



**Australian Government**  
**Department of Health**  
Therapeutic Goods Administration

# Biologicals regulatory framework proposed changes to start on 1 July 2018

## Including changes to regulation of autologous human cell and tissue products and classification of biologicals

*This guidance concerns proposed amendments to the Therapeutic Goods Regulations 1990. The proposed amendments have not yet become law and may be subject to change. The purpose of this guidance is to make you aware of these proposed changes if/when they take effect.*

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**TGA** Health Safety  
Regulation

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**Disclaimer**

*Amendments to the regulations do not become law until they have the Governor General's approval. The purpose of this guidance is to inform stakeholders about these proposed changes. While reasonable care is taken to ensure that the information is an accurate description of the proposed changes, TGA does not guarantee or warrant the accuracy, reliability, completeness or currency of the information or its usefulness in achieving any purpose. To the fullest extent permitted by law, including but not limited to s 61A of the Therapeutic Goods Act 1989, the Therapeutic Goods Administration (TGA) will not be liable for any loss, damage, expense or cost incurred or arising as a result of any use or reliance on this information.*

The Biologicals Regulatory Framework is being modified through changes to therapeutic goods legislation and legislative instruments following public consultation in 2015 and 2016.

These proposed changes are not yet law. This guidance represents TGA's interpretation and intention of the upcoming changes to:

- the regulation of autologous human cell and tissue products which could be regulated either:
  - under the Biological framework or
  - or as Medicine products as blood and blood components
- [biologicals classification and terminology definitions](#) (associated with biologicals classification)

TGA welcomes feedback on this guidance at [bloodandtissues@tga.gov.au](mailto:bloodandtissues@tga.gov.au).

We will be publishing an updated version of the [Australian Regulatory Guidelines for Biologicals \(ARGB\)](#) in July 2018 when the changes to the *Therapeutic Goods Regulations 1990* enter into force.



This guidance has been developed by the TGA and therefore the use of 'we' and 'us' throughout refers to TGA.

## Autologous human cell and tissue products

Human cell and tissue (HCT) products are those that comprise, contain or are derived from human cells and tissues.

Autologous human cell and tissue (HCT) products are those that are removed from, and applied to, the **same person**, i.e. the donor and the recipient are the same. These include some products commonly referred to as 'stem cell treatments'.

The definition of autologous HCT covers [products defined as biologicals](#), and regulated under the biologicals framework, and also blood and blood components. Where an autologous HCT meets the definition of a blood component it is likely to be regulated as a medicine. Further information on the [regulation of blood components](#) is provided on the TGA website. Where the blood component is subject to significant processing (more than minimal manipulation), the definition of a blood component would not apply and it would be regulated as a biological.

## Examples of autologous human cell and tissue products

Examples of autologous HCT products that this guidance applies to include:

- blood and blood components (red cells, plasma, serum, platelets, and [platelet-rich plasma \(PrP\)](#))
- skin grafts for treatment of burns
- bone grafts
- bone marrow transplants
- [conditioned serum](#)
- genetically-altered lymphocytes to target cancers
- bone marrow-derived stem cells for non-haematological indications
- adipose-derived cell extracts (including stromal vascular fraction (SVF))

Most of these HCT products would be regulated as biologicals under the [biological regulatory framework](#), except blood components.

Where an autologous HCT product meets the definition of a blood component it may be regulated under the medicines framework as a blood and blood component rather than under the biologicals framework. Further information on the [regulation of blood components](#) is provided on the TGA website.



Where a blood component is subject to significant processing (more than minimal manipulation), the definition of a blood component does not apply and such a product would be regulated as a biological.

## Non-TGA regulation applying to autologous human cell and tissue products

This guidance only outlines TGA regulatory requirements for these products. Regulation of autologous HCT products in Australia also involves several other regulatory bodies. Providers of autologous HCT products should be aware of all applicable regulation, such as the requirements of:

- the Australian Health Practitioner Regulation Agency (AHPRA)
- state, territory and national medical and dental boards or councils
- the Australian Competition and Consumer Commission (ACCC)
- states and territory management and administration of public hospitals
- state and territory licensing of private hospitals.

## Advertising to consumers is prohibited

Autologous HCT products cannot be advertised to consumers from 1 July 2018.

Before an autologous HCT product can be administered to a particular patient, a medical or dental professional needs to assess whether the therapeutic good is appropriate and suitable for that patient. Advertising that encourages consumers to seek out such treatments prior to such an assessment may undermine the 'medical or dental practitioner-patient' relationship, and is prohibited under the *Therapeutic Goods Act 1989* (the Act).

## Advertising of services is permitted

Services (that do not mention specific products) will still be permitted to be advertised.

However the advertisement must comply with:

- The Act and associated subordinate legislation,
- Health Practitioner Regulation National Law (and applicable advertising guidelines),
- Australian Consumer Law, and
- State and Territory Laws.

When non-compliant advertising comes to the TGA's attention, the advertiser is notified (see [Penalties for non-compliance](#)).



An advertisement for a health service that specifies the use of any autologous HCT product associated with that service is not permitted as it would promote the product also.

To advertise services and comply with the therapeutic goods legislation, the advertising should:

- ✓ Focus on the services that your business provides **without referencing** *the autologous HCT product*.
- ✗ Not make any specific reference to autologous cell and tissue products associated with the services.
- ✗ Not provide information and/or advice, on medical or dental professional's websites, for patients to consider particular types of treatments involving autologous cells and tissue products (however, such information can be provided to patients as part of a consultation with the professional).
- ✗ Not reference trade names of autologous HCT products (e.g. abbreviations, acronyms) or colloquial names such as 'stem cells'.

These requirements apply to health professionals, professional bodies, media outlets and commercial ventures. The requirements apply to all forms of media, including traditional media (such as television, radio, print media and posters/displays) and electronic media (such as websites, emails, blogs, discussion forums and social media). Testimonials that refer to autologous HCT products are also likely to be considered advertising and are subject to the same requirements.

## Penalties for non-compliance

In the first instance, the TGA seeks to inform, educate and assist advertisers to comply with the rules relating to advertising. However, if this approach fails, we may take further action to achieve compliance.

The Act provides for financial penalties for advertising breaches. Fines for such offences can be up to \$840,000 for individuals and up to \$4,200,000 for corporations<sup>1</sup>.

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<sup>1</sup> These amounts are current as at the date of publication.

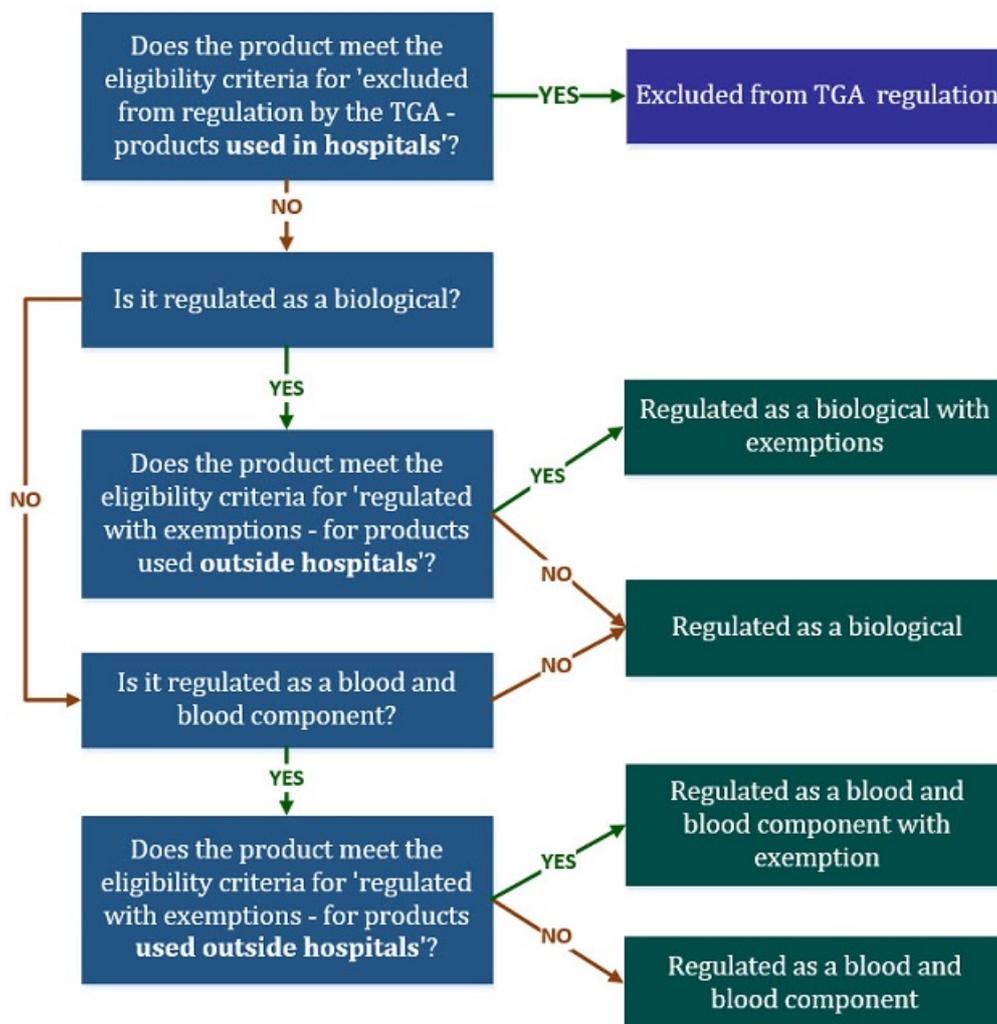
# Regulatory pathways for supply of autologous human cell and tissue products

The level of regulation for autologous HCT products is based on the level of risk to the public associated with the manufacturing processes and/or intended use of the autologous HCT product. The following categories apply (from lowest to highest risk):

- [excluded from regulation by the TGA - products used in hospitals](#)
- [regulated with some exemptions - for products used outside hospitals](#)
- [fully regulated](#)

The diagram below provides an overview of how autologous HCT will be regulated based on their level of risk.

## Regulatory pathways for supply of autologous cell and tissue products



For further advice on the classification of your autologous HCT please [contact the TGA](#).

## Excluded from regulation by the TGA – products used in hospitals



Where the product is subject to processing that is more than minimal manipulation, the definition of a blood component does not apply and such a product would be regulated as a biological

If a product is excluded from regulation by the TGA, it is excluded from all of our regulatory requirements, including the TGA clinical trials provisions.

### Eligibility criteria

We will not regulate autologous HCT products if they meet **all of the following**:

1. collected from a patient who is under the clinical care of a medical or dental practitioner registered under a law of a State or an internal Territory
2. manufactured by that medical or dental practitioner, or by a person or persons under the professional supervision of that medical or dental practitioner **in a hospital**, for that patient who must be a patient of that hospital
3. for therapeutic use in that patient by the same medical or dental practitioner, or by a person or persons under the professional supervision of the same medical or dental practitioner
4. not advertised or promoted directly to consumers.

**All** of the above criteria **must** be met for this exclusion to apply. Where one or more of the criteria are not met, including if advertising occurs directly to consumers, a higher level of regulatory requirements will apply.

These requirements for exclusion for certain autologous human cells and tissues will be included in the legislative instrument for Therapeutic Goods (Human Cells and Tissues) Determination 2018.

Medical devices or equipment used for manufacture of these products may be regulated as medical devices.



The conditions for exclusion **do not include any restrictions** on:

- the level of manufacturing (including storage and processing beyond minimal manipulation)

OR

- on the treatment that can be used by practitioners within the hospital.

Further information on the regulation of the '[manufacture and use in a hospital](#)' is provided in the definitions.

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## Examples of products likely to be excluded from regulation

The following include examples of clinical procedures/treatments that are likely to be excluded, when performed by medical or dental practitioners in a hospital. This list is not exhaustive, and the manufacturing and use should be carefully considered in the context of the eligibility criteria.

### **Skin grafts (including keratinocyte sprays)**

Where healthy skin is removed from one area of the body (leg, arm, buttocks) and transplanted to an injured area (used in burns) of the same patient. In addition, 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. This processing is considered greater than minimal manipulation and the intended use may also involve storage of the cells and multiple treatments over the course of the treatment, but is still likely to meet the exclusion criteria.

### **Craniotomy and parathyroidectomy**

Under specific circumstances sections of tissue may be removed and temporarily stored, to facilitate treatment of traumatic injuries and other disorders. The removed sections of tissue may be stored for a number of days and then returned to the patient when appropriate.

### **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.

### **Pancreatic islet cells**

Some patients with chronic or recurrent inflammation of the pancreas may need the pancreas surgically removed. The insulin-producing islet cells are isolated from the removed pancreas and transplanted into the liver to prevent diabetes. This procedure is considered minimal manipulation as the dissociation of the pancreas maintains the function of the islets. If a patient already has diabetes, islet cell transplantation decreases the risk of the diabetes becoming worse.

### **Bone grafts**

Small sections of bone may be taken from healthy sites (usually the iliac crest of the hip bone) and transplanted into injured sites of the same patient 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.

### **HPCs for reconstitution of blood after treatment of cancer (i.e. bone marrow transplants)**

Patients with a range of blood cancers often undergo powerful chemical therapies to destroy the cancerous cells. Haematopoietic cells (HPCs) are collected before the treatment and stored while the patient undergoes treatment. After the treatment the patient is re-infused with the cells to help the blood re-establish. Australian hospitals providing HPC transplants are currently subject to National Pathology Accreditation Advisory Council (NPAAC)/ National Association of Testing Authorities (NATA) accreditation.

## Autologous blood to seal cerebrospinal fluid leaks

The brain and spinal cord are cushioned by a clear fluid called cerebrospinal fluid (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.

## Autologous blood components

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 salvage).



Autologous platelet-rich plasma is not likely to meet the criteria for exclusion, unless collected and manufactured in a hospital.

## 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). Adipose tissue 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.

## Regulated with some exemptions – for products used outside hospitals

### Eligibility criteria

In order to qualify for certain regulatory exemptions autologous HCT products **must** meet **all** of the following criteria:

1. Collected from a patient who is under the clinical care of a medical or dental practitioner registered under a law of a State or an internal Territory.
2. [Manufactured by that practitioner](#), or by a person or persons under the [professional supervision](#) of that practitioner, for a [single indication](#) and in a single procedure on that patient by the same practitioner, or by a person or persons under the professional supervision of the same practitioner.
3. For therapeutic application in a [homologous use](#).
4. [Minimally manipulated](#).

All four criteria specified above must be met for the exemptions to apply. Where one or more of the criteria are not met, a higher level of regulatory requirements will apply. The conditions are set to limit this option to only low risk products, where there is still a high level of clinical oversight by a medical or dental practitioner. To achieve this there are restrictions on the degree of manufacturing (only minimal manipulation) allowed, and on the intended clinical use (to

treatment for a single indication, in a single procedure and when the intended use is homologous).

These exemptions apply equally to autologous HCT products that would be classified as biologicals and blood and blood components (regulated as medicines).

## The exemptions

Autologous HCT products that meet **all** of the [eligibility criteria](#) for 'regulated with some exemptions' would be **exempt** from the requirements for:

- using 'unapproved' product pathways (e.g. clinical trials under CTN route, Special Access schemes):
  - however, if you choose to investigate the safety or efficacy of the product as part of a clinical trial, a human research ethics committee (HREC) should approve the trial
- inclusion on the Australian Register for Therapeutic Goods (ARTG)
- holding evidence that the manufacturing facility satisfies [good manufacturing practice \(GMP\) requirements](#). The exemption from GMP requirements also applies to any contracted testing facilities used e.g. for sterility testing.

## Regulation requirements still applying

An autologous HCT product that meets all of the criteria would be exempt only from the requirements mentioned above. Other applicable regulatory requirements will apply, such as:

- compliance with all [applicable standards](#)
- need to [report adverse events](#) to the TGA (as a condition of this exemption)
- the autologous HCT product cannot be advertised directly to consumers

Criminal penalties may apply if the quality, safety or efficacy of the product is found to be unacceptable, the advertising requirements are breached, the product does not comply with applicable standards or the sponsor does not respond to TGA questions about the product.

Under most circumstances the TGA will not review such products with regard to compliance to applicable standards, or evidence to demonstrate safety and efficacy. However, [you should hold the information](#) and we may request information to be provided about the product concerning any of these aspects, for example, when a safety issue arises.

Medical devices or equipment used for manufacture of these products may also be regulated under the [medical devices framework](#).

## Examples of products likely to be regulated with some exemptions

The following includes examples of autologous HCT products that are likely to fall within this category of regulation and exemptions, if their use satisfies all of the outlined criteria.

### Bone graft for dental procedures

A dental practitioner may take a section of bone from another area of the body, and graft it onto the jaw bone (or other orofacial region) of the same patient in a single procedure, following major dental extraction (or maxillofacial surgery). This procedure would meet the conditions as the processing of the bone is considered minimal manipulation, the use is considered to be homologous, and this procedure would usually not occur in a hospital.

## Platelet-rich plasma

Platelet-rich plasma (PrP) is prepared from blood collected by a single uninterrupted venepuncture. The plasma is generally separated from the red blood cells by centrifugation, with the platelets present in the plasma. The next steps vary between protocols but are intended to discard both the red blood cells and the acellular plasma layers and to collect only the platelet rich plasma layer. Commercial kits are now available to assist in the preparation of PrP. Importantly, the preparation of PrP only separates and concentrates the cells without manipulating them.

An example of PrP that would meet the exemptions would be where a medical practitioner collects some blood from a patient outside of a hospital and manufactures the PrP using [minimal manipulation](#). The intended use of the PrP must also be [homologous](#).

The following points should be noted for the manufacture and use of PrP:

- The intended clinical use of PrP under these exemptions still needs to be justified based on proven evidence of safety and efficacy.
- PrP product would likely be considered a blood component (and regulated as a medicine), being prepared only by centrifugation, and filtration.
- The exemptions only apply when the PrP is manufactured and administered by or under the supervision of a registered medical practitioner for a patient under their care. **This exclusion does not apply to other health practitioners.**
- Where equipment (such as a commercial kit) is used in the manufacture of PrP or conditioned serum it may also be subject to regulation as a medical device.
- Cosmetic use of injected PrP is likely to be regulated by TGA where therapeutic claims are made or inferred. Generally, injectable products fall under the Australian legal definition for therapeutic use (for example, as they are intended to cure a defect or modify the anatomy, even if it is only for 'aesthetic' purposes).

## Fully regulated

Autologous HCT products will be regulated as [biologicals](#) or [blood components](#) if they do not satisfy any of the criteria for exclusion/exemption criteria specified above.

Where an autologous blood component has been subject to processing beyond minimal manipulation, it would no longer meet the definition and would be regulated as a biological. If an autologous blood component is to be used for a non-homologous use it would be regulated as a medicine.

## Regulatory requirements

These autologous HCT products, which are usually more than minimally manipulated and/or for non-homologous use, and manufactured and used outside of a hospital, will be subject to all the regulatory requirements such as:

- compliance with all [applicable standards](#)
- [reporting adverse events](#) to the TGA
- compliance with conditions relating to records and reporting
- [advertising restrictions](#)

- inclusion in the ARTG (where applicable)
- the [manufacturer](#) of the autologous HCT products and any facilities performing testing on the product must hold a TGA-issued manufacturing license or certification (where applicable).

## Inclusion in the ARTG

Where the autologous HCT product is required to be included in the ARTG it will be subject to the following:

- The TGA must be satisfied (based on a dossier) as to the quality, safety, and efficacy (for their intended purpose) of the autologous HCT product to be included in the ARTG.
- The TGA can [recall goods](#) supplied in the event that the autologous HCT product does not comply with an applicable standard or if it appeared that the quality, safety or efficacy is unacceptable. These recall procedures include requiring the supplier to make information available to the TGA and the public about the products.
- The TGA can suspend or cancel the inclusion in the ARTG if it appeared that the quality, safety or efficacy was unacceptable, a condition of inclusion was breached, the advertising requirements were breached, the product did not comply with [applicable standards](#) or the sponsor did not respond to TGA questions about the product.

## Examples of products likely to be regulated as biologicals or blood components

The following section includes examples of clinical procedures or treatments that were **previously excluded** from regulation but are **now likely to be regulated** as [biologicals](#) or [blood and blood components](#) if the processing is performed outside a hospital.



### *Medical devices*

Medical devices or equipment used for manufacture of these products may also be regulated as [medical devices](#).

## Adipose-derived cell extract (including stromal vascular fraction)

There are a wide range of methods used to collect and process adipose tissues to isolate cells prior to re-injection in the patient. We would consider almost all of them to fall outside of the eligibility criteria for exclusion or the exemptions from regulation.

The methods used to prepare adipose-derived cell extracts are generally considered to be more than [minimal manipulation](#).

The intended clinical use of adipose-derived cell extracts would result in a product being fully regulated as a biological when the clinical uses are [non-homologous](#) and subject to greater safety concerns (e.g. intrathecal or intravenous injection), or the cell preparation is used in more than a single procedure, for example, if extra cells left over from the initial treatment cycle are stored for a later procedure.

More information on the classification of cells extracted from adipose tissue (including stromal vascular fraction (SVF)) is provided in the [explanation of key terms](#).

## Conditioned serum

Autologous conditioned serum is the term used for products made from a blood collection, where the serum is cultured for several hours to induce the white blood cells to secrete anti-inflammatory compounds into the serum. This product does not contain platelets and should not be confused with [platelet-rich plasma \(PrP\)](#).

The processing of the blood component, in this case, is considered **more than minimal manipulation**; and thus conditioned serum products will be **fully** regulated as a biological.

## Access to ‘unapproved’ autologous HCT products

For autologous HCT products that will become regulated, the provisions to access unapproved therapeutic goods will still be available to patients and their treating doctors via access to ‘unapproved’ autologous HCT product, subject to fulfilment of specific requirements.

## Clinical trials

Importation into and/or supply in Australia of ‘unapproved’ therapeutic goods for use in a [clinical trial](#) may fall under either the Clinical Trial Notification (CTN) scheme or the Clinical Trial Exemption (CTX) scheme.

The CTX scheme is mandatory for a trial of any Class 4 biological unless (a) use of the biological is supported by evidence from previous clinical use; or (b) the use of the biological in a clinical trial has been approved for an equivalent indication from a national regulatory body with comparable regulatory requirements. For more information about the [Clinical Trials schemes](#) see the guidance.



[GMP licensing or certification of manufacturing sites](#) is required, unless the persons or goods are exempt e.g. first-in-human trials.

## Special Access Scheme (SAS)

The [Special Access Scheme \(SAS\)](#) applies to all regulated therapeutic goods and refers to arrangements that provide for the import and/or supply of an ‘unapproved’ therapeutic good for a single patient, on a case-by-case basis.

- Category A is a notification pathway which can be accessed by a prescribing medical practitioner or a health practitioner on behalf of a prescribing medical practitioner for patients who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.
- Category B is an **application** pathway that can be accessed by health practitioners for patients that do not fit the Category A definition. Category B applications must be reviewed and approved by TGA before the unapproved product may be accessed. Category B applications must be completed in full and include the patient diagnosis and indication for which the product is sought. The application also requires a thorough clinical justification for the use of the product, which includes the seriousness of the condition, details of previous treatment and reasons why a therapeutic good currently included on the ARTG cannot be used for the treatment of the individual patient in the particular circumstance. The application must also include sufficient safety and efficacy data to support the proposed use of the product. This may include references to clinical trial results and published peer-

reviewed data, or evidence that the product has been approved for an equivalent indication by a national regulatory body with comparable regulatory requirements. The request should include details of intended monitoring for adverse events and patient response to treatment. **The SAS Category B pathway is intended for exceptional circumstances and not for routine use of an unapproved product.** In addition, the applicant has responsibilities when seeking to use unapproved therapeutic goods that include adherence to relevant standards of good medical practice. For further information about the [SAS](#), see the guidance.



The product to be accessed via the SAS B pathway must be manufactured in accordance with appropriate good manufacturing practice (GMP).

- Category C is a notification pathway that allows health practitioners to supply goods that are deemed to have an established history of use. Most autologous HCT products that do not satisfy the criteria for exclusion from regulation by the TGA, or the criteria for exemption from some parts of the *Therapeutic Goods Act 1989*, will not be considered appropriate for inclusion in the pathway.

### Authorised prescribers

In some circumstances a medical practitioner may be granted authority to become an [authorised prescriber](#) of a specified 'unapproved' therapeutic good (or class of unapproved therapeutic goods) to specific patients (or a class of patients) in their immediate care with a particular medical condition. The authorised prescriber must obtain approval from a Human Research Ethics Committee (HREC) or endorsement from a specialist college.



[GMP certification of manufacturing sites](#) is required when accessing unapproved therapeutic goods under the authorised prescriber scheme.

## Transition arrangements

From 1 July 2018, transitional arrangements will apply to autologous HCT products currently excluded from regulation by the TGA under item 4(q) of the [Therapeutic Goods \(Excluded\) Order](#) that will not meet the conditions for exclusion or exemptions under the new arrangements. During the transition period certain autologous HCT products may be exempt from:

- using ‘unapproved’ product pathways (e.g. clinical trials under CTN route, Special Access schemes)
- requiring inclusion on the ARTG
- holding evidence that the manufacturing facility satisfies [good manufacturing practice \(GMP\) requirements](#). (The exemption from GMP requirements also applies to any contracted testing facilities used, e.g. for sterility testing.)

All other regulatory requirements will apply to these autologous HCT products from 1 July 2018, such as:

- the autologous HCT product cannot be advertised directly to consumers
- the need to [report adverse events](#) to the TGA (as a condition of the exemptions)
- compliance with all [applicable standards](#).

Any autologous HCT product stored beyond the transition period, which do not comply with the new requirements, including manufacturing in a GMP licenced facility, can only be supplied using the ‘unapproved’ product pathways (e.g. clinical trials under CTN route, Special Access schemes), where appropriate. Alternatively, justification for supply of stored product could be considered and potentially approved as part of the review of any CTX or market authorisation application.

At any time during the transition period an application can be made for GMP certification of a manufacturing site, a clinical trial exemption (CTX) or for inclusion of your autologous HCT product in to the ARTG.

## When transitional arrangements apply

The transitional arrangements may apply in specific circumstances, including:

- when autologous HCT products have been supplied before 1 July 2018 (including clinical trials)
- where the intent is to submit an application for GMP certification, a CTX or inclusion in the ARTG.

## Autologous HCT product supplied before 1 July 2018 (including clinical trials)

Where an autologous HCT product has been supplied prior to 1 July 2018 this can continue until **30 June 2019**. This is intended to allow patients that have been scheduled for treatment to complete the procedure. Similarly, any clinical trials (CTN or CTX) that have been approved by a HREC and are underway prior to 1 July 2018 can continue, but patient treatment must be completed by 30 June 2019.

If you were not supplying autologous HCT product prior to 1 July 2018 this provision does not apply.

Note that the following requirements will still apply:

- the autologous HCT product cannot be advertised directly to consumers
- [reporting of adverse events](#) to the TGA (as a condition of the exemptions)
- compliance with all [applicable standards](#).

## Where the intent is to submit an application for GMP certification, a CTX or an application for inclusion in the ARTG

Further transition provisions may be available in the following circumstances:

- **Application for GMP certification.** Where an autologous HCT product is being supplied as part of an HREC-approved clinical trial prior to 1 July 2018, and the recruitment and supply of the product will not be completed by 30 June 2019. If you have notified the TGA of the trial under the clinical trial notification (CTN) scheme and have made an application for GMP certification of the manufacturing site before the end of the transition period (i.e. by 30 June 2019) you may continue to supply without satisfying the GMP requirements under Part 3-3 of the *Therapeutic Goods Act 1989*, until a decision is made on your application. You would need to be ready for an inspection of the manufacturing site at any time following submitting the application for GMP compliance, which would generally occur between 2-6 months from when the application was made.
- Where the trial is not 'first-in-human', GMP certification of the manufacturing sites must be sought during the transition and obtained before the CTX is approved.
- **CTX application.** Where an autologous HCT product is being supplied as part of an approved HREC clinical trial for a Class 4 biological prior to 1 July 2018, and the recruitment and supply of the product will not be completed by 30 June 2019. If you submit a CTX application before the end of the transition period (i.e. by 30 June 2019) you may continue to supply without satisfying the requirements for inclusion in the ARTG under Part 3-2A and the GMP requirements under Part 3-3 of the Act, until a decision is made on your application. Where the trial is not 'first-in-human', GMP certification of the manufacturing sites must be sought during the transition and obtained before the CTX is approved.
- **Inclusion on the ARTG.** Where an autologous HCT product is being supplied, but there is the intent to transition from supply under the current exclusion to supply following inclusion in the ARTG. Where an application for inclusion in to the ARTG has been made and successfully completed preliminary assessment before the end of the transition period (i.e. by 30 June 2019) you may continue to supply without satisfying the requirements for inclusion in the ARTG under Part 3-2A and the GMP requirements under Part 3-3 of the Act, until a decision is made on your application. Note that GMP licencing or certification of the

manufacturing sites must be sought during the transition and obtained before the application can be approved.

## Explanation of key terms

The specific terms used in the *Therapeutic Goods Regulations 1990* associated with autologous HCT products are explained below.

### Clinical care and treatment

For exclusion and exemptions to apply a registered medical or dental practitioner must have and assure the prime responsibility for the clinical care of their patient throughout the course of treatment in which the autologous HCT product is used. This provision **does not** apply to other health practitioners.

### Registered medical and dental practitioners

Medical and dental practitioners are the health care providers that most frequently prescribe or administer therapeutic goods including medicines, medical devices and biologicals. The conduct of these practitioners (including advertising of services) is regulated by Australian Health Practitioner Regulation Agency (AHPRA) and the relevant state, territory and national boards and councils. To maintain registration in their respective specialities, medical and dental practitioners are required to participate in appropriate continuing professional development, to work within their scope of practice and to maintain recency of practice. Guidance for professional practice is contained in "[Good medical practice: A code of conduct for doctors in Australia](#)" and in the "[Code of conduct for registered health practitioners](#)".

We accept that clinical/dental practice is sufficiently regulated such that, if the conditions outlined in the exclusion or the exemptions are satisfied, additional regulation by the TGA of some autologous HCT products may impose unnecessary burden.

The exclusion or exemptions from regulation by the TGA of autologous HCT products used under the outlined conditions has no effect on the professional obligations of health practitioners to maintain satisfactory standards of practice that are appropriate to their profession. A registered medical or dental practitioner:

- Must have prime responsibility for the clinical care of his/her patient throughout the course of treatment in which the autologous HCT products are used.
- Should be mindful of adherence to professional standards when using products that have not been evaluated for safety and efficacy by the TGA. This would include consideration of whether the treatment being undertaken is necessary and safe and whether its efficacy is supported by credible clinical evidence.
- Should ensure that prior to treatment of any patient with a product that has not been approved for use in Australia, that patient receives appropriate and adequate information about the material risks and benefits of that product to allow informed consent.

The [Australian Health Practitioner Regulation Agency \(AHPRA\)](#) also has the power to prosecute for particular advertising offences which may infringe the Health Practitioner Regulation National Law Act (in force in each state and territory). The [Medical Board of Australia](#) also publishes Guidelines for Advertising of Regulated Health Services.

## Manufacture and use in a hospital

We believe that there is sufficient regulation of hospitals to mitigate possible risks that may arise as a result of manufacturing and using excluded autologous HCT products, and that credentialing processes applied by hospitals should be sufficient to ensure that medical/dental practitioners do not work outside of their scope of practice.

Public and private hospitals in Australia are subject to regulation under various state, territory and national provisions. Accreditation of hospitals is a requirement for funding by governments and other funding organisations. A national accreditation scheme for health service organisations and the National Safety and Quality Health Service (NSQHS) Standards were endorsed by the Australian Health Ministers in September 2011.

## Commonwealth Hospital Declaration

The Australian Government Department of Health regularly updates a [list of Commonwealth declared hospitals](#). Inclusion on this list of public hospitals requires State or Territory Department of Health confirmation of a public hospital and evidence of accreditation. Inclusion of private hospitals requires a copy of a state or territory hospital licence and evidence of accreditation.

## NSQHS Standards considered applicable to biologicals and blood components

While the following [National Safety and Quality Health Service \(NSQHS\) Standards](#) do not specifically apply to biologicals, we believe that the principles applied to achieve the required standards are relevant and applicable to the safe use of biologicals, specifically autologous HCT products, in accredited hospitals:

- NSQHS Standard 3: 'Preventing and controlling healthcare associated infections' includes criteria for governance and systems of infection prevention, control and surveillance, and for cleaning, disinfection and sterilisation.
- NSQHS Standard 4: 'Medication safety' includes criteria for governance and systems for medication safety and medication management processes that outline mechanisms for "safe prescribing, dispensing, administering, storing, manufacturing, compounding and monitoring..." of medicines.
- NSQHS Standard 7: 'Blood and blood products'. While blood and blood products are not currently regulated as biologicals by the TGA, the principles that underlie safe and appropriate prescribing and use of blood and blood products are also applicable to autologous HCT products. The criteria for Standard 7 apply to governance systems and systems to 'receive, store, transport and monitor wastage of blood and blood products safely and efficiently'.

## **Institutional credentialing of health practitioners**

Health practitioners who work in hospitals are subject to mandatory institutional credentialing processes, to ensure the quality and safety of patient care. Credentialing includes review of qualifications, professional standing and professional registration and indemnity. Credentialing also requires the practitioner to undertake to work within his or her professional scope of practice. In 2015 the Australian Commission on Safety and Quality in Health Care released a guide to “Credentialing health practitioners and defining their scope of clinical practice – A guide for managers and practitioners”. The “Standard for credentialing [sic] and defining the scope of clinical practice: a national standard for credentialing [sic] and defining the scope of clinical practice of medical practitioners, for use in public and private hospitals” was published in 2004.

## **Professional supervision over the manufacture of the product**

For the exclusion or exemptions to apply, the autologous HCT product is to be 'manufactured by that medical/dental practitioner or by a person or persons under the professional supervision of that medical/dental practitioner'. The fact that the products being used for a patient are not directly manufactured by the treating medical/dental practitioner does not mean that the exemptions do not apply.

## **Professional supervision**

Professional supervision in this context requires that the medical/dental practitioner with primary responsibility for the clinical care of a patient is party to all manufacturing steps that are performed in a formal governance arrangement with the person or persons undertaking the manufacturing. This would include input into the protocols and quality systems used in the manufacturing process. This enables use of goods that are not directly manufactured by the treating medical/dental practitioner.

For example, pancreatic tissue may be collected from a patient by a surgeon in collaboration with an endocrinologist, for processing of the islet cells in a laboratory. Subsequent to processing, the islet cells are infused into that same patient as an autologous transplant.

The collection, processing and infusion must however remain under the professional supervision, as described above, of the endocrinologist caring for the patient.

Specialised testing on a representative sample of the product by a third-party facility, for example sterility testing, would still be considered to fit within the professional supervision of the medical or dental practitioner.

## **Therapeutic application for a single indication in a single procedure**

Where a HCT is removed from a patient and transplanted back into the patient during a single clinical procedure the risks to the patient are the same as those typically associated with surgical procedures. These operations will normally be exempt from regulation by the TGA. In contrast, any treatment that involves more than a single procedure, especially where storage of the HCT is required, can significantly increase the risks to safety associated with traceability, sterility and quality of the product. Treatments involving storage of the HCT do not fall within the scope of the exemption provisions.

The therapeutic application must also be limited to a single indication. Sometimes the therapeutic purpose of the cell or tissue therapy is clear from the context of the admission or the description of a surgical treatment.

For example:

- Use of a saphenous vein to replace an occluded coronary artery during coronary artery bypass grafting
- Use of an autologous skin graft to cover a burn
- Use of small volumes of autologous bone to fill bony defects in dental practice.

However, clinical users of autologous HCT products, may conclude that some HCTs have therapeutic value in more than one indication. The primary indication for the autologous HCT product in any procedure or treatment should be clearly documented.

## New definitions related to classification

The definitions and guidance below relate to any HCT covered by the biologicals regulatory framework, in addition to the exemption and exclusions proposed for autologous HCT products.

### Classification of biologicals



The definitions for Class 2, 3 & 4 biologicals have been modified, and we do not expect that the changes will affect any previous decisions on classifications of biologicals. The definitions improved clarity and international harmonisation.

The new definitions are below.

#### Class 2 biological

*Class 2 biological* means a biological that:

- has been subject to a process that is minimal manipulation and is for homologous use

OR

- is mentioned in Schedule 16 as a Class 2 biological.

#### Class 3 biological

*Class 3 biological* means a biological that:

- has been subject to a process that is more than minimal manipulation and/or is not for homologous use

OR

- is mentioned in Schedule 16 as a Class 3 biological

## Class 4 biological

**Class 4 biological** means a biological that:

- is mentioned in Schedule 16 as a Class 4 biological

High risk products must be specified in the Schedule 16 instrument to be classified as Class 4 biologicals. This list includes viable animal HCT products and human HCT products that are considered to pose a high risk, due to the level of manipulation and/or the current lack of safety data to appropriately classify them. As the level of safety data and experience with a specific group of HCT products increases, it is possible that they could be removed from the list.

### Defined in Schedule 16

Class 4 biologicals are defined in the Schedule 16 instrument as:

- Things that comprise or contain live animal cells, tissues or organs.
- An HCT that has been modified to artificially introduce a function that was not intrinsic to the donor cell or tissue.
- Pluripotent stem cells and products that were derived following *ex vivo* differentiation of pluripotent cells to a defined lineage.

### 'Artificial' altering of function

The 'artificial' altering of the function or functions of the HCT is intended to capture only modifications that are **not intrinsic** to the HCT *in vivo*.

Examples of intrinsic modifications that are considered to artificially alter the function include:

- Genetic modification of cells (e.g. CAR T cells, iPSCs)
- Induction of pluripotency in cells (iPSCs).

The techniques used to alter the function may include the use of recombinant nucleic acid technologies, liposome modification, nanoparticles and/or pharmaceutical treatment, or equivalent technology.

Examples of intrinsic modifications that are not considered to artificially alter the function include:

- Many compounds and growth factors are used to expand, maintain or induce differentiation of cells in culture, but these only influence the intrinsic functions, ability and plasticity of the HCTs
- Cells where exogenous proteins or peptides (non-pharmaceutical) have been taken up by normal endocytic processes (e.g. tumour antigen-pulsed dendritic cells) would not be considered to have artificially altered the function of the HCTs.

### Pluripotent cells, including *ex vivo* differentiation

By definition pluripotent cells are able to give rise to cells found in all tissues of the embryo, except for germ cells, so the use of these cells raises significant safety concerns. The *in vitro* differentiation of these cells may address some safety concerns, but raises others over the ability to control the quality and safety of the defined population. Other biologicals that contain or are derived from stem cells may still have multipotent potential, but the safety concerns are not as great as for pluripotent cells. These other stem cell derived products will generally be treated as Class 3 biologicals.

## Minimal manipulation

Minimal manipulation is defined as:

- cells and tissues are subjected to a process of minimal manipulation if the process does not result 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:

- introduces a 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 generally consistent with that used in the EU and by the FDA. (However, the FDA definition differentiates between structural and non-structural tissue, which is a complexity not considered relevant in the Australian regulatory context.)
- removes definitional issues around the listed actions.

## Importance of the link between processing and intended use

Where relevant characteristics of the HCT are altered it raises issues around the product consistency and quality, safety and efficacy of the processed HCT, as product function in the recipient cannot be predicted.

In determining whether any processing step(s) altered the characteristics of the HCT, the properties of the HCT in the donor should be considered. Not all functions may be preserved during processing, but the manufacturer must be able to show that the activity of relevant characteristics related to the intended use is sufficiently maintained. This may require a reasonable understanding of the mechanism(s) of action.

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
- the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents
- irradiation for the purpose of bioburden reduction.

However, the intended use of the HCT may dictate whether or not any of the above listed actions would amount to only minimal manipulation.

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

- cell culture
- *in vitro* differentiation of cells or tissues
- genetic modification
- mixing demineralized bone with a gelatinous carrier, e.g. glycerol
- mixing demineralized bone with a medicine e.g. recombinant bone morphogenetic proteins (BMPs)
- seeding of cells on to a medical device
- enzymatic dissociation of tissue.

## Examples to demonstrate minimal manipulation

### 1. Musculoskeletal tissue example:

- a. A manufacturer performs mechanical machining to shape bone during total knee replacement. This would generally be considered to be **minimal manipulation** as the structural element is maintained and is the crucial characteristic of the tissue relating to its intended use.
- b. A manufacturer grinds the bone to form morselised chips and particles for filling of bone voids. The structural element of the bone is no longer maintained, but this would still generally be considered to be **minimal manipulation** as the strength and resistance to compression is maintained, which is the crucial characteristic of the tissue relating to its intended use.
- c. A manufacturer demineralises morselised bone sufficiently to increase the malleability of the bone, with the intended use restricted to void filing. This is considered **minimal manipulation** as it maintains the utility to support bodily structures.
- d. A manufacturer demineralises the bone sufficiently to increase the exposure of the bone morphogenetic proteins, for use in bone grafts where osteoinductive potential is desired. This may still be considered to be minimal manipulation, as osteoinductivity is an inherent property of mineralised bone. However, the manufacturer must be able to demonstrate that the manufacturing process does not substantially diminish the osteoinductive potential (to a clinically relevant level). Note that due to batch variation in osteoinductive potential (presumably due to variation between donors), most demineralised bone matrix (DBM) preparations would require batch testing where an osteoinductive claim is made. Mixing the DBM with a carrier is considered more than **minimal manipulation**.

### 2. Skin example:

- a. A manufacturer processes skin to decellularise it, leaving the collagen matrix, for use in covering burns. The utility of the skin to provide a protective covering is not substantially compromised by the processing, so this is considered **minimal manipulation**.

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3. Adipose tissue example:

- a. Adipose tissue is collected from one area of the patient and used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is **minimal manipulation** because the processing does not alter the cushioning and support of the adipose tissue.
- b. A manufacturer processes adipose tissue (enzymatic or physical dissociation) with the aim to dissociate cell-cell contacts and isolate the cellular portion. The resultant product (such as stromal vascular fraction (SVF)) is injected back in to patients for reputed anti-inflammatory uses. In this case the cells responsible for the intended use and to which the determination of minimal manipulation applies (e.g. mesenchymal stem cells) would be considered the autologous HCT product. Such methods used to disrupt adipose tissue would be considered **beyond minimal manipulation**. The process applied to isolate the cells is likely to result in changes to their properties, e.g. activation state or surface molecule expression, which could significantly impact the cells characteristics or functions.

4. Amniotic membrane example:

- a. A manufacturer processes amniotic membrane to preserve it and package it in sheets, for use in wound covering. This is considered **minimal manipulation** as the barrier function of the membrane is not altered by the processing.
- b. A manufacturer processes amnion and then grinds it in to particles for injection into a wound to improve healing. This may be considered to be **minimal manipulation**, as long as the manufacturer can demonstrate to the satisfaction of the TGA that the mechanism of action for the clinical claim is a result of the intrinsic characteristics and functions of amniotic tissue, and that the manufacturing process does not alter these relevant characteristics. Note that although the processing step may be considered minimal manipulation, the intended use may not be considered to be homologous.

5. Platelet-rich plasma and conditioned serum example:

- a. Preparation of platelet-rich plasma from a single uninterrupted venipuncture, for injection in to damaged tissue. Generally the processing involved does not alter the functions of the platelets so is considered **minimal manipulation**.
- b. Culturing blood to produce a conditioned serum for injection in to damaged tissue. The serum is cultured to induce the white blood cells to produce anti-inflammatory compounds in to the serum, so this processing is considered **more than minimal manipulation**. In addition, the culturing raises safety concerns around the growth of microorganisms.

## Homologous use

Homologous use refers to:

- The repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with cells or tissue that perform the same basic function or functions in the recipient as the donor

Where this definition is not met, compared with a homologous use, there would be increased safety and efficacy concerns with the use of the HCT as there is less information on which to predict the behaviour of the product.

For clarity, distinguishing between homologous or non-homologous use also applies to autologous use of HCTs, with the donor and recipient being the same person.

In determining whether the use of the HCT is homologous, the intended clinical treatment will be carefully considered, including review of the manufacturer's labelling and advertising material.

When the use of HCT is identical in the donor and the recipient, e.g. skin grafts collected from one area and used to replace damaged skin in another location, this is accepted as a homologous use.

The determination of homologous use may be complex in some circumstances where the donor HCT is not identical to the cells or tissue that will be repaired, reconstructed, replaced or supplemented in the recipient, but it performs the same basic functions. Generally, in this situation it would be considered to be homologous use if the manufacturer provides sufficient evidence to support the claim. Where treatment involves an unproven clinical use it is likely to be considered to be a non-homologous use.

### Defining basic functions of human cells and tissues

When defining the basic function or functions of HCTs we mean those that are well understood (scientifically) to apply to the donor tissue, and where functionality can be assumed in the recipient in the absence of a need to perform testing. It is not necessary for all functions of the HCT to be maintained and performed in the recipient, only those claimed in the intended use.

The HCT may perform the same basic function or functions even when it is not used in the same anatomic location where it occurred in the donor.

### Examples to demonstrate homologous use

Some of the examples provided are taken from the [FDA guidance on the definitions and interpretation of homologous use](#), but others differ in interpretation from their guidance and represent TGA's current interpretation.

1. **HPC examples:** Sources of hematopoietic stem/progenitor cells (HPCs) include cord blood, peripheral blood, and bone marrow. The basic functions of HPCs include forming and replenishing the lymphohematopoietic system.
  - a. HPCs from mobilized peripheral blood are intended for transplantation into an individual with a disorder affecting the hematopoietic system that is inherited, acquired, or the result of myeloablative treatment. This is **homologous use** because the peripheral blood product performs the same basic function of reconstituting the hematopoietic system in the recipient.

- b. HPCs from bone marrow are intended for infusion into an artery with a balloon catheter for the purpose of limiting ventricular remodelling following acute myocardial infarction. This is **not homologous use** because limiting ventricular remodelling is not a basic function of bone marrow.
- c. HPCs from cord blood are intended for intravenous infusion to treat cerebral palsy purportedly through the repair of damaged tissue in the brain through paracrine signalling or differentiation into neuronal cells. This is **not homologous use** because there is currently insufficient evidence to support that repair of neurologic tissue through paracrine signalling or differentiation into neuronal cells is a basic function of these cells in the donor.

**2. Amniotic membrane example.** Some basic functions of amniotic membrane include:

- serving as a selective barrier for the movement of nutrients between the external and in utero environment, and
- protecting the foetus from the surrounding maternal environment, and
- serving as a covering to enclose the foetus and retain fluid in utero.

FDA also recognise **potential functions** for the tissue including reducing scarring, angiogenesis, and inflammation, but advise that they are not basic functions of the amniotic membrane when associated with the foetus. Therefore, where any of potential functions are claimed as the intended they are considered to be non-homologous uses of amniotic membrane by the FDA.

In contrast, where these additional functions can be demonstrated (experimentally) by a manufacturer to also be active in the donor, we will consider these functions to be homologous. Therefore, the following represents our current position on homologous use of amnion.

- a. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane.
- b. Amniotic membrane is used to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.
- c. An amniotic membrane product is to be used for wound healing and/or to reduce scarring and inflammation. The barrier function of the membrane is considered homologous use. However, based on current evidence, the other functions are not considered to be homologous use, unless these additional functions can be demonstrated by a manufacturer to also be active in the donor.

**3. Adipose tissue and cell extracts example.** Adipose tissue may be collected and then re-injected with minimal manipulation, or may be subjected to processing to extract the cellular portion from the tissue. Generally the HCT extracted from adipose includes various cellular fractions (of varying purity), and are collectively referred to as Stromal Vascular Fraction (SVF). Where the adipose tissue is the HCT to be provided to the recipient the basic functions include:

- a. providing cushioning and support for other tissues, including the skin and internal organs
- b. storing energy in the form of lipids, and

- c. insulating the body.

In contrast, where the HCT provided to the recipient is a cell extract, the determination of homologous use would make reference to the basic functions of the cells located in the adipose, rather than those of the tissue collectively. This may be complicated by the need to understand the cells and mechanisms responsible for the desired mode of action. The following represents our current thinking on homologous use of adipose tissue and cell extracts from this tissue:

- a. Adipose tissue is used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is homologous use because providing cushioning and support is a basic function of adipose tissue.
  - b. Stromal Vascular Fraction (SVF) isolated from adipose tissue is used to treat musculoskeletal conditions, such as arthritis or tendonitis by regenerating or promoting the regeneration of articular cartilage or tendon. This application is not considered a homologous use because regenerating or promoting the regeneration of cartilage or tendon is not a basic function of the cells isolated from adipose tissue.
4. **Platelet-rich plasma example.** The mechanism of platelet-rich plasma action in the treatment of musculoskeletal disorders remains to be determined and evaluation of platelet-rich plasma in clinical trials is in its infancy. The basic functions that would apply to platelet-rich plasma are based on the understanding of the normal healing process of musculoskeletal tissue. The repair response of musculoskeletal tissues starts with the formation of a blood clot and degranulation of platelets. This degranulation of platelets releases a range of growth factors and cytokines into the local environment that trigger a cascade of events that lead to healing of the wound. Where it can be demonstrated or justified that the intended use of PrP can augment or stimulate healing by turning on the same repair response it could be considered to be a homologous use.

## Version history

| <b>Version</b> | <b>Description of change</b> | <b>Author</b>                   | <b>Effective date</b> |
|----------------|------------------------------|---------------------------------|-----------------------|
| V1.0           | Original publication         | Scientific Evaluation<br>Branch | April 2018            |

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