Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Regulation of autologous cell and tissue products and proposed consequential changes to the classification of biologicals

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TGA Health Safety Regulation

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Chapter 1 – Context and purpose of this paper

Part A – Context

In January 2015, the Therapeutic Goods Administration (TGA) published a Consultation Paper on the regulation of autologous stem cell therapies (Regulation of autologous stem cell therapies - Discussion paper for consultation - January 2015).

The January 2015 Consultation Paper outlined:

- the current regulation of autologous cells by the TGA;
- concerns that have been raised by stakeholders in recent years about the current regulation; and
- five possible options for the future regulation of autologous cells. The options described different levels of regulation based on factors such as, whether the autologous stem cells were minimally manipulated and whether the cells were used as part of a single procedure. Regulatory options ranged from maintaining the status quo, to small increases in regulation (such as prohibiting advertising to consumers), through to full regulation as a biological under the *Therapeutic Goods Act 1989* (TG Act).

Eighty written submissions were received by the TGA and meetings were held with a number of individuals and organisations. Overall, there was general agreement that some increase in regulation was needed, but views differed widely on the appropriate extent of any changes. Some expressed concern that regulatory change may hinder their business operations and thus proposed that limited change was appropriate, while others proposed the need for greater regulation.

Stakeholders variously noted that:

- regulation needs to be more specific about which autologous cells and tissues should be captured by the therapeutic goods regulation and which should be excluded;
- regulation needs to be carefully considered and targeted to areas of risk;
- patients may be misled about a treatment (through advertising and false claims) and this may have financial implications for them, and expose them to unnecessary medical procedures with associated risk. Some stakeholders also expressed concern that human cells and tissues were being used without the benefit of first undergoing clinical trials;
- some definitions used in the therapeutic goods legislation relating to the regulation of autologous cells should be reviewed including the definitions of 'medical practitioner' and 'minimal manipulation';
- TGA regulation was not the most appropriate regulatory scheme to deal with all of the potential issues or risks associated with emerging human cell and tissues therapies. For example, it was recognised that the Australian Competition and Consumer Commission (ACCC) plays an important role in regulating false and misleading advertising, and the Australian Health Practitioner Regulation Agency (AHPRA) also plays a role in regulating the conduct of medical practitioners; and
- TGA regulation should not adversely impact the use of cells and tissues that have been part of established medical practice for decades. Rather, TGA regulation should focus on new and emerging, unproven treatments.

The TGA has closely reviewed all submissions and re-examined international approaches to the regulation of autologous cell and tissue products.

Part B – Purpose of this paper

The two main objectives of this paper are to present revised options that address the issues raised by stakeholders in response to the January 2015 Consultation Paper, and to describe in more detail the impacts of the options including the implications for the broader biologicals framework.

This Consultation Paper includes two substantive Chapters:

- ***Chapter 2 - Regulation of autologous cell and tissue therapies***. The structure of this Chapter loosely follows the structure of a Regulation Impact Statement. The Chapter has been drafted in this way so that the TGA can ensure that it elicits all relevant information from stakeholders in order to inform future decisions about the preferred option. This Chapter describes:
  - the problems proposed to be addressed through any changes to the regulation of autologous cell and tissue products;
  - the objectives of any government action;
  - the revised options under consideration; and
  - the impacts of the revised options. As noted in the description of the impacts, we recognise that there is limited information or evidence about the costs and benefits of some of the options. Specific questions have therefore been included for stakeholders.
- ***Chapter 3 - Changes to the definition of 'minimal manipulation' including impacts on the biologicals framework.***
  - A number of the options described in Chapter 2 differentiate between cell and tissue products based on the level of manipulation of such products. Recognising the potential for increased risk associated with increased manipulation, some of the options propose different levels of regulation based on whether or not the cells and tissues are subject to minimal manipulation. In developing these options, the TGA reviewed the current definition of *minimal manipulation* in the therapeutic goods legislation and identified a number of problems. Stakeholders also queried the relevance of the current definition which is not reflective of that used by a number of other regulators.
  - The TGA is therefore proposing a new definition of *minimal manipulation* which is better aligned with those used by the European Medicines Agency (EMA) and USA Food and Drug Administration (FDA), removes existing uncertainty and introduces the link between the manufacturing step and the intended clinical function of the product, which is crucial for assigning an appropriate risk classification.
  - The TGA considers that it would be desirable to adopt the new definition regardless of which option for the regulation of autologous cell and tissue products is preferred. For both legal and practical reasons, it is also desirable for the definition of minimal manipulation (currently in regulation 2 of the Therapeutic Goods Regulations 1990) to be used consistently across the entire biologicals framework. As the term is used to categorise biologicals (Class 2, 3 and 4 biologicals) this change will have impacts on the biologicals framework.

- Chapter 3 therefore describes the proposed definition of minimal manipulation and the implications for the biologicals framework and seeks stakeholder input about the proposals.

Your input is sought

TGA invites comments from interested parties. Comments can address any or all of the issues discussed in this Consultation Paper.

Submissions must be lodged using the online consultation submission form to upload your submission in either pdf or word format. Alternatively, hardcopy submissions with a printed coversheet may be mailed to:

Biological Science Section
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

For accessibility reasons, please email responses in a Word or rich text format (RTF) format.

Closing date for comments is Thursday, 6 October 2016

Chapter 2 – Regulation of autologous cell and tissue therapies

Part A – Background

Since 2011, the TGA has regulated human cell and tissue-based products as a distinct group of therapeutic goods called 'biologicals' under the TG Act and the Therapeutic Goods Regulations 1990 (the TG Regulations).

Before biologicals can be legally imported, exported, manufactured or supplied in Australia, they must be included on the Australian Register of Therapeutic Goods (ARTG) or otherwise exempted, approved or authorised.

The TG Regulations allow for the inclusion in the ARTG of four classes of biologicals based on the risk posed by the products, which relate to the methods used to prepare and process the products during their manufacture, and whether their intended use is the same as their usual biological function.

The risk of the biological determines the level of scrutiny that it must undergo before being included on the ARTG.

After biologicals have been included on the ARTG, ongoing (post-market) controls include manufacturing surveillance, targeted review and adverse events reporting.

The therapeutic goods legislation includes provisions for biologicals which do not require them to be included in the ARTG to allow legal supply under certain circumstances (such as for clinical trials, emergency situations or use by individual patients with the approval of medical practitioners). However, such biologicals are still subject to certain controls under the TG Act, including the ban on advertising and the obligation to comply with relevant standards.

Certain types of biologicals are excluded from the operation of the therapeutic goods legislation entirely.

One such group of products is known as autologous cells and tissues, used in certain circumstances by registered medical practitioners. Autologous cells and tissues are those that are removed from and applied to the same person, i.e. the donor and the recipient are the same. Examples of the use of autologous cells and tissue include skin grafts, skull flaps, bone grafts, bone marrow transplants and adipose-derived stem cells.

Item 4(q) of the *Therapeutic Goods (Excluded Goods) Order No. 1 of 2011* (the TG Order) currently provides that, if certain conditions are met, autologous cells and tissues are not considered therapeutic goods. Specifically, Item 4(q) provides that human cells and tissue are not therapeutic goods if they are:

- 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
- manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner; and
- 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.

The effect of this item is that the use of autologous cells and tissues in this way is outside the scope of the TG Act.

The main reasons for the decision to exclude autologous cells and tissues used in this way from the biologics framework in 2011 were because:

- they had, historically, been seen as part of medical practice which is subject to state and territory health legislation (along with certain national standards such as the National Safety and Quality in Healthcare Standards, depending on where the patient is treated) and medical practitioners were (and remain) subject to professional regulation by AHPRA;
- historically, the autologous cells and tissue had not been extensively manipulated and the procedures utilising autologous cells and tissue largely occurred in hospitals under the direct supervision of medical practitioners; and
- there were a number of procedures utilising autologous cells and tissue that are well established and proven to be efficacious and safe within the context in which they were applied.

Part B – The problem

Whilst some uses of autologous cells and tissue continue to be appropriately regulated as medical practice (and excluded from regulation as therapeutic goods), there are emerging examples of practices that have the potential for increased risk, and where the processes applied to the autologous cells or tissue are more akin to manufacturing processes rather than routine medical practice.

Since the TG Order was made in 2011, the following can be observed:

- in some cases, greater manipulation of the cells is occurring before they are used to treat the patient. This includes, for example, extensive ex vivo culture for cell expansion and differentiation. The more significant the manipulation, the greater the potential risk relating to a lack of control over manufacturing processes and the need for increased oversight to ensure consistency of product potency, purity, identity, traceability, safety, and product stability;
- there is emerging evidence that cells are being used via routes of administration that introduce the potential for higher risk to the patient (such as intravenous and intrathecal administration). These routes of administration introduce increased risk of infection, embolism and ectopic tissue formation;
- some treatments using autologous cells and tissue, for which there is little or no peer reviewed/established evidence of efficacy, are being marketed directly to patients/consumers. For example, treatments are being offered for diseases such as multiple sclerosis, with little or no supporting evidence. As there are risks associated with any medical procedure, this means that patients are potentially exposing themselves to risk for no definable, demonstrable benefit;
- where these uses of autologous cells and tissue are excluded from the therapeutic goods regulation, the limitations on direct-to-consumer advertising in the TG Act do not apply. A number of stakeholders have expressed concern that such advertising of unproven treatments is inappropriate. This is notwithstanding the fact that the Health Practitioner Regulation National Law (administered by AHPRA) prohibits advertising of a service provided by a health practitioner that: is false, misleading or deceptive or is likely to be so;

creates an unreasonable expectation of beneficial treatment, and/or encourages the indiscriminate or unnecessary use of health services. Advertising direct to patients could represent a health risk if it results in patients failing to get more suitable or efficacious treatment in a timely way or if it exposes them to unnecessary risk;

- experimental uses of autologous cells and tissue (provided the use meets the conditions of Item 4(q) of the TG Order) are not required to be approved or notified as clinical trials under the TG Act. Any medical practitioner can collect cells, manufacture the cells through an unproven process, and treat a patient with the processed cells without being required to meet the TGA's requirements relating to clinical trials;

- there have been some international reports highlighting the risks associated with the use of unproven cellular treatments. For example, the International Society for Cellular Therapy Presidential Taskforce recently published a report on unproven cellular treatments (http://www.celltherapysociety.org/?page=PTF2015). The Report highlighted a number of risks associated with their use:

  > *"many cell-based interventions are advertised in a direct-to-consumer fashion without first being tested to determine levels of safety and efficacy. Such premature commercialisation represents a significant risk to both individual patients and to healthcare systems. For patients, such risks include the clear risk of physical harm caused by poorly characterised products of unknown safety and efficacy. Patients and their families are also exposed to financial risks and the possibility of psychological harm";*

- in July 2016 the NSW Coroners Court made recommendations following an inquest into the death of a patient following an autologous cell treatment (http://www.coroners.justice.nsw.gov.au/Documents/Findings%20Drysdale.pdf). While the patient's death was due to adverse events associated with the surgery used to obtain the cells and not the cells themselves, the case raises issues around patients undergoing unproven and unnecessary procedures.

- because these products are not regulated as therapeutic goods, there are no obligations to report adverse events and thus there is no consolidated knowledge of adverse effects involving particular cell types. The absence of reporting contributes to there being limited evidence about either the risks or the safety of autologous cells or tissue. There are, however, requirements under the Australian Consumer Law for suppliers to notify the relevant Commonwealth Minister if they become aware that a person has suffered serious injury, illness or death associated with a consumer good they supplied; and

- the current Australian exclusions under the TG Act are broader than the exclusions of other regulators including the FDA and the EMA which include additional restrictions such as on the level of manipulation that can be performed on the cells and tissue and how and where they can be used. In other words, in both Europe and the USA, a wider range of autologous cells and tissues are subject to oversight by the therapeutic goods regulators. Throughout the world, countries are considering the appropriate regulation of autologous cells and tissue.

Quantification of the problem

The above problems have been identified through stakeholder consultations, anecdotal reports, observation of international practice, and changes in practice that are known to be occurring both locally and internationally.

The nature of the current regulation (and the fact that the use of autologous cells and tissue is currently outside the scope of the therapeutic goods legislation) presents difficulties in collecting reliable, national evidence about:

- the number of practitioners that are currently using autologous cells and tissue;
- the nature of the procedures being undertaken and the percentage of such procedures that involve significant manipulation of the cells or higher risk routes of administration (such as intravenous or intrathecal administration);
- the efficacy and safety of the procedures being used; and
- adverse effects and the extent to which they relate to the autologous cells or tissue.

This information is not collected nationally by hospitals, clinics or the Australian Institute of Health and Welfare (AIHW), so the nature and extent of the problem cannot readily be established.

In many cases, the absence of reliable evidence of a problem would tend to support the proposition that the status quo be maintained (i.e. that there is no issue to be addressed). However, in this case, the potentially significant health effects that have been reported internationally in association with some of these procedures warrants consideration of action despite those difficulties.

Developments over recent years, coupled with the recognition of the existence of potential and recent examples of problems warrants re-consideration of the assumptions that formed the basis on which the 2011 TG Order was formulated as described above.

Your views are sought

The TGA description (above) takes into account the response of stakeholders to the previous consultation.

Does the description of the problems adequately reflect the actual or potential problems associated with the existing regulation of autologous cells and tissue?

Are you able to provide specific evidence particularly in the Australian context, in relation to the practices outlined above, that demonstrates risk to patient health?

Part C – Objectives of any government action

The objectives of any government action in relation to autologous human cells and tissues would be as follows:

- to minimise public health and safety risks;
- to maintain consumer confidence in the regulation of therapeutic goods, specifically the national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods;
- to avoid duplication of regulatory effort, particularly where the regulation of therapeutic goods intersects with the regulation of medical practice (by AHPRA and State/Territory regulators) and the regulation of consumer goods more generally (via the ACCC);

- to align, as far as possible, with international best practice; and
- to minimise unnecessary regulatory burden.

Part D – Options

Revised options

Four options are proposed for the future regulation of autologous human cell and tissue products. Each of the options represents progressively increased regulation based on the two key risks:

- the risk that direct-to-consumer advertising may result in patients failing to get more suitable or efficacious treatment in a timely way and/or expose them to unnecessary risk; and
- the risk associated with increased manipulation of the cells or tissue.

Each option describes the regulatory exclusions and inclusions that would apply:

Option 1 – Human cell and tissue products:

a. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation;

b. that do not meet one or more of the exclusion criteria (for instance, not for autologous use, not under supervision of medical/dental practitioner or not part of a single course of treatment), would be regulated under the TG Act in the same way as other biologicals in the relevant class.

Option 1 is essentially the status quo (with a minor modification to extend to dental practitioners).

Option 2 – Human cell and tissue products:

a. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation but only if the product is not advertised (in the sense of intended to promote use or supply) directly to consumers;

b. that fail to meet one or more of the exclusion criteria (for instance, not for autologous use, not under the supervision of a medical/dental practitioner, not part of a single course of treatment or is advertised), would be regulated under the TG Act in the same way as other biologicals in the relevant class.

Option 2 maintains existing exclusion for products (with a minor modification to extend to dental practitioners) provided the products are not advertised direct-to-consumers.

Option 3 – Human cell and tissue products:

a. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation only if the product is:

   i. not advertised directly to consumers; and

   ii. not more than minimally manipulated;

b. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment but more than minimally manipulated would be subject to regulation under the therapeutic goods legislation as follows:

   i. notification of the type of treatment to the TGA;

   ii. compliance with relevant TGA standards (for example, Therapeutic Goods Orders 87 and 88);

   iii. a requirement to have a system for collecting and notifying adverse events to the TGA;

   iv. subject to the public notification and recovery (recall) provisions in the event that it did not comply with relevant standards; and

   v. a prohibition on advertising the products (in the sense of intended to promote use or supply) direct to consumers;

c. whether or not they are more than minimally manipulated, they otherwise do not meet one or more of the exclusion criteria (i.e. not autologous use or not under the supervision of a medical/dental practitioner, not part of a single course of treatment or advertised to consumers), would be regulated under the TG Act in the same way as other biologicals in the relevant class.

Option 3 maintains existing exclusion for products (with a minor modification to extend to dental practitioners) provided the products are not advertised directly to consumers and not more than minimally manipulated, but introduces a new and increased intermediate level of regulation for products that involve more than minimal manipulation reflecting the level of potential risk.

Option 4 – Human cell and tissue products:

a. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation only if the product is:

   i. not advertised directly to consumers; and

   ii. not more than minimally manipulated;

b. that do not meet one or more of the exclusion criteria (i.e. not for autologous use, not under the supervision of a medical/dental practitioner, not part of a single course of treatment, more than minimal manipulation or advertised) would be regulated under the TG Act in the same way as other biologicals in the relevant class.

Option 4 maintains existing exclusion for products (with a minor modification to extend to dental practitioners) provided the products are not advertised directly to consumers and not more than minimally manipulated.

A summary of the options is shown in **Table 1**.

Characteristics of each Option	Option 1	Option 2	Option 3	Option 4
What autologous human cell and tissue products are excluded from TG Act regulation under options?				
Single medical/dental practitioner, single course of treatment and only minimal manipulation	Excluded from TGA Act	Excluded from TG Act	Excluded from TG Act	Excluded from TG Act
Single medical/dental practitioner, single course of treatment and greater than minimal manipulation	Excluded from TG Act	Excluded from TG Act	Not excluded from TG Act but exempt from being on ARTG if single medical/dental practitioner and single course of treatment	Not excluded from TG Act – regulated as Class 3 or 4 biological
Is advertising allowed?				
Direct advertising to consumers	Allowed	Not allowed under the exclusion	Not allowed under the exclusion	Not allowed under the exclusion
Regulatory outcome if not within exclusion for any reason				
	Regulated under the TG Act as a biological of whichever class is applicable (depends on reason not within exclusion).	Regulated under the TG Act as a biological of whichever class is applicable (depends on reason not within exclusion).	If not within exclusion only because more than minimally manipulated then regulated under the TG Act as biological but: · exempt from being on the ARTG; · must comply with standards and report adverse events; · notify TGA of new types; · subject to recall provisions; · no advertising. If not within exclusion for any other reason then regulated under TG Act as biological of whichever class is applicable (depends on reason not within exclusion).	Regulated under the TG Act as biological of whichever class is applicable to the product (depends on reason not within exclusion)

Explanation of key terms used in the options

Before examining the options in detail the following terms that are used within the options are explained:

- human cell and tissue products for autologous use;
- under the supervision of a medical/dental practitioner;
- as part of a single course of treatment; and
- minimal manipulation.

Two other concepts are not referenced in the above options but also require explanation before discussing the options in detail:

- homologous use; and
- human cell and tissue products that form part of established medical practice.

Human cell and tissue products for autologous use

While the original Consultation Paper was about autologous cells, it contained numerous references to 'autologous stem cells' which might have given the impression that the proposals were limited to that type of cell. As pointed out in that Paper, the current TGA exemption is broader than stem cells and applies to all human cells and tissues that meet the exclusion criteria (including for autologous use, under medical supervision and as part of a single course of treatment).

The descriptions of the options in this paper are more clearly described as applying to human cells and tissue products generally. Limiting any regulatory changes to 'stem' cells is problematic because:

- distinguishing stem cells from other cell and tissue types is not straightforward;
- preparations are often heterogeneous, i.e. mixtures of cells including some progenitor cells, such as stromal vascular fraction (SVF) isolated from digested adipose tissue. There are a number of other cell types present in this preparation and potentially more than one are responsible for any effect observed.

This clarification in relation to the scope of the framework will ensure consistency in handling for the various types of cells and tissues, help to manage boundary issues and ensure that potential future innovations in cells and tissues can be handled within a single framework.

Your views are sought

Do you support the proposed approach? Please provide reasons to support this view or not.

Under the supervision of a medical/dental practitioner

The current exclusion (in item 4(q) of the TG Order) applies to cells and tissue 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 where the cell and tissue is manufactured by that medical practitioner, or by a person or persons under the supervision of that medical practitioner.

For each of the options described above, it is proposed that this concept of supervision by a medical practitioner continue. It is, however, proposed that it be extended to dental practitioners. Use of autologous tissues is accepted practice for a number of dental procedures that do not take place under the supervision of a medical practitioner but instead are undertaken by, or under the supervision of, a dental practitioner, such as gingival grafting for gum recession and preparing jawbones for dental implants.

Your views are sought

Do you agree that the proposed options should also apply to registered dental practitioners supervising the autologous use of human cell and tissue products as part of a single course of treatment? Please provide reasons to support this view, or not.

As part of a single course of treatment

The TG Order currently refers to human cells and tissue for autologous use in a 'single course of treatment'. The original Consultation Paper referred to such cells and tissues (in the context of the proposed options) as being used in a *single procedure*. Internationally, a range of terms are used including *single course of treatment*, *single procedure* and *single surgical procedure*.

The main difference between a 'single course of treatment' and a 'single procedure' (or single surgical procedure) is that storage of the product would be unlikely to be included in a single procedure (or surgical procedure) but would likely form part of a single course of treatment.

There is much debate about the preferred approach. Consistent with the way that the TG Order is currently framed, it is proposed the broader concept of single course of treatment be maintained under each of the Options which would mean that the exclusion would still apply even if the treatment occurred over a period of time (and thus likely to involve storage of the cells and tissue). Storage of cells and tissues introduces potential risks including those of product quarantine, stability, traceability and integrity, and management of such risks will remain the responsibility of the medical/dental practitioner.

The alternative (to limit the exclusion only to where the therapy forms part of a single procedure) would by narrowing the current exclusion, remove any therapy that involves storage of cells and/or tissues and thus increase the range of therapies that would be subject to full regulation as biologicals. For example, storage of skull fragments removed at decompressive craniectomy would become subject to full biologicals regulation even though there has been no indication that the storage required for this treatment represents a risk to the patient that could be ameliorated by regulation under the TG Act.

Your views are sought

Please provide your views regarding the proposal to retain the concept of a 'single course of treatment'. Do you consider the storage of autologous cells and tissues as part of a single course of treatment carry risks of such a nature that should require TGA regulatory oversight? Please provide reasons to support this view, or not.

Minimal manipulation

The current TG Order does not differentiate between cells and tissues based on the level of manipulation of the cells or tissue. Options 3 and 4 propose using the concept of minimal manipulation to distinguish products based on the risks that are derived from subjecting a product to processes akin to manufacturing (rather than procedures more associated with medical practice).

Based on feedback from the initial consultation, experience making classification decisions for biologicals, and an intention to align with international regulation, TGA proposes to replace the current definition of minimal manipulation in regulation 2 of the TG Regulations[1] with the following definition:

> *Cells or tissue are subject to a process that is more than minimal manipulation if the process results in the alteration of any of the biological characteristics, physiological functions or structural properties that are relevant to the intended use of the cells or tissues.*

While the term minimal manipulation is not currently used in the TG Order (describing the exclusion of autologous cell and tissue therapies) it is used to categorise biologicals regulated under the TG Act.[2] If the concept of minimal manipulation were to be introduced for the purpose of determining which autologous cell and tissue products should continue not to be regulated under the TG Act, the proposed new definition should also be used for the purposes of the therapeutic goods legislation. This would mean changes to the definition, as it is currently used in the categorisation of biologicals into classes.

Further detail about the proposed definition of minimal manipulation and the impact for the biologicals framework is included in Chapter 3.

Homologous use

None of the options described above refer to whether or not the human cell and tissue product is proposed for homologous use. 'Homologous use' refers to the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with cells or tissues that perform the same basic function or functions in the recipient, as in the donor. 'Homologous use' is used to categorise biologicals regulated under the TG Act[2].

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[1] The current definition is as follows:

"minimal manipulation " means 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).

[2] See definitions of 'Class 2 biological', Class 3 biological' and Class 4 biological' in regulation 2 of the Therapeutic Goods Regulations 1990.

For the purposes of the exclusion for autologous cell and tissue products, the TGA does not propose distinguishing between human cell and tissue products based on whether or not they are for homologous use. This is because, within the context of the exclusion, a decision on use of the product for each specific indication should rest with the medical or dental practitioners under whose supervision the treatment is occurring.

Your views are sought

Do you agree that it is unnecessary to distinguish homologous and non-homologous use in the context of the exclusion (i.e. where the product is also for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment)? Why?

Human cell and tissue products that form part of established medical practice

The first Consultation Paper included a list of autologous cells and tissue that were associated with established medical practice such as vascular conduits, skin and bone grafts, cultured keratinocytes, haematopoietic progenitor cells for reconstitution of blood after chemotherapy, blood components for autologous use, transplanted pancreatic islets following removal of the pancreas, skull flaps and skin, bone and whole fat transfers during reconstructive surgery.

In response to the first Consultation Paper some stakeholders emphasised the importance of distinguishing between new and untested cell and tissue products and existing established and identified medical procedures, and avoiding unnecessary additional regulation for the latter.

We have explored a range of ways for achieving this. For example, one option would be to draft a list of autologous cells and tissue to be excluded from TGA regulation on the basis that they form part of established medical practice. There are, however, challenges with this approach including defining the practices that should be on such a list with sufficient precision and ensuring it remains up-to-date. This approach would also be inconsistent with international practice.

Instead the TGA is proposing an approach (reflected in the Options described above) that is based on whether or not the product involves more than minimal manipulation. Depending on the Option, if the product involves more than minimal manipulation (thus increasing the risk profile) the product would be subject to TGA regulation.

This approach focuses on risk including where a product is derived from processes akin to manufacturing (more than minimal manipulation). It is proposed the approach should apply to all autologous cell and tissues avoiding any seemingly 'arbitrary' exclusion based on identifying those products that are, and are not, part of certain identified medical practices in the first Consultation Paper.

However, it is the case that most of the procedures listed in the first Consultation Paper involve only minimal manipulation and would therefore not be subject to increased regulation under Options 3 or 4. The TGA is, however, aware of two products that could be considered part of established medical practice but that are also likely to be more than minimally manipulated and as such would be subject to regulation under Options 3 or 4. These products are: cultured keratinocytes for the treatment of burns and infusion of pancreatic islets following removal of the pancreas.

As noted under Chapter 3 below, it is proposed that the TGA would publish guidance material about how to apply the definition of minimal manipulation, along with examples of processes that the TGA does (and does not) consider to involve minimal manipulation in the context of intended use.

Your views are sought

Are any other cell and tissue products currently in use that:

a. are currently covered by the TG Order; and

b. form part of established medical practice; and

c. would be more than minimally manipulated (and therefore would be subject to regulation under Options 3 or 4)?

Options 3 and 4 may impact on hospitals utilising the two types of products (identified above) that involve more than minimal manipulation but are also part of established medical practice. The TGA seeks the views from organisations (and others) on the impacts of this.

Mechanism for implementing options

Currently, section 7 of the TG Act enables the Secretary to declare that certain goods are or are not therapeutic goods. Relying on this power, the Secretary made the TG Order, item 4(q) of which provides that, if certain conditions are met, human tissue and cells are not regulated as therapeutic goods (as discussed in Chapter 1, Part A).

Under any of the options, the TGA would propose changing the mechanism by which these cells and tissues are excluded from the operation of the TG Act. Rather than declaring these not to be therapeutic goods (under section 7), they would be declared by the Minister to be excluded goods under section 7AA of the TG Act to provide legal certainty.[3] Such declarations are disallowable by the Parliament but are not subject to review by the Administrative Appeals Tribunal. The regulatory outcome would be the same i.e. the tissue and cells satisfying those criteria would continue to be free from regulation under the TG Act.

[3] In order to make a declaration under section 7AA, the Minister must have regard to the following:

(a) whether it is likely that the specified goods, if not regulated under this Act, might harm the health of members of the public;

(b) whether it is appropriate in all the circumstances to apply the national system of controls relating to the quality, safety, efficacy and performance of therapeutic goods established by this Act to regulate the specified goods;

(c) whether the kinds of risks from the specified goods to which members of the public might be exposed could be more appropriately dealt with under another regulatory scheme.

The Minister may have regard to any other matter he or she considers relevant. Under this section, the Minister does not have to come to a view about whether the products to be excluded would or would not otherwise be therapeutic goods.

Part E – Impacts of options

Option 1:

Human cell and tissue products:

a. **for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation;**

b. **that do not meet one or more of the exclusion criteria (i.e. not for autologous use, not under supervision of medical/dental practitioner or not part of a single course of treatment), would be regulated under the TG Act in the same way as any other biological in the relevant class.**

The effect of this Option is that:

- the TGA would have no oversight of autologous cell and tissue products manufactured by, or under the supervision of, a medical or dental practitioner for use in a single course of treatment for the patient. This means that there would continue to be no requirement for the manufacturing process to meet TGA standards, and there would be no advertising controls applied through the therapeutic goods legislation. This would be the case regardless of the level of manipulation of the cells and tissues;

- medical and dental practitioners manufacturing and using these cells and tissues would, however, continue to be subject to AHPRA regulation. For example, medical practitioners are expected to comply with a code of conduct for doctors in Australia (March 2014) and with the Guidelines for advertising regulated health services. These documents require doctors to minimise risk to patients, maintain professional behaviour and ensure patients are able to provide fully informed consent for any procedure to be undertaken. The guidelines also require that registered health practitioners comply with the National Law relating to advertising as administered by the ACCC. Similar arrangements also exist for dentists (refer AHPRA website for a full list of policies and codes applying to health practitioners including medical and dental practitioners – <https://www.ahpra.gov.au/>);

- clinics advertising such treatments using these cells and tissues would continue to be subject to the Australian Consumer Law (ACL) that is administered by the ACCC and state/territory consumer protection agencies. The ACL includes a general ban on misleading and deceptive conduct in trade or commerce and a general ban on unconscionable conduct in trade or commerce. If clinics were to advertise a treatment as being able to achieve a certain clinical outcome (and it cannot), action could potentially be taken by the ACCC or a relevant state/territory agency; and

- if a medical or dental practitioner wished to undertake a clinical trial of autologous cells or tissues they could do so, but the trials would not be subject to TGA regulation of clinical trials (including in relation to the reporting of adverse events). They would, however, still be subject to any requirements of their organisation or institution relating to, for example, ethics approvals and consent procedures.

If the cells and tissues were outside the bounds of the TGA exclusion (for instance, if the cells and tissues were not autologous or were not used under the supervision of a medical or dental practitioner for a single course of treatment), then the cells and tissues would be regulated in the same way as any other biological in the applicable class.

Apart from extending the exemption to dental practitioners, this option represents the status quo and therefore minimal change to existing practice. The main disadvantage is that it does not address the problems identified in Part B.

Your views are sought

Do you support maintaining the current system? Please provide reasons to support this view, or not.

Option 2:

Human cell and tissue products:

a. **for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation only if the product is not advertised (in the sense of intended to promote use or supply) directly to consumers; and**

b. **that do not meet one or more of the exclusion criteria (for instance, not for autologous use, not under the supervision of a medical/dental practitioner, not part of a single course of treatment or advertised), would be regulated under the TG Act in the same way as any other biological in the applicable class.**

Under this option human cell and tissue products for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment would only be excluded from TGA regulation so long as the product was not advertised directly to consumers.

This option would address one of the main concerns of stakeholders by prohibiting the advertising of these products directly to consumers. The TGA has evidence of such advertising and has also identified some websites that include such advertising. However, the TGA does not have a full inventory of all advertising that may be provided directly to consumers including through more targeted routes such as brochures or signs in health clinics or beauty salons.

Restricting advertising directly to consumers reduces the potential exposure of patients to misleading information about unproven treatments. This is also consistent with the approach adopted for other biologicals that are regulated by the TGA. A disadvantage of this option is that it would impose a restriction on advertising for some cells and tissue products that form part of routine medical practice (such as those products listed on page 15). However, the TGA is not aware of these products being advertised directly to consumers.

Medical practitioners and dental practitioners could continue to advertise their **services** (provided they meet relevant AHPRA and ACCC legislation) but they could not advertise the cell or tissue product directly to consumers.

Cell and tissue products not excluded (under the section 7AA determination) would be regulated under the TG Act in accordance with the normal rules for biologicals.

Your views are sought

Given that advertising a service will still be possible what is your opinion on advertising of

autologous cell and tissue products and the impact (including financial impact) of this option on those practitioners currently advertising these products to consumers?

Does this option address the issues presented in this paper?

NB: The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator).

Option 3:

Human cell and tissue products:

a. **for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation only if the product is:**

   i. **not advertised directly to consumers; and**

   ii. **not more than minimally manipulated;**

b. **for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment but more than minimally manipulated would be subject to regulation under the therapeutic goods legislation as follows:**

   i. **notification of the type of product to the TGA;**

   ii. **compliance with relevant TGA standards (for example, Therapeutic Goods Orders 87 and 88);**

   iii. **a requirement to have a system for collecting and notifying adverse events to the TGA;**

   iv. **subject to the public notification and recovery (recall) provisions in the event that it did not comply with relevant standards; and**

   v. **a prohibition on advertising of the products (in the sense of intended to promote use or supply) direct to consumers;**

c. **that do not meet the exclusion criteria (i.e. not autologous use or not under the supervision of a medical/dental practitioner, not part of a single course of treatment or advertised to consumers, whether or not are minimally manipulated), would be regulated under the TG Act in the same way as any other biological in the applicable class.**

Under this Option, autologous cells and tissues manufactured by, or under the supervision of, a medical or dental practitioner (for use in a single course of treatment) would be excluded from TG regulation only if the cells and tissues were not advertised directly to consumers and were manufactured in a manner that involves *minimal manipulation* only. It is proposed that the current definition of minimal manipulation would be changed to the following:

> *Cells or tissue are subject to a process that is more than minimal manipulation if the process results in the alteration of any of the biological characteristics, physiological functions or structural properties that are relevant to the intended use of the cells or tissues.*

This definition is discussed in more detail in Chapter 3.

Autologous cells and tissue that involve more than minimal manipulation (but are still supervised by a medical/dental practitioner, as part of a single course of treatment), would be regulated under the TG Act (though not to the same extent as other biological regulated under the TG Act). Specifically, the cells and tissue products would be subject to:

- notification to the TGA. This could include, for example, the medical practitioner's name and contact details, the cells or tissue being used, the process being applied to the cells and

tissues and the intended use of the cell or tissue product. It is expected that this would be a one-off notification of the proposed type of therapy rather than a notification each time the therapy was used. However, if the therapy was changed such that there was a change to the cells or tissues or the intended use of those cells or tissues, this would require further notification;

- relevant TGA standards, such as TGO 88 and TGO 87;
  - TGO 88 is a standard for donor selection, testing, and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products; and
  - TGO 87 describes general requirements relating to labelling of biologicals;
- a requirement that the medical/dental practitioner have a system for collecting and notifying adverse events to the TGA. This would not necessitate the medical practitioner developing a system specifically for this purpose. TGA already has a web-based system for reporting of adverse events that could be used. Where a system already exists (as is the case in many hospitals and clinics) this could satisfy this requirement. Further, the practitioner would only be required to report events that were suspected as involving the cell or tissue product and were serious;
- a prohibition on advertising directly to consumers;
- the recall procedures under the TG Act (see section 32HA).

However, the products would **not** be subject to a requirement to be included on the ARTG or subject to Good Manufacturing Practice (GMP) requirements.

If the product did not fall within the exclusion for any other reason (for example, if it was not manufactured under the supervision of a medical/dental practitioner as part of a single course of treatment), then the product would be subject to regulation in accordance with the relevant biologicals class.

The main advantage of this option is that it represents an increase in the regulation of potentially higher risk products (those that involve more than minimal manipulation) without applying the full biologicals framework. The focus of the increased regulation also reflects the main areas of concern or risk – that is, the increased regulation ensures minimum standards are met, notifications are made to the TGA (to enable monitoring to occur) and adverse events to be reported (building knowledge about the impact of cell and tissue products to enable action to be taken in the event that it is necessary to stop the use of the product).

A challenge of this option is that it creates a 'bespoke' solution for potentially higher risk cell and tissue products rather than integrating such products into the existing biologicals framework and thus creating complexity which may not be justified based on the risk. This option would also require further consideration of:

- when and how medical/dental practitioners would notify the TGA that they are undertaking processes using cell and tissue products of this type; and
- the relevant TGA standards; and
- the types of adverse events that would need notifying to the TGA. This could include, for example, any adverse reactions, any unexpected adverse reactions or only serious adverse events. Each of these concepts is currently used in the therapeutic goods framework but the type of event to be notified varies based on whether the therapeutic good is on the ARTG or

subject to clinical trials. In the case of goods on the ARTG and clinical trials, there are documents that define the expected adverse events. Anything outside these defined events are unexpected and potentially reportable to the TGA. However, in the case of cell and tissue therapies there will be no requirement for an Investigator's Brochure (as there is for clinical trials) or Product Information (as there is for most registered medicines). It will therefore be more challenging to describe the events that are, and are not, 'expected' or 'serious' in the context of the cell or tissue product. Under this Option, consideration would need to be given to defining those types of events that should be notified to the TGA for cell and tissue therapies as adverse events.

This Option also poses potential challenges in terms of enforcement by the TGA. For example, if the TGA considers that an adverse event is unacceptable, there would be limited capacity to stop supply of the product (beyond recalling where it does not comply with a standard) because the product is not on the ARTG and is not being supplied through a clinical trial or the SAS scheme.

Your views are sought

What is the impact (including financial impact) of this option on practitioners currently manufacturing and using these cells and tissues?

To what extent does the requirement to comply with the TG standards increase regulation or whether the manufacture and use currently comply?

Would a requirement to comply with these standards 'add value' in terms of addressing the risks and issues set out in Chapter 2, Part C?

Does this option address the issues? Please provide the reasons why it does or does not.

NB The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator).

Option 4

Human cell and tissue products:

a. for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment, would be excluded from TGA regulation only if the product is:

i. not advertised directly to consumers; and

ii. not more than minimally manipulated;

b. that are more than minimally manipulated or otherwise do not meet the exclusion criteria (i.e. not for autologous use, not under the supervision of a medical/dental practitioner, not part of a single course of treatment or advertised) would be regulated under the TG Act in the same way as any other biological in the applicable class.

Essentially this Option maintains existing exclusions for products provided the products are not advertised directly to consumers and are not more than minimally manipulated, but if the

product is more than minimally manipulated it is classified in the same way as other biologicals (and regulated accordingly).

The main advantages of this Option are:

- it would have very little impact on cell and tissue products that do not involve more than minimal manipulation. The only change for such products would be a ban on direct-to-consumer advertising;
- it would introduce strengthened protections for patients who are treated using human cell and tissue products that involve more than minimal manipulation. Such products would be classified according to the usual classification system for biologicals and as such the level of regulation would be aligned with the overall risk and use of the product.

The main disadvantage of this Option is that it may result in an increase in regulation for some autologous cell and tissue therapies that involve more than minimal manipulation and are part of established medical practice. The TGA is aware of only two products that are part of established medical practice that are also likely to be more than minimally manipulated - cultured keratinocytes for the treatment of burns and infusion of pancreatic islets following removal of the pancreas. Consideration could be given to excluding these specific human cell and tissue therapies (based on the strong evidence base and long-term use of these products) or a transition period could also be considered.

Your views are sought

What is the impact (including financial impact) of this option, particularly on practitioners currently using these products?

Do you consider that this option address the issues? Please provide the reasons why it does or does not.

NB: The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator)

Chapter 3 – Changes to the definition of minimal manipulation including impacts on the biologicals framework

Part A – Definition of minimal manipulation

Current definition of minimal manipulation

As noted in Chapter 2, the current TG Order does not differentiate between cells and tissues based on the level of manipulation to which they have been subject. Options 3 and 4 propose using the concept of 'minimal manipulation' to distinguish products based on the risks that are derived from subjecting a product to processes akin to manufacturing (rather than procedures associated with medical practice).

Regulation 3 of the TG Regulations currently defines minimal manipulation in the context of the classification framework for biologicals as follows:

Minimal manipulation is a process involving any of the following actions: 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; any other action that is similar to an action mentioned above.

This definition:

- is a list of actions but it does not link the level of manipulation with the intended use of the product. This link is present in the FDA definition of minimal manipulation and in the EU definitions of Advanced Therapy Medicinal Products (ATMPs). This link is crucial to understanding the risks of changes to the function of the cells or tissues as a result of the manufacturing process applied, and therefore the appropriate classification of the resulting biological; and
- has posed challenges for both the TGA and sponsors in trying to ensure an internationally consistent approach to the classification of biologicals for regulatory purposes.

> Consultation Paper - Regulation of autologous cell and tissue products
> **EU and FDA definitions**
> FDA definition of minimal manipulation -
> 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;
> 2) For cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.
> EU definitions –
> Cells ortissues shall be considered "engineered' if they …. have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant to the intended regeneration repair or replacement are achieved.
> Somatic cell therapy medicinal product ….. contains or consists of cells or tissues that have been subject to substantial manipulations so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered.
> The manipulations , in particular, shall not be considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification.

Feedback from the previous consultation suggested that there is broad agreement within the sector that alignment with the overseas approach is preferred and that ambiguities in the interpretation of the current definition should be removed.

Proposed new definition of minimal manipulation

It is proposed that the current definition be amended to the following:

> *Cells or tissue are subject to a process that is more than minimal manipulation if the process results in the alteration of any of the biological characteristics, physiological functions or structural properties that are relevant to the intended use of the cells or tissues.*

The proposed new definition:

- introduces the link between the processes to which the cells and tissue are subject and the intended clinical function of the product, which is crucial for assigning an appropriate risk classification;
- is consistent with that taken in the EU and by the FDA. However, neither of the specific definitions used in the EU or FDA are considered appropriate in the context of the Australian regulatory framework. In the EU the link between the processes to which the cells or tissues have been subject and the intended clinical function of the product is included in the definitions of the ATMPs somatic cell therapies and tissue engineered products and there is also a list of certain processes which, notwithstanding, cannot be considered 'substantial manipulation'. While the FDA definition of minimal manipulation includes this link, the FDA definition also includes reference to structural and non-structural tissue which is a complexity not considered relevant in the Australian regulatory context; and
- removes definitional issues around the listed actions.

The importance of linking the level of manipulation with the intended use of the product is highlighted in the example below:

Example:

Washing skin tissue in a strong hypotonic solution lyses the cells membranes and therefore changes the characteristics of the cells or tissues, but does not affect the structural elements of the skin (i.e. the collagen matrix is maintained). If the intended clinical use for the skin tissue is 'wound covering' then only the structural component of the skin may be required to perform its function. As a wash with a strong hypotonic solution does not affect the relevant structural element, in this situation the manufacturing step could be considered as minimal manipulation. In contrast, if 'wound healing' (which requires complex skin-graft interactions) is the intended use of the product, washing with hypotonic solution will/may affect the integrity of the tissue or critical surface markers and therefore the washing process is unlikely to meet the definition of minimal manipulation for this intended use.

The justification for classification of skin tissue for 'wound covering' as a Class 2 biological, and skin tissue for 'wound healing' as a class 3 biological, despite the same wash solution being applied, is that the complex skin-graft interaction required for the wound healing function would require a higher level of characterisation of the processed tissue, control of the manufacturing process, and clinical data to demonstrate clinical safety and efficacy.

Examples of processes falling within (and outside) the proposed definition of minimal manipulation

The following list of actions would usually be considered minimal manipulation (i.e. processes that do not result in alteration of the biological characteristics, physiological functions or structural properties relevant to the intended use of the human cell or tissue therapy):

- 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; and
- irradiation for the purpose of bioburden reduction.

However, a final view on whether or not those actions would amount to only minimal manipulation would, under the proposed definition, depend on the intended use.

Actions that would generally be considered to be more than minimal manipulation include, for example:

- cell culture and differentiation
- genetic modification
- mixing demineralized bone with a gelatinous carrier e.g. glycerol
- seeding on to a medical device

Again, a final view on whether or not those actions would amount to more than minimal manipulation would, under the proposed definition, depend on the intended use.

It is proposed that the TGA would publish guidance material about how to apply the proposed new definition of minimal manipulation, along with examples of processes that the TGA does (and does not) consider to involve minimal manipulation in the context of intended use.

It is recognised that for some processes there can be debate or lack of scientific certainty about whether or not the process results in alteration of the biological characteristics, physiological functions or structural properties relevant to the intended use.

For example, the TGA considers that enzymatic digestion or physical disruption of a tissue (e.g. adipose tissue) when the aim is to dissociate cell-cell contacts constitutes more than minimal manipulation. Enzymatic digestion of adipose tissue to produce 'vascular stromal fractions' or adipose-derived 'mesenchymal stem cells' would be considered beyond minimal manipulation as it is likely that the process to isolate the cells would result in changes to their properties, e.g. activation state or surface molecule expression, which could significantly impact the cells characteristics or functions.

Your views are sought

Please provide your views on the proposed new definition of minimal manipulation.

Part B – Implications for the biologicals framework

Impact of definition change on classification of biologicals

If a new definition for minimal manipulation were to be used in the context of the exclusion for autologous cell and tissue products from regulation under the TG Act, it would be highly desirable to have the same definition used in relation to the regulation of biologicals under the TG Act.

Currently the term minimal manipulation is integral to the definitions of Class 2, 3 and 4 biologicals as set out in regulation 2 of the TG Regulations. In summary:

A ***Class 2 biological*** is one that is:

- processed using only one or more of the actions of *minimal manipulation* and is for homologous use; or
- mentioned in Schedule 16 as a Class 2 biological.

A ***Class 3 biological*** is one that is:

- processed using a method in addition to any of the actions of *minimal manipulation*, in a way that does not change an inherent biochemical, physiological or immunological property; or
- mentioned in Schedule 16 as a Class 3 biological.

A ***Class 4 biological*** is one that is:

- processed using a method in addition to any of the actions of *minimal manipulation*, in a way that changes an inherent biochemical, physiological or immunological property; or
- mentioned in Schedule 16 as a Class 4 biological.

In turn the definition of 'minimal manipulation' in regulation 2 of the TG Regulations is currently a non-exhaustive list of actions or processes such as centrifugation, refrigeration, freezing, trimming, flushing, washing; processing steps related to preserving function or minimising contamination.

If the existing definition were to be replaced with the new definition (with its focus on whether there is alteration of the biological characteristics, physiological functions or structural properties relevant to the intended use) the existing references in the definitions of Class 3 and Class 4 biologicals to changes in inherent properties needs to be reconsidered This is because the concepts of characteristics, functions and properties relevant to an intended use (used in the proposed new definition of minimal manipulation) and inherent biochemical, physiological or immunological properties (used in the current definitions of Class 3 and Class 4 biologicals) overlap and likely make the current Class 3 redundant.

It is proposed therefore that the definition of Class 3 be changed to include any cells and tissues that are not Class 1 or 2. Class 3 would thus become a broad category of higher risk biologicals that do not come within Class 2, that is, that have the following characteristics:

- involve only minimal manipulation but are not for homologous use;
- are for autologous use but involve more than minimal manipulation; or
- are for homologous use and involve more than minimal manipulation.

It would be appropriate in those circumstances for the levels of documentation in the dossier regarding clinical evidence of efficacy, manufacturing control, safety and risk management (amongst other requirements) to vary according to product's complexity and risk.

For example:

A ***Class 3 biological*** is a biological that:

- is not a Class 1 or 2 biological; or
- is mentioned in Schedule 16 as a Class 3 biological.

Class 1 biologicals are those prescribed in TG Regulations.

It is also proposed to clarify how Class 2 biologicals are defined in TG Regulations to:

A ***Class 2 biological*** is a biological that:

- **has not been subject to a process that is more than** *minimal manipulation* and is for homologous use; or
- is mentioned in Schedule 16 as a Class 2 biological.

It is important that the regulatory framework has the capacity to accommodate changes and developments in the nature of regulated products. The definition of Class 4 could be redefined so as to allow types of products to be included in the future that had characteristics that would justify, for instance, the TGA requiring additional information than currently required for Class 3. These characteristics might include a higher degree of uncertainty and risk. Such products would need to be readily distinguishable from the proposed new Class 3, such as any biological that was genetically manipulated or involved novel technologies. The new definition might be something along the following lines:

A ***Class 4 biological*** is a biological that:

- is in a class of biologicals that has the characteristics described in Schedule 16 as being characteristics of a Class 4 biological; or
- is mentioned in Schedule 16 as a Class 4 biological.

Your views are sought

Do you support the proposed changes to the classification criteria as set out in the proposed new definitions (to rely on the new definition of minimal manipulation and, as a result, to redefine Classes 3 and 4)?

Do you support redefining of the current Class 4 as proposed above?

What are the implications of this approach for your organisation?

Implications of changing the classifications for biologicals

Implications for clinical trials

Under the TG Regulations, clinical trials involving Class 4 biologicals must be approved by the TGA under the Clinical Trials Exemption Scheme (CTX) except where a clinical trial for an equivalent indication has been approved by another national regulatory agency with comparable requirements or has a previous usage history that is supported by clinical evidence received by TGA. This requirement is in place to ensure oversight of clinical trials involving new and potentially high risk biologicals.

If Class 3 and 4 biologicals were to be redefined it is proposed that this requirement would apply to the new redefined Class 3 and Class 4. Thus clinical trials involving biologicals in the new Class 3 and 4 must be approved by the TGA under a CTX except where a clinical trial for an equivalent indication has been approved by another national regulatory agency with comparable requirements or has a previous usage history that is supported by clinical evidence received by TGA.

Your views are sought

Do you consider it is appropriate for the requirements for CTX approval apply to the new redefined Class 3 generally or just to a subset of Class 3 which represent the higher risk biologicals (as well as biologicals coming within the new Class 4 in the future)?

Do you perceive any additional risks in the change for requirements for CTX approval for biologicals in the new redefined Class 3 and Class 4? Should a distinction be maintained for higher risk biologicals in relation to clinical trials and what criteria should this consider? Please provide any information that supports your view.

Implications for fees

No changes are currently proposed to the fee schedule (Schedule 9A of the TG Regulations).

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