



Australian Government
Department of Health
Therapeutic Goods Administration

Regulation of autologous stem cell therapies

Discussion paper for consultation

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TGA Health Safety
Regulation

Historical consultation document

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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Overview

The Therapeutic Goods Administration (TGA) is considering whether the regulation applied to some autologous cells is appropriate. The autologous cells under particular consideration are 'autologous stem cells' that are taken from a patient and used under the supervision of a medical practitioner who is caring for that patient for a single indication in a single course of treatment.

The purpose of this paper is to seek your input on this issue and, in particular, on five potential options for regulation of these cells as therapeutic goods under the *Therapeutic Goods Act 1989* (the Act). We are also interested to receive your comments on the other discussion questions throughout the paper.

This paper is not intended to advance any position on the issues involved. Its purpose is to canvass the views of the public and inform the Australian Government whether a change is required to regulation under the Federal therapeutic goods regulatory scheme of the products discussed in the paper. As such, there is no preferred option presented in this paper and it should not be taken that the TGA accepts any or all of the issues that have been raised as needing to be addressed, at this time.

Feedback from the consultation may also inform whether changes need to be considered to regulation other than through the therapeutic goods regulatory scheme. For example, feedback might suggest changes to regulation of the conduct of medical practitioners, and whether other non-regulatory options should be explored, such as increased education.

As a result of considering responses to this paper any further consideration of options would be undertaken through the usual processes for implementing regulatory change, such as the preparation of a Regulation Impact Statement which will involve further public consultation.

Autologous cells and how they are regulated

Autologous cells are those that are removed from and applied to the same person, so the donor and the recipient are the same. Some autologous human cells and tissues (HCTs) are currently captured under Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 (the Order), provided they are:

- for use in the patient from which they were taken
- used under the supervision of a medical practitioner who is caring for that patient
- for a single indication in a single course of treatment.

This means that they have been declared not to be therapeutic goods for the purpose of the *Therapeutic Goods Act 1989* (the Act) by the Secretary of the Department of Health (the Secretary), therefore, they are not regulated by the TGA¹.

There are some autologous HCTs that may be captured under the Order for which there are currently no public health concerns such as autologous vascular conduits used in coronary artery bypass surgery and autologous haematopoietic cells used in bone marrow transplants. However, other autologous cells particularly 'autologous stem cells', also captured under the

¹ A copy of the Order can be found at <<http://www.tga.gov.au/therapeutic-goods-excluded-goods-order-no-1-2011>>

Order are being used in an increasing number of therapeutic applications. It is these 'autologous stem cells' in particular which are the subject of this paper.

Does the current regulatory model for stem cells need to change?

In recent years, the number of companies and medical clinics offering services involving the use of 'autologous stem cells' that are not regulated under the Act by reason of the Order has increased.

Concerns about these therapies that have been expressed to the TGA and in public forums include:

- safety of the products – either direct safety impacts or safety issues incidental to the therapy
- lack of evidence to support the efficacy of the products
- the large sums of money being charged for unproven treatments
- lack of mechanisms for reporting of adverse effects of the products
- inappropriate advertising of the products

Potential alternative options of the therapeutic goods regulation

An overview of five potential options and their regulatory effects are provided in the table below:

Overview of the options for regulation of autologous cells

	Option 1	Option 2	Option 3	Option 4	Option 5
Description of option	Exclude under s 7AA from the Therapeutic Goods Act all 'stem cells' currently covered by 4(q)	Exclude under 7AA – but only when used or presented for supply in certain ways*: <ul style="list-style-type: none"> • no advertising to consumers • no greater than minimal manipulation, homologous use • single procedure, indication, medical practitioner 	Regulate under Act, but exempt from: <ul style="list-style-type: none"> • inclusion in the ARTG (on condition that sponsor reports adverse effects), and • manufacturing requirements but only where* <ul style="list-style-type: none"> • no greater than minimal manipulation, homologous use • single procedure, indication, medical practitioner 	Regulate under Act as Class 1 biologicals but only where*: <ul style="list-style-type: none"> • no greater than minimal manipulation, homologous use • single procedure, indication, medical practitioner 	Regulate under Act as biologicals according to applicable class (2, 3 or 4)
Effect of option		<i>* Any autologous cells not in this category would be regulated under Part 3-2A of the Act as biologicals according to applicable class</i>	<i>* Any autologous cells not in this category would be regulated under Part 3-2A of the Act as biologicals according to applicable class</i>	<i>* Any autologous cells not in this category would be regulated under Part 3-2A of the Act as biologicals according to applicable class</i>	
Advertising to health practitioners only	No (but still subject to other regulation e.g. ACCC and AHPRA)	Yes	Yes	Yes	Yes
Act standards	No	No	Yes	Yes	Yes
Adverse effect reporting	No	No	Yes	Yes	Yes
Safety requirements	No	No	No	Yes (sponsor certification only)	Yes
Efficacy requirements	No	No	No	No	Yes
Manufacturing	No	No	No	No	Yes

* Any autologous cells not falling under these descriptions would be regulated under the Act, according to the applicable class of biological. ACCC is the Australian Consumer Complaints Commission. AHPRA is the Australian Health Practitioners Regulatory Authority.

Introduction

Human cells and tissues are used in many therapeutic applications. Human cell and tissue products (HCTs) can be derived and used as part of medical practice or supplied as products manufactured for therapeutic use. The boundary between HCTs derived and used solely as part of medical practice and those supplied as products manufactured for therapeutic use (usually as part of medical practice) is not always clear. Medical practice and therapeutic products are overseen by different regulatory frameworks. The conduct of health practitioners (including advertising) is regulated by the Australian Health Practitioners' Regulation Agency (AHPRA), the Medical Board of Australia and state and territory medical boards. Therapeutic products are regulated under the *Therapeutic Goods Act 1989* by the Therapeutic Goods Administration. Defining the boundary between these two regulatory frameworks is an issue for many jurisdictions internationally.

Scope of this discussion paper

The Order contains a declaration that autologous human cells and tissues that are derived and used under the direct responsibility of medical practitioners are not therapeutic goods, so that these goods are not regulated under the Act. This was intended to facilitate individual medical practitioners performing procedures, such as autologous skin grafts used to treat burns and autologous haematopoietic cells in bone marrow transplants. These intended procedures/treatments are set out in the list at [Attachment 1](#). As there is no current public health concern with these treatments they are not the subject of this paper, and there is no plan to change their status under the *Therapeutic Goods Act* (the Act); i.e. they will continue to be excluded from the coverage of the Act by an appropriate mechanism.

However, other autologous cells, particularly 'autologous stem cells', are being used in an increasing number of therapeutic applications. It is these 'autologous stem cells' in particular that are the subject of this paper.

In recent years, the number of companies and medical clinics offering services involving the use of 'autologous stem cells' that are not regulated under the Act has increased. This includes some companies that have developed business models designed to limit the regulatory oversight of the products they use.

There has recently been increased public scrutiny and concerns on the risks, benefits and availability of stem cell treatments.

This increased activity may be due to a number of factors including:

- patient driven demand, often through expectations around the promise of 'stem cells' (often in the treatment of conditions that may be chronic, such as osteoarthritis) and advertising direct to the public
- medical practitioners can directly access and use autologous human cells without the pre-market scrutiny applied to medicines and devices
- use of autologous cells and tissues may be perceived to represent a low safety risk.

The concerns related to the use of autologous stem cells in these circumstances include the:

- safety of the products – either direct safety effects or safety issues incidental to the therapy
- lack of evidence to support the efficacy of the product

- the large sums of money being charged for unproven treatments
- lack of mechanisms for reporting of adverse effects of the products
- inappropriate advertising the product

Due to these public health concerns the focus of this paper is on potential options for regulating via the Act those autologous cells that are not included in [Attachment 1](#) including, but not limited to, those described by practitioners as 'autologous stem cells' that are:

- for use in the patient from which they were taken (i.e., for autologous use)
- used under the supervision of a medical practitioner who is caring for that patient
- for a single indication in a single course of treatment.

Autologous cells when used in this context are not currently regulated under the Act, by way of item 4(q) of the Order. The five options presented in this paper are presented with this group of treatments as their focus. These will be referred to in this paper as 'autologous cells'. Any reference to 'autologous cells' in this paper includes but is not limited to those described in the media and by medical practitioners as 'stem cells'.

Background

In 2006, the Australian Health Ministers' Council (AHMC) agreed to a National Framework for the regulation of human tissues and emerging biological therapies subject to further consultation and advice on whether to include organs and un-manipulated reproductive tissue for assisted reproductive therapy (ART). An intention of the proposed framework was that some medical procedures would be excluded including:

- single medical/surgical procedures performed on one patient (autologous transplants) such as bone grafts and vein transplants
- single medical/surgical procedures involving two patients (allogeneic transplants²) such as organ donation from a live donor within the same facility as the transplant recipient³.

At this time, there was no direct consideration of stem cells and any unintended consequences of exempting this class of product.

In 2008, AHMC agreed that un-manipulated ART be self-regulated and the regulation of solid organs be referred to the (see www.donatelife.gov.au). It was agreed that otherwise, human tissues and cells would be regulated under the Act as 'biologics', (now Part 3-2A), which came into effect on 31 May 2011.

The Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 (the Order)⁴ lists goods that are declared by the Secretary not to be therapeutic goods and, therefore, do not come within the operation of the Act⁵. The Order was the mechanism chosen to enact the decision of the AHMC and was updated in 2011 at the time of the implementation of the biologicals regulatory

² Where cells or tissues are removed from one person and applied to another person

³ See now Item 4(o) of the Order

⁴ Made under section 7 of the Act

⁵ All references in this paper to sections are to sections of the Act; all references to regulations are to the Therapeutic Goods Regulations 1990 (the Regulations), unless otherwise indicated.

framework. The update included a new item (Item 4(q)) that was intended to provide clarity in regard to those exempt single medical/surgical procedures by requiring that the cells be prepared by a medical practitioner responsible for the clinical care and treatment of the patient, or a person(s) under their direct oversight.

The Order Item 4(q) declares that the following goods are not therapeutic goods and thus not regulated by the TGA:

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. 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.*

A guidance document on the TGA website⁶ outlines which products come within the Order Item 4(q) and, therefore, are not regulated by the TGA.

Potential public health risks of autologous stem cell treatments

There may be a number of potential health risks emerging because of the current regulatory approach to these products including:

2. Safety of the product, including issues related to any processing of the product

While there is little evidence from reported clinical trials of frequent serious short to medium term adverse effects of autologous cell therapies, there are reports of infrequent significant adverse effects of such therapies. One challenge is that as there is no framework that encourages reporting of adverse effects outside clinical trials, so it is likely that adverse effects are under reported.

[Attachment 2](#) contains a summary of a review recently undertaken by the TGA of safety and risk factors associated with autologous mesenchymal stem cell therapy, with particular reference to autologous adipose-derived mesenchymal stem cells. A limitation of such literature based reviews is that it is restricted to clinical trial reports and thus does not include treatments that maybe provided within medical clinics that are not reported. This review is also restricted in the scope of cell therapies reviewed.

There is potential for increased risks associated with a product the more processing (manipulation) that is required before it is used. Risks associated with increasing levels of processing include increased infectious disease risk and the introduction of significant changes to the cells being manipulated that may lead to unintended clinical outcomes.

⁶ Excluded Goods Order No. 1 of 2011: Guideline for Items 4(o), 4(p), 4(q) and 4(r)
<http://www.tga.gov.au/excluded-goods-order-no-1-2011-guideline-items-4o-4p-4q-and-4r>

3. Lack of evidence to support the efficacy of the product and the large sums of money being charged for unproven treatments

Treatments are being offered for diseases such as osteoarthritis (and charged for) with little or no supporting evidence. This means that, because there are risks with any medical procedure, patients are potentially exposing themselves to this risk for no definable, demonstrable benefit.

Because these treatments can be used in some circumstances without evidence, there is no incentive to undertake research of the kind designed to determine efficacy (including clinical trials). This means that treatments that might have a benefit are not being researched sufficiently and the public is missing out on the potential real benefits.

Without proper evidence, the public and clinicians have no way of knowing whether these products, where they might have a benefit, are being used in a way that optimises the likelihood of that benefit being realised. Research is needed not only on whether these treatments work, but also on how to make them work most effectively.

4. Lack of reporting adverse effects of the product

Because these products are not regulated as therapeutic goods, there are no obligations on either companies providing these 'products' or the medical practitioners involved to report adverse events and thus there is no consolidated knowledge of adverse effects. The absence of reporting has contributed to there being limited evidence of a direct safety risk or that supports the safety of autologous cell therapies.

5. Inappropriate advertising the product

A number of clinics and companies are advertising autologous cell treatments. Many of the diseases being targeted in these advertisements are chronic non-life threatening conditions for which currently accepted medical treatments are only minimally or moderately effective such as osteoarthritis and tendinopathy. Many of the diseases have significant negative effects on quality of life.

Although the TGA has been made aware of concerns in relation to this advertising, as of early September 2014 the TGA, the Health Care Complaints Commission and the Australian Competition and Consumer Commission have received very few direct patient complaints from consumers of autologous stem cell treatments. AHPRA has received four complaints about stem cell treatments.

Discussion questions

- What are the public health risks of 'autologous stem cells' in your view?
- What is the evidence for these risks?
- What identified risks should have the highest priority for resolving?
- Are there public health benefits, such as patient access to new and novel treatments, to consider?

Options for regulation of autologous stem cells

This section outlines five potential options, including maintaining the status quo, for addressing the potential risks raised.

Co-existence with other forms of regulation

Before considering TGA-based regulatory options in detail, it is important to remember that they are not intended to be exclusive of other existing regulatory regimes.

The Act regulates only certain dealings with therapeutic goods (import into, and export from, Australia, manufacture and certain aspects of supply). This law co-exists with laws and codes governing medical practice.

The conduct of health practitioners (including advertising) is regulated by the Australian Health Practitioners' Regulation Agency (AHPRA), the Medical Board of Australia and state and territory medical boards. These, in combination, administer different aspects of the National Registration and Accreditation Scheme for health practitioners and the Health Practitioner Regulation National Law (as enacted in each State and Territory). The regulation of any therapeutic goods by the TGA is not inconsistent with, and sits alongside, the regulation of medical practice by these bodies. This would be the case whether or not autologous cells were regulated under the Act.

Therefore, the following potential options should be considered as being likely to operate alongside these existing regulatory schemes.

Concept of minimal manipulation and homologous use and international approaches

Currently the Order does not rely on the concepts of minimal manipulation and homologous use to differentiate the goods that it excludes from goods that are not excluded under item 4(q).

Internationally, many regulatory frameworks for HCTs consider the level of product processing/manipulation and whether the product is for homologous use or not, to determine the potential risk of a product and the commensurate level of regulatory oversight.

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. Homologous use of a product (e.g. haematopoietic cells used in bone marrow transplants) is considered lower risk than non-homologous use (e.g. haematopoietic cells used for cardiac repair).

These concepts are also used in the regulatory framework for HCTs (known as Biologicals) in Australia. There is no internationally harmonised definition for these terms. The definition of these terms in regulatory frameworks in Australia and a number of other countries/jurisdictions is included in [Attachment 3](#).

For international consistency these concepts have been adopted as the basis for potential options 2 to 5 although it is important to note that international jurisdictions do not necessarily have direct equivalents of these options.

The following options for addressing the potential risks of autologous stem cells are presented in ascending order of extent of regulation.

The table below provides a summary of the practical effect of the five options on criteria such as advertising and patient access.

Summary of evidence, reporting and advertising requirements for the regulatory options for autologous cells

Issue	Option 1	Option 2	Option 3	Option 4	Option 5
Evidence to support the safety and efficacy of the product	No requirement for review under the Act.	No requirement for review under the Act but only excluded if homologous use and not subject to more than minimal manipulation thus represent less risk.	No requirement for product to be safe or efficacious.	Applicant for Class 1 must certify that the product is safe for the purpose for which it is to be used (grounds for /suspension cancellation if that statement false or misleading).	Evidence of safety and efficacy required before inclusion in the ARTG.
Advertising of the product	No requirements under the Act but subject to ACCC and AHPRA regulation.	No advertising to the public, advertising permitted to health practitioners and subject to AHPRA regulation.	No advertising to the public.	No advertising to the public.	No advertising to the public.
Reporting of adverse effects of the product	No requirements under the Act.	No requirements under the Act.	Yes, there would be a requirement for reporting adverse effects related to the product if the conditional exemption under Schedule 5A was adopted.	Yes, there would be a requirement for reporting adverse effects related to the product.	Yes, there would be a requirement for reporting adverse effects related to the product.

Patient access	<p>Direct public access to products in the absence of any limit on advertising directly to consumers.</p> <p>Patient access unlikely to be affected.</p>	<p>Access via referral from health professional in absence of advertising to the public (?)</p> <p>Whether patient access is affected will depend on extent to which currently available treatments involve homologous and minimally manipulated products.</p>	<p>Like other biologicals, access normally via referral from health professional.</p> <p>Whether patient access is affected will depend on extent to which currently available treatments involve homologous and minimally manipulated products and comply with any applicable standards.</p>	<p>Like other biological, access normally via referral from health professional.</p> <p>Whether patient access is affected will depend on extent to which currently available treatment, involve homologous and minimally manipulated products and comply with any applicable standards.</p>	<p>Like other biological, access normally via referral from health professional.</p> <p>In the absence of good clinical evidence, products likely not to be included, at least in the short term, so patient access likely to be affected.</p>
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Discussion questions for each of the potential options

- What do you see as the likely risks, benefits and costs of each option to you? If possible, please attempt to quantify these costs and benefits.
- How do you think each option addresses the risks you identified in the earlier question?
- Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address?

Option 1: Continue to exclude autologous cells from regulation under the Act

This option is aimed at effectively maintaining the status quo. However, in examining this issue, the TGA has questioned whether the types of therapies and goods that have emerged since the original declaration that these goods did not meet the definition of therapeutic goods in the Act. In other words, we have asked ourselves whether these goods do in fact meet that definition and found that it is likely that they do, based on our current understanding of contemporary usage.

In order to maintain the status quo, but address this emerging understanding, the TGA considers it is more appropriate that the Minister (or their delegate) consider issuing a legislative instrument under subsection 7AA(1) of the Act, which would specify that the autologous stem cells are not covered by the Act. This would remove the need to consider whether these meet the definition of therapeutic goods.

Effectively, this would replicate the current situation in that the specified goods would continue to be wholly excluded from regulation under the Act. However, this exclusion would be achieved by a section 7AA instrument rather than the existing section 7 order made by the Secretary.

The purpose of section 7AA is to enable the Minister to exclude from the Act goods that might meet the definition of therapeutic goods, but in relation to which regulation under the Act is not appropriate⁷. Before issuing the instrument under section 7AA, the Minister must have regard to⁸:

- whether it is likely that the goods, if not regulated under the Act, might harm the health of members of the public;*
- whether it is appropriate in all the circumstances to apply the Act to regulate the goods;*
- whether the kinds of risks from the goods to which members of the public might be exposed could be more appropriately dealt with under another regulatory scheme.*

The Minister does not need to be **satisfied** that the goods do not harm the health, or are not likely to harm the health, of the public. Rather, they need to **have regard to** the likelihood of harm to members of the public should the goods not be regulated under the Act and how that

⁷ Further details about the background to s 7AA are set out in the Explanatory Memorandum for the Therapeutic Goods Amendment (2013 Measures No. 1) Bill 2013 – see <http://www.comlaw.gov.au/Details/C2013B00231/Explanatory%20Memorandum/Text>

⁸ Subsection 7AA(3).

risk might otherwise be mitigated, for example, through concomitant and parallel regulatory schemes.

Once a good has been excluded under section 7AA, it is no longer subject to the Act and cannot (for example) be included in the Australian Register of Therapeutic Goods (the ARTG).

The criteria under section 7AA would need careful consideration against the known and likely risks and benefits from cell treatments before these products were able to be excluded from the regime under section 7AA.

This option has the advantage over the current situation of making the regulatory status of, specifically, autologous stem cells clearer, and would be made only after the Minister considers the specific public health criteria that s 7AA requires the Minister to consider. These criteria are different from those the Secretary is required to make in issuing a determination under s 7, which exists to allow clarification of whether certain goods are, or are not, therapeutic goods.

In summary, under this option, autologous stem cells would:

- remain regulated by reference to professional standards applying to medical practitioners (overseen by the Medical Boards and AHPRA) and, in relation to a live listing, by the ACCC
- not be regulated under the Act and, therefore, not be subject to standards to which other stem cell therapies are subject to or the advertising ban in the Act
- not be the subject of an obligation to report adverse effects to the TGA
- the TGA would not be able to require the manufacturer/supplier to provide information about any aspects of the supply, manufacture or use of the goods

As this option would maintain the exclusion of autologous stem cells from the Act, its implementation would not affect patient access to treatments.

Discussion question for Option 1

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

Option 2: Exclude autologous stem cells from regulation under the Act in defined circumstances

Subsection 7AA(2) of the Act permits the Minister to determine that certain goods are excluded goods when they are 'used, advertised, or presented for supply' in ways specified in the determination. Under Option 2, autologous stem cells could be excluded from coverage by the Act **only** when they are:

- for homologous use (i.e. the cells perform the same basic function in the body as they originally perform before being extracted)⁹

⁹ 'Homologous use' is defined in regulation 2 of the Regulations as means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a biological that performs the same basic function in the recipient as in the donor.

- subject to not more than minimal manipulation¹⁰
- not advertised directly to the public.

These criteria have been selected because autologous cells that meet them present the lowest risk. When cells are not used in a homologous way, that is, they are used to perform a different function than the basic function that they normally perform in the body, there are increased risks associated with how those cells may physiologically affect the body.

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.

Restricting the advertising of the goods to the public addresses the problem of a market for treatments of unknown efficacy. By removing the ability to advertise to the public, this provides incentives for medical practitioners (and others), who wish to continue to use certain treatments, to advise their patients objectively on treatment options and for research to be undertaken to demonstrate efficacy. While clinics may no longer be able to attract patients directly through advertising, when they have a proven treatment available, clinics should be able to build their practices through referrals from general practitioners or specialists.

This reasoning also applies to Options 3 and 4.

Any autologous stem cells that do not meet the above criteria (and are therefore not excluded from regulation under the Act) would be regulated under the Act as biologicals (either as Class 3 or 4 biologicals). Given the likely lack of clinical evidence to support their efficacy, it is possible that applications for inclusion may be delayed and/or be unsuccessful so these products would no longer be available to patients. Any such use that did not comply with the requirements of the Act may give rise to substantive criminal and civil penalties.¹¹ They could be used in clinical trials under the Act.

In summary, in this option, autologous stem cells in particular circumstances would:

- remain regulated by reference to professional standards applying to medical practitioners (overseen by the Medical Boards and AHPRA) and, in relation to advertising, by the ACCC
- not be regulated by the TGA under the Act and therefore not subject to standards to which other cell therapies are subject to or the advertising ban in the Act but only to the extent that there was no advertising to the public (and any other limits)
- not be the subject of an obligation to report adverse effects to the TGA

¹⁰ 'Minimal manipulation' is defined in regulation 2 of the Therapeutic Goods Regulations 1990 (the Regulations) as a process involving any of the following actions, or any other similar action – centrifugation, trimming, cutting or milling, flushing or washing, refrigeration, freezing, freeze drying (of structural tissues only), the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents, irradiation for the purpose of bioburden reduction;

¹¹ For instance, the manufacture and supply could involve a breach of subsection 19B(4) in respect of which the penalty is imprisonment for 12 months or 1,000 penalty points (\$170,000) or a breach of the civil penalties in section 19D (\$850,000 for an individual and \$8,500,000 for a company) and advertising to the public could involve a breach of paragraph 42DL(1)(fa) in respect of which the penalty is \$10,200.

- the TGA would not be able to require the manufacturer/supplier to provide information about any aspects of the supply, manufacture or use of the goods

Options 1 and 2 would have the effect of excluding autologous stem cells either generally (Option 1), or when used in particular circumstances (Option 2), from regulation under the Act. Once excluded under section 7AA, such goods are no longer therapeutic goods for the purposes of the Act and cannot be regulated under the Act.

Option 2 is likely to address the issues relating to advertising of unproven treatments, which, in turn, creates demand for these services. However, it may not provide incentives for the medical profession to conduct appropriate clinical trials to identify whether or not given treatments work for defined conditions. As there is no incentive to include the products in the ARTG as Class 2, 3 or 4 biologicals (which is predicated on evidence of efficacy and thus provide confidence and clarity in the medical profession around using these products), it is difficult to see why proponents would invest in further research.

Option 2 would not address the need to collect adverse event information.

Discussion question for Option 2

- Should autologous stem cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from regulation? Why or why not?

Option 3: Regulate autologous stem cells under Act, but exempt from registration and manufacturing requirements

If autologous cells are therapeutic goods and are not otherwise excluded from regulation, they would fall within the definition of a biological under the Act. Biologicals are things that 'comprise, contain or are derived from human cells or tissues, and that are represented to be, or likely to be taken to be¹²:

- for use in the treatment or prevention of a disease, ailment, defect or injury affecting persons; or
- for use in influencing, inhibiting or modifying a physiological process in persons'.

Autologous cells that are represented as, or likely to be taken to be, for one or both of these purposes, clearly fall within this definition of biologicals¹³.

In the absence of a specific exemption, such cells would therefore be subject to the requirements in the Act to:

- comply with applicable standards
- be included in the ARTG with the associated statutory obligations to report adverse effects

¹² Section 32A.

¹³ See also the discussion above on the meaning of therapeutic good. The paragraphs that define biologicals by reference to treatment of disease, ailment (etc.) is narrower than the equivalent paragraph in the definition of therapeutic goods, which also refers to diagnosing, curing and alleviating the disease (etc.).

- be manufactured under a manufacturing licence involving compliance with relevant manufacturing principles in relation to good manufacturing practice (GMP)
- comply with advertising requirements (it is an offence to publish or broadcast an advertisement that refers to a biological).

Requirement to be included in the ARTG

Inclusion in the ARTG is the primary means by which the TGA monitors the safety, quality and efficacy of therapeutic goods imported into, exported from, manufactured and supplied in Australia. Once a product is included in the ARTG, the sponsor is then legally responsible for these matters and the TGA is able to track any problems with the goods that arise once they are in the Australian market. For example, the sponsor is required to report certain adverse effects to the products to the TGA¹⁴.

Under the Regulations, biologicals can be exempted from the registration requirement by being included in Schedule 5¹⁵, or in Schedule 5A¹⁶ of the Regulations. For example, an exemption could be created that is subject to a condition that the sponsor report adverse events arising from use of the autologous cells, to enable the TGA to investigate.

Manufacturing requirements

Goods that are exempt from registration are not exempt from compliance with manufacturing requirements, unless they are included in Schedule 7 or 8 of the Regulations.

Schedule 7 of the Regulations exempts therapeutic goods from the requirements for manufacturing under licence unless they are supplied as pharmaceutical benefits.

Schedule 8 of the Regulations applies to persons, exempting them from the requirement to hold a manufacturing licence under the Act for the manufacture of certain goods (e.g. medical practitioners do not require a licence to 'manufacture...a medicine by a medical practitioner...specifically for a patient under his or her care' (Item 1)). Schedule 8 usually works in conjunction with an exemption under schedule 5 or 5A, for example, extemporaneous compounding.

Either schedule could be used to provide an exemption for manufacturing licences under this option, depending on the circumstances of manufacture.

There is currently no manufacturing principle that specifically governs the manufacture of autologous cells. However, the Australian Code of Good Manufacturing Practice for Human Blood, Blood Components, Human Tissues and Human cellular therapy products ('the Code'), which is made mandatory for Australian manufacturers of therapeutic goods by way of the Manufacturing Principles issued under the Act¹⁷, does apply to the manufacture of biologicals, which would include **autologous cells**¹⁸ if they were regulated under the Act.

¹⁴ Section 32DQ creates criminal offences and civil penalties for failing to do so in relation to biologicals included in the ARTG, and the TGA imposes post-market reporting and record keeping about supply requirements as a condition of inclusion of biologicals.

¹⁵ Section 32CA(2) and Regulation 12(1).

¹⁶ Section 32CA(2) and (3), and Regulation 12(2).

¹⁷ Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2013 (MP1/2013).

¹⁸ Except for Class 1 biologicals, which do not have to comply with the manufacturing requirements in Part 3-3 (see section 33B).

Compliance with standards

Goods that are exempt from inclusion in the ARTG and/or manufacturing requirements are still required to comply with any applicable standards unless they are (by case-by-case decision) permitted to depart from them¹⁹.

The relevant standards applicable to autologous cells would include Therapeutic Goods Order 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 therapeutic products*) and Therapeutic Goods Order 87 (*General Requirements for the Labelling of Biologicals*), and any other standards applicable in the circumstances.

This option would apply only to autologous cells that are:

- for homologous use (i.e. the cells perform the same basic function in the body as they originally perform before being extracted)
- subject to not more than minimal manipulation.

and would involve:

- excluding these autologous cells from the requirement to be included in the ARTG, either unconditionally or subject to conditions (including for instance that the user report adverse effects and other adverse events to the TGA)
- excluding them from the requirement that they be manufactured in premises that are the subject of a manufacturing licence, or
- excluding medical practitioner manufacturing autologous stem cells from the requirement to hold a manufacturing licence.

In summary, under this option autologous cells for homologous use and subject to not more than minimal manipulation would be regulated under the Act as follows:

- they would not be required to be included in the ARTG
- neither the 'manufacturer' of the stem cells nor the manufacturing process would be required to be licensed
- the stem cells would be required to meet the requirements of applicable product standards, including any relevant standards made under section 10 of the Act
- the TGA could require information to be provided about the products, including about their supply and handling²⁰, which would provide a mechanism for determining whether they were in fact exempt²¹

¹⁹ There is no mechanism to "exempt" goods from the application of Part 3-1. However, the Secretary can give consent for specified goods to be imported, supplied or exported without being required to comply with a standard or standards: s 14, 14A. This condition can be (and usually is) subject to conditions imposed to mitigate any risk.

²⁰ See section 32JE. It is an offence for failure to comply with a notice requiring information (under section 32JI) and civil penalties are payable if the information is false or misleading (section 32JJ).

²¹ If the products were not in fact exempt then their manufacture and supply would be an offence under the Act (section 32BC and 32BD) and civil penalties would be payable (section 32BF).

- if the exemption from registration was made under Schedule 5A of the Regulations, the sponsor could be required to report certain adverse effects to the TGA
- the TGA's recall powers²² (which include requiring the supplier to make information available about the products, including the public) would be available in the event that the products did not comply with an applicable standard or it appeared that the quality, safety or efficacy was unacceptable
- the stem cells would be required to comply with advertising requirements (it is an offence the Act to publish or broadcast an advertisement that refers to a biological)
- it would not prevent the products being used in clinical trials under the Act.

Any autologous cells that are not within the exclusion as described above would be regulated as Class 3 or Class 4 biologicals (for example any that are subject to greater than minimal manipulation)²³ (but could be used in clinical trials under the Act without be included in the ARTG). Given the likely lack of clinical evidence to support their efficacy, it is possible that applications for inclusion may be delayed and/or be unsuccessful so would no longer be available to patients.

It follows that it is possible that some autologous cells currently being supplied under the Order exemption would not come within this description and thus would be regulated under the Act as Class 3 or 4 biologicals.

This option would address the need for more data on adverse reactions. It is unknown whether it would provide an incentive to perform further clinical trials or not. As such, patients, albeit probably a reduced number, may expose themselves to risks without any demonstrable benefits.

The extent to which this option affects patient access depends on the extent to which existing treatments are for homologous use and minimally manipulated, and whether they comply with existing standards.

Option 4: Regulate under the Act as Class 1 biologicals

Autologous cells could be required to be included in the ARTG as biologicals, but at the lowest level of regulation applying to biologicals, namely Class 1.

The requirements for inclusion in the ARTG as a biological depend on the class to which the biological belongs. There are four classes of biologicals. Class 1 biologicals represent the lowest level of risk. They are required to be included in the ARTG, but are not required to be evaluated by the TGA for their safety, quality and efficacy prior to registration, as are higher classes²⁴. So long as the applicant has made all the required certifications, the Secretary must include the Class 1 biological in the ARTG²⁵.

²² While typically, a recall is not possible for products that are used immediately, there are other requirements such as advising patients and taking action to prevent recurrence that service the public interest during a recall.

²³ They would not come within the definition in regulation 2 of Class 2 biologicals.

²⁴ A Class 1 biological is one that is specified in regulation 16; at present there are no Class 1 biologicals in Schedule 16.

²⁵ Subdivision B of Division 4, especially s 32DB of the Act.

The kind of biological must first be included in Schedule 16 of the Regulations, as a Class 1 biological. Companies can then apply to include biologicals that come within that description in the ARTG, subject to the applicant certifying that²⁶:

- a. the biological is a Class 1 biological
- b. the biological is safe for the purposes for which it is to be used
- c. the biological conforms to every standard (if any) applicable to it
- d. the applicable provisions of the Therapeutic Goods Advertising Code and other requirements relating to advertising are complied with
- e. the biological complies with all prescribed quality or safety criteria that are applicable to it
- f. the biological does not contain substances that are prohibited imports under the *Customs Act 1901*.

Class 1 biologicals are exempt from manufacturing requirements. Further, there are currently no prescribed quality or safety criteria for Class 1 biologicals and no products have been included in Schedule 16 as Class 1 biologicals. The applicant is not required to certify as to the efficacy of the product.

Applicants must certify that:

- the biological is a Class 1 biological
- it is safe for its intended purpose
- it conforms with applicable standards²⁷
- that the advertising requirements are met (which would involve certifying that no advertising to the public mentions the relevant products, noting that it is an offence under the Act to publish or broadcast an advertisement that refers to a biological).

Sponsors of Class 1 biologicals must report certain kinds of adverse effects to the TGA²⁸. It would be possible to include additional conditions on the inclusion relating to the keeping of records about supply and reporting to the TGA as with the inclusion of other classes of biologicals.

This option would apply only to autologous cells that are (for the reasons set out above):

- for homologous use (i.e. the cells perform the same basic function in the body as they originally perform before being extracted)
- subject to not more than minimal manipulation.

In summary, under this option these **autologous cells** would be regulated under the Act as follows:

- the product must be included in the ARTG if the relevant certifications are made by the applicant and it is of the kind described as a Class 1 biological

²⁶ Section 32DA(2).

²⁷ Therapeutic Goods Orders 87 and 88 are the relevant standards.

²⁸ Section 32DQ.

- these certifications include statements about safety, compliance with applicable standards and advertising, but not efficacy
- providing a false or misleading certification would be a grounds for suspension or cancellation
- the TGA could require information to be provided about the products, including about their safety and efficacy and compliance with standards²⁹; failure to provide would be grounds for suspension/cancellation³⁰
- their inclusion in the ARTG (and thus supply in Australia) could be suspended or cancelled if it appeared to the TGA that the quality, safety or efficacy of the products were unacceptable, there was a breach of condition of inclusion, the advertising requirements were breached, the product did not comply with relevant standards or the sponsor did not respond to TGA questions about the product
- neither the 'manufacturer' of the cells or the manufacturing process would be required to be licensed
- the cells would be required to meet the requirements of applicable product standards, including any relevant standards made under section 10 of the Act
- the sponsor would have to report certain adverse effects to the TGA and, depending on any additional conditions imposed, be required to keep supply records, etc.
- the TGA's recall powers (which include requiring the supplier to make information available to the TGA and the public about the products) would be available in the event that the products did not comply with an applicable standard or it appeared that the quality, safety or efficacy was unacceptable
- the stem cells could not be referred to in any advertising to the public
- it would not prevent the products being used in clinical trials under the Act.

Any autologous cells that are not within the description of Class 1 biologicals as described above would be regulated under the Act as Class 3 or Class 4 biologicals (for example any that are subject to greater than minimal manipulation).³¹

It follows that it is possible that some autologous cells currently being supplied under the Order exemption would not come within this description and thus would be regulated under the Act as Class 3 or 4 biologicals (though could be used in clinical trials under the Act without being included in the Register). Given the likely lack of clinical evidence to support their efficacy, it is possible that applications for inclusion may be delayed and/or be unsuccessful so would no longer be available to patients.

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. This option may, inadvertently, provide an inappropriate level of confidence in the products as they will be seen to be regulated by the TGA, but without strict assessment of safety, quality and

²⁹ See section 32JA. It is an offence for failure to comply with a notice requiring information (under section 32JB) and civil penalties are payable if the information is false or misleading (section 32JC).

³⁰ Subsection 32FA(1) and paragraph 32GC(1)(d).

³¹ They would not come within the definition in regulation 2 of Class 2 biologicals.

efficacy. This may then perpetuate patients exposing themselves to risk with insufficient evidence of benefit.

This option would address the issues around adverse event reporting.

Option 5: Regulate under the Act as Class 2, Class 3 or Class 4 biologicals

All classes of biological above Class 1 must be evaluated by the TGA against a number of criteria³² before they can be included in the ARTG. The most important of these is whether the quality, safety and efficacy of the biological for the purposes for which it is to be used have been satisfactorily established³³.

Class 2 biologicals are biologicals that are³⁴:

- processed using only one or more actions of minimal manipulation¹¹
- for homologous use.

Depending on the circumstances, those cells that are not autologous cells (as defined at the commencement of this paper)³⁵ would constitute Class 2 biologicals. If a biological does not meet the definition of a Class 2 biological, then, depending on the circumstances of its use and manufacture, it will be a Class 3 or Class 4 biological³⁶. All biologicals that are Class 2 and above, must be evaluated by the TGA for their quality, safety and efficacy for their intended purpose, prior to being included in the ARTG.

As for Class 1 biologicals, sponsors of Class 2 biologicals must report certain kinds of adverse events arising from the use of the biologicals to the TGA and would be required to keep supply records and be subject to other reporting requirements.

Class 2 biologicals (and above) must also comply with applicable standards (which would include TGO 88 and TGO 87), and their manufacture must be covered by a manufacturing licence issued under Part 3-3 of the Act.

In summary, under this option autologous cells used in a single medical procedure would be regulated under the Act as follows:

- the TGA would need to be satisfied (based on a dossier and clinical evidence) as to their quality, safety, efficacy (for their intended purpose) in order for them to be included in the ARTG
- the 'manufacturer' of the cells and the manufacturing process would be required to be licensed

³² Section 32DE.

³³ Paragraph 32DE(1)(a).

³⁴ Regulation 2 defines the various classes of biologicals, and terms such as minimal manipulation and homologous use.

³⁵ For instance, if they were not being used under the supervision of one medical practitioner in the course of one treatment for one indication.

³⁶ Class 3 and Class 4 biologicals are defined in regulation 2 of the Regulations. The difference between them is that the former cannot involve the use of a processing method in a way that changes an inherent biochemical, physiological or immunological property.

- the TGA could require information to be provided about the products, including about their safety and efficacy and compliance with standards³⁷; failure to provide would be grounds for suspension/cancellation³⁸
- their inclusion in the ARTG (and thus supply in Australia) could be suspended or cancelled if it appeared to the TGA that the quality, safety or efficacy of the products were unacceptable, there was a breach of condition of inclusion, the advertising requirements were breached, the product did not comply with relevant standards or the sponsor did not respond to TGA questions about the product
- the cells would be required to meet the requirements of applicable product standards, including any relevant standards made under section 10 of the Act
- the 'sponsor' (i.e. the person in relation to whom the goods were included in the ARTG) would have to report certain adverse effects to the TGA and comply with conditions relating to records and reporting
- the TGA's recall powers (which include requiring the supplier to make information available to the TGA and the public about the products) would be available in the event that the products did not comply with an applicable standard or it appeared that the quality, safety or efficacy was unacceptable
- the cells could not be referred to in any advertising to the public
- it would not prevent the products being used in clinical trials under the Act.

This option provides the clearest incentives for gaining good quality clinical evidence as it would be the only avenue for marketing. It would also give medical practitioners sufficient confidence to refer patients for these treatments. The current marketing model would shift from advertising unproven treatments to referring for proven treatments.

It would address the need for adverse reaction data.

If it is the case that there is limited clinical evidence about the efficacy of autologous stems currently available, this option may see these products not available, unless made available under an exemption under the Act.

³⁷ See section 32JA. It is an offence for failure to comply with a notice requiring information (under section 32JB) and civil penalties are payable if the information is false or misleading (section 32JC).

³⁸ Subsection 32FA(1) and paragraph 32GC(1)(d).

Attachment 1

List of clinical procedures/treatments potentially within the current Item 4 (q) exclusion not covered by the discussion paper

Note inclusion of alternative regulatory schemes where they exist.

Autologous

1. Skin grafts (including keratinocyte sprays)

A procedure where healthy skin is removed from one area of the body (leg, arm, buttocks) and transplanted to an injured area (most commonly burnt). Some hospital burns centres are taking keratinocytes (skin cells) and culturing them before applying the cells to the injured area as part of mesh grafts or sprays. Skin grafts may also be used in reconstructive surgery. International centres have reported on transplants of autologous melanocytes, another skin cell type, for treatment of vitiligo.

2. Skull flaps

Sections of skull may be removed to facilitate brain surgery to treat traumatic brain injuries (fractured skull, swelling, bleeding in the brain), tumours (cancerous and non-cancerous), and other disorders. The removed sections of skull may be stored and then returned when any swelling within the skull cavity has settled.

3. Vascular conduits

Blood vessels (usually veins) are used to replace injured or blocked arteries in a different area. Vascular conduits are commonly used in coronary artery bypass grafting for heart disease and in the treatment of peripheral vascular disease (poor blood flow to the lower limb/s). Autologous blood vessels may also be transplanted to facilitate heart transplants.

4. Pancreatic islet cells

The pancreas is a large gland that lies behind the stomach and is responsible for producing the hormones insulin and glucagon to control blood sugar levels. Some patients with chronic or recurrent inflammation of the pancreas may need the pancreas surgically removed. The insulin-producing islet cells are taken from the removed pancreas and transplanted into the liver to prevent diabetes. If a patient already has diabetes, islet cell transplantation decreases the risk of the diabetes becoming worse.

5. Bone grafts

Small sections of bone may be taken from healthy sites (usually the iliac crest of the hip bone) and transplanted into injured areas to assist healing after elective orthopaedic surgery (for example knee reconstruction), and traumatic bone injuries. Osteochondral transfer (OATS, transfer of small sections of bone and attached cartilage) procedures may be used for repair of well-defined cartilage defects in joints like the knee.

6. Haematopoietic cells (HPCs) for reconstitution of blood after treatment of cancer (also called bone marrow transplants)

Patients with a range of blood cancers often undergo powerful chemical therapies to destroy the cancerous cells. HPC are taken before the treatment and then restored after the treatment to

help the blood re-establish, particularly the infection fighting cells. Hospitals providing HPC transplants are currently subject to NPAC/NATA accreditation

7. Blood to seal cerebrospinal (CSF) leaks

The brain and spinal cord are cushioned by a clear fluid called CSF, encased in a protective membrane called the meninges. If the meninges are torn as a result of injury, surgery or sometimes spontaneously, the CSF may leak out and the patient is at risk of infection and other complications. Small tears in the meninges may be closed by applying fresh blood, which clots and seals the opening.

8. Blood components

Donated (allogeneic) whole blood, packed red blood cells, platelets and plasma may be transfused for a large number of reasons. Some patients with rare blood types that are difficult to match may need to prepare for surgery by providing autologous donations a few weeks in advance of surgery. The blood is stored and reinfused when needed. Another approach to autologous blood replacement is the process of catching, filtering and reinfusing lost blood during surgery (Cell Savers).

9. Cosmetic/reconstructive procedures (skin, bone and fat transfers)

Bone grafts and mucous membranes may be used as autologous transplant materials for patients requiring dental and maxillofacial surgery (dental implants for crowns or bridges, gum recession, facial prostheses). Fat cells may be collected from one area (usually stomach, thighs or waist) using a procedure termed liposuction, and reinjected into another area to increase fat content in the receiving site. This is often used for breast reconstruction after breast cancer surgery, and other cosmetic and reconstructive surgery.

Attachment 2

Summary of TGA review of the safety of autologous adipose derived mesenchymal stem cell therapies

Summary

The TGA has very recently undertaken a literature review of safety and risk factors associated with autologous mesenchymal stem cell therapy, with particular reference to autologous adipose-derived mesenchymal stem cells. This attachment briefly summarises the salient features of the review, which will aid in formulating a suitable regulatory framework for autologous cell therapies.

The key findings of the review are as follows:

- No significant safety issues pertaining to therapeutic use of mesenchymal and/or adipose derived stromal cells were identified based on published data for multiple indications, using multiple delivery routes and up to 6.8 years of follow-up evaluations (including published meta-analyses).
- Sporadic reports of adverse effects pertaining to adipose-derived stromal cells were identified. The effects were diverse in nature and ranged from cyst formation, fat necrosis, microcalcifications, pulmonary embolism, microthrombosis, bone formation, high blood pressure and fever, suggesting a context-dependent manifestation.
- Pulmonary embolism and infarction are theoretical risks of IV administration of mesenchymal stromal cells, and literature reports indicate that a large proportion of injected cells are detected in the lungs of humans upon first passage; however, only one human case report of pulmonary emboli after cell infusion was identified in the scientific-medical literature. This is in contrast to the situation in small animal species, where fatal pulmonary emboli after IV injection of mesenchymal stromal cells is commonly reported.
- Additional risk factors that may affect clinical safety were also identified based on pre-clinical studies, both *in vitro* and *in vivo*. These risk factors included recruitment of adipose derived stromal cells into tumour propagation, bi-modal immunomodulatory response *in vivo* to high or low cytokine levels and potential to develop cytogenetic aberrations *in vitro* that may have tumorigenic potential *in vivo*.
- A general lack of standardised cell characterisation and expansion protocols combined with paucity of knowledge with regards to biological context in which the cells operate *in vivo* are also confounding risk factors.

In order to minimise ambiguity and risks associated with the safe and efficacious therapeutic application of mesenchymal and adipose-derived stromal cells, this review identified the need to have:

- unambiguous and scientifically accurate nomenclature to describe the cell therapy product, based on up-to-date and peer-reviewed data
- standardised lists of *in vitro* and *in vivo* characteristics that are reproducible and allow for direct and meaningful comparisons between pre-clinical and clinical studies
- standardised protocols for harvesting and expansion of mesenchymal and adipose-derived stromal cells, which are also reproducible.

The TGA review concluded that there may be under-reporting of adverse events for stem cell treatments outside the framework of approved clinical trials and that safety data on long-term follow-up of cell therapies are very limited. There is the possibility that a lack of adverse events and/or efficacy may be due to a lack of persistence of cells in the host. The review also noted that most stem cell treatments are in early stage clinical trials and safety data on long-term follow-up are very limited.

Background

Stem cells have the potential to divide to produce either more identical stem cells (self-replicate) or to differentiate into a range of different cell types. The majority of stem cell treatments are still under development and have not been demonstrated to be safe and effective.

In recent times, there has been an increase in the number of companies and medical clinics that offer 'autologous stem cell' treatments in Australia. Concerns have been expressed on the safety of and proliferation of unproven autologous stem cell treatments, particularly autologous adipose-derived stem cells. Numerous 'stem cell clinics' in Australia claim to treat indications such as headache, hamstring muscle injury, tendinopathy, osteoarthritis, multiple sclerosis and cosmetic enhancements utilising 'stem cells'. However, no stem cell-based therapies (that are not excluded from the Act under the Order) are included in the ARTG at present.

The TGA is currently exploring options for regulation of autologous stem cell therapy that would include adipose-derived mesenchymal stem cell therapies. A suitable regulatory framework would encompass issues of safety, efficacy, promotion and/or advertising. The TGA has undertaken a literature review to assess the safety and risk factors associated with autologous stem cell therapy, specifically, adipose-derived stem cells.

Characterisation of the stem cells

Stem cells isolated from adipose tissues demonstrate characteristics similar to that of mesenchymal stem cells isolated from other mesodermal tissues, such as marker expression, *in vitro* growth characteristics, differentiation and pre-clinical therapeutic potential.

There is currently no standardised definition of mesenchymal stem cells as the defining characteristics are broad within the scientific and clinical therapy fraternity and often lacks consistency. The term is commonly applied to 'plastic adherent cells isolated from bone marrow, adipose or other tissues with multipotent differentiation capacity *in vitro*'.

Mesenchymal stem cells can be isolated from a wide range of tissues and expanded *in vitro* using different protocols. This makes it difficult to enable appropriate and direct comparisons between different studies, especially in the context of cell therapy, and to provide clarity within a regulatory framework.

Stem cells for autologous therapy are derived either from the patient's own bone marrow or from adipose (fat) tissue. The easy and less-invasive access to adipose tissue and the simple isolation procedures provide a distinct advantage over harvesting of bone-marrow derived cells. No universal consensus exists in terms of distinguishing adipose-derived mesenchymal cell characteristics from other stromal cell types.

Before cells can be used, the cells need to be cultured *in vitro*. A major contributory factor to the ambiguity in cellular identity *in vitro* is the variation observed in tissue processing, isolation and cell expansion protocols. At present there is no common stringent, reproducible procedure followed for pre-clinical or clinical cell harvest and expansion. A key consideration of *in vitro* culture is the number of 'expansion cycles' employed to generate the necessary number of cells, which is also used to compare studies. Most studies report expansion cycles in terms of 'passage number' (the number of times cells in the culture have been sub-cultured). In addition, for the

cells to increase in number, they need to be cultured in culture medium containing serum. Experiments have shown that it is preferable to use human serum rather than the more common use of fetal calf serum as different gene expression patterns have been observed in the stem cells; stem cells grown in human serum appear to be more stable.

Adverse effects

Several clinical studies have used allogeneic or autologous bone marrow-derived human mesenchymal stem cells. The indications of these studies varied from haematological diseases, cancers, cardiovascular diseases, neurological (inherited diseases), auto-immune diseases, refractory wounds and bone/cartilage defects/fractures. Few studies utilised cells of adipose origin (one auto immune, two refractory wounds and one bone/cartilage defect). The follow up period for all studies varied from one month to 6.8 years. Depending on indication, the routes of administration were intra-arterial, intra-venous, intra-bone marrow, intra-coronary, intra-ventricular, intra-techal, intra-spinal or local applications. Of the 54 studies examined (and over 700 patients), no reports of tumour or ectopic tissue growth were reported.

Adverse effects following autologous cell therapies have been reported, some of which are related to adipose-derived cell treatment. These include the following:

- cyst formation, microcalcifications, fat necrosis and at least one incident of ectopic fibrogenesis for breast augmentation;
- pulmonary embolism one month following *iv* infusion for cervical herniated intervertebral disc - *the only case report of pulmonary emboli after stromal cell infusion identified in the scientific-medical literature;*
- microthrombosis in diabetic patients treated for critical limb ischemia;
- cerebrovascular events (stroke) in three patients, in both the treatment and placebo groups; (It was unclear whether the injected cells, treatment with anticoagulants, or catheterization of the left ventricle contributed to the adverse events.);
- spinal cord multi-cystic mass eight years following autologous olfactory mucosal cell transplant for spinal cord injury;
- cellular masses in kidney following injection of autologous haematopoietic stem cells for end-stage renal disease; and
- bone formation in eyelid after eye injection for cosmetic purposes.

It is clear from the above reports that the potential for adverse effects following autologous adipose-derived cell therapy is realistic, and that the type of effects are diverse, and likely dependent on many different variables. However, in some instances the inclusion of patients with a poor prognosis and pre-existing medical conditions could obscure potential long-term harmful effects of the treatment.

Recent studies have demonstrated an immunomodulatory role for mesenchymal stem cells. That is, they appear to be involved in immunological processes that can have adverse effects on the immune system either by immunosuppressing a process or by enhancing one. The immunosuppressive processes include maintenance of dendritic cell in an immature state, monocyte and macrophage recruitment to tumour sites, induction of cytokine secretion by macrophages, suppression of natural killer cells and suppression of T-cell and B-cell proliferation. These may arise from a strong proinflammatory cytokine response. Conversely, these cells can potentiate an enhanced immune response by a weak inflammatory cytokine response. This immunomodulatory response facilitated by these stem cells necessitates a context-dependent utility at different stages of the same disease or unrelated indications to

minimise risk of adverse effects and maximize efficacy. This is of particular importance given that the effects of stem cells can be long lasting, even in the absence of engrafted tissue *in situ*.

Because of the immunomodulatory properties of mesenchymal stem cells there is an urgent requirement for further standardised characterisation of immunological properties of these cells, including those derived from adipose tissue.

A robust assessment of tumorigenic potential of stem cells in clinical trials must include assessment of efficacy of the trials as absence of efficacy may be an indication of minimal or absent cell integration or transplantation (amongst other reasons), thus, masking potential tumorigenic effects. The source, preparation and dose of cells utilised, and route of administration may also likely be of consequence (e.g. potential for locally administered bolus to create tumorigenic microenvironment depending on site of implant). Pulmonary embolism and infarction are theoretical risks of IV administration of mesenchymal stromal stem cells in humans, as it has been reported that a large proportion of IV injected mesenchymal stem cells are trapped in the lungs of humans upon first passage.

Conclusion

Overall, no direct and significant safety issues pertaining to therapeutic use of mesenchymal and/or adipose derived stromal cells were identified based on published data for multiple indications, using multiple delivery routes and up to seven years of follow-up evaluations (including published meta-analyses).

While there is little evidence from clinical trials of serious short to medium term adverse effects of autologous cell therapy, sporadic reports of adverse effects pertaining to adipose-derived stromal cells were identified. The effects, which were diverse in nature, range from cysts formation, fat necrosis, microcalcifications, pulmonary embolism, microthrombosis, high blood pressure and fever, and suggest a context dependent manifestation.

Additional risk factors that may affect clinical safety were also identified based on pre-clinical studies, both *in vitro* and *in vivo*. These risk factors included recruitment adipose derived stromal cells into tumour propagation, bi-modal immunomodulatory properties sensitive to *in vivo* cytokine response and potential for tumorigenic cytogenetic aberrations propagated *in vitro*.

A general lack of standardised cell characterisation and expansion protocols combined with paucity of knowledge with regards to biological context in which the cells operate *in vivo* also appear to be confounding risk factors.

Attachment 3

Definitions of manipulation and homologous use

'Minimal manipulation'

Health Canada

Minimally manipulated means:

- a. in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement; and
- b. in respect of cells and non-structural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility

TGA

Minimal manipulation: A process involving any of the following actions:

- a. centrifugation;
- b. trimming, cutting or milling;
- c. flushing or washing;
- d. refrigeration;
- e. freezing;
- f. freeze drying (of structural tissues only);
- g. the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents;
- h. irradiation for the purpose of bioburden reduction;
- i. any other action that is similar to an action mentioned in paragraph (a), (b), (c), (d), (e), (f), (g) or (h).

EU

Non substantial manipulation is:

- cutting,
- grinding,
- shaping,
- centrifugation,
- soaking in antibiotic or antimicrobial solutions,
- sterilization,
- irradiation,

- cell separation, concentration or purification,
- filtering,
- lyophilization,
- freezing,
- cryopreservation,
- vitrification.

FDA

Minimal manipulation means:

1. For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and
2. For cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

'Homologous use'

Health Canada

In respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation.

TGA

The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a biological that performs the same basic function in the recipient as in the donor.

FDA

Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

'Non homologous use'

EU

The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Historical consultation document

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<http://www.tga.gov.au>

Reference/Publication #