

Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
Canberra ACT

To Whom It May Concern,

Comments on “*Regulation of Autologous Stem Cell Therapies: Discussion paper for consultation v1.0 January 2015*” (“Discussion Paper”)

1.0 Cell Therapies Pty Ltd and the Centre for Blood Cell Therapies at Peter Mac

This submission represents the views of Cell Therapies Pty Ltd (“CTPL”). CTPL is a leading provider of manufacturing and distribution infrastructure for cell based therapies in the Asia Pacific region. CTPL provides contract translation and clinical trial manufacturing services to product development companies, and then supports commercialisation in the region via in-licensing and marketing or further contract manufacturing and distribution. Our expertise is needle-to-needle ensuring complete product security and control and includes collection management (especially apheresis), cryopreservation, cell processing, distribution and marketing.

CTPL is a subsidiary of the Peter MacCallum Cancer Centre in Melbourne (“**Peter Mac**”) and provides quality oversight and services to Peter Mac’s Centre for Blood Cell Therapies (“**CBCT**”) a hospital-based cell therapy provider of HPC transplants. CBCT provides clinical and medical advice and governance to CTPL and has contributed to this submission.

CBCT is NPAC/NATA accredited and holds a TGA Licence to manufacture therapeutic goods (HPC-A products). CTPL has maintained numerous cGMP manufacturing licenses with TGA for manufacturing under CTX clinical trial approvals scheme. Together our cellular therapy manufacturing and clinical delivery experience spans products currently exempt from regulation under the Excluded Goods Order (“**the Order**”) Item 4(q), through to highly manipulated and gene-modified cells for immune therapy for clinical trials.

CTPL is a member of the International Society for Cellular Therapy (“**ISCT**”) and the Alliance for Regenerative Medicine (“**ARM**”). We have contributed to, and endorse, the comments on this Discussion Paper made by ISCT.

2.0 Summary Comments

1. CTPL strongly agrees that broadly exempting autologous cells from TGA regulation creates significant and unnecessary risks of unsafe products of

- unproven efficacy being inappropriately advertised and administered to patients without adequate adverse event reporting
2. CTPL endorses the concept of regulating autologous cells according to risk and utilising the concept of “autologous, homologous *and* minimally manipulated” to identify low-risk products. This would bring Australia into line with FDA and EMA
 3. CTPL endorses the recommendation that products which do not meet the definition for “autologous, homologous and minimally manipulated” be regulated as Class 3 or 4 Biologics under Part 3-2A of the Therapeutic Goods Act (“**the Act**”). Definitions should be clarified, as per point 5b below.
 4. CTPL recommends and endorses proposed option 4 of the Discussion Paper as striking the most appropriate balance of regulation, risk management and patient access
 5. Should TGA adopt option 4, factors to consider during implementation include
 - a. Ensure option 4 is not limited to “stem” cells but extends to all cellular therapies
 - b. Ensuring a robust definition of “autologous, homologous and minimally manipulated”
 - c. Ensuring, subject to efficiency and cost effectiveness, that the TGA rather than the applicant determine whether a product meets the definition of “autologous, homologous and minimally manipulated”
 - d. Consider amendment of Item 4(q) of the Order rather than Section 7AA of the Act as a more efficient means of implementation
 - e. Require immediate compliance with advertising standards
 - f. Specify standards against which class 1 biologics must be certified eg manufacturing standards such as FACT, cGMP; adverse event tracking requirements such as registries, and adverse event reporting requirements
 - g. Ensuring that the requirements for, and process for obtaining, manufacturing licensure for clinical trials manufacture of products that do not meet the “autologous, homologous and minimally manipulated” test do not unduly restrict or delay access to clinical trials of products pre-registration and do not undermine the efficiency of the CTN framework

3.0 Importance of the Discussion Paper

CTPL appreciates the issuance of the Discussion Paper as we consider the exemption in Item 4(q) of the Order to be largely unsuitable for ensuring the safety (and efficacy) of cell therapies administered to Australian patients. Our concerns are specifically around the unrestricted (and wholly unregulated) availability of potentially dangerous (no regulation of manufacturing or adverse events) and/or unproven (no independent assessment of efficacy) cell therapy treatments being promoted aggressively and inappropriately (unethically – no/limited regulation of advertising and appropriateness of physician qualifications) to Australian patients. Current practices and technology have moved well beyond what was possible when the exemption was first considered and its breadth is out of step with regulation by FDA and EMA.

Item 4(q) of Order provides a medical exemption from TGA regulation and oversight for:

human tissue and cells from regulation by the TGA that are:

a) collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and

b) that are manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner

This allows an exceptional scope of therapeutic products to go unregulated and explicitly does not take into consideration any handling or processing (manipulation) associated with the collected tissue or cells.

In the absence of any product registration, or recording of exempted treatments, it is not surprising to observe that:

- There has been very rapid growth in the number of clinicians and centres advertising “autologous stem cell treatments”¹
- Several commercial business models have evolved based on centralised or local “black box” manufacturing processes where treating physician oversight and understanding of manufacturing is highly likely to be minimal and practitioners are able to shelter behind “commercial in confidence claims” in order to avoid divulging materials and methods
- Anecdotal evidence suggests the exemption is being applied to products prepared using higher levels of cellular manipulation than would normally be classified as “minimal” and/or these products are being used for indications well beyond what would normally be classified as “homologous”
- There is clear evidence of promotional standards falling well short of the evidence-based standards expected of registered products. For example one commercial website promotes the benefits of its technology largely by reference to its registry (in itself commendable) but with only limited reference to the observation, supported by its own data, that its technology performs no better than placebo in controlled clinical trials²
- The sector has attracted significant adverse publicity as a result, to the detriment of the whole industry including regulators, commercial enterprises and physicians.³

As the Discussion Paper points out, this medical exemption system is out of step with other developed markets who qualify their medical exemptions according to risks defined by homologous use and levels of manipulation. It is also worth noting that Australia still has an exceptionally rapid and broad exemption available to patients and clinicians under the Special Access Scheme (SAS), the Authorised Prescriber

¹ M Munsie and M Pera, *Stem Cells and Development*, Vol. 23, Supp. 1 2014. DOI: 10.1089/scd.2014.0332

²

³ See for example, ABC's 7.30 Report 25 August 2014

Scheme (APS) and via the Clinical Trials Notification Process (CTN) to enable access to unregulated therapies in a controlled environment. There can be no clinical or patient justification for the current breadth of the Item 4(q) exemptions, when these already highly appropriate and well utilised medical exemptions are available. The review of regulation of autologous cell therapies initiated by the Discussion Paper is therefore welcomed.

4.0 Discussion questions

4.1 What are the public health risks of 'autologous stem cells'?

4.2 What is the evidence for these risks?

The National Health and Medical Research Council (NHMRC), Australia's peak funding body for medical research, which is responsible for establishing, developing and maintaining health standards, has simply summarised the issues in its own policy statements:

Unproven stem cell treatments can result in serious health complications such as infection, allergic reaction or immune system rejection and in some cases, the development of cancer. In addition to the health and safety risks, these treatments often involve significant financial costs. Undergoing unproven treatments may also interfere with or delay a patient accessing proven and potentially beneficial therapies or treatment plans.⁴

The level of manipulation or processing of a product can increase its risk by modifying the product's characteristics or function, leading to unintended clinical outcomes and increased infectious disease risk. The risks associated with higher levels of manipulation include increased microbiological contamination of the material via external exposure, infectious disease risk (from cross-contamination from other products) and the introduction of significant changes to the cells being manipulated that may lead to unintended clinical outcomes.

It should not be assumed that, just because the cells are obtained from the patient undergoing treatment, that there is no risk associated with these procedures. Serious adverse events have been reported as a result of unproven stem cell treatments, including the development of tumours and abnormal bone growth as a result of stem cell injections. Infection, allergic reaction and immune system rejection are also side effects reported as a result of stem cell therapies, a point illustrated by the recent report where the development of angiomyeloproliferative lesions occurred after direct injection of autologous stem cells into the renal parenchyma of a patient with lupus nephritis. The time course, multifocal nature of the lesions, and the identification of both myeloproliferative and angioproliferative components provided strong circumstantial evidence that the tumor lesion arose from injected stem cells.⁵

Although the mode of stem cell-based treatment in this patient was not an established therapy, it underscores a growing risk associated with the proliferation of private clinics that offer "stem cell" and other cellular therapies to patients without

⁴ Stem Cell Treatments. A Quick Guide for Medical Practitioners. www.nhmrc.gov.au/your-health/stem-cell-treatments (accessed 2 July 2014)

⁵ Thirabanasak et al. (2010) J Am Soc Nephrol 21(2):1218- 1222 - Pubmed

providing any guidance from safety or efficacy studies and without appropriate oversight by the regulatory authority (TGA).

Of course regulating stem cell, or indeed any cell-based treatment will not eliminate adverse events, however it will ensure significantly improved assessments of safety and efficacy through requirements for evidence of safety and efficacy, control of manufacturing and monitoring of adverse events.

A further public health risk comes from the lack of regulation of advertising and promotional standards. While physician promotional practices are in theory regulated by AHPRA, the fact that complaints may only be raised by patients or other healthcare professionals and the lack of resourcing of AHPRA mean that enforcement is both rare and weak. This results in providers motivated by commercial interest being able to engage in direct to consumer advertising using messages and data that would never meet the standards expected of the pharmaceutical industry for example (see note 2). The consequence is vulnerable patient populations being potentially misled into significant personal expenditure on therapies that are either unproven or for which the risks have not been appropriately explained. Aside from the impact on individual patients, such practices undermine the confidence in and integrity of healthcare practitioners and the regulatory system as a whole.

CTPL strongly agrees that broadly exempting autologous cells from TGA regulation creates significant and unnecessary risks of unsafe products of unproven efficacy being inappropriately advertised and administered to patients without adequate adverse event reporting

4.3 What identified risks should have the highest priority for resolving?

Based on the analysis above, the risks having the highest priority for solving are:

- The risk of patients receiving unproven autologous therapies, or therapies of dubious efficacy
- The risk of the autologous therapies being unsafe due to uncontrolled or inconsistent manufacturing processes or due to more than minimal manipulation or non-homologous use
- The risk that autologous therapies are promoted to patients without appropriate disclosure of risks and/or with inflated promises of efficacy that are not supported by evidence
- The risk that there is no way of determining, either by clinical trials or on-market surveillance, whether the autologous therapy is safe

4.4 Are there public health benefits, such as patient access to new and novel treatments, to consider?

There should remain avenues for expedited and compassionate patient access for unproven cell therapies. This does not require an unrestricted medical practice exemption. There is already an efficient and risk-adapted framework available through the SAS and the APS schemes (and these could easily be made subject to more robust tracking of rationale, outcomes and adverse events if required via compulsory reporting to the TGA).

As a general rule, it would seem desirable to demonstrate evidence for a claimed positive benefit, and we endorse the use of clinical trials to demonstrate a clinical

benefit. The CTN clinical trial route remains one of the most permissive clinical trial schemes in developed markets.

If patients or medical practitioners require access, these well-utilised pathways are available – and ensure that ongoing safety and efficacy monitoring and appropriate promotion occur. Any changes to the scheme should encourage the use of clinical trials to build an evidence base for new uses of cell therapy, for example by ensuring the requirements for manufacturing licensure for clinical trials do not act as a *de facto* limit to the efficiency of the CTN process.

4.5 Is there an argument that autologous stem cells are not therapeutic goods and, therefore, should remain under the current Section 7 declaration?

4.6 Should autologous cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from the regulation?

There is no credible justification for considering manipulated cells as not being a therapeutic good. No developed market other than Australia exempts non-homologous, more than minimally manipulated autologous cells from some form of regulatory oversight in addition to practice of medicine self-regulation.

Even for autologous, homologous, minimally manipulated products, there can be no justification for an absence of standards against which therapies can be measured, an absence of tracking of outcomes and adverse events and an absence of standards of advertising and promotion. In the absence of effective procedures for standard setting and regulation outside the Act, autologous cells (whether stem cells or not) should be regulated by the TGA. There should be a presumption of regulation with explicit, risk assessed exceptions, rather than a presumption of non-regulation.

CTPL endorses the concept of regulating autologous cells according to risk and utilising the concept to “autologous, homologous and minimally manipulated” to identify low risk products. This would bring Australia into line with FDA and EMA

4.7 What do you see as the likely risks, benefits and costs of each option?

4.8 How do you think each option addresses the risks you identified earlier?

	Risks	Benefits	Costs
Option 1	Existing risks of unqualified Item 4(q) exemption remain: Substantial patient risk (safety – lack of manufacturing control, lack of clinical data, lack of adverse event reporting), patient exploitation (questionable efficacy combined with inappropriate promotion) Market distortion: discouraging legitimate product development through risk of being undercut by less rigorously tested products delivered under the exemption, product safety issues, lack of either manufacturing or product control, no efficacy data	Maintains the status quo: less disruption and no incremental regulatory cost	No incremental costs – but public health costs remain
Option 2	For autologous, homologous and minimally manipulated products the risks of Option 1 remain. The risks associated with these products are lower, however there remains no improvement in manufacturing, promotional and adverse event tracking standards	Removes risks associated with non-homologous or non-minimally manipulated products as they will now be regulated Reduces risk of exploitation by prohibiting DTC promotion (however reliance on current enforcement mechanisms means this is likely to be ineffectual)	Costs associated with registration of more than minimally manipulated, non-homologous products will exist but be low as few are expected to have the necessary evidence

	Risks	Benefits	Costs
Option 3	As for option 2 except that manufacturers are expected to have a (self-disclosed) manufacturing standard/control and there is adverse event reporting. No mechanism by which patients or their treating doctors can determine if a product/provider is regulated because not listed on ARTG	Adverse event reporting required – however not clear what will happen should adverse events occur	There will be an expectation of review of adverse events, imposing a compliance burden on regulators
Option 4	Risk of products lacking efficacy being marketed still exists (but significantly reduced)	Listing requirement makes it possible for patients to determine that a product is regulated. Brings advertising and adverse event surveillance enforcement within remit of TGA	There will be an expectation of review of adverse events, imposing a compliance burden on regulators
Option 5	Risks no different to any other therapeutic goods; low risk products no longer available	Full transparency of product performance	Significant regulatory burden on TGA and applicants

Option 1 is unacceptable as this retains the current unsatisfactory status quo with an ongoing risk to patient safety and potential patient exploitation. There would be a substantial disincentive to normal product development, and there would be a substantial risk of more credible technologies not entering the Australian market due to the unfettered nature of the medical exemption. Additionally the lack of adverse event recording is unacceptable. As higher levels of manipulation and non homologous use of cells is associated with the greatest patient risk there can be no justification for excluding these from regulation.

Options 2-5 are significant improvements because they narrow the 'exemption' from full regulation to "autologous, homologous and minimally manipulated, in line with major international jurisdictions. We believe that even relatively low risk "autologous, homologous and minimally manipulated" products require adverse event reporting, enhanced control of promotion relative to that available now and objective, peer reviewed or better manufacturing control. Therefore we support listing on the ARTG (bringing TGA advertising standards into play and making it easier for consumers to determine that a product they are being offered is compliant/regulated); mandatory adverse event reporting and some form of objective manufacturing control or standards. Self-controlled manufacturing control of exempt products is one cause of product failure/risk as evidenced by recent scandals related to compounding pharmacies in the US.

On the other hand, we recognise that many of these lower risk products are valuable in niche markets and would never be able to generate the kind of data necessary to support a full application and the risk-benefit profile does not require regulation as a class 3 or 4 biologic in the same way allogeneic or more than minimally manipulated products do. Peer reviewed manufacturing and promotion should be adequate for these products (as occurs for IVF and HPC-A) and the TGA can always reserve the right to specifically exempt individual therapies. Although the benefits of option 5 would be full control, optimal product and patient safety with assured manufacturing quality, the risks would be the major discouragement of market entry for lower risk products.

The benefits of Option 4 are improved control of higher risk products, with low risk products lightly controlled with self-certification (manufacturing, safety) and providing a false or misleading certification would be a grounds for suspension or cancellation. Requirements to provide product information to the TGA, (including safety and efficacy and compliance with standards) and inclusion in the ARTG (and thus supply in Australia) allow proper understanding of the products being manufactured and their intended uses, and permit recall, suspension or cancellation if it appears to the TGA that the quality, safety or efficacy of the products were unacceptable. This option allows for peer assessment to manufacturing standards for low risk products, a position that many in industry have already proposed.⁶

The concern raised in the Discussion Paper that "Option 4 may not address the issues around clinical trials as the sponsor is not required to hold evidence of efficacy; therefore, the product could still be supplied without this evidence" is not a reason to reject Option 4 (none of the options address this concern). There is an

⁶ Self-regulation of autologous cell therapies Med J Aust 2014; 200 (4): 196

existing requirement that all clinical trials within Australia must undergo Institutional Review Board (IRB) approval by a Human Research Ethics Committee. Regulation of this process already exists, and requires that adequate demonstration of rationale, preclinical and non-clinical data plus any clinical data be provided in the Trial protocol before approval for a clinical trial can be given. IRB review of the Protocol and the Patient Information and Consent Form should therefore protect patients from an inappropriate level of confidence in the products. If there is concern, as some have anecdotally expressed, the IRB's are not fulfilling their function, this should be addressed elsewhere and not by creating a new level of regulation for products being investigated under properly constituted clinical trials.

CTPL endorses the regulation of products that fail the "autologous, homologous and minimally manipulated" test as Class 3 or 4 biologics under Part 3-2A of the Therapeutic Goods Act (**"the Act"**)
CTPL recommends and endorses proposed option 4 of the Discussion Paper as striking the most appropriate balance of regulation, risk management and patient access

4.9 Are there additional issues with the regulation of autologous stem cells that any changes should consider and or address?

Should TGA adopt option 4, factors to consider during implementation include

- Ensure option 4 is not limited to "stem" cells but extends to all cellular therapies*
- Ensuring a robust definition of "autologous, homologous and minimally manipulated"*
- Ensuring, subject to efficiency and cost effectiveness, that TGA rather than applicant determine whether a product meets the definition of "autologous, homologous and minimally manipulated"*
- Consider amendment of Item 4(q) of the Order rather than Section 7AA of the Act as a more efficient means of implementation*
- Require immediate compliance with advertising standards*
- Specify standards against which class 1 biologics must be certified eg manufacturing standards such as FACT, cGMP; adverse event tracking approaches such as registries, and adverse event reporting requirements.*
- Ensuring that the requirements for, and process for obtaining, manufacturing licensure for clinical trials manufacture of products that do not meet the "autologous, homologous and minimally manipulated" test do not unduly restrict or delay access to properly constituted and approved clinical trials of products pre-registration and do not undermine the efficiency of the CTN framework*

In relation to recommendation b) above, our proposal is that the TGA definition of 'homologous' be refined, similarly to the current FDA guidance, where the definition of 'homologous use' is used in conjunction with their definition of minimal manipulation. This has the desired effect of defining low risk products as those where the cells have not been removed from their original milieu to be used to reinstate a function elsewhere (ie restricted to use in the same cell system).

This would not change our perspective that Class I products merit less oversight, but would simply ensure that cells isolated from one system (say adipose-derived

mesenchymal stem cells) aren't used without oversight in an unrelated system (say spinal cord).

In relation to recommendation c) above, it is absolutely essential that the definition of products in Option 4 as being Class 1 or no more than minimally manipulated or homologous use only be objectively assessed, and not be through some form of self-assessment. Our preference would be for this classification to be adequately and precisely defined by TGA, such that there is no question that the autologous cells must not have undergone processing that alters the original characteristics that are relevant to the claimed utility of the product for reconstruction, repair or replacement. Additionally, that minimally manipulated cells must not have been removed from their original milieu to be used to reinstate a function elsewhere, and still possess the biological characteristics (and thus potentially the function or integrity) that are relevant to their claimed utility.

The more that cells are manipulated, the greater the chance of changing the cells such that they affect the body in an undesirable fashion and the greater the risk of introducing contamination leading to infection. This is generally recognised within the regulatory framework for biologicals, where increasing controls are placed on classes of products based, largely, on the degree of manipulation.

Any autologous cells that are not within the description of 'minimally manipulated' Class 1 biologicals would be required to be regulated under the Act as Class 3 or Class 4 biologicals. The TGA Biologicals Framework (and the associated cGMP for Human blood, blood components, human tissues and human cellular therapy products 2013) contain safety requirements with respect to collection/retrieval, processing, testing, storage, packaging and labelling, distribution, record keeping and accident and adverse reaction investigation and reporting. We are confident that non-exempt products subject to these regulations will (as intended) result in improved protection of the health and safety of Australian patients.

In relation to recommendation d) above, the most straightforward solution would appear to be to modify the current medical exemption system that applies in Australia (Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 Section 4(q)).

We would endorse immediate application of a risk adjusted medical practitioner exemption as follows:

4 (q) human tissue and cells that are:

a) collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and

*b) that are manufactured with cells that are minimally manipulated by that medical practitioner, or by a person or persons under the direct professional supervision of that medical practitioner, for homologous use in therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the direct professional supervision of the same medical practitioner; **or***

c) utilised in one of the following recognised medical interventions:

- i) skin grafts inclusive of sprayed and/or cultured skin;*
- ii) skull flaps;*

- iii) vascular conduits;*
- iv) transplantation of pancreatic islet cells;*
- v) bone grafts;*
- vi) blood to seal CSF leaks and re-infused during surgery;*
- vii) cosmetic/reconstructive procedures utilising skin, bone and fat transfer as skin, bone or fat.*

These changes would immediately address the risk of highly manipulated products being marketed to patients, whilst allowing a more considered risk-adapted framework to be evolved for the lower risk homologous and minimally manipulated products. There is little doubt that with higher levels of manipulation, and non-homologous use there is a considerably greater risk- addressing this risk should be the most urgent priority. This would allow, in the meantime, for a more considered approach for low risk product, given the extensive period of time required before the Act can be changed.

Thank you for the opportunity to comment on this important topic.

Yours sincerely,



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