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

Dear Sir/Madam:

Subject: Consultation Comments—Code of GMP and 5 standards for Cell and Tissue Products, Office of Devices Blood and Tissues

Genzyme Australasia Pty. Ltd and Verigen Australia Pty. Ltd., collectively known and hereinafter referred to as "Genzyme Corporation" thank the TGA for allowing us the opportunity to comment on 5 proposed tissue-specific standards and a revised Code of GMP for human blood and blood components, human tissues and human cellular therapy products in a consultation released by the TGA on December 7, 2009.

About Genzyme,
Genzyme Australasia Pty. Ltd and Verigen Australia Pty. Ltd:

Genzyme is one of the world's leading biotechnology companies dedicated to making a major positive impact on the lives of people with serious diseases. Since 1981, the company has grown from a small start-up to a diversified enterprise with more than 12,000 employees in locations spanning the globe and 2008 revenues of $4.6 billion.

With many established products and services helping patients in nearly 100 countries including Australia, Genzyme is a leader in the effort to develop and apply the most advanced technologies in the life sciences. The company's products and services are focused on rare inherited disorders, kidney disease, orthopaedics, cancer, transplant and immune disease, and diagnostic testing. Genzyme's commitment to innovation continues today with a substantial development program focused on these fields, as well as cardiovascular disease, neurodegenerative diseases, and other areas of unmet medical need.

In 2005, Genzyme broadened its cell therapy portfolio and acquired the Verigen Group in Australia, which, since its licensing by the TGA in 2002, has grown to become one of the largest Autologous Biotherapy providers to the Orthopaedic industry in Australia. As such, Genzyme, by way of this acquisition and partnership, is now one of the largest cellular therapy manufacturers in Australia. By way of background Matrix-induced Autologous Chondrocyte Implant (MACI®) is a human tissue product, which consists of a collagen membrane containing the autologous chondrocyte cells. MACI is implanted into the joint for the treatment of defined symptomatic cartilage defects to enable the regeneration of hyaline or hyaline-like cartilage, thereby restoring normal joint function

General Comments:

We understand the five new TGOs are proposed to mandate a standard for minimising the risk of transmission of infectious diseases and four tissue-specific standards for banked cardiovascular tissue, musculoskeletal tissue, ocular tissue and skin. Their main purpose is to clarify best practice requirements, increase the degree of international harmonisation and ensure ongoing flexibility to respond to new technologies. Finally, we understand that the draft Code of GMP is an amended version of the current Code of GMP for human blood and tissues (2000) which has applied to manufacturers and has been in place for almost 10 years. Specifically, the code has been re-written in such a way as to describe more explicitly the way in which Human Blood and Blood components, Human Tissues and Human Cellular Therapies should be manufactured to ensure that they consistently meet specifications and are safe to use.

This is an area of increasing regulatory significance and one in which the technology is growing so substantially. We applaud the TGA for taking the initiative to draft these new standards and revise its current code of GMP accordingly.

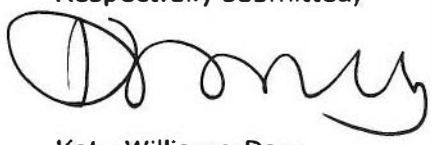
Overall, we feel these new requirements largely reflect requirements currently in place in the European Union and in the US and this appears to be a fairly straight forward quality system implementation with all the standard quality system elements that companies like Genzyme already incorporate for medical devices and therapeutic products. While the Code describes benchmark practices that should be followed, it also maintains a level of flexibility, allowing for alternative approaches that meet the intent and quality objectives of the Code in a timely and effective manner. We agree with such a flexible approach, however, we also believe it would be helpful to explain further how companies appropriately document and/or report on such deviations. Further, we believe the documents can be made stronger and clearer by:

1. Using common terminology across the 5 tissue-specific standards and code GMP;
2. Providing a more comprehensive set of definitions for key words to ensure clarity and transparency of requirements;
3. Correlating these documents in places where it makes sense so they more clearly and uniformly correspond with one another at key touch points.

Apart from these general comments, we outline in the tables that follow specific areas wherein we believe the Agency can further clarify and/or strengthen its guidelines. Our comments focus on 3 of the 6 documents as most applicable to Genzyme: (1) the Draft Code GMPs; (2) the Draft Standards for Minimising Infectious Disease Transmission; and (3) the Draft Standards for Banked Human Musculoskeletal Tissue.

If you have any questions at all regarding this submission, please contact me at (02) 9978 3901 or by email katy.williamsday@genzyme.com.

Respectfully submitted,



Katy Williams-Day
Director Regulatory & Scientific Affairs

On behalf of Genzyme Australasia Pty. Ltd and Verigen Australia Pty. Ltd, collectively Genzyme Corporation

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Specific Comments to
Draft Australian Code of Good Manufacturing Practice
Human Blood and Blood Components, Human Tissues and Human Cellular Therapies

Section Topic Page/Paragraph	Provision	Comments/Proposed Change
Section 1: Quality Management-General Page 5, Paragraph #104	"The system of Quality Assurance appropriate for the manufacture of products should ensure that: therapeutic products are designed and developed in a way that takes account of the requirements of this Code and Good Laboratory Practice."	In other countries like the US, for example, this would be related to the conduct or pre-clinical studies in a GCP like way. Would it mean something different in Australia? Please clarify what is meant by Good Laboratory Practices.
Section 3: Premises and Equipment-Premises General Page 12, Paragraph #304	"Where appropriate, contingency plans for breakdowns in critical services or equipment should be developed and regularly reviewed. For example, in the event of power failure, where necessary there should be access to a power source to allow the maintenance of critical services and equipment to permit the safe conclusion of activities in progress."	Contingency planning is an effective business planning tool, but may not need to be in the code for GMPS. Please clarify the rationale for including contingency planning provisions in a Code for GMP? It would also be helpful to identify under what circumstances contingency planning would need to be cGMP code element.
Section 3: Premises and Equipment-Premises General Page 13, Paragraph #307	This paragraph provides: "Donor interview facilities should enable interviews to be conducted in private."	This does not always apply, for example, facilities strictly dedicated to autologous therapies do not conduct donor interviews. Please qualify this requirement and/or insert "where appropriate."
Section 3: Premises and Equipment-Equipment Page 15, Paragraph #324	This paragraph provides: "There should be contingency plans in place for instances where routine equipment cannot be used. In such instances, the contingency plan equipment should meet the same acceptance criteria as for routine."	We recommend rewording this section to provide that "when backup equipment is identified for routine production equipment, it should meet the same acceptance criteria prior to use." Contingency planning is an effective business planning tool, but may not need to be in the code for GMPS
Section 3: Premises and Equipment-Equipment Page 15, Paragraph #328	"Where controlled temperature conditions (including during transport, where appropriate) are required, the environment should be monitored as follows: There should be temperature recording devices, and records kept and reviewed..."	Applying clause 328 to current manufacturing practices may be difficult as we do not routinely employ temperature tracking/loggers for patient material and/or reagents during transport. Further, such a provision may unduly complicate transport mechanisms into Australia from other countries that don't bear these same requirements and/or have the means to track/log temperature. We recommend separating "transport" from "storage" conditions and require that "transport" allow validation/qualification of the packaging system itself.

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Specific Comments to
Draft Australian Code of Good Manufacturing Practice
Human Blood and Blood Components, Human Tissues and Human Cellular Therapies (Continued)

Section Topic Page/Paragraph	Provision	Comments/Proposed Change
Section 4: Documentation	[entire section]	Please add in a clause that describes documentation and reporting requirements for any deviations from the cGMPs.
Section5: Control of Material	[entire section]	We recommend being more specific in this section with regard to minimum quality testing requirements.
Section 7: Complaints and Recalls	[entire section]	Please add a clause on deviations and/or errors discovered post distribution of product what are the requirements for regulatory authority notification.
Section 8:	[entire section]	Please add a clause specifying a timeframe for maintaining donor traceability records.
Section 8: Collection and Processing Page 24, Paragraph #808	"For Cellular Therapies, there should be a documented procedure for defining the medical assessment requirements including the acceptable timeframe for assessment, if not able to be done on the day of procurement."	Paragraph 808 appears to be in conflict with the TGO guidelines being proposed for infectious diseases. The TGO document states a medical assessment is require to occur on the day of the procedure or within 7 days of the event. Paragraph 808 declares that the manufacturer of a cellular therapy may state the time frame. Please clarify how paragraph 808 of the revised Code GMP should be interpreted in the context of the TGO proposed standards for infectious diseases.

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Specific Comments to
Therapeutic Goods Order No. XX, Draft Standards for Minimising Infectious Disease Transmission via Therapeutic Goods that are Human Blood and Blood Components, Human Tissues and Human Cellular Therapies

Section Topic Page/Paragraph	Provision	Comments/Proposed Change
Schedule 3—Medical and Social History, Page 10, section (2) (a)	"This Schedule sets out the requirements relating to the collection, recording and assessment of medical and social history of prospective donors or donors of human blood and blood components, human tissues and cellular therapies. Section (2) (a) provides as follows: "Human blood and blood components, human tissues or human cells must not be collected from a living donor unless the Medical and Social History interview has been conducted by a qualified interviewer at a face-to-face interview with the donor or guardian/next-of-kin. (a) The interview must occur as close as possible to, but at no more than 7 days prior to donation, unless (b) or (c) or (d) applies, and the history must be documented at that time."	For allogeneic products, we are not certain whether such a narrow time frame is warranted. Autologous procedures involve a step-wise approach over the course of several weeks where the patient undergoes consultation and initial pre-screening prior to being cleared for and admitted to the hospital for the tissue biopsy. The consultation between the patient and surgeon may occur 4 to 6 weeks prior to the surgical event. Please explain why this 7-day window is warranted for autologous procedures.

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Specific Comments to
Therapeutic Goods Order No. XX, Standards for Banked Human Musculoskeletal Tissue

Section Topic Page/Paragraph	Provision	Comments/Proposed Change
Section 7, General Requirements Page 5, (3)	"A biological must not be manufactured from musculoskeletal tissues obtained from a donor who is known to have a disease or condition compromising the quality and safety of the cells or tissue, including...[(a) – (h)]..."	Current health assessment forms used during the donor screening process for autologous chondrocyte implant procedures do not cover all these disease areas and/or conditions. While these forms can always be expanded to include these areas, we would welcome an understanding of the perceived benefit in the case of autologous transplants.
Section 7, General Requirements Page 5, (6)(b)	This section provides: "A musculoskeletal tissue that is to be transported to the manufacturing facility must be... (b) Packaged using aseptic technique with at least one moisture impermeable barrier and maintained at or below 10°C prior to and during transportation."	We disagree with the statement that that the tissue be maintained "at or below 10°C". We have a validated transport system for 2-25°C. Our range indicates that at least certain types of tissue can be exposed to refrigeration (2°C) and room temperature (25°C). We would ask you to revise this provision to permit a greater range in temperature of up to 25°C. Alternatively, we would ask that you include an exemption clause that states; "Unless well-documented validation studies confirm viability of a different range of temperatures for the specific tissue type."