



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

# Changes to the regulation of autologous cells and tissues

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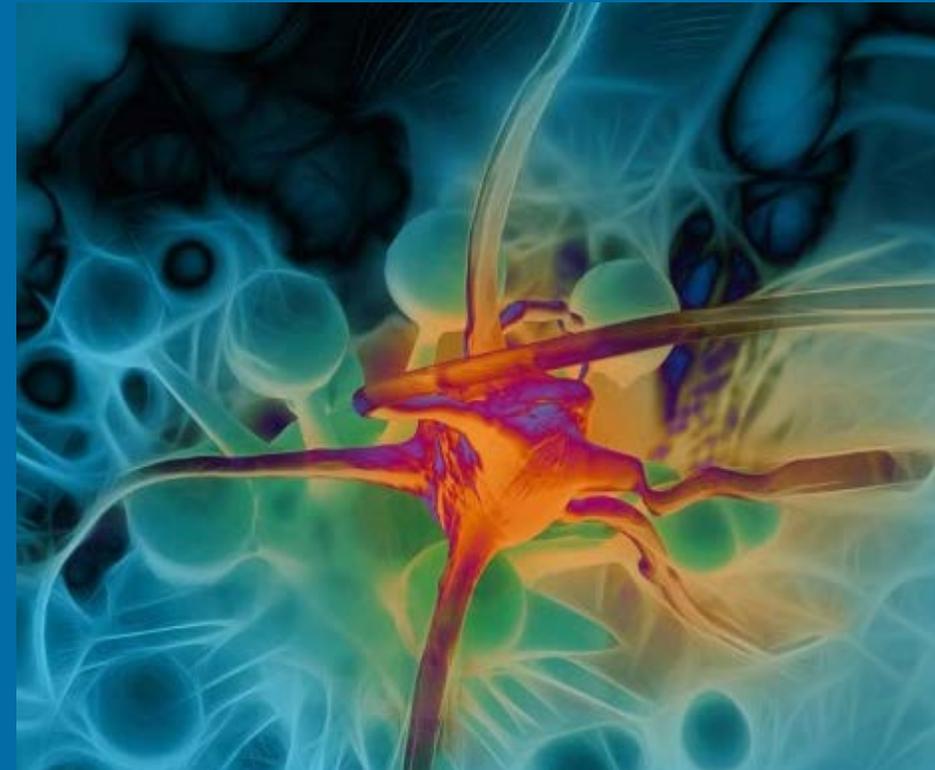
June 2018



**TGA** Health Safety  
Regulation

## Overview

- Background
- Changes to regulation of autologous cells & tissues (HCT)
  - Subject to approval commence 1 July 2018
  - Transition provisions
  - Excluded from TGA regulation
  - Exempt from certain regulatory requirements
  - Regulated as a biological
  - Minimal manipulation and homologous use
  - Examples: Platelet-rich plasma (PrP), Stromal vascular fraction (SVF)
- Implementation
- Questions



# Some regulators of products & practices

Therapeutic use/ clinical trial products in humans

- Regulated by TGA
- *Therapeutic Goods Act 1989*

Food

- Regulated by Food Standards Australia New Zealand
- *Australia New Zealand Food Standards Code*

Research (potential therapeutic) products

- Research process regulated by the National Health and Medical Research Council
- *Australian Code for the Responsible Conduct in Research*
- Australian Health Ethics Committee

Single patient compounded pharmaceuticals

- Regulated by Pharmacy Board of Australia
- *Guidelines on the Compounding of Medicines* by the Pharmacy Board of Australia

Veterinary medicines

- Regulated by Australian Pesticides & Veterinary Medicines Authority
- *Agricultural and Veterinary Chemicals Act 1994*

Cosmetics & industrial chemicals

- Regulated under then National Industrial Chemicals Notification and Assessment Scheme
- *Industrial Chemical (Notification and Assessment) Act 1989*

Medical practice derived products

- Regulated by Medical Board of Australia/Australian Health Practitioner Regulatory Agency
- *Health Practitioner Regulation National Law, National Registration and Accreditation Scheme*

# Autologous human cells & tissues

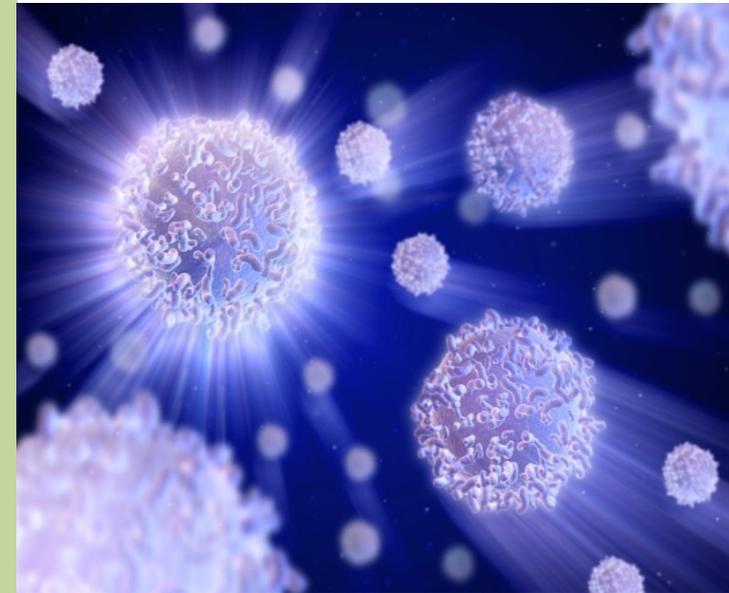
- Human cell and tissue (HCT) products are those that comprise, contain or are derived from human cells and tissues.
- Autologous human cell and tissue (HCT) products are those that are removed from, and applied to, the same person, i.e. the donor and the recipient are the same.
- These include some products commonly referred to as 'stem cell treatments'.

- 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))
- blood and blood components (red cells, plasma, serum, platelets, and platelet-rich plasma (PrP))



# Current Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 (EGO)

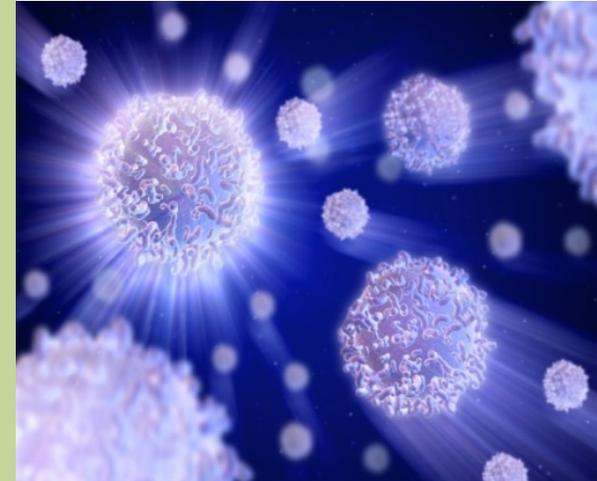
- **Autologous cells and tissues (Medical practice)**
  - collected **under the care of a medical practitioner, and**
  - manufactured for treatment of a **single indication, and**
  - in a **single course of treatment** of that patient **by the same medical practitioner**, or by a person under their supervision
  - Other autologous uses are not exempt in Australia
- Position reviewed in response to concerns





# Changes to regulation of autologous cells & tissues

- Increase the level of oversight by TGA of autologous HCT
- Three levels of regulation of autologous HCT
  - Excluded from TGA regulation
  - Exempt from certain regulatory requirements
  - Regulated as a biological
- Aligns more closely with international practice
- Some changes come in to effect from 1 July 2018; other changes will be subject to transition provisions



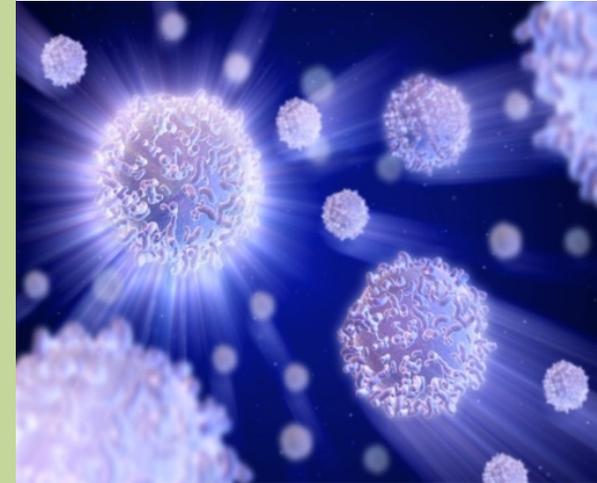
# Changes in place from 1 July 2018

Applies to **all** autologous HCT products:

- No direct advertising to consumers of autologous cell and tissue products from 1 July 2018 (Jenny Mason)

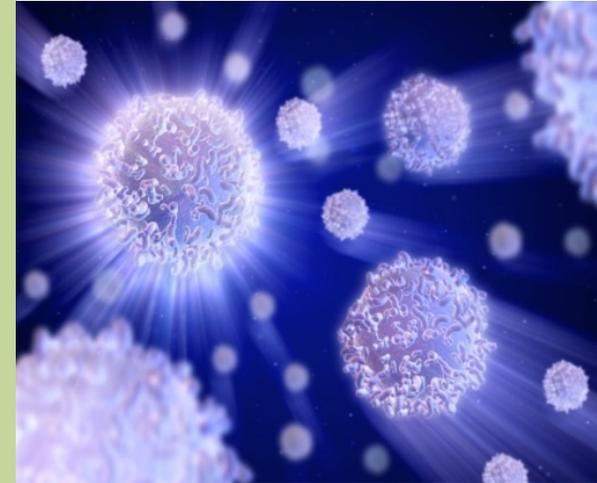
The following conditions also apply to **Exempt** and **Fully Regulated** products:

- Reporting of adverse events to TGA
- Compliance with all applicable standards
  - Donor screening and testing (Therapeutic Goods Order 88)



# Transition provisions

- When autologous HCT products have been supplied before 1 July 2018
  - ➔ supply may continue until 30 June 2019
- Further transition provisions
  - Exemption from GMP requirements where an application is received to seek GMP certification before 30 June 2019
  - Where a full market authorisation or a CTX application is made and accepted for evaluation by 30 June 2019
  - Supply can continue under the provision until a decision is made on the application



# Changes to regulation of autologous cells & tissues

## Excluded from TGA regulation

Exclude from regulation by the TGA only those autologous cell and tissue products that are manufactured and used in an accredited hospital

- the goods were collected and manufactured by, or under the professional supervision of, the practitioner in an accredited hospital
  - For use in that patient by that practitioner or persons under their supervision
  - the goods are not advertised or promoted directly to consumers;
- Designed to exclude certain autologous cells and tissues that are associated with established medical practice
  - Accredited hospitals are responsible for decisions on the appropriateness of procedures and products manufactured in their institution
  - For example, vascular conduits, skull flaps, cultured keratinocytes and hematopoietic progenitor cells for reconstitution of blood after chemotherapy



# Changes to regulation of autologous cells & tissues

## Excluded from TGA regulation – Hospital accreditation

- Public and private hospitals in Australia are subject to regulation under various state, territory and national provisions
- Credentialing processes are applied by hospitals to ensure that practitioners do not work outside of their scope of practice
- Hospitals are accredited to the National Safety and Quality Health Service (NSQHS) Standards
- Hospitals should have governance and procedures in place to ensure manufacturing and use of autologous HCT is appropriate



# Changes to regulation of autologous cells & tissues

## Excluded from TGA regulation – Manufacturing

- Collection and manufacturing must occur within the hospital and under the professional supervision of the medical practitioner
- Professional supervision 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 through a formal arrangement with the person or persons undertaking the manufacturing.
- ✓ Specialised testing on a representative sample of the product by a third-party facility, for example sterility testing.
- ✗ Offsite or third-party manufacturing of the product

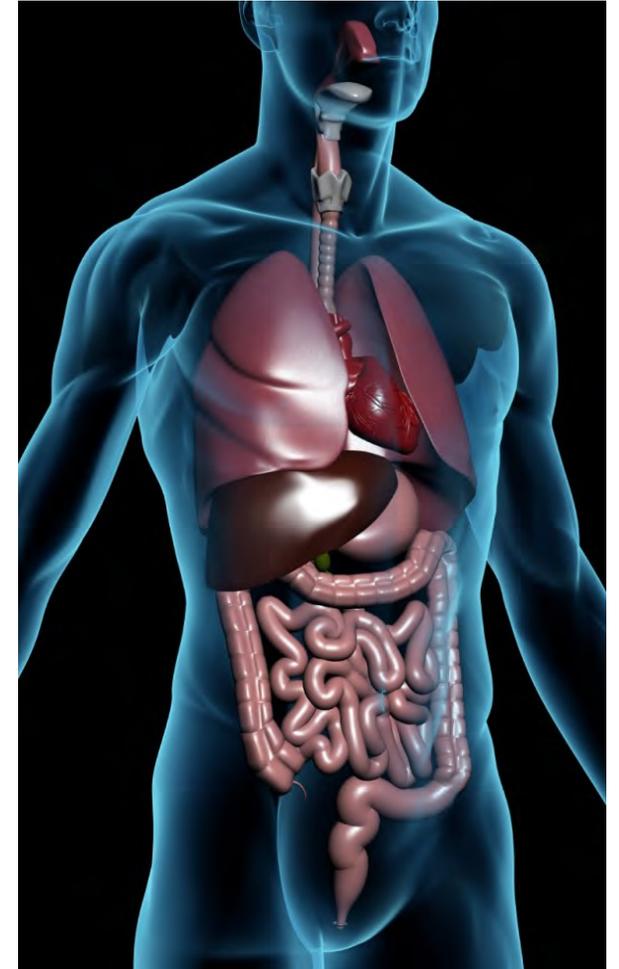


# Changes to regulation of autologous cells & tissues

## Exempt from certain regulatory requirements

Regulation under Biologicals Regulatory framework with exemptions from some requirements for autologous HCT that are:

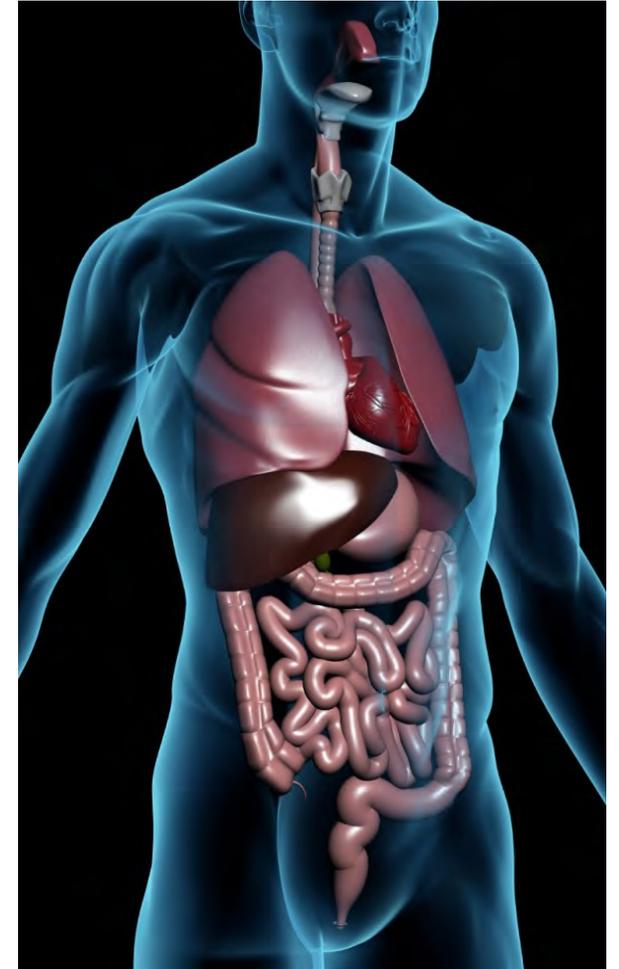
- minimally manipulated, and
  - for homologous use only, and
  - manufactured and used outside a hospital by a medical or dental practitioner,
  - for a patient in the same practitioner's care.
- Conditions set to limit this option to only low risk products, where there is still a high level of clinical oversight by the practitioner.
  - Exempt from being on the Register (no market authorisation), and GMP



# Changes to regulation of autologous cells & tissues

## Exempt from certain regulatory requirements – continued

- No advertising to consumers
- Single indication/single procedure
  - Any treatment that involves more than a single procedure may 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 primary indication for the autologous HCT product in any procedure or treatment should be clearly documented
- Guidance on what meets the definitions of minimal manipulation and homologous use
- Standards, advertising restrictions, and adverse event reporting will apply. Enforcement options will include the ability for TGA to request information and take appropriate action.



# Minimal manipulation

The goods have been subjected to ***minimal manipulation*** if no process or processes to which the goods have been subjected have altered any of the biological characteristics, physiological functions or structural properties of the original cells or tissues that are relevant to the purpose for which the manufacturer of the goods intends the goods to be used

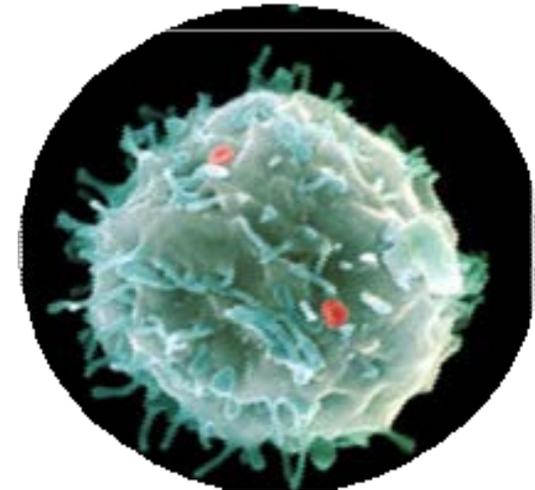
- Introduces a link between the processes to which the cells and tissue are subject and the intended clinical function of the product, which is crucial for assigning an appropriate risk classification
- Removes definitional issues around the previous list of actions
- Designed to draw a line between medical practice and product manufacturing
- 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.



# Homologous use

**Homologous use** of the goods is use of the goods to repair, reconstruct, replace or supplement the cells or tissues of a person (the **recipient**), if the goods will perform the same basic function or functions in the recipient as the original cells or tissues performed in the person from whom they were collected.

- 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.
- 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.



# Exempt from certain regulatory requirements – Example

- Platelet-rich plasma:
- 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.
- The mechanism of platelet-rich plasma action in the treatment of musculoskeletal disorders is not fully determined and evaluation of platelet-rich plasma in clinical trials is incomplete. The basic principles that would apply to platelet-rich plasma are based on the understanding of the normal healing response 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. If it can be demonstrated or justified that the intended use of PrP can augment or stimulate the same repair response it could be considered to be a homologous use.



# Exempt from certain regulatory requirements – Example

- Platelet-rich plasma:
  - 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 medicinal product) 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 and do not apply to other uses
  - Where equipment (such as a commercial kit) is used in the manufacture of PrP or collection, the equipment may also be subject to regulation as a medical device
  - Cosmetic use of injected PrP is likely to be regulated by TGA where therapeutic claim is not explicitly or implicitly 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).



# Changes to regulation of autologous cells & tissues

## Regulated as a biological

Regulate under the Biologicals Regulatory Framework those autologous human cell and tissue products that are:

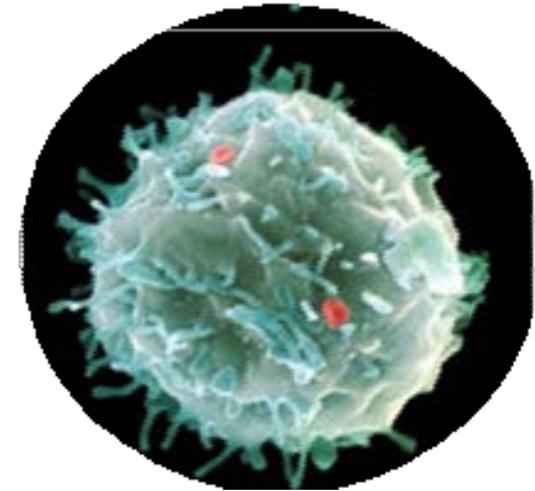
- manufactured and used outside an accredited hospital, and
  - more than minimally manipulated, or
  - for non-homologous use.
- Products may still be accessed through clinical trials or compassionate use schemes
- Market authorisation and GMP requirements apply.



# Regulated as a biological - Example

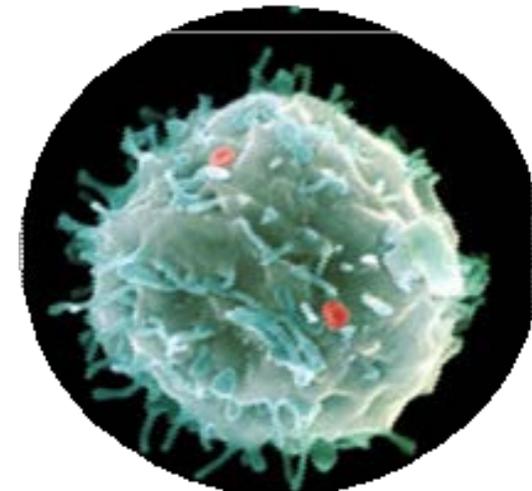
Adipose tissue example:

- a. 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.



# Regulated as a biological - Example

- Adipose tissue may be collected and then reinjected with minimal manipulation, or may be subjected to processing to extract the cellular portion from the tissue.
- The HCT extracted from adipose includes various cellular fractions (of varying purity), and are collectively referred to as Stromal Vascular Fraction (SVF).
- **Homologous uses** include:
  - providing cushioning and support for other tissues, including the skin and internal organs
  - storing energy in the form of lipids, and
  - insulating the body.
- 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.
- 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 considered a **non-homologous use**.



# Implementation

- Staged implementation – advertising restriction, transition
- In the first instance, we seek to inform, educate and assist stakeholders
- Communication strategy over next 12 months to target different stakeholder groups, including consumer groups
- Teleconferences and face-to-face meeting options
- Submitted questions after the Advertising presentation
- Primary contact for further enquiries is [bloodandtissues@tga.gov.au](mailto:bloodandtissues@tga.gov.au)
- Link to current guidance: [Biologicals regulatory framework proposed changes to start on 1 July 2018](http://www.tga.gov.au/publication/biologicals-regulatory-framework-proposed-changes-to-start-on-1-july-2018) (www.tga.gov.au/publication/biologicals-regulatory-framework-proposed-changes-start-1-july-2018)



# Advertising Unapproved HCT Therapies

- Unapproved autologous HCT products which are regulated as exempt biologicals from 1 July 2018 will be prohibited from being advertised to consumers under the *Therapeutic Goods Act 1989* (the Act).
- Likewise, autologous HCT products which are proposed to be excluded from the operation of the Act from 1 July 2018 may not be advertised to consumers.

# Making claims to arrange supply of unapproved HCT therapies

- Making claims to arrange supply of unapproved HCT therapies (as distinct from advertising) is also prohibited under the Act unless :
  - Those goods are subject to an exemption, approval or authority under one of a number of different schemes included in the Act.
  - The claim is limited to the terms of that exemption/ approval; and
  - communicated between the relevant parties to that exemption, approval or authority
- This means that claims to arrange supply of unapproved HCT therapies cannot be broadly made to consumers or health professionals.

## Education / guidance

- New “Advertising hub” planned for website
  - Easier to locate from homepage
  - Access to education, guidance, complaint form, inquiry form etc
- Three e-learning modules under development
- Australian Regulatory Guidelines on Advertising Therapeutic Goods
- Consumer-specific materials:
  - Fact sheets – lodging complaints, identifying non-compliant ads
  - Short video on advertising requirements



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