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Purpose and scope

The purpose of this briefing paper is to:

- Engage with individuals, health care practitioners, patients and patient representatives, industry and State and Territory Governments to confirm the understanding of the Therapeutic Goods Administration (TGA) of the sector engaged in the collection, manufacture and supply of material used in faecal microbiota transplantation (FMT)
- Clarify the operation of current regulatory requirements for FMT materials under the Therapeutic Goods Act 1989 (the Act) and the Therapeutic Goods Regulations 1990 (the TG Regulations),
- Seek feedback on three potential options for achieving greater clarity on the operation of the regulatory framework; either development of product specific guidance or one or both of two possible regulatory measures for the collection, manufacture and supply of FMT material.

Faecal microbiota transplantation material refers to 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 rectal enema, sigmoidoscopy, colonoscopy, nasogastric or nasoduodenal tube. The materials also include human faecal matter that has been filtered, or otherwise prepared to allow oral ingestion. The focus of this paper is on allogeneic use of FMT material, where the donor and the recipient are different. The regulatory principles that arise from this discussion may also be used in the future to inform the development and implementation of regulation of allogeneic microbiota transfer material collected from other human tissues (for example, nasal or vaginal secretions).

Background

A Health Policy Advisory Committee on Technology (HealthPACT) analysis of FMT in 2014 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 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 vancomycin or placebo, although the authors also recommended further studies are required to establish the best approaches to preparation and administration of FMT materials. FMT has been acknowledged as an appropriate treatment for recurrent CDI by a number of specialist groups including the Australasian Society for Infectious Diseases, the European Society of Clinical Microbiology and the American College of Gastroenterology, and by the National Institute for Health and Care Excellence (NICE).

FMT material meets the definition of a biological in subsection 32A(1) of the Act. This follows because, as we understand it, FMT materials manufactured in Australia at present always contain human cells, that is colonocytes (or, if relevant, any other kinds of human cells or tissues). It will also meet that definition, regardless of what the processed material contains, if FMT material would be used in the treatment or prevention of a disease, ailment, defect or injury affecting humans. In these circumstances, most FMT material currently used in Australia falls to be regulated as a biological under the Act. FMT material that is processed by methods that include separation from, and the discard of, human cells may or may not be a biological for the purposes of the Act. In this case, whether FMT is a biological will partly turn on whether there is evidence that the material responsible for the therapeutic use could be said to have been derived from human cells or tissues.

FMT material poses similar risks as other goods currently regulated as biologicals, including the risk of infectious disease transmission. Risks are of particular concern if the material is banked, where a single batch can be administered to multiple patients, or pooled, where FMT material from more than one donor may be mixed prior to use.

Internationally, the approaches to regulation of FMT vary. Most policies 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.

In May 2013, the US FDA announced that it would regulate FMT as a drug, 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.

5 https://www.nice.org.uk/guidance/ipg485/chapter/1-Recommendations
6 There are potential situations where FMT material might not be considered a biological, for example if the FMT material is centrifuged and the pellet discarded removing all human cells. We are not aware of these manufacturing methods anywhere in Australia, but we are aware of this method being used internationally in clinical trials.
Canada has followed the US. Health Canada published a guidance document regarding FMT used in the treatment of CDI in 2015\(^9\). Health Canada regulates FMT matter as a biologic drug under the *Food and Drugs Act*. 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. 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 GMP-compliant processes 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 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 Medicine and Healthcare Products Regulatory Agency (MHRA) classifies FMT as a medicinal product\(^10\). 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.

**The 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.

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TGA regulations

Supply compliance

Biologics must be included in the Australian Register of Therapeutic Goods (ARTG) prior to supply, unless they are exempt or supplied as unapproved goods. The only legal pathways to supply unapproved biologics 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.

At the time of writing, there are no FMT products included in the ARTG. Since 2013, ten clinical trials using FMT materials have been notified to the TGA using the clinical trial notification (CTN) scheme, and/or have been registered in the Australian New Zealand Clinical Trials Registry.

Manufacturing compliance

With the exception of supply for a first in human clinical trial, the requirement for manufacture of biologics (including FMT material) under a Good Manufacturing Practice (GMP) licence applies. Information on how to apply for a GMP licence is available on the TGA website.

Advertising compliance

Biologics 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 clear policy choice made on introduction in 2009 of the regulatory framework for biologics. The explanatory memorandum to the Therapeutic Goods Amendment (2009 Measures No. 3) Bill 2009 states:

This is necessary as it is inappropriate for biologics 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

The prohibition casts its net widely: a 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 of 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.
Further guidance on the advertising restriction is provided on the [TGA website](https://www.tga.gov.au).

### Other regulation in Australia

The Australian Health Practitioner Regulation Agency (AHPRA) is responsible for the National Registration and Accreditation Scheme for registered health practitioners including medical practitioners, dental practitioners, nurses and midwives, chiropractors, optometrists, osteopaths, pharmacists, physiotherapists, podiatrists, psychologists, Aboriginal and Torres Strait Islander health practitioners, Chinese medicine practitioners, medical radiation practitioners, occupational therapists and shortly, paramedics. 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.

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. The Australian Commission on Safety and Quality in Health Care (the Commission) works with the State and Territory governments 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.

### Providing clear regulatory guidance and measures

Stakeholders are asked for their views on the following possible guidance or regulatory measures intended to assist with clarity on the application of the regulatory framework. Your views will assist the TGA to ensure that the guidance or relevant measures are appropriate, having regard to the ultimate objective of ensuring the safety of patients as they access the therapy. Those potential measures may include:

1. Guidance on donor and product screening requirements for FMT material;
2. A new standard for donor and product screening requirements for FMT material;
3. Where GMP is required, allow manufacturers and suppliers a limited transition period to implement GMP licensing requirements.

More detail on these options follows; the TGA will continue its work with you on the terms of the chosen guidance or regulatory measure.

### Screening requirements for FMT material

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. Individual hospitals may apply their own screening criteria, and more recently a number of specialist groups have published consensus opinions either highlighting principles that should
be applied or providing specific recommendations for selecting donors or for screening products \textsuperscript{11,12,13}.

Developing and implementing guidance or a new standard that carves out screening requirements relevant to donation of FMT material would 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. However, the current TGO 88 requirements around donor and product screening do not appear to be sufficient to capture all of the risks of FMT identified in the published guidances.

### Discussion point

What critical elements of screening, directed at minimising the risk that these therapeutic goods will harm a recipient, should be included in an Australian guidance or standard for FMT materials? Please consider how these critical elements may be applied to:

- Donor selection – what risk criteria should be assessed for donor suitability
- Donor testing – what testing should be considered for donor suitability
- Stool testing – what testing should be applied to ensure pathogenic agents are minimised? Is identification of microorganisms required?
- Manufacturing considerations – what controls are required to prevent contamination?
- What is required to identify and quantitate the active component (potency) to ensure product consistency?

### Discussion point

We recognise that several groups consider FMT an effective treatment for recurrent CDI. Use of FMT in other conditions is still considered investigational. Given the evolving nature of the therapeutic FMT sector, should the TGA publish information regarding screening requirements for FMT as guidance, or is there sufficient certainty in the sector to support publication of a Standard for FMT materials?

### A transition period

GMP licensing is generally required for sites that manufacture therapeutic goods, including all biologicals. Unless FMT is classified as a Class 1 biological or an exemption is introduced to allow


manufacture of FMT material without a GMP licence, there is currently no mechanism to allow the supply of FMT material outside a ‘first in human’ clinical trial.

Consideration is being given to a transition period that will allow manufacturers and suppliers of FMT to meet the quality management system and facility requirements to satisfy GMP licensing requirements. During the transition period, we recommend that potential applicants for a manufacturing licence contact the Manufacturing Quality Branch at TGA at GMP@tga.gov.au for assistance with the application process.

**Discussion point**

What is a reasonable transition period that will allow current manufacturers to satisfy GMP licensing requirements?

**Discussion point**

Some manufacturers may consider GMP requirements for manufacture and supply of FMT materials overly restrictive. What alternative accreditation, directed at minimising the risk that these goods will harm a recipient, may be applicable to Australian facilities involved in FMT manufacture and banking?
## Version history

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<tr>
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