Introduction

This submission contains the response of the Steering Committee for the Centre for Cell and Gene Therapy (CCGT) at the Westmead Research Hub Campus in NSW to the Draft Australian Code of Good Manufacturing Practice human blood and blood components, human tissues and tissues and human cellular therapies.

Members of this Steering Committee represent research and clinical groups on the campus from the bone marrow transplantation, pancreatic islet transplantation and gene therapy fields. It contains representation from Westmead Hospital, Westmead Millenium Institute, The Children's Hospital at Westmead, the Kid's Research Institute and the Children's Medical Research Institute.

This committee is charged with the oversight of the development of a campus-wide GMP compliant quality system to provide the platform for the provision of cellular therapies to patients as an ARTG listed product where applicable, or in a GMP compliant manner where possible if the cellular product is considered as exempt, or under the provisions of "Exceptional Release".

General comment

This Draft Code of GMP contains many elements which are already underway in Australian hospitals and their associated Research Institutions. However, implementation as written will require an upgrading of all of the processes involved in production of a variety of human tissues for therapeutic use, including quality management, process development, facilities structure, review and training. On the Westmead campus all clinical and research groups have been actively involved in instituting quality based programs to underpin their activities over the past decade, with the major constraint on progress being the ascertainment of funding to support these activities and the procurement of appropriately experienced staff.

Implementation of the Draft Code of GMP will require a major increase in both human resources and funding for facilities development. Implementation without enhancement via :

1. an immediate increase in the staffing of these facilities and
2. immediate availability of funds to support physical alterations to facilities to allow them to comply with the demands of the code

will impact adversely on patient care, as it will result in the cessation of function of a high percentage of currently practicing transplant and cell therapy facilities.

The implementation of a campus wide quality system, under the direction of the CCGT Steering Committee is currently externally funded by both Federal and NSW government grants, administered through Research Infrastructure Support Services (RISS Pty Ltd). These grants were gained via a competitive application process in 2009. This funding is

sufficient to provide salaries for a minimal number of staff, minor refurbishment of existing infrastructure and the provision of consulting services to direct the design and implementation the system. It is limited, however, to two years funding (ending mid 2011), and does not provide for on-going maintenance of the quality system, nor the physical faciltities. The past and future maintenance of current infrastructure is expected to be funded from within the budgets of the Area Health Services represented on the campus.

It is the opinion of the CCGT Steering Committee that a co-ordinated approach to implementation of the Draft Code is a necessity, with input simultaneously through regulatory bodies, state and federal health departments and treasury departments. The major issue to be addressed by all of these stakeholders is resourcing of the implementation to avoid withdrawal of existing services and the abandonment of research programs which seek to adopt emerging cell therapies for the clinical benefit of patients in NSW.

Comment on Introduction

"Product standards to be established." The definition of a technical standards file and proposed "product groups" need to be clarified as soon as possible, as it is important that the TGA again understands there is no point of comparison between a drug and an cellular therapy product.

In addition, it must be recognised that the volume of preparation of some cellular therapy products is small, with each product, in general, being manufactured on a patient specific basis. Centres are in danger of being saddled with a regulatory impost for such products that will swamp their ability to undertake or introduce the therapy.

Specific Comments on Sections

Section 1 Quality Management

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The quality system should provide a structured and organised approach for quality to be achieved. There should be resources at all levels to enable objectives to be met effectively.

The major barrier to implementation of a quality system to meet the required standard is the lack of perceived need to undertake this activity by under-funded hospitals and area health services. The need for these systems is well understood by both clinical and technical staff working in these areas, but the systems required are complex, time consuming to implement and require prolonged input from different individuals with clinical, scientific, quality, engineering and possibly pharmaceutical experience. In particular, it is extremely rare to find quality staff that have any knowledge or experience in the areas of cellular therapies, as the complexity and uniqueness of many cellular therapy manufacturing processes is very high. It will be impossible for technical and

scientific and clinical staff to meet the QM requirements in addition to their current duties. Implementation of adequate quality systems will require major funding support to include direct employment of additional staff and release cover for all currently employed staff to allow for their input into the development of a relevant and workable system.

The Steering Committee of the CCGT at Westmead is committed to implementing a campus-wide GMP compliant quality system for existing and future cellular therapies, however, this process faces all of the existing problems as stated above. That is, difficulty in sourcing funding to underpin the development of the quality system, procurement of suitably experienced staff and the ability to provide the required amount of input by existing staff given their current level of clinical and/or research activity. Existing staff involved in the process are not funded by their current employers to undertake these additional activities.

Solutions to these problems may include :

- centralisation of cell processing into adequately funded larger facilities which to a certain extent is the model being adopted by the Westmead CCGT. However, the funding issues still exist on this scale. Further centralisation across NSW would be problematic as it would be likely to meet vigorous local opposition, with delays in agreeing and identifying the site and administration of such facilities, and likely disagreement on who and how funding would be arranged under current state and health area models

- federal takeover of cell processing with centralised federal funding for single or dual state facilities. This however would be unlikely to occur rapidly, and would require considerable time and negotiation to implement at government and health administration levels

- diversion of other quality management officials from other duties predominantly in diagnostic pathology laboratories. However, these staff are not skilled in production facility quality management and would take a considerable amount of time to develop the necessary expertise.

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In relation to the supply of therapeutic product:

Nearly one half of all products used for unrelated allogeneic HPC transplantation in Australia have been sourced from overseas. The most widely used system of verification that these products have been produced and controlled adequately is an international standard, the FACT standard, which is already being used in several centres in Australia. Since TGA will have no control over this majority of material sourced from overseas many Australian HPC transplant centres are already in the process of implementing the FACT standard. This standard includes both the clinical process of transplantation, and manufacture of the product. Consequently, implementation of any system through the TGA will be ineffective for many of HPC products, duplicates some elements of what is

being done, and falls short of the FACT standard that already being adopted. It has nothing to offer except significant cost.

Section 2 Personnel and Training

There are significant staffing implications beyond the employment of QM officers. The draft code requires that all staff receive initial and continuing training relevant to needs. The Committee estimates that a 30-50% increase in staff complement would be required based on the needs for ongoing training and the requirements in day to day work for fulfilment of the code principles. This increase in training activities cannot be absorbed by existing staff within their current schedules and responsibilities.

The requirement of the Draft Code that that the manufacturer employ an adequate number of personnel with appropriate qualifications and practical experience is not liley to be met where the manufacturer is a person or persons employed by a hospital or area health service. **It is essential that the TGA recognize that most often, the manufacturer (ie the product manager in the facility) does not have authority over the capacity for staff employment.** There is a serious danger that the necessities of the code will not be comprehended or if comprehended, not heeded by hospital/area health service administrative staff with no prior experience of manufacturing in a medical environment. The issues of resource constraint mentioned above may lead to inappropriately poor staffing and dangerous conditions.

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The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

While this sentiment is noble, it is also naive. In an environment of constrained resources, it would be far better for the TGA to mandate a ratio of quality management to technical staff and to dictate certain terms of employment to ensure that administering institutions are not able to escape the responsibility for employment of appropriate individuals.

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The quality and production nominees should have a relevant tertiary level qualification, (eg. in medicine, science, medical laboratory science, nursing), and have had practical experience, at management level, in the manufacture of therapeutic products.

It will be possible to meet this requirement only for a limited number of positions. This requirement will be especially difficult to meet in relation to quality nominees due to the specialist nature of the products being manufactured within the areas of HPC transplantation, pancreatic islet transplantation and gene therapy. This is not only due to the complexity of both well established and newly adopted processes being used, but also most importantly due to the complexity of the clinical context in which patients receiving cellular therapy products are being treated. The current and past experience in several groups on the Westmead Campus has demonstrated that, for example, quality systems staff coming from a blood manufacturing background have almost no experience in

clinical HPC transplantation and have a perspective which requires significant re-education before such staff can start working usefully in these positions.

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The duties laid out in 207 are duties of the manufacturing staff, not the quality staff, as all these items must be completed before each product is released.

Section 3 Premises and Equipment

Section 3 of the Draft Code describes requirements of Premises and Equipment that for many facilities will be of a standard in excess of those currently available. For such facilities, constraints on rectification will include money, space, availability of local services within larger health institutions, facility constraints based on physical needs of adjacent parts of institutions and availability of appropriate personnel to implement equipment protocols. Since many facilities are part of larger institutions (eg pathology services, hospital departments, state networks etc) some of these issues are also constrained by political processes that will take time to work through. It is appropriate that any introduction of a draft code be sensitive to this fact or have an alternative strategy for rapid resolution. Although the regulatory body may take the view that implementation is not an issue with which it needs to concern itself, it would be foolish to imagine that the implications of service limitation will not ultimately and probably rapidly return to impact upon the originating regulatory document. This will apply particularly in areas of established cell provision where established lobbies within areas such as leukaemia and stem cell transplantation are most unlikely to tolerate service limitation (resulting in certain death) even if aimed at overall quality improvement.

Section 5 Control of Material

Some physical requirements of the draft code such as locked and controlled storage areas may be impossible for facilities working within larger organisations and constrained by the factors outlined above to implement. A cell processing facility may not have the luxury of being able to provide a lockable storage area within a reasonable distance of the laboratory. Materials for some processes may not be manufactured to the standard that the draft suggests is mandatory. This is particularly the case given the strong translational research focus of many cell therapy facilities. In such cases, products that are known to be life saving or reduce disease morbidity may be available only in forms that are not licensed for human use or not manufactured as clinical grade materials. The code must take account of these situations and allow for a mechanism that permits ongoing work with these products where experts deem the risks if adequately explained to and accepted by the patient are justified by the potential benefits.

Section 7

The working in this section reflects the drug product origin of the whole document. It is too late to issue a recall for a product which has already been infused into a patient. This sections requires significant input from the manufacturers of cellular therapy products, rather than rely on the current drug manufacturer perspective.

Section 8 Collection and Processing

Overall, almost all of these points are so general that they are of no value when compared to the NPAAC standard or FACT standards in relation to HPC.

More specifically, it is essential that the TGA understand that for many cell processing facilities, collection from the donor takes place in facilities, cities and countries far from the production facility itself and completely outside the jurisdiction of that production facility. Excellent examples include the use of unrelated donors where the starting material from the donor is collected in a variety of health facilities in countries overseas. This includes the use of cord blood units collected most often in birthing facilities in a variety of nations worldwide. It would be absurd to expect that the production facility could influence the procedures of each of these institutions or could collect information on the procedures for each product produced. Control of these facilities is largely vested in administrative structures charged with ensuring that standards of collection are maintained to an acceptable level for the purposes of clinical transplantation. The regulations imposed on the production facility in relation to collection must be limited to collection outside these internationally accepted norms (eg the Red Cross, the International Bone Marrow Donor Registry, the various national cord blood banks etc) and where the production facility has a reasonable chance of being able to exert influence for change (probably limited to institutions within its own area health service and even that not definitely). While it is understandable to imagine that manufacturing of the product must control collection, in reality the process of collection for product manufacturing is frequently intimately involved with surgical, medical, obstetric nursing and other departments outside the production facility. Where possible locally, time and quite possibly an entire renegotiation of duties will need to be considered for many of the draft code principles to be enacted and of course once again, resource implications must also be raised in terms of staff to undertake the necessary assessments, money for testings, follow up and documentation. It is likely that is will take time and some reflection for all areas to accept the need for restructuring, both physical and financial, to allow this process to proceed. It will be much better done in a concerted way using a combination of regulatory and statutory influence than by imposing requirements on manufacturers whose only alternative to inadequate requests for change will be restriction or termination of services.

Section 9

905

It is very difficult to work out what sort of laboratories will be adequate to carry out the Infectious Disease markers in cellular therapy patients. Terms used include “Competent lab” and “Licensed lab”. There is a lot of overlap with the NPAAC document; it would be better to stick to one type of lab standard (eg NATA, as per NPAAC) than TGA talking about ‘certified”. Most/all of these tests re already done, in local hospital labs

(without an adequate, or indeed any, item number). Limiting these tests to other labs will involve more and more cost.

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All products for human allogeneic transplantation are infused after completing pre-defined acceptance criteria. Ill-informed, incorrect and unnecessarily complex regulatory requirements have the ability to stop patients undergoing life-saving procedures, or even dying if a product is not released for an individual patient.

Research

Where products generated in the laboratory are in Phase I or II clinical trial, a significant reduction in the applicability of the code will be required and flexibility will be essential to allow for continuation of cell therapies research. Such products should be designated research and all attempts should be made to apply the code to such products, recognising that standards will need to be altered to allow ongoing product development. Such reductions in stringency will need to be recognised by appropriate patient information and consent by trial participants to accept those risks that are associated with clinical research. The code should specifically recognise that some products fall into the research area and should acknowledge that the risks associated with failure to comply with all tenets of the code may be far outweighed by the potential benefits available to patients receiving products that fall into this category.