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REVIEW

Raising the standard: changes to the Australian Code of Good Manufacturing Practice (cGMP) for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products

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Summary

In Australia, manufacture of blood, tissues and biologicals must comply with the federal laws and meet the requirements of the Therapeutic Goods Administration (TGA) Manufacturing Principles as outlined in the current Code of Good Manufacturing Practice (cGMP). The Therapeutic Goods Order (TGO) No. 88 was announced concurrently with the new cGMP, as a new standard for therapeutic goods. This order constitutes a minimum standard for human blood, tissues and cellular therapeutic goods aimed at minimising the risk of infectious disease transmission. The order sets out specific requirements relating to donor selection, donor testing and minimisation of infectious disease transmission from collection and manufacture of these products. The Therapeutic Goods Manufacturing Principles Determination No. 1 of 2013 references the human blood and blood components, human tissues and human cellular therapy products 2013 (2013 cGMP). The name change for the 2013 cGMP has allowed a broadening of the scope of products to include human cellular therapy products. It is difficult to directly compare versions of the code as deletion of some clauses has not changed the requirements to be met, as they are found elsewhere amongst the various guidelines provided. Many sections that were specific for blood and blood components are now less prescriptive and apply to a wider range of cellular therapies, but the general overall intent remains the same. Use of 'should' throughout the document instead of 'must' allows flexibility for alternative processes, but these systems will still require justification by relevant logical argument and validation data to be acceptable to TGA. The cGMP has seemingly evolved so that specific issues identified at audit over the last decade have now been formalised in the new version. There is a notable risk management approach applied to most areas that refer to process justification and decision making. These requirements commenced on 31 May 2013 and a 12 month transition period applies for implementation by manufacturers. The cGMP and TGO update follows the implementation of the TGA regulatory biologicals framework for cell and tissue based therapies announced in 2011. One implication for licenced TGA facilities is that they must implement the 2013 cGMP, TGO 88 and other relevant TGOs together, as they are intricately linked. This review is intended to assist manufacturers by comparing the 2000 version of the cGMP, to the new 2013 cGMP, noting that the new Code extends to include human cellular therapy products.

Key words: Blood, cellular therapy, cGMP, code, manufacture, standard, tissue.

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INTRODUCTION

The Code of Good Manufacturing Practice (cGMP) for Human Blood and Tissues has been the relevant standard for licensed Therapeutic Goods Administration (TGA) manufacturing facilities since its introduction in August 2000.[1] The GMP code has finally seen the release of a long awaited update in the 2013 version that has been expanded to include human cellular therapy products[2] (see Fig. 1). Since 2000 an increasing shift of interest and activity towards use of cell based therapies has changed the regulatory landscape worldwide toward immunotherapy and regenerative medicine products. In Australia this led to the implementation of the initial Australian Regulatory Guidelines for Biologicals in 2011,[3] often referred to as the biologicals framework, for cell and tissue based therapies. This new framework is based on applying increased regulatory oversight in line with perceived or potential increased risk of the product to the recipient. As such, the new framework sets out four classes of products, Class 1 to Class 4, where Class 1 provides minimal risk and Class 4 products provide the highest level of potential risk to the patient. In this framework manufacturing sites need to comply with defined standards for quality, safety and efficacy to attain a TGA manufacturing licence. All regulated biological products manufactured within the guidelines will also be listed in the Australian Register of Therapeutic Goods (ARTG). The Biologicals Regulatory Framework is a system to manage these products and a series of requirements to be completed by manufacturers, sponsors, healthcare professionals and interested parties before products are marketed in Australia. The biologicals framework currently excludes examples such as human haemopoietic progenitor cells (HPC), organs for direct transplantation and reproductive materials. However, it is notable that the cGMP update and the application of the Therapeutic Goods Order (TGO) No. 88[4] specifically reference and include human HPC. The cGMP update and TGO 88 provide further guidance for stakeholders to achieve compliance and are intrinsic to the implementation of the TGA biologicals framework. There are also many other

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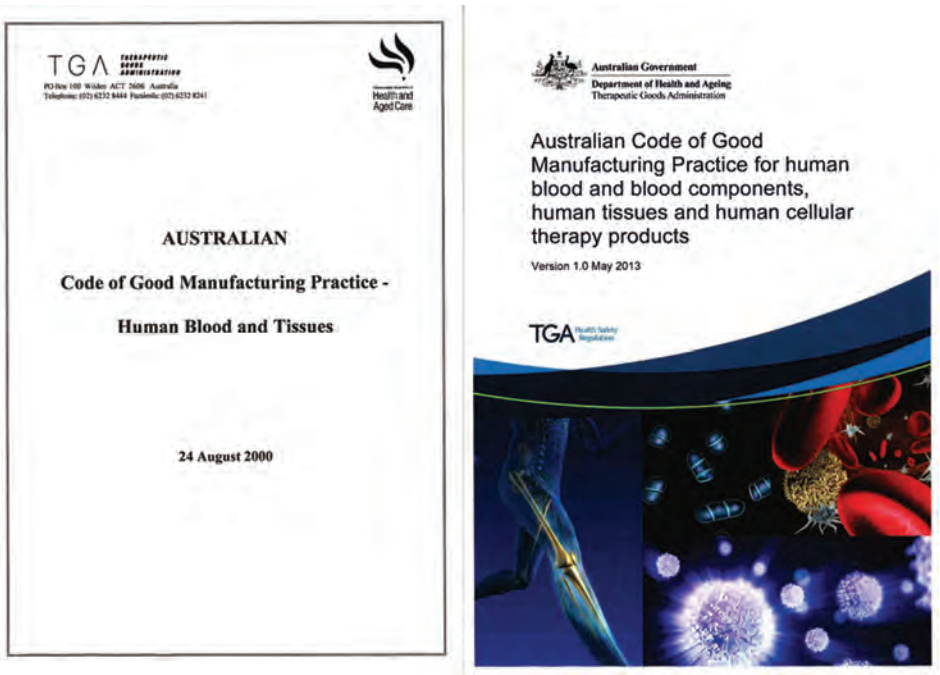

Fig. 1 Title pages of the 2000[1] and 2013[2] versions of the Code of Good Manufacturing Practice

framework documents and other relevant Therapeutic Goods Orders (TGOs) that are updated frequently and are available on the TGA website.[3,5] Examples of these include (but are not limited to):

- TGO 75 Standard for Haematopoietic Progenitor Cells Derived from Cord Blood
- TGO 81 Standards for Blood and Blood Components
- TGO 83 Human Musculoskeletal Tissues
- TGO 84 Human Cardiovascular Tissues
- TGO 85 Human Ocular Tissue
- TGO 86 Human Skin
- TGO 87 General Requirements for the Labelling of Biologicals
- TGO 88 Standards for Donor Selection, Testing and Minimising Infectious Disease Transmission via Therapeutic Goods that are Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.

The legislation works in a hierarchical manner. Initially a product must be deemed a therapeutic good, noting organs and some HPCs are excluded from this definition. The new cGMP and TGO 88 covers all human cell and tissues including those defined as biologicals and medicines. The TGA has currently excluded certain products such as reproductive technology, fresh organs for transplantation, and also specifically defined products as excluded by listing them as such in associated legislation. This is documented in the Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011.[6–9] For example, the new biologicals framework currently excludes HPC used for haemopoietic reconstitution, *in vitro* diagnostic devices (IVDs), samples of human cells or tissues used solely for diagnostic purposes, blood and blood components, biological medicines, including vaccines with no living human cells, recombinant products, and plasma derived products.[10,11] It is currently unclear if these exemptions will be maintained in the longer term. The National Association of Testing Authorities (NATA) has published the National Pathology Accreditation Advisory Council (NPAAC) Requirements for Procedures Related to the Collection, Processing, Storage and Issue of Human Haemopoietic Progenitor Cells (Third Edition 2009).[12] Many Australian HPC transplant and apheresis collection centres are accredited by NATA to these guidelines. TGO 75 indicates that manufacturers of HPC from cord blood use the FACT-NETCORD International Standard.[13,14] All three AusCord unrelated cord blood banks in Australia have attained and maintain TGA manufacturing licences. TGA compliance is assessed during audit conducted by TGA inspectors and provision of a Technical Master File that documents standards for product compliance, efficacy and quality. For non-cord blood HPCs, the British Pharmacopoeia, European Pharmacopoeia and the US Pharmacopeia are other standards also used.[15]

HIGHLIGHTS AND OBSERVATIONS

This comparison and review of the 2000 cGMP, Human Blood and Tissues, with the new 2013 cGMP recognises the scope to include human cellular therapy products. However, the comparison between the versions does not define any particular elements relating solely to human cellular therapy products within the text of the 2013 cGMP. Instead, the quality requirements are now applied over the range of cellular therapies as well as blood, blood components and tissues. Overall, the 2013 cGMP is generally less prescriptive across all areas, with a risk assessment approach being adopted for most process related decision making. Most of the specific requirements relating to donor selection, testing and product release are removed from the new cGMP and are now described within the TGO 88 standard. The notable requirements and clauses removed from the previous cGMP version are summarised in Table 1. Many of these omissions may be re-interpreted as requirements within other more generic clauses of the 2013