



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Options for the regulation of Faecal Microbiota Transplantation materials

Consultation paper

Version 1.0, January 2019

**TGA** Health Safety  
Regulation

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## Purpose and scope

The purpose of this consultation paper is to detail potential options for developing product specific requirements, standards and regulatory measures, for the collection, manufacture and supply of faecal microbiota transplantation (FMT) material. Submissions received in response to this consultation will inform policy decisions by the Australian Government regarding the quality, safety and efficacy of FMT material for therapeutic use.

FMT material refers to donated human faecal matter and the therapeutic material that may be processed from donated human faecal matter. For the purposes of this paper, FMT materials include fresh or frozen human faecal matter that may be introduced to the bowel by a range of methods including rectal enema, sigmoidoscopy, colonoscopy, and nasogastric or nasoduodenal tube. The materials also include human faecal matter that has been filtered, centrifuged, cultured, encapsulated, or otherwise prepared to allow oral ingestion. Regulation of microbes derived from sources other than human faecal matter is not in the scope of this consultation, although the regulatory outcomes may be used in the future to inform the development and implementation of a policy on regulation of allogeneic microbiota transfer material collected from other human tissues (for example, nasal or vaginal secretions).

## Why is FMT material a therapeutic good?

FMT material meets the definition of a [therapeutic good](#), regardless of what the processed material contains, if FMT material is used in the treatment or prevention of a disease, ailment, defect or injury affecting humans. At present, FMT materials that contain human cells, that is, colonocytes (even though these may be incidental to the mechanism of action of the materials in treating a disease) would meet the definition of a [biological](#). FMT material that is processed by methods that include separation from human cells may or may not be a biological for the purposes of the Act. Feedback on this definition will be obtained as part of this public consultation.

The focus of this paper is on allogeneic use of FMT material, where the donor and the recipient are different.

### Your input is sought

The Therapeutic Goods Administration (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.

***The closing date for comments is March 15, 2019***

## Background

In 2014, a Health Policy Advisory Committee on Technology (HealthPACT) analysis of FMT<sup>1</sup> concluded that:

“Faecal microbiota transplantation therapy is disseminating across Australian clinical practice and its use is likely to increase over time. The development of clinical practice guidelines in regard to donors, route of administration and patient preparation would be helpful before the use of bacterial replacement therapies became widespread”.

In 2015 The Gastroenterological Society of Australia (GESA)<sup>2</sup> recommended that

“FMT should be made available as a treatment option for all patients in the Australian healthcare system with recurrent or refractory [*Clostridium difficile* infection (CDI)]. This requires that FMT services be developed in at least one public hospital in each state or territory”

and

“FMT for indications other than for CDI should be carried out only in the clinical trial setting and with careful evaluation and transparent reporting of efficacy and safety”.

More recently, a systematic review and meta-analysis of 10 randomised controlled trials of FMT for *Clostridium difficile* associated diarrhoea (CDAD) concluded that FMT is more effective than either the antibiotic vancomycin or placebo, although the authors also recommended that further studies are required to establish the best approaches to preparation and administration of FMT materials<sup>3</sup>. FMT has been acknowledged as an appropriate treatment for recurrent CDI by a number of specialist groups including the Australasian Society for Infectious Diseases (ASID), the European Society of Clinical Microbiology and the American College of Gastroenterology<sup>4</sup>, and by the UK National Institute for Health and Care Excellence (NICE)<sup>5</sup>.

Internationally, the approaches to regulation of FMT vary – for example, in some jurisdictions FMT is regulated as a medicine, not a biological (cell or tissue) product. Many regulatory frameworks have confined their scope to the regulation of FMT for recurrent CDI, with use of FMT for other indications being subject to clinical trial requirements. Some international approaches are summarised in Appendix 1.

On 10 October 2018, the TGA hosted a [stakeholder forum](#) in Melbourne to confirm its understanding of the health care sector engaged in the collection, manufacture and supply of material used in FMT. At the forum, invited speakers described the collection, manufacture and supply of material used in FMT in Australia, and provided views on the future regulation of these products. Individual patients, gastroenterologists, infectious disease specialists and Commonwealth and State Department of Health representatives discussed potential and preferred mechanisms for ensuring continued supply of FMT material that is safe and fit for purpose. Three sessions covered the Australian regulatory environment, requirements for donor selection and donor and product screening, and manufacturing requirements. The stakeholder forum concluded with agreement on the following points:

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<sup>1</sup> Technology Brief Update: Faecal microbiota transplantation, HealthPACT, July 2014

<sup>2</sup> GESA Position Statement on Faecal microbiota transplant (FMT), Gastroenterological Society of Australia, September 2015

<sup>3</sup> Moayyedi P, Yuan Y, Baharith H, Ford AC (2017) Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea; a systematic review of randomised controlled trials *MJA* 207(4): 166-72

<sup>4</sup> Brandt LJ (2017) Faecal microbiota transplantation: past, present and future *MJA* 207(4): 151-2

<sup>5</sup> <https://www.nice.org.uk/guidance/ipg485/chapter/1-Recommendations>

- There is a broad spectrum of processed FMT materials. A range of models for the oversight of manufacturing facilities should be considered, and these should be developed in anticipation of pharmaceutical-type products being developed in the future.
- Further consideration must be given to the level of accreditation or licensing required for laboratories that test donor material, in line with the current TGA framework for in vitro diagnostic tests, to address issues such as test method validation.
- The participants recognised the need for Australian standards for donor selection criteria and considered the possibilities of adopting appropriate international standards, and of developing specific standards relevant to Australia and New Zealand, to supplement the existing TGA standard, [Therapeutic Goods Order \(TGO\) No. 88: Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products](#). It was noted that donor exclusion criteria for FMT may be broader than those within TGO 88, and the breadth of such donor exclusion criteria would need to be clearly explained.
- A robust regulatory framework/s that recognises the rapid growth and evolution of this sector and minimally affects innovation should be applied.
- Any new regulatory requirements should be introduced with a reasonable transition period.

Additional detail regarding discussions at the stakeholder forum is included in Appendix 2.

## The nature of human faecal material

FMT materials encompass a broad range of products that may have been subjected to varying degrees of processing prior to administration. This section outlines the nature of the different faecal material products (summarised in Table 1) as well as factors that may affect the level of regulatory oversight by TGA (summarised in Table 2).

### Fresh faecal material

After frozen material, fresh faecal material for the treatment of recurrent CDI is the most common FMT product in the relevant literature<sup>6,7,8,9</sup>. At its simplest, fresh faeces have been sourced from single screened donors either known or unknown to the recipient, most frequently homogenised in saline (or in some studies in tap water), filtered, strained and/or decanted to remove undigested food and other large particles, and used within four to eight hours. For such donors, the donor screening tests have been performed prior to donation, but the short time frame between collection and administration limits the level and nature of testing that can be performed on the product and the results available prior to release. Samples are usually collected and stored frozen for later testing, as required.

### Risks

The potential risks specific to fresh faecal transplants, and not associated with the procedural risks dependent on the method of administration or with the medical condition of the recipient patient, are:

<sup>6</sup> Van Nood E, Vrieze A et al. *NEJM* 368(5): 407-15 (2013)

<sup>7</sup> Goldenberg SD, Batra R et al. *Infect Dis Ther* 7:71-86, 2018

<sup>8</sup> Satokari R, Mattila E et al. *Alimentary Pharmacology and Therapeutics* 41: 46-53, 2015

<sup>9</sup> Cammarota G, Masucci L, et al. *Alimentary Pharmacology and Therapeutics*, 41: 35-43, 2015

- Inadvertent transmission of infection as a result of incomplete test results on the faecal material. This may be considered acceptable if FMT is required as an emergency therapy, for example in fulminant CDI, but may also be easily mitigated by having appropriate banked stores of fully screened faecal material readily available for emergency use.
- Donations from known donors may be more acceptable to some recipients, particularly in emergency applications, but there is also a credible risk that known donors may be reluctant to reveal behaviours that could increase the risk of disease transmission.
- There is a possibility that homogenisation in tap water or other hypotonic solutions may lyse some cellular organisms and potentially interfere with the efficacy of the FMT treatment, although in the reviewed published literature FMT mixed with water and with saline have been equally effective in treating rCDI.

## Frozen faecal material

The use of frozen (particularly cryopreserved) faecal material is most frequently described in the literature<sup>10,11,12,13</sup>. Faeces are generally collected from single screened donors either known or unknown to the recipient, sampled for testing, and homogenised under aerobic or anaerobic conditions in a mixture of normal saline and around 10% glycerol. The unprocessed product may be stored at 4°C for up to six-eight hours before processing. The processed product may be stored at -80°C for between four and six months, and may be filtered before cryopreservation and storage, or after thawing and prior to administration.

## Risks

The potential risks specific to frozen faecal transplants, not associated with the procedural risks dependent on the method of administration or with the medical condition of the recipient patient, are:

- The impact of the freezing procedure on the viability of specific flora<sup>14</sup>. Glycerol is included in the storage medium to minimise effects on viability, but is still known to result in loss of some viruses and bacteria<sup>15,16,17</sup>.
- Some authors advocate anaerobic processing of faeces, as it appears to have less effect on the viability of a proportion of the flora. However, published data does not seem to indicate a meaningful clinical difference in treatment outcomes of patients with rCDI and CDAD treated with fresh or frozen faeces<sup>18</sup>.
- There is insufficient evidence to allow extrapolation of success in CDAD to other conditions.

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<sup>10</sup> Goldenberg SD, Batra R et al. *Infect Dis Ther* 7:71-86, 2018

<sup>11</sup> Satokari R, Mattila E et al. *Alimentary Pharmacology and Therapeutics* 41: 46-53, 2015

<sup>12</sup> Costello SP, Tucker EC et al, *Clinical Infectious Disease* 62(7):908-14, 2016

<sup>13</sup> Lee CH, Steiner T, et al. *JAMA* 315:142-9, 2016

<sup>14</sup> Fouhy F, Deane J et al, *PLOS One* 10(3)(e0119355), 2015

<sup>15</sup> Costello SP, Conlon MA et al, *Alimentary Pharmacology and Therapeutics* 42: 1011-8, 2015

<sup>16</sup> Hooper LV, Littman DR et al, *Science* 336:1268-73, 2012

<sup>17</sup> Choi H, Cho Y-S, *Clinical Endoscopy* 49:257-65, 2016

<sup>18</sup> Cammarota G, Ianiro G et al, *Gut*, doi:10.1135/gutjnl-2016-313017

## Centrifugation and encapsulation

Some authors include additional processing steps, for example centrifugation to concentrate gut flora in a pellet which then is mixed in a small volume of glycerol and frozen<sup>19</sup> or lyophilised (freeze-dried) prior to encapsulation<sup>20</sup>. Alternatively, the faecal slurry is first mixed with glycerol and then centrifuged, with the final sediment encapsulated and frozen<sup>21</sup>. These reports describe storage of the capsules for up to two months before use. The supernatant in both these methods is discarded.

### Risks

The list below is in addition to the potential risks specific to frozen faecal transplants listed above:

- The potential risks associated with centrifugation and discarding of the supernatant would be the loss of potential effective “agents”, the absence of which may impact on the efficacy of the encapsulated product. Such agents may include bacterial products, bile and other gut excretions as well as phages or other viruses.
- There is insufficient research at this time to assess the relative contributions of products retained in supernatant after centrifugation to the mechanism of action of FMT in CDAD or other conditions.
- The efficacy of lyophilised and encapsulated product, as reported in the published literature, is often not as great as with fresh or frozen product, but has better response rates reported than with current standard of care antibiotics.
- Large numbers of capsules may be required to “cure” a patient, with protocols describing 15 – 25 capsules being taken on consecutive days, and possibly at repeated time intervals. Provision of an encapsulated product may mitigate the procedural risks of introduction of slurry via endoscopy, and may be more acceptable to patients.
- Depending on the mechanism of action and the indication for the use of FMT, the efficacy of capsules may vary. There is insufficient research at this time to make unequivocal statements.

## Isolated and cultured microbes, spores, microbe banks

Some groups are already investigating administering specific therapeutic gut flora as alternatives to fresh or frozen FMT. In these processes, faecal material is collected from screened donors and stored frozen. Specimens from several donors may be pooled, then suspended, homogenized and filtered as in the earlier examples.

A process stated to preserve spore viability while selectively killing vegetative microorganisms and removing pro-inflammatory macromolecules adds a processing step that includes mixing with ethanol and centrifugation to separate supernatant containing bacterial cells and spores from other faecal material<sup>22</sup>. Further steps include additional centrifugation, washing, resuspension and encapsulation. The contents are characterised.

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<sup>19</sup> Youngster J, Russell G et al JAMA 312(17):1772-78, 2014

<sup>20</sup> Chehri M, Christensen A et al. Medicine 97:31(e11706), 2018

<sup>21</sup> Kao D, Roach B, Silva M, JAMA 318(20):1985-93, 2017

<sup>22</sup>Khanna S, Pardi DS et al, Journal of Infectious Diseases 214:173-81, 2016

A second manufacturing process also describes isolating a standardized mixture of microbes from faecal material collected and pooled from a number of selected and screened donors<sup>23</sup>. The standardized microbe mixture is stored frozen at -80°C and administered by enema.

Rectal bacteriotherapy, a treatment method that also depends on the culture of bacterial strains isolated from healthy persons<sup>24,25</sup> (whether from stools or another source), is likely to be considered administration of organisms collected from biologicals of human origin. Further clarification of the regulatory controls over products used in rectal bacteriotherapy, through a legislative instrument, may be necessary to avoid any ambiguity in law.

## Risks

The risks of these processes may be similar to those of encapsulated whole material, except:

- Pooling material from multiple donors increases the risk of inadvertent transmission of infection, potentially to multiple recipients.
- Developing a standardised microbial population is likely to involve short or long term culturing.
- Such a product and manufacturing process would require a higher level of oversight and control of the product quality.

## Faecal filtrate

Another proposed FMT material for which there is only a very early experimental report is material described as “sterile” faecal filtrate<sup>26</sup>. In this report faecal material collected from known donors is filtered to remove small particles and bacteria. The resultant product is stated to contain “bacterial debris, proteins, antimicrobial compounds, metabolic products, oligonucleotides/DNA”, with diverse bacterial DNA signatures and bacteriophage signatures in the filtrates.

- There is a risk that the processing by filtration would result in the discarded material containing effective “agents”, which may impact on the efficacy of the product.
- Further studies are required to determine if this is an effective and safe therapeutic approach.
- Further clarification of the regulatory controls over products of this type, through a legislative instrument, may be necessary to avoid any ambiguity in law (such as whether faecal filtrates would be regulated as a medicine or a biological by TGA).

## Risks common to most FMT products

The importance of a comprehensive donor selection process is central to the safety of any product derived from faecal material.

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<sup>23</sup> Dubberke ER, Lee CH et al, *Clinical Infectious Diseases* 67(8):1198-204, 2018;

<sup>24</sup> Emanuelsson F, Claesson BEB et al, *Scandinavian Journal of Infectious Diseases* 46:89-97, 2014

<sup>25</sup> Tvede M, Tinggaard MD, Helms M. *Clinical Microbiology and Infection* 21: 48-53, 2015

<sup>26</sup> Ott SJ, Waetzig GH et al, *Gastroenterology* 152(4):799-811, 2017

## Transmission of non-infectious conditions

- Transmission of non-infectious conditions traditionally considered “non-communicable”, for example metabolic syndrome and diabetes. There does not appear to be sufficient literature available at present on the relative importance of these possible risks, nor is there a clear mechanism of action that explains how a condition, or the propensity to develop a condition, may be transferred.
- Because of a lack of knowledge about the transferability of tumourigenesis or autoimmune, metabolic and neuropsychiatric diseases, the long-term side effects of FMT, if any, are unknown.

## Transmission of antibiotic resistance genes

- Horizontal gene transfer from other bacterial populations is a mechanism of transferring antibiotic resistance genes. Donor screening will need to include screening for highly resistant bacteria, for example vancomycin-resistant enterococci (VRE).

## Processing methods for FMT

- Effect of aerobic vs anaerobic processing – fastidious anaerobic organisms are less likely to survive aerobic processing, but there is a body of research that indicates that the “metabolome” is unaffected, at least with regard to outcomes of treatment for rCDI. Clarification of the actual mechanism of action of FMT, and whether the mechanism is the same for rCDI and other gastrointestinal disorders, or in fact systemic disorders, is essential to establish whether anaerobic processing should be controlled when FMT is being prepared for disorders other than rCDI.

## Methods of administration

- Risks of different methods of administration – Despite few reports of adverse events related to the use of FMT, there are tangible risks of severe and less severe adverse events associated with different administrative procedures, including risks of general anaesthesia, aspiration of gut contents with upper GI administration, bowel perforation and subsequent sepsis with instrumentation, and failure to retain rectal enema. While risks associated with administration are not within the scope of TGA, they should be taken into consideration in any assessment of benefit-risk balance of a therapeutic good. Note that because of the current ambiguity around the regulatory status of FMT it is likely that some adverse events are not being reported to TGA.

## Donor pooling

- Risks of FMT from a single donor vs from a pool of donors – while some users of FMT material have expressed preference for providing treatments based on material from a single donor, to more easily control traceability and minimise risks of inadvertent transmission of disease from donor to recipient, others advocate the broader microbial spectrum that can be transferred to recipients with FMT material pooled from multiple appropriately screened donors.

## Facilities used for FMT procedures

- It is understood that private facilities currently perform more FMT procedures and for a broader range of conditions.

- Health service organisations are responsible for the provision of safe, quality services, in the context of a range of requirements of the states and territories in relation to these facilities. Health service organisations are also required to comply with the National Safety and Quality Health Service (NSQHS) Standards. The [Australian Commission for Safety and Quality in Health Care](#) developed the NSQHS Standards in collaboration with the Australian Government, states and territories, clinical experts, the private sector, patients and carers. The primary aims of the NSQHS Standards are to protect the public from harm and to improve the quality of health service provision. Whilst the NSQHS do not specifically detail requirements in regard to FMT, each of the eight NSQHS Standards has relevance to the delivery of FMT services. Due to the nature of FMT services, the Clinical Governance, Preventing and Controlling Healthcare-Associated Infection, and Communicating for Safety are particularly relevant.

**Table 1: Examples of variously processed FMT materials, some characteristics and variations**

Finished product	Characteristics and variations
Fresh faecal product	Sourced from known or unknown donor, usually single donors; various routes/method of administration; homogenisation in water or saline; infectious disease testing on donor and faecal material not complete at the time of release. Usually prepared and administered at the same facility
Frozen (cryopreserved) faecal product	Sourced from known or unknown donor, single donors or pooled donors; various routes/method of administration. Frozen at below -80°C in around 10% glycerol; various thawing approaches. May be prepared and administered at same facility, or delivered to an alternate facility for administration
Frozen encapsulated faecal product	Freeze-dried product; encapsulation; sourced from known or unknown donor, single donors or pooled donors; may be prepared and administered at the same facility; potential to deliver to an alternate facility, or away from a health facility
Frozen encapsulated faecal product – microbial spores only	Frozen at below -80°C in around 10% glycerol; treated with ethanol (50% w/w) to remove bacteria, fungi, parasites and viruses; sourced from known pooled donors; may be prepared and administered at the same facility; potential to deliver to an alternate facility, or away from a health facility
Faecal filtrate	Filtered to remove all small particles and bacteria. Administered via colonoscopy or rectal enema?
Cultured strains isolated from faecal donor (Bacteriotherapy)	Frozen at below -80°C in around 10% glycerol; isolation and further culture of selective strains; sourced from unknown single donors; Administered via colonoscopy or rectal enema

**Table 2: Factors that may influence the level of TGA regulatory oversight**

	Activities likely to require only low level TGA regulatory oversight	Activities likely to require a higher level of TGA regulatory oversight
Processing	<p><b>Minimal manipulation</b> (where the processing would not be expected to impact on the quality and efficacy)</p> <ul style="list-style-type: none"> <li>• Mixing with saline</li> <li>• Particulate filtration</li> <li>• Freezing of cells</li> <li>• Encapsulation</li> </ul>	<p><b>More than minimal manipulation</b> (where there is potential that quality and efficacy could be impacted)</p> <ul style="list-style-type: none"> <li>• Substantial <i>in vitro</i> culturing</li> <li>• Synthetic manufacturing to re-create microbiome</li> <li>• Pooling of donor material</li> <li>• Inadequate quality and safety testing on the FMT material prior to release. Product used fresh, so infectious disease testing on sample and donor not complete at time of release</li> <li>• Third party manufacturing (off-site storage excluded)</li> </ul>
Governance models	<p>Being performed in hospitals</p> <p>Medical practitioner oversight of manufacture and administration</p>	<p>Supply to patients under the clinical care of a different practitioner</p> <p>Supply to patients outside of the manufacturing hospital</p> <p>Importation of FMT product (equivalent to 3<sup>rd</sup> party manufacture)</p>

## Current regulatory approaches to human cells, tissues and organs for therapeutic use

In addition to the biological regulatory framework, there are a limited number of alternative regulatory approaches currently in place in Australia for the oversight of the manufacture or processing and use of human cells, tissue and organs. These models are applied to therapeutic goods that are excluded from regulation by TGA, or exempt from some TGA requirements. These examples highlight TGA's risk based approach and the graduated regulatory options that are currently in place to ensure that quality, safety and conformity to a set of rules and standards can be achieved.

With the potential exception of the biologicals regulatory requirements, none of these models are directly applicable to FMT materials, but the models (see Appendix 3 for more details) may be helpful when considering options for various regulatory approaches for this sector.

### Regulation of Class 2 - 4 biologicals

The TGA regulatory requirements for Class 2 – 4 biologicals include compliance with general and product-specific [Therapeutic Goods Orders](#) including TGO 88, manufacture under the Australian Code of Good Manufacturing Practice (GMP) and a prohibition on advertising to consumers. Currently there are no products classified as Class 1 biologicals.

### Supply compliance

**Biologicals must be included in the Australian Register of Therapeutic Goods (the Register) prior to supply**, unless they are exempt or supplied as unapproved goods. The only legal pathways to supply unapproved biologicals are as part of a [clinical trial](#), or by using the [Special Access Scheme](#) (SAS) or [Authorised Prescriber](#) (AP) scheme. These pathways are subject to conditions.

### Manufacturing compliance

**The manufacture of medicinal products and allogeneic biologicals must be performed at a TGA licenced facility.**

The GMP code for biologicals is the Australian Code of Good Manufacturing Practice for human blood and blood components, human tissue and human cellular therapies (2013, “the Australian Code”), whereas the GMP Code for medicinal products is the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE009-13, 01 January 2017 (the PIC/S Code). Therapeutic goods that are microbial in nature but are not derived from a human source are subject to the PIC/S Code, and are not considered in this consultation.

### Advertising compliance

**Biologicals are prohibited from being [advertised](#) to the public** (see, for example, subsection 42DL(11) of the Act). The prohibition is given effect by various criminal and civil penalty offences included in the Act, the terms of which are reasonably broad; for example, a person advertising by any means, or causing the advertising by any means, if the advertisement *refers* to a biological (relevantly) commits an offence. The prohibition does not apply in circumstances where the reference is authorised or required by a government or government authority that is not a foreign government or foreign government authority.

The breadth of the application of the prohibition was a decision by Government made on introduction in 2009 of the regulatory framework for biologicals. The explanatory memorandum to the *Therapeutic Goods Amendment (2009 Measures No. 3) Bill 2009* states:

“This is necessary as it is inappropriate for biologicals to be advertised as the nature of the good means that they are only suitable to be supplied and used by appropriately qualified healthcare professionals and, therefore, it is not necessary or appropriate for them to be advertised to the public. The provision of information about these goods can be made to healthcare professionals and other relevant professionals, including through advertisements in professional publications, under section 42AA if the Act”

**Therefore a medical practice that promotes to the public that it carries out FMT procedures would contravene the prohibition** and by doing so, that practice would commit a criminal offence. This follows because that promotion would, in contravention of subsection 42DL(11), necessarily include a *reference* to a biological, FMT.

It is important to note, however, that an offence or contravention of a civil penalty is only potentially committed if the reference to the biological is in an advertisement. The Act defines ‘advertise’ in relation to therapeutic goods to include ‘make any statement, pictorial representation or design that is intended, whether directly or indirectly, to promote the use and supply of the goods ...’ A statement, for example, that is not designed or calculated to draw public attention to and to promote supply, sale or use of FMT is not an advertisement. A reference to FMT in a statement of that kind would therefore not contravene the prohibition against advertising a biological.

The TGA functions under a cost-recovered model. This means that among other things, sponsors or manufacturers are required to pay to have their therapeutic goods evaluated for quality, safety and efficacy, and for licensing and audits of manufacturing facilities.

## Examples of other regulatory approaches

### Reproductive tissue for assisted reproductive therapy

Reproductive tissue for use in assisted reproductive therapy (ART) is excluded from regulation by the TGA.

ART clinics are required to be licensed to [industry practice standards](#), with monitoring of compliance managed through the [Reproductive Technology Accreditation Committee](#) (RTAC) accreditation process.

### Fresh viable human organs

The use of organs for direct donor-to-host transplantation is excluded from regulation by the TGA. Regulation of organ donation is the responsibility of the states and territories, with each having separate legislation covering organ donation and transplantation.

### Haematopoietic progenitor cells (HPC)

The government has adopted a graduated regulatory oversight approach for HPC products. HPC products may be:

- **Excluded from regulation** by TGA if fresh viable human haematopoietic progenitor cells (HPCs) are for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution.

These cells may be obtained from the patient themselves (autologous transplantation), or collected from the bone marrow or peripheral blood of another person (allogeneic transplantation).

- **Exempt from some TGA regulatory requirements** if the HPC is for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution, and is subject to storage that is outside the governance of the requesting physician e.g. storage of cord blood units for future patient matching. These products are exempt from being included in the Register, but must still comply with TGA GMP requirements and demonstrate compliance with specific standards, subject to TGO 88 and [TGO 94 Standard for Haematopoietic Progenitor Cells derived from Cord Blood 2017](#).
- **Regulated as biologicals:** HPC products not meeting the above exclusion or exemption criteria are regulated by the TGA under the Biologicals Regulatory Framework according to their risk based classification.

## Autologous human cell and tissue products

Similar to the regulation of HPCs, the government has recently introduced a [graduated regulatory oversight approach](#) for autologous HCT products. The level of TGA oversight varies based on the level of external governance and clinical oversight, or depending on the manufacturing processes or intended use of the autologous HCT product. Under this approach autologous HCTs may be:

- [Excluded from TGA regulation](#) if HCTs are manufactured and used in a hospital under the [supervision](#) of a registered medical or dental practitioner, who has clinical care of the patient.
- **Exempt from some aspects of TGA regulation:** autologous HCT products are regulated under the *Therapeutic Goods Act 1989* but are exempt from certain requirements, including manufacturing under GMP, where the material is:
  - [minimally manipulated](#), and
  - [for homologous use only](#), and
  - manufactured outside a hospital, only if
    - collected, manufactured and used by persons under the supervision of the medical or dental practitioner who has clinical care of the patient, for a
    - single indication in a single clinical procedure
- Regulated as biologicals: Autologous HCT products that do not satisfy the above exclusion or exemption criteria are regulated by the TGA under the Biologicals Regulatory Framework according to their risk based classification.

## Autologous FMT

The use of FMT material for autologous use is likely to fall under the current [autologous human cells and tissues products regulation](#).

It is understood that autologous use of FMT material is likely to be:

- solely for the purpose of restoring gut homeostasis (homologous use); and
- minimally manipulated; and

- collected, manufactured and used by persons under the supervision of the medical practitioner who has clinical care of the patient; and
- manufactured and used in a hospital OR manufactured **outside** of a hospital but for a single indication in a single clinical procedure.

Based on this, most autologous FMT material is likely to be excluded or exempt from some requirements (including manufacturing at a GMP licenced facility) of TGA regulations.

## Alternative facility accreditation

A number of other accreditation bodies have been established to provide some assurance of compliance with specific standards that ensure the quality, safety and effectiveness treatments performed in different sectors.

None of these are likely to be considered appropriate for the accreditation of a facility processing FMT material; they provide examples of how standards are set and accreditation determined by an independent body. If such an alternative set of facility standards and independent accreditation is established for the manufacture of FMT materials, it may be appropriate to exempt clinics that comply with these alternative standards from the requirement to be TGA licenced.

- [NATA](#) accredits testing and pathology laboratories. There are a number of standards against which NATA can accredit a facility, including the NPAAC standards, ISO 15189, ISO 17025, and the OECD Principles of Good Laboratory Practice. However, the scope of NATA accreditation does **not** include clinical manufacturing and so it would not be suitable for manufacturers of FMT material.
- The [Foundation for the Accreditation of Cellular Therapy](#) and [the Joint Accreditation Committee – ISCT-Europe and European Society for Blood and Marrow Transplantation \(FACT-JACIE\)](#) develop international standards for collection, processing and administration of haematopoietic progenitor cells and cellular therapies, and accredit facilities to these standards. However, in Australia this accreditation scheme is currently limited to bone-marrow transplant facilities.
- Assisted Reproductive Technology (ART) clinics are required to be licensed to industry practice standards, with monitoring of compliance managed through the [RTAC](#) accreditation process.



**It should be noted that even for products excluded from TGA regulation, equipment and materials used for the manufacture of the product may be therapeutic goods to which the therapeutic goods legislation applies, and thus be subject to regulation.**

**For example, IVF solutions are regulated as a medical device, as are fluids used to transport whole organs for donation.**

## Facility licencing

GMP licencing is required for all sites that manufacture therapeutic goods, including all biologicals, unless otherwise exempt or excluded. The exemptions or exclusions from GMP licencing exist where a lower level of manufacturing oversight is required to ensure product quality and safety (e.g. early clinical development), or there is an alternative level of facility standards and usually independent accreditation to these standards. Below is a summary of possible options for implementing more limited TGA oversight that may be appropriate to some facilities processing FMT materials.

## Exclusions and exemptions from TGA licencing

Some sites processing biological products may be either **exempt** or **excluded** from the requirement to be a TGA licensed facility. For example, facilities performing ART and human organ transplants, as described above, are excluded from regulation by TGA, including GMP requirements.

While those particular processes are not directly applicable to facilities manufacturing FMT material, there are provisions for exclusions or exemptions from TGA licencing requirements that could be appropriately adapted for application to FMT manufacture under specific and defined circumstances.

- **Manufacture of FMT material for first-in-human clinical trials** is exempt from the TGA licencing requirement. Where the clinical trials are not first-in-human, i.e. where some early stage clinical data has been generated, then the exemption no longer applies.
- **Manufacture and use of FMT autologous material in a hospital** under the [supervision of a registered medical practitioner](#), who has clinical care of the patient. This exclusion from TGA legislation is currently only applied to some autologous cell and tissue products and may not be appropriate for processing of allogeneic material. To apply a similar exclusion to FMT facilities would require a change to the *Therapeutic Goods Regulations 1990* (TG Regulations).
- **Facilities processing allogeneic FMT material may be exempted from licence requirements, but not from other parts of the Therapeutic Goods legislation, if the manufactured product satisfies criteria applied to Class 1 biologicals.** For this potential option the FMT material must be determined to be a low risk to public health and have a high level of practitioner oversight. The material would be required to comply with TGO 88 and would be required to comply with any product-specific standard for FMT materials that would be developed in consultation with the sector. To apply this option to FMT facilities would require a change to a Therapeutic Goods instrument, to define certain FMT materials to be Class 1 biologicals.
- **Facilities processing allogeneic FMT material may also be exempted from licence requirements if the Government were to introduce other, specific exemptions in the TG Regulations.** Such exemptions for specific activities would need to be based on evidence of low risk for those activities.

## TGA licencing of manufacturing sites

**Where the exemptions and exclusions described above do not apply - or are not considered appropriate - facilities manufacturing FMT material must be TGA licenced**

irrespective of whether the FMT material is regulated as a biological under the Australian Code, or as a medicinal product under the PIC/S GMP Code.

The Australian Code includes clauses related to both the requirements to assess the suitability of donors of cells and tissues and clauses related to the specific processing steps commonly used in the manufacture of biologicals such as freeze drying (lyophilisation) and cryopreservation. The Australian Code also includes minimal requirements for manufacturing facilities and does not include any specific facility standards. The level of control expected is commensurate with the risk of the product. Minimal facility requirements for low risk products are acceptable to meet compliance with the Australian Code. A number of Australian hospital sites already have TGA licences for the manufacture of biological products and can meet minimum facility requirements.

## **FMT specific GMP guidance**

It is proposed to develop specific GMP Guidance for FMT materials in consultation with the sector. This guidance will adopt a risk-based approach and also include further interpretation of the evidence required to demonstrate compliance with Code Clauses. This will assist manufacturers by clarifying the type of information required to show GMP compliance.

Examples of product-specific GMP Guidance, which may be similar in application to FMT processing facilities, are published on the TGA website. One example is for sunscreen manufacturers who wish to demonstrate [compliance with the PIC/S Guide](#).

## **Licensing of testing facilities**

Under the Biological Framework facilities that perform:

- mandatory donor screening tests required by TGO 88; or
- any product tests that are required specifications to release the product;

are also required to hold a TGA manufacturing licence and comply with the requirements of the Australian Code. NATA accreditation alone is not considered sufficient for testing performed on therapeutic goods.

## **Use of validated tests**

Several tests used for screening stool samples will necessarily utilise in house (laboratory-developed or adapted) in vitro diagnostic tests, given that few relevant commercial tests have been validated for faecal material at this time. Although not all test kits are classified as in vitro diagnostic medical devices (IVDs) which need TGA approval, all tests used to screen donors and the FMT material must be shown to be validated for their intended use.

## **Donor screening tests**

Under the IVD framework all donor screening tests for infectious diseases are regulated as Class 4 IVDs (or Class 4 in-house IVDs) regardless of whether they are mandatory under TGO 88 or non-mandatory donor screening tests. This includes first line donor screening tests as well as any supplementary or confirmatory donor screening tests.

Commercially supplied test kits for the infectious agents indicated in TGO 88 are already included in the ARTG as Class 4 IVDs. However, tests to screen donors for any additional viruses, bacteria or parasites relevant to FMT, would need to be registered with the TGA as Class 4 medical devices (or Class 4 in-house IVDs). If tests for new agents were identified, transition periods would be introduced to allow testing facilities time to meet the IVD requirements.

## Tests used in the manufacture of FMT material

Tests performed during the course of manufacture of FMT material would not necessarily be considered IVDs and would not need to comply with the regulatory requirements for IVDs (unless also intended for a therapeutic purpose). However, laboratories are required to demonstrate that any tests used in the manufacturing process for FMT products are fit for purpose. This would include providing validation/verification of any 'off-label' use of the test, and similarly providing validation for a *de novo* test used to test the FMT material during the manufacturing process.

Testing performed on the FMT material to satisfy product specifications before release of the product is considered a 'release for supply' test. Release for supply tests are required to be validated, fit for purpose and performed at a TGA licensed laboratory. More information about ['release for supply'](#) is available on the TGA website.

## Transition period

For facilities that are processing FMT material that must be TGA licenced, an appropriate transition period will be introduced to allow time for facilities to comply.

# Regulatory options for FMT materials

## Objectives of any new regulatory scheme

The objectives of any government action to develop a new regulatory scheme in relation to FMT materials are:

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

The following section and Table 3 describe four regulatory options for FMT materials. They have been developed on the premise that all FMT materials would be defined as biologicals. However, there is no clear agreement whether a product would meet the definition of a biological if any human cells were removed through the processing. Therefore, in this section we also seek your input on whether all material isolated from human faeces should be defined as biologicals, or whether there are alternatives that could be considered.

## Define all material isolated from human faeces as biologicals

At present, which FMT materials would meet the definition of a biological is not entirely clear.

A product which **contains** human cells, that is colonocytes (or, if relevant, any other kinds of human cells or tissues), would clearly meet the definition of a biological for the purposes of the Act; it would be excluded from being considered a medicine.

There is a real issue, however, as to whether FMT processed from human faecal matter may be said to be, for the purposes of the definition of biological in the Act, **derived** from human cells or tissues.

In addition, if human cells are removed during processing, whether the product is appropriately considered a biological or a medicine may also not be entirely clear. On the one hand, the product may be considered as a biological because, notwithstanding the removal of the cells, there is a reasonable argument that, as provided for by section 32A(1)(a) of the Act, it is **derived** from human cells or human tissues. On the other hand, because of the removal of the human cells it is not unreasonable to conclude that it may no longer be capable of being described to contain or be derived from human cells or tissues and because it is represented to achieve or likely to achieve its principal intended action by chemical, immunological or metabolic means in the body of a human it may appropriately be considered a medicine.

This lack of clarity is likely to result in confusion within the sector. In addition, the position may become more complex as the sector continues to innovate so that a product which might have once clearly been a biological evolves to such an extent as to more clearly be a medicine – an example may be a highly purified sterile product that does not contain cells of any type.

Different GMP standards would also apply to those regulated as either a medicine or a biological although the processing and FMT material are very similar.

For the following reasons, the proposal from TGA is that the position is clarified in law through a legislative instrument so that all FMT material which is originally sourced from human donors is considered to be a biological:

- Standards applicable to screening of donors would apply to all FMT material
- The Australian Code of GMP that covers biologicals is suitable for products where donor screening is required and material may be banked
- The biologicals framework is designed to recognise the need to approve a manufacturing process rather than a 'product'. For example, all autologous cell therapies are unique, but the manufacturing process and testing is designed to ensure sufficient product consistency.

To achieve this, the definition of what is a biological would be changed in law to incorporate FMT material that is derived from human faecal matter.

Under all biologicals options (1-4 below) the regulatory framework for IVDs will apply to all donor screening (Class 4 IVD or Class 4 in-house IVD) tests.

### **Your views are sought**

Do you support the proposal to consider all FMT material that has been originally sourced from human donors as biologicals, irrespective of the presence or absence of human cells in the final product, or of the regulatory approach? Or do you support an alternative proposal – for example considering all FMT material as medicines, or a hybrid situation where only some products (for example sterile, cell free and/or highly purified products) are regulated as medicines?

Please provide reasons to support your view.

## Option 1: Regulation under the Biologicals Framework

Regulation of FMT products under the Biologicals Framework based on the level of manipulation during processing.

- FMT material collected from appropriately screened donors that has been processed using **minimal manipulation** (mixing with saline, filtration, adding glycerol, freezing or cryopreservation) would likely be subject to TGA regulation as **Class 2 biologicals**.
- FMT material collected from appropriately screened donors, that has been processed using methods that **may have altered any of the biological characteristics or physiological functions of FMT** (for example *in vitro* culture, isolation or purification of specific microbes, lyophilisation that impacts on the viability of crucial microbes, pooling material from several donors) would be subject to TGA regulation as **Class 3 biologicals**.

### For both class 2 and 3 biologicals

- Manufacturers or sponsors must submit a dossier to the TGA for inclusion of their product in the Register.
- The only legal pathways to supply unapproved biologicals are as part of a [clinical trial](#), or by using the [Special Access Scheme](#) (SAS) or [Authorised Prescriber](#) (AP) scheme. These pathways are subject to conditions.
- FMT materials must satisfy relevant Therapeutic Goods Orders including TGO 88 and any product-specific standard developed in consultation with the sector.
- All manufacturing facilities and testing facilities will require GMP licencing.

### Features

The framework is already in place and is aligned with the regulatory approach to other cells and tissues derived from a human source.

International guidelines for donor selection and screening of FMT material have been published, which can be relatively easily adapted and adopted for Australia. Most clinics already have established procedures consistent with these guidelines, although some variation exists.

The level of regulation can be applied incrementally to minimally versus more than minimally manipulated FMT products.

The approach will introduce consistency to the applicable standards and manufacturing principles across the sector, resulting in patients having increased confidence in the FMT materials supplied.

Reporting of adverse events by product sponsors to the TGA will be mandatory.

Advertising restrictions would apply.

### Considerations

The costs of establishing a GMP licensed facility may be high and the level of evidence required demonstrating compliance with GMP standards would be defined in FMT specific GMP guidance to be developed.

Each clinic supplying FMT material would need to have their product included in the Register to continue to supply after any transition. The costs of developing and submitting a dossier for evaluation would have to be considered, including for small and medium size enterprises.

The current level of evidence to support an application for inclusion in the Register as a Class 2 biological is only likely to be sufficient for rCDI. It is likely that supply for any other indication at this stage could only occur through clinical trials.

The testing requirements would require testing facilities to also have a GMP licence and all kits used for donor screening would need to be registered as Class 4 IVDs.

In the absence of easily accessed services, some patients may resort to self-treatment, as has been reported.

## Likely transition

It is likely that up to three years would be required to allow implementation of this option. This would allow time for a standard for FMT material to be developed and implemented, as well as for providers to seek GMP licensing for processing and testing facilities and to submit an application for inclusion in the Register. In addition, consideration would need to be given to allow test kits to be registered as Class 4 IVDs, where the standard has mandated new infectious disease agents.

### Your views are sought

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

Do you consider that this option appropriately addresses requirements for public health and safety? Please provide the reasons why it does or does not.

## Option 2: Regulate under the Biologicals Framework, introducing a Class 1 category for some FMT materials

Regulate FMT materials under the Biologicals Framework based on the level of manipulation during processing, but identify facilities that have sufficient clinical governance and oversight, and the FMT materials manufactured in those facilities to be sufficiently low risk, to allow that FMT material to be defined as a Class 1 biological.

- It is proposed that the following conditions would need to be met for FMT material to be regulated as a **Class 1 biological**:
  - Minimally manipulated FMT material (mixing with saline, filtration, addition of glycerol, freezing/cryopreservation) from appropriately screened donors, which is
  - Manufactured in a hospital and used in that hospital under the [supervision](#) of a registered medical practitioner who has clinical care of the recipient patient
- The sponsor of the product would have to show that the FMT material complies with a TGA standard or standards, but the facility would not need to be TGA licenced. The appropriate clinical indications for use of the FMT material would be determined by the hospital.
- Minimally manipulated FMT material from appropriately screened donors, manufactured in a facility that is not a registered hospital, regardless of the relationship between the manufacturer, the treating medical practitioner and the recipient patient, would be

regulated as Class 2 biologicals. The facility must be TGA licenced. The FMT material must comply with any applicable standards.

- All other FMT material from appropriately screened donors, manufactured in any facility using methods that may have altered any of the biological characteristics or physiological functions of FMT (for example *in vitro* culture, isolation or purification of specific microbes, lyophilisation that impacts on the viability of crucial microbes, pooling material from several donors) would be regulated as Class 3 biologicals. The facility must be TGA licenced.
- The only legal pathways to supply unapproved biologicals are as part of a [clinical trial](#), or by using the [Special Access Scheme](#) (SAS) or [Authorised Prescriber](#) (AP) scheme. These pathways are subject to conditions.
- FMT materials must satisfy relevant Therapeutic Goods Orders including TGO 88 and any product-specific standard developed in consultation with the sector.
- Some tests, materials and equipment used in the process of manufacturing Class 1 biologicals may be therapeutic goods to which the therapeutic goods legislation applies, and thus be subject to regulation by the TGA.

## Features

The basic framework is already in place and is aligned with the regulatory approach to other cells and tissues derived from human source, with just a minor change to define certain materials as Class 1 biologicals.

International guidelines for donor selection and screening of FMT material have been published, which can be relatively easily adapted and adopted for Australia. Most clinics already have established procedures consistent with these guidelines, although some variation exists.

The level of regulation can be applied incrementally, minimally versus more than minimally manipulated FMT products with an additional low level of regulation by TGA for specific FMT materials.

The approach will introduce consistency to the applicable standards and manufacturing principles across the sector, resulting in patients having increased confidence in the FMT materials supplied.

Use of minimally manipulated FMT materials for acknowledged indications of rCDI and CDAD can continue in accredited hospitals.

Reporting of adverse events to TGA will be mandatory.

Advertising restrictions will apply.

## Considerations

There is a risk that implementation of applicable standards, manufacturing principles and intended use will be inconsistent among the hospitals, and patients may be uncertain of the safety and efficacy of the FMT materials supplied.

The costs of establishing a GMP licensed facility need to be considered and more information on the level of evidence required demonstrating compliance with GMP standards would need to be developed and communicated.

Each clinic supplying FMT material would need to have their product included in the Register to continue to supply after any transition. The costs of developing and submitting a dossier for evaluation would need to be considered.

The current level of evidence to support an application for inclusion in the Register as a Class 2 biological is only likely to be sufficient for rCDI. It is likely that supply for any other indication at this stage could only occur through clinical trials.

The testing requirements would require testing facilities to have a GMP licence and all kits used for donor screening would need to be registered as Class 4 IVDs.

Some services may no longer continue, and some patients may resort to self-treatment.

## Likely transition

The change to include certain FMT material as Class 1 biologicals could occur relatively quickly, but no standard for FMT material is in place at this time to determine whether a specific product satisfies the low-risk requirement. Therefore, it is likely that two years would be required to allow implementation of this option. This would allow time for a standard for FMT material to be developed and implemented, as well as for providers to seek GMP licensing for processing and testing facilities and to submit an application for inclusion in the Register. In addition, consideration would need to be given to allow test kits to be registered as Class 4 IVDs, where the standard has mandated new infectious disease agents.

### Your views are sought

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

Do you consider that this option appropriately addresses requirements for public health and safety? Please provide the reasons why it does or does not.

## Option 3: Regulate under the Biologicals Framework, introducing exclusions and/or exemptions for some FMT materials

A more graduated regulatory oversight approach could be adopted, with the level of regulation varying based on the external governance and clinical oversight of FMT processing and administration, and on the manufacturing processes that are applied.

Under this approach FMT materials may potentially be:

- **Excluded from TGA regulation – Minimally manipulated FMT material** (mixing with saline, filtration, addition of glycerol, freezing/cryopreservation) from appropriately screened donors, manufactured and **used in a hospital** under the [supervision](#) of a registered medical practitioner, who has clinical care of the patient.

As part of the implementation of this Option, the health service organisation providing FMT would need to ensure that it met the requirements of all relevant regulatory and standards organisations such as:

- State and territory administration of public hospitals and regulation of private hospitals

- The Australian Commission on Safety and Quality in Health Care
- The Australian Health Practitioner Regulation Agency (AHPRA)
- **Exempt from some aspects of TGA regulation – Minimally manipulated FMT material** from appropriately screened donors, manufactured and used **outside of an accredited hospital but under the [supervision](#) of a registered medical practitioner** who has clinical care of the patient, **for the treatment of rCDI.**

These products would be regulated under the *Therapeutic Goods Act 1989*, but exempt from certain requirements, including manufacturing in TGA licenced facilities.

**Providers of exempt FMT materials** must still comply with TGA regulatory requirements including:

- all standards applicable to FMT materials
- the need to report adverse events to the TGA
- not advertising directly to consumers
- being responsible for conducting a recall, if necessary

The use of allogeneic FMT products carries a higher risk to recipients than do autologous products (for which this exemption is currently restricted for human cells and tissues). Development and application of an appropriate standard to mitigate risk with allogeneic FMT products is proposed.

- **Regulated as biologicals – FMT materials that do not satisfy the above exclusion or exemption criteria** would be regulated by the TGA under the Biologicals Regulatory Framework according to their risk based classification, as in the above options.
- Some tests, materials and equipment used in the process of manufacturing excluded or exempted FMT materials may be therapeutic goods to which the therapeutic goods legislation applies, and thus be subject to regulation by the TGA.

## Features

The basic framework is already in place and is aligned with the regulatory approach to other cells and tissues derived from a human source, with minor changes to specific legislative instruments to allow exclusions and exemptions of specific products.

International guidelines for donor selection and screening of FMT material have been published, which can be relatively easily adapted and adopted for Australia. Most clinics already have established procedures consistent with these guidelines, although some variation exists.

The level of regulation can be applied incrementally, minimally versus more than minimally manipulated FMT products with an additional low level of regulation by TGA for specific FMT materials.

The approach would introduce consistency to the applicable standards and manufacturing principles across the sector, resulting in patients having increased confidence in the FMT materials supplied.

Use of minimally manipulated FMT materials for rCDI can continue in accredited hospitals and in private clinical practice with limited change to regulatory requirements.

Reporting of adverse events to TGA by sponsors would be mandatory.

Advertising restrictions would apply.

Only a limited number of facilities manufacturing and providing FMT materials would need to satisfy GMP licensing requirements.

## Considerations

For those facilities that manufacture FMT material that is not excluded or exempted, the costs of a GMP licensed facility would need to be covered and more information on the level of evidence required demonstrating compliance with GMP standards would need to be developed and communicated.

A wider range of options for regulatory approaches based on the facilities in which the procedure is being performed may result in less consistency of applicable standards, manufacturing principles and intended use in exempt and excluded facilities, resulting in patient uncertainty regarding the safety and quality of FMT materials supplied at different sites.

The use of allogeneic products as therapeutic goods carries a higher risk to recipients than do autologous products, so the risks around the option to exclude and/or exempt some FMT material need to be carefully considered.

The intended use of FMT material in private clinics is restricted to rCDI. These providers would be required to establish GMP licensed facilities for any other use of FMT material.

## Likely transition

The change to include certain FMT material as excluded or exempt biologicals requires changes to the Regulations, and no standard for FMT material is in place. Therefore, it is likely that up to three years would be required to allow implementation of this option. This would allow time for a standard for FMT material to be developed and implemented, as well as for providers to seek GMP licensing for processing and testing facilities and to submit an application for inclusion in the Register. In addition, consideration would need to be given to allow test kits to be registered as Class 4 IVDs, where the standard has mandated new infectious disease agents.

### Your views are sought

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

Do you consider that this option appropriately addresses requirements for public health and safety? Please provide the reasons why it does or does not.

Should the exempt and/or excluded status be restricted to use of materials only for the treatment of rCDI? Please consider:

- i. The consequences of restricting either excluded therapeutic good status, or exemptions from some TGA requirements, to FMT materials used for a specific condition (rCDI) or conditions.
- ii. The consequences of applying either excluded therapeutic good status, or exemptions from some TGA requirements, to all FMT materials regardless of the condition/s being treated.
- iii. Mechanisms for ensuring that FMT materials are being used to treat a condition only when sufficient evidence of safety and efficacy has been established for that condition, in the absence of TGA requirements for a dossier to include a biological in the Register.

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## Option 4: Self-regulation options

Under this option, all FMT materials, regardless of the level of manipulation during processing would be subject to applicable standards and manufacturing requirements, but these would be set and accreditation or compliance determined by nominated bodies. Oversight by these other bodies will need to ensure that the possible risks that may arise as a result of manufacturing and using FMT materials are appropriately mitigated. Under this option:

- Manufacturing and product standards would be developed and supervised by an overarching expert body or bodies.
- Facilities processing FMT materials would be required to be accredited to the industry standards.
- Compliance with these standards must be managed through an independent accreditation or licensing process.

There are a number of regulatory models that could apply, depending on the level of external governance and accreditation. For example, FMT materials may be excluded from regulation by TGA or only exempt from certain requirements. This would be akin to the models of regulation in place for ART and exempt HPC, as outlined in the section on current regulatory approached to other cells and tissues.

- The regulatory Framework for IVDs will still apply to all donor screening tests (Class 4 IVDs or Class 4 in-house IVDs)
- Some tests, materials and equipment used in the process of manufacturing may be therapeutic goods to which the therapeutic goods legislation applies, and thus be subject to regulation by the TGA.

### Features

A self-governance model may allow more flexibility in the standards and manufacturing controls as the field evolves.

### Considerations

It will take significant time for the sector to develop, approve and implement an alternative oversight approach for FMT materials. It may not be appropriate for the sector to remain unregulated until a self-regulation model could be established.

Sector may not be sufficiently mature to apply effective self-regulatory mechanisms, particularly with respect to manufacturing quality.

The overall time and costs of establishing effective accreditation and licensing may be equivalent or greater to regulation by the TGA

No currently available laboratory accreditation system is suitable for assessing manufacturing aspects.

Substantially manipulated FMT materials (i.e. equivalent to Class 4 biologicals) may not be subject to sufficient assessment of quality, safety and efficacy.

If an alternative accreditation process is established, the government would still need to separately consider the effectiveness of the process and its standards in protecting public health and safety, and whether genuine compliance and enforcement powers exist.

There is currently no funding arrangement that would assist the sector in establishing an alternative process.

**Your views are sought**

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

Do you consider that this option appropriately addresses requirements for public health and safety? Please provide the reasons why it does or does not.

Is there an alternative (non-TGA) body or bodies for developing and setting both product and facility standards for FMT material? If not, is there a body or bodies that could assume this role, and how long would this take to occur? Please describe the body and detail how that body is appropriately placed for developing and setting standards.

Is there an alternative (non-TGA) body or bodies capable of performing independent accreditation of manufacturing to product and facility standards? If not, is there a body or bodies that could assume this role, and how long would this take to occur? Please describe the body and detail how that body is appropriately placed for accreditation and licensing activities.

**Table 3: Summary of regulatory options for consultation**

Characteristics of each Option	Option 1	Option 2	Option 3	Option 4
<b>Regulatory approach</b>	Biologicals framework	Biologicals framework, with Class 1	Graduated regulation including limited exemptions and exclusions	Exclusion of all FMT material from regulation by TGA
FMT products excluded from regulation by TGA	None	None	Minimally manipulated Accredited hospital Single supervising doctor	All
FMT products exempted from GMP requirements and inclusion on the register	None	As Class 1 Minimally manipulated Accredited hospital Single supervising doctor	Minimally manipulated, but manufactured outside an accredited hospital for a single supervising doctor, for the treatment of rCDI	Not applicable
FMT products regulated under Biological framework	All products as Class 2 – 4 biologicals	As Class 2 - 4 Manufacture outside accredited hospital Beyond minimal manipulation in accredited hospital Commercial supply Supply outside manufacturing facility	Class 2 - 4 Beyond minimal manipulation at any site Treatment of conditions other than rCDI outside of an accredited hospital Commercial supply Supply from an external manufacturing facility	None

Characteristics of each Option	Option 1	Option 2	Option 3	Option 4
Subject to TGA standards	All	All	All but excluded FMT materials	None
Subject to standards other than TGA	Site and state specific standards may also be applied	Site and state specific standards may also be applied	Site and state specific standards continue to apply to excluded FMT	Specific standards to be developed, approved and implemented by an appropriate governing body
Manufacturing facility subject to Australian cGMP	All	Class 2 - 4	Class 2 - 4	None
Manufacturing facility subject to alternative licensing	No	Potentially Class 1	Potentially exempted and excluded goods	Yes. This would require alternative accreditation to be developed under site, state, or other jurisdictional structure
Donor Screening Tests Subject to IVD framework	Yes	Yes	Yes	Yes
Materials and equipment may be subject to TGA regulation	Yes	Yes	Yes	Yes
Advertising restrictions	Yes	Yes	Yes	As determined by appointed governing body

## Conclusion

There is strong support across many areas of medical practice for the use of FMT in the treatment of rCDI and CDAD, and emerging (but not yet conclusive) evidence for its use in the treatment of inflammatory bowel diseases. In clinical trials, FMT is also being investigated for treatment of a variety of other diseases, including metabolic syndrome, non-alcoholic fatty liver disease, and some psychiatric conditions, based on the recognition of the gut-brain vagus nerve link<sup>27</sup>.

Whatever regulatory process is selected, the Australian population must be reassured that the supply and use of FMT occurs under rigorous standards and for evidence-based conditions.

Irrespective of the preferred regulatory option chosen, the following actions will be required to ensure public health and safety with respect to the use of FMT materials for CDAD and other unrelated conditions.

1. Drafting guidance or a new standard with donor and product screening requirements for FMT material;
2. Applying an appropriate risk classification to FMT material to determine what regulatory standards should apply;
3. Consideration of what is the appropriate standard to apply to manufacturing;
4. If GMP is required, implementing a transition period that will allow manufacturers and suppliers to satisfy GMP licensing requirements.

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<sup>27</sup>Montiel-Castro A, González-Cervantes R, Bravo-Ruiseco G, et al. The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality. *Front Integr Neurosci* 2013; 7: 70).

## Appendix 1

### International approaches to the regulation of FMT materials

In May 2013, **the US FDA** announced that it would regulate FMT as a drug<sup>28</sup>, but indicated that the use of FMT to treat CDI in patients not responding to conventional therapies would be subject to 'enforcement discretion'.

FDA will exercise this discretion providing that (1) the patient gives informed consent, (2) the FMT product is obtained from a donor known to either the patient or from a licenced health care facility and (3) the faecal matter is screened and testing performed under the direction of the licensed health care provider.

The draft guidance was updated in March 2016 with a recommendation that use of FMT product obtained from a stool bank would require an application for an investigational new drug (IND), as the FDA expressed some additional safety concerns with banked materials<sup>29</sup>.

**Canada** has followed the US. Health Canada published a guidance document regarding FMT used in the treatment of CDI in 2015<sup>30</sup>. Health Canada regulates FMT matter as a biologic drug under the Food and Drugs Act.

To date, no individual or company has been granted a marketing authorisation for FMT and therefore the only way to access FMT is by authorised clinical trial or under the "Health Canada Interim Policy on FMT used to treat patients with *Clostridium difficile*". This policy clearly states that CDI not responsive to other therapies would be the only condition for which FMT merits consideration outside the direct regulatory provisions of an investigational clinical trial. FMT providers must comply with conditions outlined in the guidance document. The guidance document proposes that donor screening 'may include and may not be limited to' an extensive list of microorganisms, and included recommendations for a lookback program and the application of inspector powers for Health Canada Inspectors.

Regulation of FMT in the **Member States of the European Union** falls within the remit of the national competent authorities and not the European Medicines Agency. In 2014, the European Commission provided a legal opinion that the cells found in FMT materials are not the active component and therefore are not "intended for human applications" within the meaning of the EU Tissue and Cell Directive (2004/23/EC).

As a result, some Member States regulate FMT materials as medicinal products while others may apply Tissues and Cells legislation. There is no specific guidance available for FMT products, although manufacturers are expected to use processes compliant with the relevant Code of Good Manufacturing Practice (cGMP) and validated assays for purity, potency and identity for release testing.

**Swissmedic** considers FMT materials as medicinal products, which are subject to authorisation. All manufacture, including as part of a clinical trial, requires a Swissmedic manufacturing licence. An exception from the requirement for authorisation is applied only to FMT that is prepared by a limited number of manufacturing steps (lyophilisation and encapsulation) and is

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28Food and Drug Administration (July 2013)

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM488223.pdf>

29<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceinformation/guidances/vaccines/ucm488223.pdf>

30 Fecal microbiota therapy used in the treatment of *Clostridium difficile* infection not responsive to conventional therapies. Guidance Document. Health Products and Food Branch, Health Canada. 27/3/2015

for autologous use. From 2019, the process of manufacturing these autologous “drugs that cannot be standardised” will be subject to an approval process.

In 2015, **the UK** Human Tissue Authority (HTA) published an opinion that FMT does not fall within the scope of the UK *Human Tissue (Quality and Safety for Human Application) Regulations 2007*, but also recommended that establishments conducting FMT should act in accordance with the HTA “Guide to Quality and Safety Assurance for Tissues and Cells” for patient treatment.

The **UK Medicine and Healthcare Products Regulatory Agency (MHRA)** classifies FMT as a medicinal product<sup>31</sup>. All medicinal products should be produced according to the principles of GMP under MHRA licence. The MHRA position paper emphasised the importance of informed consent, performing donor serology and ensuring the traceability of samples from donor to recipient, which is in line with the HTA guidance.

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<sup>31</sup> Medicines & Healthcare Products Regulatory Agency (June 2015), [http://www.bsg.org.uk/images/stories/docs/clinical/guidance/fmt\\_mhra\\_position\\_june2015.pdf](http://www.bsg.org.uk/images/stories/docs/clinical/guidance/fmt_mhra_position_june2015.pdf)

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## Appendix 2

### TGA Stakeholder Forum on the regulation of FMT

#### The Australian regulatory environment

TGA is the Australian regulator responsible for safeguarding and enhancing the health of the Australian community through effective and timely regulation of therapeutic goods. TGA does not regulate clinical practice, which is the role of National Health Practitioner Boards and the Australian Health Practitioner Regulation Agency (AHPRA). TGA also does not regulate hospitals or clinics where FMT may occur.

[The Australian Health Practitioner Regulation Agency \(AHPRA\)](#) is responsible for the National Registration and Accreditation Scheme for registered health practitioners including medical practitioners and a wide range of other health care practitioners. The National Health Practitioner Boards represent each of these health professions, and are responsible for registering their practitioners, ensuring that they work within their registered scope of practice. Clinical practice of FMT falls within the scope of gastroenterologists and infectious disease specialists.

Hospitals and health services are generally regulated by State or Territory Governments, and the registration and licensing requirements may vary between the states and territories, and between public and private hospitals. Whilst the [Australian Commission on Safety and Quality in Health Care](#) (the Commission) is not a regulator, it does work with the State and Territory governments and the private sector to drive the implementation of nationally coordinated improvements in safety and quality systems in health care. The Commission has published several National Safety and Quality Health Service Standards to guide these improvements, however there are none that specifically apply to the use and management of biologicals, including FMT materials, within hospitals or other health services.

#### *Key discussion points:*

- Forum participants emphasised that it was important to identify and clearly elucidate the risks that arise from all steps of “production”, “manufacture” and dosing of FMT. Some participants considered that none of the existing regulatory frameworks were appropriate for FMT, while others considered that the class 1 biologicals classification could be used for these products, with specific requirements developed for this risk category.
- Participants also emphasised that it was important that potential regulatory requirements be “future proofed” given that it is possible that within five years transplant of raw faeces may be superseded and that purified pharmaceutical products could be commercially available and used as the norm for therapy. Regulatory requirements need to be sufficiently flexible or graded to address the full continuum from raw faecal material to registered pharmaceutical products.

#### Donor selection and donor and product screening

While some jurisdictions have published guidance documents with regard to the use of FMT, there are no agreed international standards for donor selection or screening of FMT material. A number of specialist groups have also recently published consensus opinions either highlighting principles that should be applied or providing specific recommendations for selecting donors or

for screening products <sup>32,33,34</sup>. The Gastroenterology Society of Australia has established an Australian Consensus Working Group for the use of Faecal Microbial Transplantation in clinical practice which anticipates developing guidelines for many aspects of FMT over the course of 2019. At the TGA stakeholder forum invited speakers described the donor selection and testing criteria at their facilities and within the international context.

*Key discussion points:*

- Indirect transmission of disease by FMT materials is possible and therefore a risk-based approach to regulation is appropriate.
- The international position on donor screening and testing of blood and stool samples is relatively mature and in reasonably close consensus.
- Screening is very strict and only a low percentage of potential donors are deemed to be suitable.
- Given that the various screening requirements for FMT applied by stakeholders in most cases exclude donors that would be able to donate blood (such as obese individuals or those with moderate or serious mental illness) the rationale for such exclusion would need to be explained in implementing any new framework.
- Self-regulation options should be considered.

In view of the information gained at the forum, developing and implementing guidance or a new standard specific to screening requirements relevant to donation of FMT material and testing on the stool, is likely to mitigate some safety risks associated with infectious disease transmission. Most aspects of [Therapeutic Goods Order \(TGO\) No. 88: Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products](#), particularly with regard to donor screening requirements, may be applicable to FMT donors.

## Manufacturing

Invited speakers at the TGA forum described the manufacturing processes adopted at their facilities. They also emphasised that although the bacterial composition of the material was highly variable, the functionality of the biome was consistent and predictable. It was noted that while FMT material is not a sterile implanted product per se, the risk from introduced agents is minimal. This was proposed as a reason for requiring only limited controls on the manufacturing environment.

*Key discussion points:*

- Participants expressed concerns with manufacture under the current codes of GMP, such as the cost and need for additional infrastructure. The TGA clarified that the GMP Codes generally are not prescriptive, and that different requirements apply under the PIC/S Code<sup>35</sup> for medicines, say to topical products, complementary medicines, and prescription medicines and under the Australian Code<sup>36</sup> for biologicals implanted through surgical or

<sup>32</sup> Mullish BH, Quraishi MN, Segal JP et al (2018) The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* epub ahead of print 28/8/2018 doi:10.1136/gutjnl-2018-316818

<sup>33</sup> Kraft, C.S. (2017). [Laboratory Testing of Donors and Stool Samples for Faecal Microbiota Transplantation for Recurrent Clostridium difficile Infection, Journal of Clinical Microbiology.](#)

<sup>34</sup> Cammarota, G. et al. (2017). European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*.

<sup>35</sup> PE009-13, the PIC/S guide to GMP for medicinal products

<sup>36</sup> The Australian Code of Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products, April 2013

other procedures. Therefore if a GMP approach is utilised, a risk based approach to the GMP requirements could be applied following public consultation. Some participants were keen that TGA explore alternatives to standard biologicals GMP.

- Some attendees supported implementation of centralised manufacturing facilities, modelled on the Australian Red Cross Blood Service.
- Some attendees proposed that National Association of Testing Authorities, Australia (NATA) accreditation of the laboratory responsible for screening tests may be sufficient. It was noted that several of the tests used for screening stool samples will necessarily utilise in house (laboratory-developed or adapted) in vitro diagnostic kits, given that few relevant commercial tests have been validated for faecal material.
- All manufacturing facilities would need to ensure that processing and handling of FMT material would be isolated from other products.
- The requirement for manufacture under cGMP could impede a number of ongoing clinical trials, particularly if it was interpreted that all clinical trials require manufacture of products under full cGMP.
- Several attendees advocated a framework for regulation of FMT material modelled on the 'organ' self-regulatory framework. This approach would require legal interpretation whether faecal material could be described as an organ for regulatory purposes.
- There was an important level of agreement that manufacture should occur at a licensed or accredited facility, with some level of quality control, especially around traceability and record keeping. Greatest concerns were raised regarding standardisation of FMT materials.
- The group also considered proposals to establish a national FMT registry and to ensure that provision of FMT was restricted to health practitioners with an appropriate scope of practice. These proposals were recognised as potentially beyond TGA jurisdiction.

## **Concluding remarks**

- There is a broad spectrum of processed FMT materials. A range of models for the oversight of manufacturing facilities should be considered, and these should be developed in anticipation of pharmaceutical-type products in the future.
- Further consideration must be given to the level of accreditation or licensing required for testing laboratories in line with the current TGA framework for in vitro diagnostic tests, to address issues such as test method validation.
- The participants recognised the need for Australian standards for donor selection criteria and considered the possibilities of adopting appropriate international standards, and of developing specific standards relevant to Australia and New Zealand, to supplement the existing TGA standard, TGO 88.
- A robust regulatory framework/s that recognises the rapid growth and evolution of this sector and minimally affects innovation should be applied.
- Any new regulatory requirements should be introduced with a reasonable transition period.

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## Appendix 3

### Examples of other regulatory approaches for human cells, tissues and organs

#### Reproductive tissue for assisted reproductive therapy

Reproductive tissue for use in assisted reproductive therapy (ART) is excluded from regulation by the TGA. This exclusion reflects the decision of the Australian Health Ministers' Conference in July 2008 that reproductive tissues should not be regulated by the TGA because at that time the use of these tissues was considered to be coherently and consistently managed.

ART clinics are required to be licensed to [industry practice standards](#), with monitoring of compliance managed through the [Reproductive Technology Accreditation Committee](#) (RTAC) accreditation process. The RTAC is part of the Fertility Society of Australia (FSA), and is charged with the responsibility of setting standards for the performance of ART through an audited [Code of Practice](#) and the granting of licences to practice ART within Australia. They are also required to meet the National Health and Medical Research Council (NHMRC) [Ethical Guidelines on the use of Assisted Reproductive Technology in Clinical Practice and Research](#) (2017). The sector uses testing laboratories that have been accredited by [National Association of Testing Authorities](#) (NATA). Some test kits, equipment and materials used for ART are also therapeutic goods to which therapeutic goods legislation also applies.

#### Fresh viable human organs

The use of organs for direct donor-to-recipient transplantation is excluded from regulation by the TGA. Governance of organ donation and transplantation is the responsibility of the states and territories, with each having separate legislation addressing organ donation and transplantation.

At the national level, the Australian Government funds the [Australian Organ and Tissue Donation and Transplantation Authority](#) (OTA) that works with states and territories, clinicians, and the community sector to improve organ and tissue donation and transplantation rates and processes in Australia. The OTA leads and funds the implementation of a national program in collaboration with state and territory governments and the DonateLife Network (DLN). The DLN comprises State and Territory Medical Directors, DonateLife Agencies and hospital based medical and nurse donation specialists who work to ensure that all donation opportunities are identified and explored to maximise the number of donor organs available for transplantation in Australia.

Additionally, the OTA works with professional associations to develop and implement clinical guidelines for organ donation and transplantation. The Transplantation Society of Australia and New Zealand (TSANZ) publish [Clinical Guidelines for Organ Transplantation from Deceased Donors](#). This document, most recently updated in December 2018, includes standards for donor suitability, including donor screening and testing requirements, and also transplant recipient eligibility. The Australia and New Zealand Intensive Care Society (ANZICS) publish the [ANZICS Statement on Death and Organ Donation](#). This document provides guidance to intensive care specialists and other clinicians on the determination of death in the context of deceased organ donation, physiological supportive treatment of potential donors and other processes related to deceased donation.

Further, the NHMRC publishes [guidelines](#) for health professionals [on the ethical principles](#) of both deceased and living organ donation and provides guidance on how these principles can be put into practice.

Some equipment and materials used for the testing of organ donors and recipients are regarded as therapeutic goods to which therapeutic goods legislation applies, and are subject to regulation by TGA. Infectious disease screening tests are regulated as Class 4 *in vitro* diagnostic (IVD) medical devices by the TGA under the IVD regulatory framework.

## Haematopoietic progenitor cells (HPC)

The TGA has adopted a graduated regulatory oversight approach for HPC products. The level of regulation by TGA may vary due to the level of external governance and clinical oversight, or depending on the manufacturing processes or intended use. HPC products may be:

- **Excluded from regulation** by TGA if fresh viable human haematopoietic progenitor cells (HPCs) are for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution.

These cells may be obtained from the patient themselves (autologous transplantation), or collected from the bone marrow or peripheral blood of another person (allogeneic transplantation).

Facilities performing these collections and transplants must meet specific standards to facilitate access to MBS reimbursement for testing and processing services. The [National Pathology Accreditation Advisory Council](#) (NPAAC) document "[Requirements for Procedures Related to the Collection, Processing, Storage and Issue of Human Haematopoietic Progenitor Cells](#)" outlines the minimum standards to be met by HPC manufacturers whose operations come under the pathology quality management system. Assessment is carried out against these NPAAC requirements as a component of NATA/Royal College of Pathologists of Australasia (RCPA) accreditation for medical testing facilities under ISO15189 – Medical laboratories – Particular requirements for quality and competence.

- **Exempt from some aspects of TGA regulation** if the HPC is for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution, and is subject to storage that is outside the governance of the requesting physician e.g. storage of cord blood units for future patient matching. These products are exempt from being included in the Register, but must still comply with TGA GMP requirements and demonstrate compliance with specific standards, subject to TGO 88 and [TGO 94 Standard for Haematopoietic Progenitor Cells derived from Cord Blood 2017](#).
- **Regulated as biologicals:** HPC products not meeting the above exclusion or exemption criteria are regulated by the TGA under the Biologicals Regulatory Framework according to their risk based classification.

## Autologous human cell and tissue products

Similar to the regulation of HPCs, TGA has recently introduced a [graduated regulatory oversight approach](#) for autologous HCT products. The level of TGA oversight varies based on the level of external governance and clinical oversight, or depending on the manufacturing processes or intended use of the autologous HCT product. Under this approach autologous HCTs may be:

- [Excluded from TGA regulation](#) if HCTs are manufactured and used in a hospital under the [supervision](#) of a registered medical or dental practitioner, who has clinical care of the patient. Regulation by other bodies is considered sufficient to mitigate possible risks that

may arise as a result of manufacturing and using autologous HCT products that are excluded from TGA regulation.

Generally, if any part of the manufacturing process occurs outside the direct supervision of the responsible medical practitioner (for example, manufacture of a vector used to transduce cells), the HCT is no longer excluded from regulation by TGA.

- **Exempt from some aspects of TGA regulation:** autologous HCT products are regulated under the *Therapeutic Goods Act 1989* but are exempt from certain requirements, including manufacturing under GMP, where the material is:
  - [minimally manipulated](#), and
  - [for homologous use only](#), and
  - manufactured outside a hospital, only if
  - collected, manufactured and used by persons under the supervision of the medical or dental practitioner who has clinical care of the patient, for a
  - single indication in a single clinical procedure

If any part of the manufacturing process occurs outside the direct supervision of the responsible medical practitioner (for example, manufacture of a vector used to transduce cells), the HCT is no longer exempt from TGA regulatory requirements. Providers of exempt autologous HCT products must still comply with some TGA regulatory requirements, such as:

- all standards applicable to [blood components](#) or [biologicals](#)
  - the need to [report adverse events](#) to the TGA
  - [no advertising to consumers](#)
  - being [responsible for conducting a recall](#), if necessary
- **Regulated as biologicals:** Autologous HCT products that do not satisfy the above exclusion or exemption criteria are regulated by the TGA under the Biologicals Regulatory Framework according to their risk based classification.

Costs of manufacture and supply may be covered by patients, public hospitals and insurers, if products are excluded from TGA regulation. Providers or manufacturers are responsible for the costs of satisfying any regulatory requirements, and may pass these on to patients or insurers if there is no public funding model, as for organ transplantation or ART.

## Version history

<b>Version</b>	<b>Description of change</b>	<b>Author</b>	<b>Effective date</b>
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