Options for the Regulation of Faecal Microbiota Transplantation materials Consultation Paper

Stakeholder Submission

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Introduction

Faecal microbiota transplantation (FMT) has extensive literature supporting its use as a first line therapy in patients with recurrent or severe *Clostridium difficile* infection.[1, 2] It is widely regarded as the most effective treatment for this condition.

There is also increasing evidence for the effective use of FMT in the treatment of Inflammatory Bowel Disease (IBD). Five randomised controlled trials have demonstrated effective induction of remission with FMT in patients with drug-resistant ulcerative colitis.[3-7] Evidence is emerging of the specific microbial changes associated with clinical benefit.[6, 8 9, 10]

Despite the advent of a range of traditional immunosuppressive and biologic drug therapies for ulcerative colitis many patients have severe or ongoing active disease. A substantial number require surgical treatment, with elective colectomy associated with a mortality rate of at least 1.5%.[11, 12]

There are clear unmet therapeutic needs for patients with IBD. FMT is currently the most promising therapy to address this therapeutic need; patients require access to it. When considering the established evidence of therapeutic benefit and safety of FMT use in *Clostridium difficile* and ulcerative colitis, we believe the TGA's regulatory position should avoid limiting patient access to this effective therapy, while ensuring the quality and safety of preparation.

We recognise that FMT involves the transfer of human cells from donor to recipient, and therefore requires stringent donor screening for infections and medical co-morbidities. However, regulation of FMT as a Class 2 biologic or higher under the current biologic regulatory framework would impose Good Manufacturing Practice (GMP) requirements, and would be excessively onerous. We wish to reiterate that FMT is a consortium of bacterial, viral and fungal organisms, and would introduce a contamination risk to current GMP approved facilities.

In contrast to the biologic and pharmaceutical agents regulated under GMP, there is no logical requirement for FMT to be produced in a sterile environment as faecal matter is not sterile. Further, in screened donors the risk of transmissible infection is very small.

Upon review of the TGA 'Options for the regulation of Faecal Microbiota Transplantation materials' document we do agree that clarification is needed to establish the actual mechanism of action of FMT, including the effect of aerobic vs anaerobic processing methods, transmission of antibiotic resistance genes and most effective methods of administration. However, it has been demonstrated in retrospective studies even in high risk patients who are immunosuppressed there are few related serious adverse events or related adverse events secondary to FMT.[13, 14]

There are further risks of imposing GMP approved FMT processing facilities, for the preparation of FMT:

1) GMP approval for FMT facilities would place significant financial burden on public hospitals, to create, staff and maintain this facility
2) The financial and regulatory requirements of hospitals needing to meet GMP would supress the research and development of new indications for FMT
3) In the setting of community popularity and ease of performing FMT at home, over regulation and the absence of public FMT services would lead to increased unregulated FMT use, in unsafe conditions related in part to unscreened donors.

Option 1: Regulation under the Biologicals Framework

This option would regulate FMT products as Class 2 or 3 biologicals. These classes require all manufacturing facilities and testing facilities to obtain GMP licencing. Although there is scope to develop FMT-specific GMP guidance documents, this does not replace the need for FMT to be registered on the ARTG. This would require the submission of a dossier to the TGA by any site wishing to perform FMT, so that these "products" may be included on the register of therapeutic goods. This raises a number of issues:

1. The dossier structure required for registration of a class 2 biologic under the current biologics framework does not, and cannot apply to minimally modified FMT for the following reasons:
    a. Although (as stated in the consultation paper) the biologics framework is designed to approve a manufacturing process to ensure "consistency", the product composition of a minimally modified FMT varies depending on donor, potentially requiring dossier submission for each dose/donor as the composition cannot be generalised.
    b. Analysis of the final product would require extensive molecular characterisation, a process that using current technology would take months and the input of a specialist bioinformatician.
    c. The manufacturing and compliance requirements for the dossier would be above what a public hospital would be able to implement

2. According to the technical requirements for the TGA dossier for Class 2 biologics, the starting material is required to be "validated" to "demonstrate starting material quality". This is currently beyond the capability of public hospitals as a) what defines a quality FMT donor is as yet undefined in the literature, and b) the technical aspects of validation (high dimensional microbiome sequencing and analysis) is outside of the scope of normal clinical practice and achievable timelines.

3. The current structure of the dossier requires GMP manufacturing. Additionally the dossier requires validation of microbiological methods, microbial control/stability and endotoxin limits – none of which are easily applied to a product that is by definition, an unsterile microbial consortium with high variability.

Additionally, no currently approved GMP manufacturing facilities within the public hospital system (which would be either pharmacy based drug preparation or transplant laboratories) are suitable or usable for the manufacture of FMT due to the absolute requirement of these facilities to be sterile for drug production. This would require construction, staffing, registration and maintenance of specific facilities for the preparation of FMT. This is out of reach of publicly funded hospital facilities without additional streams of funding.

We recommend:

This option does not provide an appropriate resolution for FMT regulation. This option severely impedes public health and safety by limiting the ability of public hospital's to provide timely and effective FMT treatment for refractory *Clostridium difficile*. GMP registration and licencing is costly and financially out of reach for public hospitals and their testing facilities. We do not recommend regulating all FMT products under Class 2 or 3 biologicals.

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

This option would regulate some FMT products as Class 1 biologicals, a class which has not previously been implemented in Australian Biologicals Framework. Minimally manipulated FMT material or FMT material manufactured in a facility that is not a registered hospital will be regulated as a class 2 biological. Furthermore, it is stated that there would likely be a requirement for hospitals to again register Class 1 biologics (FMT) as per option 1 above. This is subject to the same issues as outlined above.

We recommend:

Current FMT practice in hospital is overseen by medical professionals using an evidence based approach, follows hospital practice and protocol and does not require TGA regulation in order to be safely monitored. TGA regulation requiring implementation of a new Biologics Class 1 would be considered an unnecessary administrative burden and will not add additional safety when FMT could be performed in a registered hospital as described in Option 3. We do not recommend regulating FMT under Option 2.

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

This option would provide a more graduated regulatory oversight approach. The level of regulation would vary based on external governance and clinical oversight of FMT processing and administration.

This option provides flexibility within the Australian healthcare system to provide timely access to expanded indications for FMT. While refractory *Clostridium difficile* is the current major indication, there is sufficient evidence now that FMT is an effective treatment for drug-resistant ulcerative colitis. By allowing FMT to be excluded from regulation if delivered in a registered hospital or approved specialist clinic, this will expand timely access for new indications where the data on the use of FMT is still expanding. This is important to ensure that an onerous regulatory framework does not prevent access to the best possible evidence-based care for patients, provided in a timely manner and at a reasonable cost. FMT provided within a hospital or approved specialist clinic will be subject to the same oversight as any other procedure or medication, with the oversight of policies, procedure and clinical standards.

We agree that outside of a hospital environment or approved specialist clinic, access to FMT should be limited to refractory *Clostridium difficile* only. There is a lack of evidence for many of the indications for which FMT is suggested by private clinics such as weight loss, irritable bowel syndrome, chronic fatigue syndrome, multiple sclerosis and autism. Delivery of extended indication FMT within the Australian hospital system ensures that normal evidence based standards of practice can be maintained while still adapting to changing evidence.

This option also would allow for a sliding scale of manipulation, with minimally manipulated FMT (mixing with saline, filtration, addition of glycerol, freezing/cryopreservation) being exempt from GMP and registration, while more highly manipulated products would still be subject to appropriate regulatory oversight.

We recommend:

Due to the varying nature of FMT therapies and modes of delivery, this option provides more flexibility in regulating incrementally based on degree of manipulation of FMT products.

This regulatory design would allow FMT to be delivered under the care and supervision of a capable clinician in a registered hospital or approved specialist clinic. Registered hospitals or approved specialist clinics will still be able to deliver safe and effective FMT treatment to patients with refractory *Clostridium difficile* (and potentially other indications) with minimal disruption – maintaining public health and safety. Although some providers are exempt from TGA regulation – there is still a reporting requirement for adverse events – positively impacting public health and safety.

This option would not have an insurmountable financial impact of practitioners delivering FMT currently in a registered hospital or clinic environment with the absence of GMP requirements for minimally modified FMT delivered in a hospital environment.

<u>We recommend a more graduated regulatory oversight approach to FMT delivery as outlined in Option 3.</u>

<u>Option 4: Self-regulation options</u>

With this option, all FMT materials, regardless of the level of manipulation during processing would be subject to standards set by an overarching expert body or bodies.

We recommend:

Although a self-governance model may allow more flexibility in standards and manufacturing we believe that:

1. **It will take significant time for the development and approval of this oversight approach.**
2. **The application of FMT currently is diverse, consisting of both public and private providers. FMT as it stands is widely self-regulated; this lacks sufficient assessment of quality, safety and efficacy. We suggest TGA involvement – such as detailed in Option 3.**
3. **We do not believe that this option would appropriately address requirements for public health and safety. Self-regulation may lead to non-evidence based practice and uncontrolled FMT production.**
4. **The financial impact to practitioners and providers of FMT of this option is currently unknown due to the lack of an existing governing body and laboratory accreditation system.**

We do not recommend a self-regulation option for FMT.

<u>Other comments on the regulation of Faecal Microbiota Transplantation</u>

In all potential regulatory options, we support the implementation of restrictions on advertising of FMT treatment for any indication, in line with all current regulations on direct-to-consumer advertising of medical and pharmaceutical products.

Currently, there is no TGA stance on FMT, including for use in clinical trials. When considering the established evidence of therapeutic benefit and safety of FMT use in *Clostridium difficile* and ulcerative colitis, we believe the TGA's regulatory position should avoid limiting patient access to this effective therapy, while ensuring the quality and safety of preparation.

The requirements for donor screening as laid out in the current legislation *(Therapeutic Goods Order 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)* are necessary and fair. Amendments to the legislation will be required in regards to section 12 (Requirements in relation to microbial control) to include testing for parasites, antibiotic resistant bacteria (VRE, ESBL), food borne pathogens and *Clostridium difficile*.[15]

However, there is no discussion within the TGA documentation on the administrating of multi-donor/pooled FMT or banking of stool, even if prepared using highly screened donors. Any regulatory framework considered should explicitly deal with these scenarios. Furthermore, consideration should be given as to how a national registry could be developed to facilitate tracking donor and recipient health long term.

We do not recommend registration of medical practitioners applying FMT.

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