with the flexibility to apply tailored approaches to manufacturing controls suitable to their product.

Any additional level of regulatory certainty attained by including newly emerging tissue and cell therapy products in the scope of the existing Code is unlikely to prevent unregulated products being used in the marketplace. There are other existing mechanisms in place to address this: National, State and Territory legislative provisions, institutional review boards and professional standards which govern medical practice. However, formalisation of TGA's expectations by clarifying the manufacturing scope of the Code will lead to greater acceptance that this is the industry standard for manufacture of these types of products.

Inflexible requirements

The existing Code is prescriptive in its requirements, often using terminology such as 'must'. Although this ensures enforceable, high standards of manufacturing, difficulties arise for both manufacturers and the TGA where advances in technology cannot be accommodated or require a different practice than that prescribed, or manufacturers have developed a justified alternative.

For example, the existing Code mandates initial donor testing and also 180-day retesting of certain tissue donors before the products can be released for supply. Since 2000, more sensitive tests have become available that could replace the requirement for 180-day testing. Industry is adversely affected by the requirement to continue 180-day testing as the logistics of donor contact and retesting requires significant resources, and the supply of tissue can be adversely affected where a donor cannot be located, or is unwilling to be retested.

Leading international regulatory agencies in the U.S and Europe are discovering the need for flexibility when dealing with HCTs. In many cases, each application and cell manufacturing process is evaluated on a case-by-case basis to determine the level of compliance with GMP and to ensure that standards are acceptable for the particular product.

Regulatory basis for requirements

The existing Code contains technical standards including donor selection and testing criteria and technical requirements for infectious disease minimisation. At the time the Code was introduced these requirements were included as this was the principal means of regulating HCTs. Since that time, a new Biologicals framework has commenced and there has been considerable effort by the TGA towards more regulatory certainty and transparency of regulation for each type of therapeutic good.

Separation of requirements for infectious disease minimisation would align with the regulatory processes for HCTs to be consistent with those applicable to other therapeutic goods and thus provide more transparent regulation of HCTs. In addition, the Act allows the TGA to mandate technical requirements by legislative instrument in a TGO. The existing placement of technical requirements in the Code creates a regulatory discrepancy, as manufacturing principles and TGOs operate from different parts of the Act.

To reconcile this discrepancy, and to improve the clarity of the scope of the Code, it has previously been recommended by the TGA that all technical requirements be transferred from the existing Code into a newly developed infectious disease minimisation standard and product specific standards. These standards would then be implemented as TGOs under section 10 of the Act (for further background, see approved RIS for biologicals ORR ID 5066). Product specific standards for human cardiovascular, ocular, musculoskeletal tissue and skin have already been developed and implemented under section 10 of the Act to support the inclusion of biologicals in the ARTG.

Objectives

The objective of GMP is to provide a set of principles and procedures that, when followed by manufacturers of therapeutic goods, helps to ensure that the products manufactured will have the required quality. A basic tenet of GMP is that quality cannot be tested into a product but must be built into each product during all stages of manufacture.

A revised Code of GMP for HCTs will reduce the likelihood of risks associated with quality and safety of all HCTs, and to ensure timely access to these types of therapies. For regulatory effectiveness it is imperative that the Code, applicable legislative instruments and guidelines are reviewed regularly or whenever significant concerns are raised regarding adequacy.

There are a number of ways that the objective of GMP can be achieved, including:

- ensuring that there is a uniform and minimum set of manufacturing requirements established for all HCTs, including emerging technologies, which are well-accepted by industry;
- facilitating compliance with manufacturing and technical requirements through clearly written requirements;
- achieving international harmonisation of manufacturing requirements, where possible and appropriate, to better facilitate global trade and reduce regulatory burden;
- ensuring the existing manufacturing requirements will allow for advances in technology or changes in industry practices
- correcting any legislative discrepancies identified with including technical requirements in the existing Code.

Options

Four options have been considered to address the concerns regarding the inadequacies of the existing Code, and include different risk management options. The options include:

Option 1 – Maintain the *status quo* (i.e. do nothing)

Option 2 – Rescind the existing Code and allow industry self-regulation via an industry-based Code or principles

Option 3 – Adopt an international Code

Option 4 – Revise the existing Code and applicable technical standards

Option 1: Maintain the status quo

The existing Code has been in place since 2000 and during this time there has been significant change to the range of HCTs manufactured and supplied in the clinical setting.

As previously identified the current code no longer adequately addresses the requirements for modern and emerging HCTs. Feedback from stakeholders and comments during consultation for the Biologicals Framework indicated support for revision of the existing Code.

A decision to maintain the *status quo* and retain the existing Code will not satisfy the two major objectives of clarity and removal of product specific requirements.

Potential issues that may result from maintaining the status quo include:

- performance based requirements in the existing Code not addressing certain types of manufacturing operations such as those used for advanced cellular therapy products
- some requirements remaining unclear, while other requirements will not reflect the underlying legislation, such as the inclusion of some technical product requirements for all types of HCTs under the manufacturing principles
- the industry would continue to interpret requirements and/or seek clarification from the TGA
- lack of clarity may lead to industry behaviour that is not compliant with contemporary GMP which can subsequently lead to sub-standard therapeutic product quality which in turn may pose a risk to public health and safety
- a potential flow-on effect to additional health and welfare costs, and a reduction in productive life of recipients who could otherwise provide further benefit to the Australian economy.

For these reasons, this option is not recommended.

Option 2: Allow industry self-regulation

Under this option manufacturers would be required to assure the TGA that basic GMP principles have been followed. These guidelines would be established by the industry, however there may be difficulties associated with enforcing the requirements if manufacturers are not members of the industry group that is responsible for administering the requirement of GMP (the Code). Furthermore there are HCT manufacturers who are publicly funded organisations, and there is no peak industry association or co-ordinating body through which to develop an appropriate Code. Given the higher risk associated with HCTs it is appropriate for these products to be subject to independent government regulation.

In addition, self-regulation in this area is inconsistent with the agreement of the Australian Health Ministers Council which agreed that the TGA would introduce a new regulatory scheme for human tissue and cell therapy products, including revised manufacturing principles and technical product standards.

For these reasons, this option is not recommended.

Option 3: Adopt an international GMP Code

This option involves reviewing and adopting a suitable Code of GMP used by a comparable international regulator to replace the existing Code.

Most regulatory bodies have found it necessary to develop GMP guidelines or codes that describe the principles and practices required to provide assurance that therapeutic goods are safe, reliable and of consistently high quality. There are currently different levels of regulation internationally, such as no regulation of the manufacturing activities by the regulator, regulations under development, or regulation by international or national regulatory codes. There are currently countries that are only inspecting blood manufacturing establishments, and few countries that inspect human blood, human tissues and cellular therapy product manufacturers.

The European Union has relevant GMP requirements for therapeutic products. However, the requirements are written into the EU legislation and refer to many different parts of the EU legislative Directives. If the EU GMP was to be adopted, all of the Directives would also have to be adopted or considerable effort undertaken to ensure requirements in the directives are referred to, are captured in an EU GMP amended for use in Australia. Additionally there would be an overlap with technical requirements and potential confusion with the current TGOs legislated for HCTs.

In an effort to address different international regulatory requirements, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) provide an active and constructive international co-operation in the field of GMP. The purpose of PIC/S is to facilitate networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors. Australia is a member of the PIC/S. A GMP guide for medicinal products has been developed under this scheme: "*PIC/S Guide to Good Manufacturing Practice for Medicinal Products*".

The TGA has reviewed the applicability of this GMP guide, "*PIC/S Guide to Good Manufacturing Practice for Medicinal Products*" for applicability to HCTs in the Australian context. Adoption of the entire guide was assessed as inappropriate as some critical requirements for HCTs are not covered by this GMP guide such as requirements for the selection of donors (including medical assessment, consent and collection) and requirements for handling non-sterile source starting material. The need for these specific requirements reflects the unique nature of HCTs in that they are sourced from human donors, the source starting material is not sterile and the HCT is often not able to be sterilised due to the nature and sensitivity of the HCT.

Amending either the EU GMP or the PIC/S GMP for Australian conditions would require considerable stakeholder consultation to ensure the issues associated with the current Code are addressed and no further problems are created by this approach. As much of the consultation on how to address the issues associated with the current Code was conducted as part of the development of the Biologicals framework, further consultation would create additional burden on industry and further delay attempts to reform the Code.

Whilst adoption of a suitable code and the resulting harmonisation is desirable, neither the EU GMP Code nor the PIC/S Code was appropriate for adoption for the Australian market. This option is thus not recommended.

Option 4: Revise the existing Code and associated technical standards for infectious disease minimisation

Under this option, the existing Code would be replaced with a revised Code, the “*Code of GMP and standards for human blood and blood components, human tissues and human cellular therapy products*” with all technical requirements removed. These technical requirements would be transferred to a newly developed TGO: “*Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products*” (ID TGO).

This option specifically addresses the manufacturing processes for therapeutic products that are associated with more recent therapeutic advances and the need for clarity, flexibility and harmonisation with both national and international regulations. Revision of the code would involve:

- where appropriate bringing the requirements into closer alignment with major international codes, including the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* for greater harmonisation.
- restructuring and rewriting to improve clarity and provide substance to identified problem areas
- revising sections specific for blood and blood components to be applicable to a wider range of cellular therapy products, in particular to incorporate a degree of flexibility to deal with the range of products regulated under manufacturing licence by the TGA.

A summary of the changes to the revised Code are included in **Appendix A**. Some examples are provided below:

- specific requirements for handling of product returns from the customer (Clause 512)
- specific requirements for maintenance of freeze – drying and cryopreservation records (Clause 831, 832)
- regular periodic quality review of all products to verify the consistency of processes and appropriateness of current specifications for both starting materials and finished products Clause 113).

The infectious disease minimisation requirements that would be removed from the existing Code will be incorporated into a draft standard for infectious disease minimisation and implemented as a TGO. The introduction of a TGO for these infectious disease minimisation requirements will also align regulation of HCTs with the regulation of other therapeutic goods in Australia and internationally. Technical requirements for most therapeutic goods are legislated in TGOs to facilitate TGA evaluation of quality and safety of the products that are being supplied, which is distinct from the quality that is assured through compliance to appropriate manufacturing principles.

The ID TGO will clarify the requirements in relation to:

- the medical and social history of prospective donors
- donor blood sampling, test kits, test protocols and test management
- donor physical assessment and testing
- microbial control
- critical materials used in collection and manufacture

A summary of the requirements in the TGO for infectious disease minimisation, and the source of these requirements from the existing Code, is provided in **Appendix B**.

Option 4 Impact analysis

Key stakeholders affected by a revised Code for HCTs include:

- consumers, i.e. persons who receive treatment with HCTs
- healthcare professionals who administer HCTs
- the industry- comprising tissue banks, hospitals, hospital supply units, clinics, not-for-profit and commercial organisations, and
- government agencies, including the TGA as the regulator of HCTs and other areas of the Department of Health and Ageing.

Consumers

The regulation of therapeutic products directly impacts on the recipients of such therapies who have an expectation of quality, safety and efficacy of the therapies they receive. A Code that better aligns with the modern HCT environment will improve confidence that those expectations can be met.

Health care professionals

Appropriate regulation of manufacturing processes and technical specifications provides confidence to medical practitioners that human-derived products have been manufactured to the highest quality standards and are safe for use. For example, they will have confidence that products have been manufactured using processes to minimise the risk of contamination or infectious disease transmission.

Industry

Manufacturers of therapeutic products may potentially include:

- commercial organisations specialising in the manufacture of human products
- medicine and medical device manufacturers who produce goods that can be utilised with human products, such as blood products, biomolecules, biomaterials, cell scaffolds and matrices
- Laboratories performing mandatory screening and testing the therapeutic products
- Cellular therapy product manufacturers and advanced tissue manufacturers.

In the past, HCTs have primarily been manufactured by not-for-profit organisations that process and store products for future clinical use, and by hospitals, which develop products “in-house” for use in specific patients. However, with recent advances in tissue and cell technology there is increasing involvement of the commercial sector in the manufacture of tissue and cell therapy products, and the creation of small start-up companies and clinics within larger hospitals.

There are approximately 130 Australian manufacturers licensed to manufacture therapeutic products where the existing Code applies. It is expected that most of these

manufacturers will be impacted by any revision to the existing Code, however the impact of the changes vary greatly between manufacturers, depending on:

- which products are manufactured and degree of processing undertaken
- the range of products manufactured
- level of compliance achieved with existing GMP (minimum or higher)
- whether other existing industry standards are in place with similar or more stringent requirements such as accreditation standards which some parts of the sector voluntarily comply with.

For these reasons it is difficult to quantify the impact of the revised Code on any given group of stakeholders, however where possible an estimate of the number of affected facilities has been provided. The impact will be greatest for new manufacturers and advanced HCTs.

Scientific and clinical research institutions involved in research and development may also be affected by changes to the Code. Although these institutions are not regulated, early manufacturing process development in accordance with good manufacturing principles is strongly encouraged from the point of product concept for human-derived products. Incorporating regulatory requirements into process development increases the likelihood of a successful marketing application and that a product will be consistently manufactured to the quality and safety specifications.

There are approximately 10 international manufacturers of HCTs that must meet the requirements of the Code and any applicable standards to supply goods to Australia. Additionally there are estimated to be 10 international laboratories that are required to meet the current Code. Most of these manufacturers are located in North America, and the GMP requirements of leading international regulators, including the FDA, are comparable with the requirements of the revised Code. As such, the changes in the revised Code are expected to have little or no impact on the manufacturing operations or supply for international manufacturers.

Governments

With the introduction of any changes to the regulation of therapeutic products, including the introduction of product specific standards, there may be increased demand for funding to ensure publicly funded organisations can meet compliance requirements. Government agencies may be further affected by altered requirements resulting in changes to inspection measures and assessments.

Costs

Industry

Under the existing TGA regulatory arrangements, all affected HCT manufacturers meet costs associated with maintaining a GMP licence. These existing TGA regulatory fees applicable to the HCT sector are outlined in **Appendix C**. No new fees or inspections would be introduced with the revision of the Code and ID TGO.

There are a number of changes proposed in the revised Code which primarily involve changes to documentation. The main changes include:

- more clearly defining the requirement for review of process records by detailing the scope and content of reviews;
- specific training requirements for personnel working where contamination is a hazard;
- more clearly defining the requirement that sterile biological products should meet Annex 1 of the PIC/S PE 009-9 document in the code; and
- providing additional clarity on the requirements/factors that need to be considered for the monitoring of environmentally controlled processing areas.

The impact on business compliance costs of these changes is expected to be low. This is because the revised Code is principles-based, describing benchmark practices that should be followed, but permitting alternative approaches provided it can be demonstrated that the intent of the Code is met in a timely and effective manner.

For example, the most significant potential impact of the revised clause in relation to regular product review is the requirement for process trend analysis which may require implementation of a software package. However, this work can be (and is being) done through the use of Excel spreadsheets; therefore, the decision to buy specialist software for this purpose would be a business decision; made on the basis of a benefit/cost analysis that showed returns on the investment.

To assess the possible impact on a large manufacturer, the Australian Red Cross Blood Service (ARCBS)'s current systems were reviewed by the Office of Manufacturing Quality. In addition, a gap analysis was provided by the ARCBS. The ARCBS has already implemented statistical process control software for the monitoring of blood and blood components as required under the blood product specific standard. The Review indicated that the existing controls in place at ARCBS would meet the requirements of the revised clause of the Code.

Similarly, manufacturers of cord blood have procedures and processes in place for regular product review as required under the cord blood product specific standard.

For smaller manufacturers where the number of products released is significantly less, the annual review process would not require the use of sophisticated software packages. These manufacturers could use generic software packages such as Microsoft Excel which they most likely have available to undertake the necessary process trend analysis.

During the public consultation for the revised Code and ID TGO in 2010, stakeholders were asked to provide comment on potential compliance costs associated with the revised Code and ID TGO. The consultation feedback did not indicate that the proposed changes to the Code were likely to increase compliance costs for the regulated industry.

Proposed changes to the ID TGO are expected to have minor impacts on direct compliance costs. Most ID requirements are already in existence as principles based requirements in the Code, and more explicitly in industry-accepted standards for many HCT products including blood, HPC, and some tissues. In some cases, particularly in the private sector larger manufacturers of blood and blood products, manufacturers already exceed many of the requirements of the proposed ID TGO.

The proposed ID TGO may impose indirect costs on industry by affecting the current supply of HCTs. Donor screening criteria are a fundamental risk management tool for minimising infectious disease transmission in HCTs, however, the degree to which certain criteria are applied between manufacturers and products is inconsistent. Consultation identified that the revised ID requirements primarily impact the tissue sector (n=19).

The extent to which the ID TGO may affect supply cannot be quantified - most requirements are already met. However two concerns raised in the consultation include:

- deferral of donors at risk of having malaria: this was raised as a likely impact on donor numbers in Western Australia (n=4 facilities) due to travel demographic. These facilities have been asked to quantify the potential impact of this requirement however to date this information has not been provided, although a risk assessment from these facilities may result in exemption from this requirement for the irradiated bone products;
- deferral of donors at risk of prion disease (mad cow/ bovine spongiform encephalopathy): raised by the ocular tissue sector (n=4 facilities) and estimated to potentially decrease supply by up to 20%.

In both cases, the affected stakeholders have acknowledged that the proposed requirements align with international practice and accept the implementation of these deferrals is appropriate based on the currently available scientific information regarding infectious disease transmission in tissues.

The TGA is committed to ensuring that the level of regulation remains appropriate, and ID requirements will be reviewed on an ongoing basis as further information becomes available on the transmission of disease through HCTs.

Consumers and Health Care Professionals

It is difficult for the TGA to predict whether the changes to the Code will incur extra costs to consumers and health care professionals. There is no quantitative information available about costs to these stakeholders for HCTs. In reviewing the Code, the TGA has endeavoured to keep costs to a minimum by working with industry to ensure the revised requirements are practical and cost-effective.

It is conceivable that there may be some flow-on costs from manufacturers resulting from implementation of improvements to product safety and quality, although it is difficult to predict what these costs might be for consumers and health care professionals.

Government

As a majority of Australian HCT manufacturers are not-for-profit or publicly funded facilities (approximately 110), costs to industry arising from changes to the Code may flow to Commonwealth, State and Territory Governments, through:

- 1) additional operational funding requests to the Commonwealth or State Government bodies by not-for-profit organisations
- 2) an increase in costs for use of these products and subsequent increase in Medicare benefits payable to manufacturers and recipients.

While the actual cost to industry could not be quantified due to disparity in existing manufacturing and quality management practices, any flow on costs to government are expected to be minimal.

The costs to the TGA, are fully cost recovered in accordance with TGA's cost recovery model.

Benefits

Consumers

The major benefit to consumers will be increased assurance in the safety and quality of therapeutic products. It is not possible to quantify these effects. In some instances, the benefits may be relatively minor as many of the revised requirements are "industry standards". However, by strengthening some quality assurance requirements, consumer benefit may be derived from a reduction in the rate of product quality defects and product recalls. While such occurrences may be relatively infrequent, their cost can be significant depending on the nature and volume of the product involved. Revised requirements provide continual assurance of a quality product and aim to reflect improved health outcomes for the recipients and a reduction in health costs in the longer term.

Health Care Professionals

Regular review and updates to TGA's Code and standards assure health care professionals that all of the products have been manufactured to highest quality standards and, if applicable, subjected to a pre-market approval process to ensure that they are safe for use, i.e. they are not likely to be contaminated or contain infectious diseases.

Industry

The revision of the Code is to provide greater clarity of requirements for HCTs and is intended to be less prescriptive and allow for justification of alternative practices, thus facilitating product innovation. While the revised Code seeks to improve clarity, there are instances where regulatory requirements will have flexibility that allows manufacturers to use an alternative approach. Details of all proposed changes to the Code are summarised in **Appendix A**. The recent consultation confirmed that the HCT industry supports the proposed revisions to the Code, including introduction of the ID TGO for ID requirements. Furthermore industry expressed that specific changes will benefit them immediately, for example the existing Code mandates initial testing and 180-day follow up testing of certain tissue donors, which is resource intensive and can affect supply where donors cannot be located. The revised requirements, which will be in the ID TGO, permits the manufacturer to perform initial testing by using a more sensitive test and forego the requirement to perform 180 testing if preferred.

The removal of requirements for infectious disease minimisation from the Code will increase the general utility of the Code, and the creation of a separate ID TGO for these provisions will ensure targeted application of these requirements.

Government

The provision of more detailed guidance in the revised MP and revised Code will provide the TGA with greater confidence that its requirements are understood by industry, and that all therapeutic products manufactured locally are manufactured in compliance with the legislative requirements.

The revised Code addresses requirements for all products within its scope, providing greater regulatory certainty and transparency.

Distribution of costs and benefits

The costs, in the first instance, will be borne by the sponsor/manufacturer of the product who wishes to supply a product for use in the Australian market. However, it is conceivable that costs will flow on to the Australian public in the price of the product or the broader Australian health system through requests for more public funding or Medicare rebates.

In some cases, manufacturers already comply with a number of the proposed changes to the Code and ID TGO requirements, and the changes mostly represent a formalisation of current practice. Therefore, minimal compliance costs are anticipated, but will be subject to ongoing review.

The benefits to be derived from assurance of ongoing high quality and safe products will equally flow to the Australian consumers and the Australian health system. Benefits to manufacturers are that a clear standard/code can accommodate innovation and changes to technology.

Option 4 - Summary

The manufacturing industry for therapeutic products already has costs associated with the maintenance of licensing under the existing Code, including ongoing quality assurance and quality control systems required to comply with the Act. The TGA anticipates the revision of the Code will result in no or minimal additional compliance costs to the Australian manufacturing industry. Some manufacturers may need to strengthen certain quality assurance aspects of their manufacturing operation in order to comply with the revised requirements. In these cases, the imposition of such costs is justified in the interest of product quality and public safety. Any costs of complying with the revised Code and ID TGO are expected to be partially off-set by savings associated with simplified and standardised quality systems and possible reductions in defective products due to greater emphasis on quality assurance activities.

Consultation

Public consultation

The revision of the Code was initially developed in consultation with representatives from Medsafe, the Australian and New Zealand blood services and the tissue sector between 2005 and 2008. Parallel to that process was the transferral of technical requirements from the Code into a new ID TGO where the consultation process occurred with representatives from the tissue sector between 2005 and 2007 (including in the Regulatory Impact Statement no. 5066).

The TGA then undertook two extensive rounds of national public consultation in 2009 and 2010 to inform the development of the revised Code, ID TGO, and the technical product standards for the Biologicals Framework. The consultations were advertised on the TGA website for a period of 8 weeks during each round, and the documents were distributed via email to all stakeholders on the TGA stakeholder database². The documents were also available to all other interested parties, including the general public on the TGA website. The consultation process and the objectives of consultation were clearly described in the supporting documents.

The consultations were combined as part of the development of the Biologicals Framework. All manufacturers not subject to the regulatory requirements of the Biologicals framework, including those who manufacture blood and blood components and haematopoietic progenitor cells, were clearly identified and included in the consultation process. The TGA has also engaged directly with the major stakeholders involved in the production of blood, blood components and haematopoietic progenitor cells, for example the Australian Red Cross Blood Service, on numerous occasions to ensure that the requirements of the revised Code and ID TGO can be met.

The TGA has attended a number of industry meetings and conducted information and education sessions during the course of the consultation rounds and beyond those. The major views of stakeholders expressed in written responses to the consultations were also relayed during these meetings. Any additional stakeholder feedback at these meetings was noted and where relevant, incorporated in the development of the revised Code and infectious disease minimisation standard. Regular updates on the development of the revised Code and ID TGO has been included in TGA newsletters, which are provided on the TGA website and distributed via email to all individuals who have registered their interest in being included on TGA's stakeholder database.

All of the public submissions received during consultation and information on how they have been addressed by the TGA, including a detailed tabulation of issues in Round 2, are available on the TGA website: Round 1 <http://www.tga.gov.au/newsroom/consult-bt-standards-0912.htm> and Round 2 [http://www.tga.gov.au/newsroom/consult-bt-](http://www.tga.gov.au/newsroom/consult-bt-standards-0912.htm)

² The stakeholder database contained the names of 490 stakeholders that have registered with TGA to receive updates on the Biologicals Framework and includes federal and state government bodies, industry associations (e.g. Australian Medical Association, Australasian Tissue and Biotherapeutics Forum) and individuals from industry covering tissue banks, cord blood banks, HPC collection/processing centres, pharmaceutical/biotechnology companies, lawyers/consulting firms, and education and clinical research institutions.

[standards-1012.htm](#). A summary of the concerns raised during consultation and the steps taken to address them are detailed below separately for the Code and the ID TGO.

The TGC Subcommittee on Biologicals (see below) had a significant role in the development and endorsement of the initial documents released for first round consultation in Dec 2009. All feedback was considered by the subcommittee in TGA's further development of the documents. The ID TGO was significantly amended in response to the first round of stakeholder comments. The revised documents were endorsed by the TGC Subcommittee in July 2010 for a second round of public consultation in November 2010. Further public consultation was not required for the revised Code, as feedback from the first consultation resulted in only minor amendments. As per advice from the subcommittee, the revised Code was included in the second round for information. An enthusiastic response was received from 42 organisations during both rounds of consultation, including industry stakeholders, public health organisations and specialists, and government departments.

Therapeutic Goods Committee- Subcommittee on Biologicals

The revised Code and infectious disease minimisation standard were developed in close association with the Therapeutic Goods Committee (TGC) Subcommittee on Biologicals. The TGC is established under regulation 34 of the Regulations to advise and make recommendations to the Minister for Health and Ageing on the adoption of standards for therapeutic goods, matters relating to standards for therapeutic goods and various other matters. Membership to this committee is appointed by the Minister for Health and ageing and includes experts in various fields relevant to therapeutic goods regulation, and nominees of organisations which represent the interests of the therapeutic goods industry as well as consumers of health services. The Subcommittee on Biologicals was comprised of a group of subject matter experts and reported to the TGC.

The Code

Overall there was industry support for the revised Code. Stakeholder concerns regarding the revised Code can be summarised into four main categories:

- Editorial
- Requests for addition/deletion of clauses
- Clarification of intent of certain clauses and aspects
- Suggestions for separate codes for tissue manufacturers.

To address these concerns a glossary has been included in the Australian Regulatory Guideline for Biologicals (ARGB) (<http://www.tga.gov.au/industry/biologicals-argb.htm>), and further information has been published on the TGA website to assist interpretation (<http://www.tga.gov.au/industry/biologicals-framework.htm>). Where required, the draft Code was edited to improve clarity.

Following the above amendments to address stakeholder concerns, the TGC Subcommittee for Biologicals endorsed the revised Code at its 5th meeting on 10 March 2011.

Infectious Disease Minimisation Order

To remove the technical requirements from the Code to make it more universal, requirements for infectious disease minimisation were transferred to a specific TGO. The ID TGO is intended to complement the revised Code to ensure that public health and safety is protected during the manufacturing of HCTs, but still allowing flexibility for emerging technologies to comply with the Code.

Similar to the Code, the ID TGO was also subject to two rounds of consultation. The issues that were raised during the first round of consultation included:

- Donor selection and testing issues
 - Timing and requirements for the examination and consent of living donors
 - Disease and age exclusion criteria for living donors
 - Timing and requirements for sampling and testing of donors
- Assessment of microbial contamination and minimisation of bioburden
- Requirements for transport, storage, quarantine and banking
- Standards for plasma for fractionation products.

The draft ID TGO was amended to address these concerns and was subject to a second round of consultation. The following points outline the issues raised during the second round of consultation; further details relating to the concerns and the approach endorsed by the TGC Subcommittee are included in **Appendix D**.

1. Transition arrangements for implementation of the ID requirements as a TGO.
2. Proposed amendments to timeframes to conduct donor medical and social history interviews.
3. Applicability of donor social and medical history criteria for autologous donors.
4. Ineligibility time period for non-medical drug injection.
5. Ineligibility time period for risk of malaria.
6. Malarial deferral for eye and cornea donations.
7. Six month deferral of donor with prior exposure to risk of acquiring blood borne transmissible infection.
8. Ineligibility periods for donors with risk of prion disease.

Following amendments to the ID TGO to address the concerns identified (as detailed in **Appendix D**), the TGC Subcommittee for Biologicals endorsed the revised ID TGO at its 5th meeting, March 10 2011.

There was also feedback on the potential impacts that any newly imposed requirements might have on the continuing supply of products or new supply of novel tissue and cell therapy products into the Australian market. Parts of the industry warned that if the regulation hurdles to enter the Australian market exceed those of other regulatory agencies, given the small market share of Australia that products may not be supplied into this country. Parts of Industry also expressed concern that the costs of implementing new requirements may lead to a cease in the supply of particular tissue products. All of these views were taken into account by the TGA and TGC during the development process.

Conclusion

As demonstrated above, an update to the current Code is required to ensure requirements for HCT manufacturers remain relevant and adequate in the current regulatory and technological environment.

The preferred approach to implement this update is option 4, which provides for the revision of the current Code, and development of a separate standard for infectious disease minimisation. This option addresses the problems with the current situation while remaining aligned with the key objectives of the TGA and the good manufacturing principles, without imposing significant regulatory burden.

It is recognised that there are uncertainties surrounding the costs of this option and the level of benefits applicable to the industry and the Australian public. The impact on business compliance costs of these changes is expected to be low because the revised Code is principles-based, describing benchmark practices that should be followed, but permitting alternative approaches. It is also the revision of an existing Code, to which all affected manufacturers must already comply. The introduction of the ID TGO may introduce some initial resource costs for industry, and potentially a small reduction in the number of eligible HCT (specifically tissue) donors, but these costs are expected to be minimal and in most cases, changes are underway as a result of other regulatory changes recently introduced in the HCT industry.

The benefits of increased relevance to contemporary manufacturing practices, and increase in safety of HCTs through clearly defined infectious disease safety criteria, are also difficult to quantify. The improvement in clarity and international consistency is expected to facilitate regulatory compliance for Australian and overseas manufacturers, and in turn increase consumer confidence that all therapeutic products in the Australian marketplace are manufactured to a similar standard regardless of whether they were manufactured locally or overseas.

Implementation

The TGA proposes to implement the revised Code and ID TGO in the following manner:

1. the revised Code be implemented via revised manufacturing principles under Section 36(1) of the TG Act, and
2. the ID requirements are to be implemented as a TGO under Section 10 of the Act contemporaneously.

Sponsors and manufacturers of existing products

1. A transition period of 12 months will be given from the time of implementation of the Code and ID TGO, to provide sufficient time for manufacturers of therapeutic products to address the updated requirements.
2. Sponsors and manufacturers of relevant therapeutic products will continue to be informed of significant updates in regard to implementation of the updated requirements via the TGA website and will be further advised soon after the transition period commences of the need to transition their existing products.
3. If a periodical or unscheduled inspection is to occur within the 12-month transition period, manufacturers both locally and internationally will have the option to be inspected against the existing Code or the revised Code (2012) and the new ID TGO. This will ensure the existing manufacturing licence or certificate remains current.
4. Prior to the conclusion of the transition period, relevant manufacturers will be reminded of the need to review their existing manufacturing practice against the revised Code (2012) and put the appropriate compliance measures in place for their products.
5. At the conclusion of the transition period, all manufacturers of affected therapeutic products must comply with the revised Code (2012), as demonstrated at the inspection. Any non-compliant manufacturers will be notified of TGA's intent to withdraw or suspend their manufacturing licence, or be issued with a licence on the basis that specific conditions apply.
6. As is consistent with other Codes and product standards, TGA will review the impact of the update following implementation. These reviews may incorporate audit findings, complaints, appeals and applications for exemptions from specific requirements introduced with the regulatory change.

Sponsors and manufacturers of new products

1. Sponsors and manufacturers of relevant products will continue to be informed of significant updates in regard to implementation of the updated requirements via the TGA website and

2. Must comply with the requirements of the revised Code (2012) and new ID TGO at the time of application for a new manufacturing license and submission of a dossier if required.

Acronyms and Glossary

Code	<i>Code of Good Manufacturing Practice for Blood and Tissues (2000)</i>
GMP	Good manufacturing practice
Standards	As specified under section 10 of the <i>Act</i> or contained within monographs of British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia-National Formulary
TGA	Therapeutic Goods Administration
HCT	human cell and tissue therapy
HPC	Haematopoietic progenitor cells
MP	Manufacturing principles
TGO	Therapeutic Goods Order
DoHA	Department of Health and Ageing
the Act	<i>Therapeutic Goods Act 1989</i>
the Regulations	<i>Therapeutic Goods Regulations 1990</i>
Biologicals	Human cell and tissue-based therapeutic goods
vCJD	Variant Creutzfeldt-Jakob disease
WHO	World Health Organisation
CDC	Centres for disease control and prevention
TGC Subcommittee	Therapeutic Goods Committee Subcommittee on Biologicals
ID TGO	Therapeutic Goods Order for infectious disease minimisation
Autologous	Obtained or used in the same individual
Allogeneic	Tissues or cells that are genetically dissimilar

Appendix A: Summary of Changes to the Code

There are a number of changes proposed in the revised Code. Following is a summary of selected changes that reflect increased clarity and flexibility in the revised code:

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>Clause 911:</p> <p>There must be stated regular reviews of process records. The frequency of review may depend on the incidence of non-conformances discovered at internal audit and/or the frequency of product out of specification.</p>	<p>Clause 113: Regular periodic quality reviews of all products should be conducted with the objective of verifying the consistency of processes and the appropriateness of current specifications for both starting materials and finished product. Quality reviews may be grouped by product type where scientifically justified. Trends should be highlighted to identify necessary product and process improvements. Such reviews should be conducted and documented annually, taking into account previous reviews, and should include, as applicable:</p> <ul style="list-style-type: none"> • A review of material used for the product, especially those from new sources. • A review of critical in-process controls and finished product results. • A review of all products that failed to meet established specification(s) and their investigation. 	<p>An updated and less prescriptive requirement for regular (normally annual) review to verify process consistency, appropriateness of specifications, highlight trends and identify the need for product and process improvements.</p> <ul style="list-style-type: none"> • The results of the review will continue to be assessed during a TGA inspection to identify the need for corrective and preventive action or revalidation • There may be compliance costs for manufacturers with a large product range who do not already have systems in place -in most cases manufacturers are already complying with the requirements, as it represents a formalisation of current practice • The most significant impact will be the requirement for process trend analysis, which may require implementation of new software for some manufacturers although standard issue software (e.g. MS Excel) can be used to perform these analyses in cases where the product range is small (e.g. tissue banks). • Many manufacturers have already implemented product review

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
	<ul style="list-style-type: none"> • A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken. • A review of all changes carried out to the processes or analytical methods. • If applicable, a review of the results of the stability monitoring program and any adverse trends. • A review of all quality-related returns, complaints and recalls and the investigations performed at the time. • A review of adequacy of any other previous product process or equipment corrective actions. • The qualification status of relevant equipment and utilities, e.g. HVAC, water, gases, temperature controlled equipment; A review of Contractual Agreements to ensure that they are up to date. 	<p style="text-align: center;">to comply with other sector specific standards.</p>
<p><i>Clause 906:</i></p> <p>There should be data validating each critical process in the manufacture of product, and where applicable, quality control data to demonstrate that the process is under adequate control.</p>	<p><i>Clause 835:</i></p> <p>The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document. Validation studies should reinforce Good Manufacturing Practice and be conducted in</p>	<ul style="list-style-type: none"> • Provides additional clarity on the requirements • Provides more flexibility to the manufacturer to adopt or develop, suitable/new procedures • There will be no cost or operational impacts on manufacturers arising from the change

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>Clause 908:</p> <p>There must be a re-validation performed whenever there is a significant change in any of the critical processes of manufacture of the product. The data should identify the change which should be documented, reviewed and approved by the quality assurance manager, or nominee, before implementation.</p>	<p>accordance with defined procedures. Results and conclusions should be recorded.</p> <p><i>Clause 836:</i></p> <p>The manufacturer should identify what validation work is required to demonstrate control of the manufacturing process. A risk assessment approach should be used to determine the scope and the extent of the validation.</p> <p><i>Clause 837:</i></p> <p>Significant changes to the manufacturing process, including any change in equipment or materials which may affect product quality and/or reproducibility of the process should be validated.</p> <p><i>Clause 838:</i></p> <p>When any changes to the manufacturing process are adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.</p>	
<p>Quality Assurance and Production Nominees</p>	<p>Clause 104: The system of Quality Assurance appropriate for the</p>	<ul style="list-style-type: none"> Requirements have been made less prescriptive allowing more flexibility to develop procedures conducive to the

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>108 The responsibility for quality assurance and production must be allocated to a person(s) as required by the manufacturing licence. Those nominated for these responsibilities should be different persons, neither responsible to the other, unless other arrangements acceptable to the TGA are made. The licensed site must be able to demonstrate supervisory control over any manufacturing step(s) carried out at another site.</p> <p>109 The quality assurance nominee (manager) must have the necessary independence and authority to ensure that quality measures are employed in the manufacture (including testing) of product. This person should report to the Director.</p> <p>110 The production nominee (manager) must have the necessary authority to control the manufacture of product.</p> <p>111 The quality assurance and production nominees should usually have a relevant tertiary level qualification, (e.g. in</p>	<p>manufacture of products should ensure that:</p> <ul style="list-style-type: none"> • therapeutic products are designed and developed in a way that takes account of the requirements of this Code and Good Laboratory Practice; • production and control operations are clearly specified and Good Manufacturing Practice adopted; • managerial responsibilities are clearly specified; • arrangements are made for the manufacture, supply and use of the correct starting and packaging materials; • all necessary controls on intermediate products, and any other in-process controls and validations are carried out; • the finished product is correctly processed and checked, according to the defined procedures; • therapeutic products are not supplied before an authorised person has verified that they have been produced and controlled in accordance with the requirements and any other regulations relevant to the production, control and release of therapeutic products; <p>Satisfactory arrangements exist to ensure, as far as possible, that the therapeutic products are stored,</p>	<p>new/emerging therapy development</p> <ul style="list-style-type: none"> • Provides additional clarity on the requirements/factors that need to be considered • Harmonisation with the international regulations/practice • There will be no cost or operational impacts on manufacturers arising from the change

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>medicine, science, medical laboratory science, nursing), and have had practical experience, at management level and under professional guidance, in the manufacture of blood and/or tissue products, in accordance with GMP requirements.</p> <p>112 Where operational events and quality policy conflict, the Director (or nominee), must have the authority to make a decision to resolve the conflict. The circumstances and the decision taken should be recorded.</p>	<p>distributed and subsequently handled so that quality is maintained throughout their shelf life.</p>	
<p>Clause 116: A system must be established and maintained to identify, document, review and approve all process and product changes. The results of the review must be recorded and any changes or modifications approved by the quality assurance manager, or nominee, before implementation.</p>	<p>Clause 116: A formal change control system should be in place to evaluate and document all changes that may affect the collection, preparation, storage, dispatch, quality control and quality assurance of product.</p>	<ul style="list-style-type: none"> • Requirements made less prescriptive allowing significant flexibility to develop procedures conducive to the new/emerging therapies • There will be no cost or operational impacts on manufacturers arising from the change
<p>Training Clause 207</p>	<p>Training Clause 208:</p>	<ul style="list-style-type: none"> • Less Prescriptive requirements • Provides additional clarity, inclusion of specific training requirements for personnel working where contamination is a

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>Learning and development programs must be developed in accordance with identified needs. Programs should be documented and include on-going training and refresher training.</p> <p>Clause 208</p> <p>Personnel must be made aware of the principles of GMP relevant to their duties.</p> <p>Clause 209</p> <p>There should be a formal mechanism for determining the competency of the workplace trainer and assessor to deliver training and assess the competency of the trainee.</p> <p>Clause 210</p> <p>For personnel at sites remote from the licensed site, who undertake a step in manufacture, (such as at tissue retrieval), there must be documentation to demonstrate that the work practice(s) undertaken are under the control of, and acceptable to, the licensed site.</p> <p>Clause 211</p>	<p>The manufacturer should provide training for all personnel whose duties take them into processing areas or into laboratories, and for other personnel whose activities could affect the quality of the product.</p> <p>Clause 209:</p> <p>Beside the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.</p> <p>Clause 210:</p> <p>Personnel working in areas where contamination is a hazard, (e.g. clean areas or areas where infectious materials are handled), should be given specific training.</p> <p>Clause 211:</p>	<p>hazard.</p> <ul style="list-style-type: none"> • Removal of superfluous clauses such as Clause 212 • There will be no cost or operational impacts on manufacturers arising from the change

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>All personnel must be shown to have undergone learning and development for the documented procedure relevant to the work practice being performed. There must be records to show that all personnel have acknowledged subsequent changes to a procedure(s).</p> <p>Clause 212</p> <p>Learning and development related to sanitation and personal hygiene should be included in staff learning and development programs.</p>	<p>Visitors or untrained personnel should not be taken into the processing and Quality Control areas. If this is unavoidable, they should be given appropriate information in advance and they should be closely supervised.</p>	
<p>Environmental control</p> <p>305 The environment must be suitable for the particular operation carried out. Processing steps must take place in an appropriately controlled environment.</p> <p>306 Where critical material is being stored, temperatures or other critical parameters must be</p>	<p>Processing areas</p> <p>Clause 308:</p> <p>Materials of construction should not pose a source of contamination to the product. Critical surfaces in processing areas should be non-porous, smooth, and easily cleanable.</p> <p>Clause 309:</p> <p>Where environmental conditions (e.g. temperature, humidity, air quality)</p>	<ul style="list-style-type: none"> • Provides additional clarity on the requirements/factors that need to be considered • Less Prescriptive requirements provide more flexibility to the manufacturer to incorporate emerging technologies and establish relevant monitoring systems • Removal of superfluous clauses such as 308 • It is not expected that this change will incur costs as manufacturers currently are required to show that the environment is suitable for the operations carried out

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>monitored and demonstrated to be in accordance with the manufacturer's instructions.</p> <p>307 Product manufactured in an "open" system must have the environmental conditions and monitoring of the area clearly defined, (such as for a "clean room" or laminar flow cabinet). Where environmental conditions are required to be monitored, records must demonstrate that</p> <p>The area is monitored frequently for microbiological contamination and air control.</p> <p>308 Access to environmental-controlled areas should be from corridors or other manufacturing areas. Where internal doors are a barrier to avoid cross-contamination, they must be kept closed when not in use and signposted to that effect.</p>	<p>could have an adverse effect on product quality, appropriate conditions should be defined, implemented and monitored.</p> <p>Clause 310:</p> <p>For products requiring control of microbiological bioburden, the manufacturer should establish and document the environmental requirements to which product is exposed during processing.</p> <p>Environmentally controlled processing areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. The suitability of the manufacturing environment should be verified by a documented monitoring program.</p> <p>The frequency of environmental monitoring should be based on the assessment of risk to the product.</p> <p>Records of environmental monitoring should be kept.</p>	
<p>Clause 307</p> <p>References the Annex 1 of the medicines cGMP, where clean air is required in the manufacture of a</p>	<p>Updated requirement that manufacturers must meet Annex 1 of the medicines cGMP, where applicable.</p>	<ul style="list-style-type: none"> • There may be costs incurred by manufacturers where clean air is required for the manufacture of product or where the product is labelled sterile

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
<p>product or where the product is labelled sterile, but does not require that manufacturers meet Annex 1.</p>	<p>Clause 300: Premises, facilities and equipment should be located, designed, constructed, adapted, maintained, and suitable for its intended purpose. Their layout and design should aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, build up of dirt and, in general, any adverse effect on the quality of products.</p> <p>In order to minimise the risk of microbiological, and particulate contamination, the manufacture of sterile products, or products required to have a low bioburden, should be subject to special environmental controls (e.g. Clean rooms, biological safety cabinets). Where required, applicable code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products should apply.</p>	<ul style="list-style-type: none"> • The TGA is not aware of any sterile human products that would be affected by this change and thus there is currently no impact • It is well accepted that if a sterile product is manufactured it should meet the same requirement as for a sterile medicine (Annex 1 of medicines Code of GMP)
<p>Clause 602: The record system must demonstrate that there is a complete history of the donation from donor selection/registration</p>	<p>Clause 415: Records should be completed at the time each action is taken and in such a way that all significant activities concerning the manufacture and</p>	<ul style="list-style-type: none"> • Less Prescriptive requirement, provides more flexibility to the manufacturer to incorporate emerging technologies and establish updated monitoring systems • No extra cost to the manufacturers

Existing Code of GMP (2000)	Revised Code of GMP (2012)	Impact on manufacturers
to the release for use as final product, and should include: identification and traceability to all critical manufacturing steps; traceability to a location, including transportation between sites; and accountability for records which have been withdrawn and archived.	disposition of products are traceable.	
None	<p>Clause 327:</p> <p>A specific requirement for labelling fixed pipe work for gases and liquids and water systems used in manufacturing.</p>	<ul style="list-style-type: none"> • Quality and safety improvement • Brings the Code on par with current practice. Manufacturers are already labelling the fixed pipe work for gases and liquids • There will be no cost or operational impacts on manufacturers arising from the change
None	<p>Clause 512:</p> <p>A specific requirement for handling of product returned from the customer.</p>	<ul style="list-style-type: none"> • Brings the Code on par with current practice. Manufacturers are already handling product returns. • There will be no cost or operational impacts on manufacturers arising from the change
None	<p>Clauses 831 and 832:</p> <p>A specific requirement for records to be maintained for freeze drying and cryopreservation of product.</p>	<ul style="list-style-type: none"> • Brings the Code on par with current practice • Clarifies requirements for record keeping of procedures • There will be no cost or operational impacts on manufacturers arising from the change.

Appendix B: Comparison of requirements between the new ID TGO and the existing Code of GMP 2000

Requirements	Principle	ID TGO	Existing Code (2000)
General requirements	Risk management	8(1)(a)	800
	Donor management	8(1)(b)	805 – 807, 815
	Acceptance and release criteria	8(1)(c)	713, 614
Requirements in relation to the medical and social history of prospective donors	Interview requirements	9(1) – (2)	608, 801 – 804, 812 – 813, 818, 821 – 824, 825-826
	Deferral criteria	9(3)-11)	621
	Donor age/ condition affecting product quality/ safety	9(12) – (13)	826
Requirements in relation to donor blood sampling, test kits, test protocols and test management	Donor sampling and testing	10 (1) – (5)	808, 827
	Test methodology	10 (6)-(8)	829, 830-838
	Contract testing laboratories	10 (7)-(8)	840-842 (contract laboratories)
	Archive samples	10 (9)-(10)	839
	Records of donor testing	10 (11)	612-613
Requirements in relation to donor physical assessment and testing	Physical assessment	11 (1)-(2)	803, 812, 821-823, 826
	Mandatory tests	11 (3)-(6)	828

Requirements	Principle	ID TGO	Existing Code (2000)
Requirements in relation to microbial control	Processes to minimise contamination	12 (1)	308
	Cell/ tissue collection times (starting material)	12 (1) - (2)	714
Requirements in relation to microbial control (cont'd)	Storage and transport conditions	12 (3)- 4)	1001, 1011 - 1013
	Release criteria - microbial	12 (5)	913
Requirements in relation to substances used in collection and manufacture	Quality and safety of solutions	13 (2) (a)	715, 902 - 903
	Quality and safety of materials	13 (2) (b) - (d)	703, 902 - 903

Appendix C: Table of regulatory costs currently applicable to the HCT sector

Fees and charges as at September 2012.

Table: Existing regulatory costs to HCT manufacturers (average)

Type of fee or charge	Average Cost	HCT sector (qty affected)
GMP Inspection fees biological manufacturer (biennially)	\$14,700	Tissues, cell therapy (all)
GMP Inspection fees testing facility (biennially) (average)	\$8000	Pathology (all)
GMP Inspection fees blood/HPC/ blood product manufacturer (biennially) (average)	\$12,000	Blood, blood products, HPC (all)
Annual ARTG inclusion charge (biologicals only)	\$5,810	Tissues, cell therapies (all)
Annual licence charges (except biologicals)	\$5600	Blood, blood products, HPC (all)
Application fee for a biological (one-off)*	\$950	Tissues, cell therapies (all)
Evaluation of dossier for a Class 2 biological (one-off)*	\$63,400	Tissues (19), cell therapies (unknown)
Evaluation of dossier for a Class 3 biological (one-off)*	\$126,700	Tissues (4), cell therapies (4)
Evaluation of dossier for a Class 4 biological (one-off)*	\$205,900	Tissues (0), cell therapies (unknown)
Evaluation of technical master file or plasma master file (annual)	\$29,600	Blood, blood products, HPC (all)

The introduction of the new regulatory framework for biologicals requires that all biologicals manufacturers (n=25 existing) submit a one-off application and dossier to the TGA. It is expected that all of these applications will be received in the next two years.

Biologicals fees and charges were developed and consulted in the Cost Recovery Impact Statement (see <http://www.tga.gov.au/about/fees-cris-biologicals-110201.htm>)

Appendix D: Issues and endorsed amendments for the revised ID Order

Issue	Comment	TGC Subcommittee endorsed response
<i>Transition arrangements for implementation of the ID Order as a TGO.</i>	Stakeholders raised concerns in relation to transition arrangements and management of long standing product inventories on implementation of the TGO. In particular, there were concerns that biological products already in inventory would need to be retested against additional tests specified for new donations. Currently a biological product can be used today if the practice at the time of collection had deemed the product suitable for release.	The TGC Subcommittee supported transition arrangements for all biological products that were collected prior to the date of implementation of the ID Order (12 months after commencement of TGO). Biologicals that do not meet requirements of the TGO must comply with the equivalent of the TGA revised version after Round 2 consultation Subsection 9(9), that is the requirement to retest is to be determined by the manufacturer based on risk and after consultation with the TGA.
<i>Proposed amendments to timeframes to conduct donor medical and social history interviews.</i>	Stakeholders had argued both for wider (30 days prior) and narrower (the day of donation) requirements. Internationally for different product sectors there was a diversity of requirements.	The TGC Subcommittee agreed that as the ID Order was to apply to a range of HCTs the timeframes should be set at 30 days prior to or 30 days after donation. It was agreed that the ID Order would establish minimum requirements and that product-specific TGOs should specify the appropriate limit that manufacturers should observe for that product.
<i>Applicability of donor social and medical history</i>	Areas of concern were raised regarding: subsequent redirection for allogeneic use when the intent at the time	The TGC Subcommittee endorsed that for autologous donations, manufacturers should determine which, if

Issue	Comment	TGC Subcommittee endorsed response
<i>criteria for autologous donors.</i>	<p>of collection was autologous use; misdirection of autologous donations for allogeneic use with a failure of quality system management; relevance of contaminated autologous donations in the total inventory. It was recognised that quality systems include multiple strategies for safety that need to operate together, and the neither questionnaires nor product labelling guaranteed safety. As autologous donations were diverse, it was proposed that manufacturers determine a risk-based approach. Dealing with this issue in product-specific orders was deemed to be not feasible, as not all tissues would be subject to product-specific orders.</p>	<p>any, of the medical and social history criteria listed in Table 1 of the ID Order should be applied. This will be informed by a risk-based assessment of the tissue or cells to be collected and must be justified in the product dossier submitted for product evaluation.</p>
<i>Ineligibility time period for non-medical drug injection.</i>	<p>Areas of concern were raised regarding: unreliability of donor's memories regarding non medical injected drug use; availability of laboratory testing for hepatitis; harmonisation of wording of this donor medical and social history criterion with current Australian Red Cross Blood Service questionnaire for blood donors wording.</p> <p>It was proposed that the guidelines for the ID Order explain non medical drug injection, including discussion on the use of medicines administered outside of</p>	<p>The TGC Subcommittee endorsed the proposal that donors who have ever injected, or been injected with, any drug for a non medical reason should be ineligible if evidence of risk behaviour occurred within the previous five years.</p>

Issue	Comment	TGC Subcommittee endorsed response
	Australia.	
<i>Ineligibility time period for risk of malaria.</i>	It was proposed that the malaria ineligibility requirements in the ID Order should be aligned with those in TGO 81 Standards for Blood and Blood Components, which are consistent with those of the Council of Europe (2009).	The TGC Subcommittee endorsed that the ineligibility time periods for the risk of malaria be those of the 14th edition (2009) Council of Europe requirements, with correction to “a malarial endemic area” in Table 1 of the ID Order.
<i>Malarial deferral for eye and cornea donations.</i>	It was suggested that as there is no significant risk of transmission of malaria via ocular tissue and this should be reflected in requirements for donations intended exclusively for ocular tissue use.	The TGC Subcommittee endorsed the inclusion of a new section in the ID Order, to the effect that testing and deferral period requirement of Table 1 relating to malaria are not requirements to be met when the donation is to be used exclusively for ocular tissue.
<i>Six month deferral of donor with prior exposure to risk of acquiring blood borne transmissible infection.</i>	A proposal was made to rely on secure quarantine arrangements to not release HCT product prior to 180 day resample and retest, and so depended on strict adherence to protocols and Code. It was suggested that the guidelines include explanations and a timeline diagram of how this deferral arrangement would work.	The TGC Subcommittee endorsed an addition to Table 1 of the ID Order, relating to a donor with exposure to risk of acquiring a blood borne transmissible infection, that the period of ineligibility prior to donation be qualified to the effect that ‘living donors who will be retested at 180 days are ineligible for 6 months from the time of exposure until collection of blood sample at 180 days for infectious disease screening’.

Issue	Comment	TGC Subcommittee endorsed response
<p><i>Ineligibility periods for donors with risk of prion disease.</i></p>	<p>Concerns were raised regarding the ineligibility criteria for risk of prion disease, in particular the applicability of donor deferral criteria to minimise risk of prion disease from ocular donors.</p> <p>After consideration of international requirements for donor referral, the impact of this on potential donor numbers and the risk of the transferral of prion disease, such as vCJD, from a donated cornea to the recipient, it was proposed that donors with a risk of prion disease should be permanently ineligible as donors, including for donations of ocular tissue.</p> <p>It was further argued that donor exclusion criteria should relate to 'blood components', and not 'blood products'.</p>	<p>The TGC Subcommittee endorsed that the requirements of Table 1 of the ID Order relating to the permanent ineligibility of donors with a risk of prion disease apply to ocular tissue.</p> <p>The TGC Subcommittee endorsed that deferral for donors apply to those who were recipient of allogeneic blood or blood components (but not blood products).</p>



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