

Regulation of cellular therapies: the Australian perspective

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Summary

The first step in the process of regulating cell-based products in Australia was taken in 1991, when the code of good manufacturing practice (cGMP) for 'Blood and Blood Components' was instituted. Paradoxically, it focused on the regulation of plasma fractionation, the non-cellular component of blood. Subsequently, Australia's regulatory body for medicinals, the Therapeutic Goods Administration (TGA), has clearly stated that all cell-based therapies utilizing components of blood and/or tissues will be regulated. The final landscape for the regulation of cellular therapies has yet to be defined, but is likely to be clarified within the next 12 months. The current cGMP for 'Blood and Tissues' is the regulatory document for all aspects of cell processing, including standard blood components (cellular and plasma), cord blood and allogeneic cells for storage. Currently, there are some exemptions to

government regulation, and the most important of these is autologous hemopoietic stem cells (HSC). Indeed, no licensing is required for processing of HSC at the moment, although most centers subject themselves to a self-imposed auditing system through the National Association of Testing Authorities, Australia. However, it is anticipated that within 12 months this and the other exemptions within the Act will be removed. The TGA will become the formal regulator of all cell-based therapies, and laboratories will be required to apply for cGMP auditing and licensing. It is likely that the Foundation for the Accreditation of Cellular Therapy (FACT) guidelines or others of a similar nature, will form the basis of one of the regulatory standards for HSC processing. Of particular note is the inclusion of apheresis as an integral component of cGMP licensing.

Regulation before 1999

Regulation of all therapeutics (i.e. pharmaceuticals, devices and cellular-based products) in Australia is governed through the Therapeutic Goods Act 1989 and the associated Therapeutic Goods Regulations 1990, which is enforced through a Federal agency known as the Therapeutic Goods Administration (TGA). The relevant web site is www.tga.health.gov.au (visited 24th May 2003). The Act has two central components relevant to manufacturers of cell therapeutics in Australia:

- Assessment of *therapeutic goods* prior to inclusion on the Australian Register of Therapeutic Goods (ARTG) under Part 3-2 of the Act.
- Assessment of *manufacturers* for licensing against a manufacturing principle, specified as a code of good manufacturing practice (cGMP) under Part 3-3 of the Act. Manufacturing is defined to include collection,

processing, assembling, labelling, storage, testing and release of any part or process involved in the production of the goods.

In 1991 blood plasma for fractionation was included in the scope for regulation, and was linked to a code of GMP for 'Blood and Blood Components'. This cGMP was used by TGA auditors who assessed blood collection and processing centers for the purpose of licensing under Part 3-3. In reality, this translated into auditing and licensing of the Australian Red Cross Blood Service (ARCBS) (the only collectors of blood products at the time) and the Commonwealth Serum Laboratories (CSL) (the only plasma fractionator). The requirements for Part 3-2 of the Act were typically addressed by CSL, who submitted detailed dossiers for evaluation of each plasma-derived product for quality, safety and efficacy, as well as being subject to their own cGMP audits using a medicinal

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(i.e. pharmaceutical) standard. This structure provided *de facto* regulation of the remaining blood components (i.e. red cells and platelets) as the ARCBS was then the only organization collecting both plasma and other blood components for homologous use, and their cGMP systems indirectly encompassed the processing of non-plasma products. As there was no direct regulation of blood components other than plasma, there was no formal government regulation of autologous red cell collection centers, hospitals collecting platelets by apheresis, or collection of autologous/allogeneic BM or mobilized peripheral blood.

At this time, there were also a number of important exemptions in the Act. The provision of safety, quality and efficacy data did not apply to:

- cGMP licensed organizations that were involved in collection or storage of human tissue for “implantation in the human body that is obtained stored and supplied without direct alteration to its biological...properties”.
- Blood and blood components manufactured by the ARCBS.
- Goods for initial use in human volunteer studies, provided that these clinical trials were *notified* to the TGA via the Clinical Trials Notification (CTN scheme) or *registered* with the TGA (CTX scheme).

Therapeutic goods could also be provided to seriously ill patients outside of trial use through a Special Access Scheme (SAS). Such treatments had to be for a specific individual's use under the direct care of the prescribing physician. Whilst whole organs have never been classified as a ‘therapeutic good’, tissues of an essentially ‘non-viable’ nature, such as bone, skin, heart valves and ocular tissue, were subject to Part 3-3 (licensing) with their own cGMP for human tissues (released in 1995), but excluded from any requirement under Part 3-2 (assessment of therapeutic goods).

Furthermore, the requirements to obtain a cGMP licence did not apply to the following.

- Human blood and components other than plasma prepared by a blood donation center from human blood. Through this exemption the TGA made a broad interpretation that other cellular products, such as HSC and other blood-derived cells, were excluded from any regulation, irrespective of autologous or allogeneic use.

- Blood and blood components collected by a medical practitioner for therapeutic application to a patient under the practitioner's care.
- Goods manufactured for Phase 1 clinical trials. Of note, whilst the requirement for licensing of facilities for Phase 2 and 3 trials was clear, there was no evidence of actual audit of facilities manufacturing cell-based therapeutics for such trials.

Regulation after 1999

At the direction of the Australian Health Ministers Advisory Council (AHMAC), progressive amendments began to appear, leading to the full regulation of *all* blood components. In the eyes of the TGA, the ultimate need for cGMP licensing of all facilities involved in blood processing remains uncompromising. However, the issue of how to implement a safety, quality and efficacy dossier system for ‘fresh cells’ has been problematic.

In 2000, the TGA issued various orders, and the Act was amended such that:

- With regard to facility licensing (Part 3-3), in August 2000 a new cGMP of “Human Blood and Tissues” was implemented.
- For the purposes of assessment of product quality (Part 3-2), centers producing cells had to submit an abbreviated form of a safety and quality data file — known as a Technical Master File (TMF).

Therapeutic Goods Order 66 (August 2000) further specified that:

- The autologous and directed patient use (under the direct control of a medical practitioner) exemption remained in place.
- Stem cells were to be classified as a blood component.
- The Council of Europe Guide to the preparation, use and quality assurance of blood components was used as the minimum standard for manufacture for the purposes of assessment.

With the loss of the blood donation center exemption, centers collecting blood for processing of HSC also lost their *de facto* exemptions. The implications for cord banks was that they were now required to apply for licensing against cGMP, and submit a TMF if these were banked for allogeneic use, or if they were banked for life for autologous use (if not under control of the recipient's medical practitioner). Collection and storage for autolo-

gous use and collection, and immediate infusion of allogeneic cells (provided the patient was under the care of the same medical practitioner responsible for collection) remained exempt. These exemptions remain in place today, but are likely to change within the next year (see later section).

Current implications of regulation

Our own experience of the licensing process indicates that most laboratories producing cellular therapeutics would not be immediately adversely affected by the requirements as audited by TGA. The items specified by the cGMP are not significantly different from those cited by local and international standards. Facilities such as clean rooms are not required for standard HSC processing. Furthermore, we are fortunate that the cGMP allows the use of non-registered components (under Part 3-2 of the Act) such as DMSO, provided this has been appropriately tested for sterility. Similarly, the cGMP allows collections from seropositive patients, provided explicit medical approval for use is documented. However, certain key issues remain, which are discussed below.

Cell therapy trials

Whilst all clinical trials are exempt from the Part 3-2 requirements of the Act (assessment of therapeutic goods), Phase 2 and 3 trials that use cell therapeutics are expected to be cGMP licensed. Those conducting Phase 1 studies, or studies involving design and prototype development of new devices, remain exempt. Indeed, in recent weeks the TGA has started ‘flexing its muscles’ by withholding approval for Phase 2 and 3 cell-therapy clinical trials in unlicensed facilities. As very few facilities in Australia have any GMP accredited components, this will inevitably slow Phase 2 and 3 cell-therapy research, until more facilities are licensed.

Change in auditor

Most Australian centers processing HSC are currently being accredited through a national pathology laboratory accreditation process, using a laboratory standard known as “Guidelines for Laboratory procedures related to the processing, storage and infusion of Haemopoietic Stem cells for Transplantation from Bone Marrow, Mobilised Peripheral Blood and Umbilical Cord Blood” issued by the National Pathology Accreditation Advisory Council (NPAAC) [8]. This standard is audited using volunteer

peer assessors, co-ordinated through the National Association of Testing Authorities, Australia (NATA).

With the new cGMP auditing requirements, it is expected that centers will now be subject to higher intensity audits, as the cGMP auditors are professional full-time auditors allocating a minimum of 2 days to each audit. Furthermore, the frequency of TGA licensing audits will be greater, with a minimum of an annual audit as opposed to a 3-year audit cycle with NATA.

Apheresis

The audit scope for cGMP will include apheresis. This is a particularly critical issue because until now, apheresis has not been part of standard NATA laboratory accreditation. Indeed, the TGA have not been willing to consider apheresis units separately from HSC processing facilities, and the impact of this should not be under-estimated. Moreover, this will cause headaches for central processing laboratories receiving collections from multiple sites, and in phase 2 and 3 clinical trials utilizing apheresis-collected cells.

Testing of cells

Accredited laboratories under the NPAAC standard will find that their existing testing arrangements will be unsatisfactory under the cGMP for Human Blood and Tissues. Some issues include the following.

- NPAAC does not specify a testing interval for product testing for mandatory virus serology. TGA cGMP auditors will require a nominated maximum interval between serology testing and harvesting (in our case, 28 days).
- Any testing that forms part of the release criteria must be performed by a TGA-licensed laboratory. This means that cell counts, mandatory serology, microbiology and flow cytometry must be provided by a TGA-licensed provider — either external or internal (included in GMP licence).

Fees and charges for regulation

The typical audit fee from TGA for a 2 day audit is \$AUD 8500. In addition to licence costs, services will need to budget for the fees for TMF assessment, which are based upon page numbers and can easily exceed \$AUD 20 000. Fortunately for not-for-profit hospitals, Section 59 (3) of the TGA Act states that “No licence or inspection fees are

to apply to non-profit hospital supply units”, and such services may be able to avoid these fees.

Preparation of a technical master file

Few centers will have experience in the requirements to prepare a file documenting the safety and efficacy of cell therapeutics, to satisfy the requirements of Part 3-2 of the Act. The requirements to develop process maps, critical check-points and methods of administration will be challenging. TGA reviewers require extensive background clinical and scientific information, including detailed information in how cross-contamination is avoided during manufacturing. Our own TME, which in first draft was nine pages long, was only deemed acceptable after substantial amendment, resulting in a document exceeding 100 pages. This review process lasted considerably longer than the audit process!

Likely regulatory changes in 2003

A new name for the regulatory and auditing sections

Recently, the Australian Health Ministers’ Conference (AHMC) and its advisory body, the Australian Health Ministers’ Advisory Council (AHMAC) approved a future focus of the TGA — the identification, audit and license of facilities that process human tissues and emerging biological therapies. Indeed, evidence of the TGA’s new regulatory focus emerged in 2003. A new TGA office, the Office of Devices, Blood and Tissues was created, which now includes the cGMP audit section — which, in turn, was renamed the Manufacturer Assessment Section.

‘Standards’ to be used for cGMP licensing

Not surprisingly, hurdles have been encountered. Up until now the standard used for HSC by the TGA has been the eighth edition of the *Council of Europe guidelines for human blood and blood components* [1] — but the ninth edition will *not* contain a chapter on HSC! The TGA convened an *ad hoc* expert Advisory Group to consider standards for HSC harvested from apheresis and cord blood. Standards considered included those in the Reference list [2–8]. They reported a preference for the following standards:

- Non-placental HSC: *Standards for hematopoietic progenitor cell collection, processing and transplantation* — FACT [3].
- For placental HSC: *International standards for cord blood collection, processing, testing, banking, selection and release* —

NETCORD and Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) [4].

The role of these standards is not only to provide a minimum benchmark for the cGMP auditors, they also advise the assessors of the TME, for instance, as to whether adequate quality control testing is documented within the TME. However, the *ad hoc* committee emphasized two important caveats over the use of these standards. Firstly, the FACT-derived standard would only apply to product quality and quality system management, and would not include the sections relating to medical practice and, secondly, the requirements of the cGMP for Human Blood and Tissues would continue to take precedence over any requirements specified in the Standards, as would other legal requirements for clinical research and state-based legislation. Formal resolution of this issue will be a priority for TGA, and a new Therapeutic Order is imminent — presumably specifying the above standards or others of a similar nature.

What about autologous and allogeneic stem cells?

Another critical issue is the TGA’s position on current exemptions in the Act — namely those of autologous and directed-product exemptions, and the exemption for medical practitioners. TGA has begun to propose a risk-based approach (rather than based upon the product *per se*), where the degree of manipulation dictates the extent of regulation. Under such a scheme, it appears that the above exemptions would no longer apply. At a recent industry workshop, a TGA representative publicly proposed the schematic shown in Table 1.

The key issue is that apheresis for the purposes of cell harvesting for manufacture of cell therapeutics is considered to require sufficient manipulation that it needs cGMP and a TME.

Resolution of outstanding issues

There is no doubt that there will be further modifications over the next few months to the proposed ‘risk-based’ regulatory structure of HSC outlined above. Further issues for discussion are whether there should be a new cGMP for cellular therapeutics, and the extent of clinical review by TGA for new cell-based therapeutics. Moreover, whilst the removal of the autologous and directed use exemption will result in capture of many otherwise exempt centers,

Table 1. The level of regulation proposed for varying degrees of manipulation of HSC

Degree of manipulation	Level of regulation
HSC removed from donor as BM and immediately transplanted (i.e. no manipulation)	No regulation
HSC removed from donor as BM — frozen and stored	CGMP
HSC removed from donor by apheresis	cGMP and TMF
HSC removed from donor/patient, manipulated genetically and transplanted	cGMP, TMF and other requirements ¹

¹*Gene-therapy trials are regulated by the submission of a Clinical Trial Registration (CTX) to the TGA, after prior approval by the Gene Therapy Research Advisory Panel.*

the exemption has been illogical when multiple products are manufactured and banked. Many centers engage in both currently regulated and exempt products, and such centers are unlikely to have segregated facilities and processes for these respective requirements. These issues are especially relevant to the many centers that have been engaged in un-audited Phase 2 and 3 clinical trials, which are at risk of having accrual in their studies suspended until cGMP licenses are issued. Last, but by no means least, the financial impact on cell-processing centers is likely to be substantial and, as yet, no compensation mechanism for the introduction of this higher level of regulation has been proposed. If no funds are allocated, it would be reasonable to anticipate that some centers may be unable to direct sufficient resources to meet the demands of the new regulatory requirements.

Recently, the TGA announced stakeholder consultations in all Australian States to consider the outstanding issues. Although many concerns are being expressed, once resolved, there is no doubt that regulation will result in improved quality and safety of cell therapeutics in Australia.

References

- 1 Council of Europe guidelines for human blood and blood components. 8th edn. Council of Europe (CoE), 2002.
- 2 Guide to safety and quality assurance for organs, tissues and cells. 1st edn. CoE, 2002.
- 3 Standards for hematopoietic progenitor cell collection, processing and transplantation. 2nd edn. FACT, 2002.
- 4 International standards for cord blood collection, processing, testing, banking, selection and release. 2nd edn. NETCORD and FAHCT, 2001.
- 5 Standards for hematopoietic progenitor cell and cellular product services. 3rd edn. American Association of Blood Banks (AABB), 2002.
- 6 Standards for cord blood services. 1st edn. AABB, 2001.
- 7 Guidelines for the blood transfusion services in the United Kingdom. 5th edn. London: The Stationery Office, 2001.
- 8 Guidelines for laboratory procedures related to the processing, storage and infusion of haemopoietic stem cells for transplantation from bone marrow, mobilised peripheral blood and umbilical cord blood. 1st edn. National Pathology Accreditation Advisory Council (NPAAC), 1999.