Faecal Microbiota Transplantation

EU-IN Horizon Scanning Report

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1. Introduction

While there is no universally accepted definition of Faecal Microbiota Transplantation (FMT)[1], in general FMT refers to the transfer of biological material incorporating faecal microorganisms from screened, healthy human donors to the gastrointestinal tracts (GITs) of patients. In some cases, there may also be autologous use. FMT is currently being investigated for the treatment of a number of different medical conditions, with one of the main uses being in the treatment of patients with recurrent *Clostridioides difficile* (*C. difficile*) infections (CDIs).

In these patients, FMT aims to achieve modification of the composition of the microbiota in the large bowel, which, in turn, re-establishes normal bacterial competition mechanisms. The desired result is a reduction in numbers of toxigenic *C. difficile,* and so, reducing the risk of further recurrences.

Based on short term follow-up, FMT has generally shown a good safety profile provided that appropriate steps are taken to ensure quality and safety.[2,3] However, further data from long-term monitoring of patients for adverse events are needed to fully evaluate the effects that donor's intestinal microbes may have on FMT recipients and the potential for transmission of diseases.[3]

Therefore, indications with sufficient evidence of a benefit greater than a potential risk should be clearly distinguished from those where the evidence is insufficient.

1.1. Use of FMT for C. difficile infection

C. difficile is one of the main nosocomial pathogens. An episode of *C. difficile* infection (CDI) is defined as clinical findings compatible with CDI and microbiological evidence of *C. difficile* free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhoea; or a clinical picture compatible with CDI and a positive nucleic acid amplification test preferably with a low cycle threshold value, or positive toxigenic *C difficile* culture; or pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic *C. difficile*.[4] The excellent sensitivity of molecular tests for the detection of *C. difficile* toxins has brought, as a counterpart, the risk of overtreatment of merely colonised patients.[5] In addition, a significant proportion of patients adequately treated for CDI persist weeks later with positive tests for toxigenic *C. difficile*. For all these reasons, it is essential to have an adequate clinical assessment of the patients and a reasonable exclusion that the symptoms are not due to other causes.

Crude mortality in patients with CDI ranges from <5% to >40% and the direct attributable mortality of CDI has been estimated to be from 4 % to 7%.[6] Although most patients respond well to treatment, up to 8% suffer from severe-complicated (or fulminant) CDI[7], defined by the presence of one of the following factors attributed to CDI: hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of the disease[4]. Their management may require a subtotal colectomy to avoid death.

Moreover, about 20% of those affected have recurrences of the disease, and in some of them, multiple recurrent episodes are difficult to control[8]. Recurrence of CDI is associated with high rates of hospital readmission, increased costs, and higher mortality.[6,9] Most recurrences occur in the 8 weeks after the diagnosis, therefore, this period is usually used to unify the definition of recurrence, for which diagnosis is essential, not only to have a microbiological confirmation of *C. difficile* in faeces but also for the return of symptoms after a previous resolution with treatment. The same criteria are required for the diagnosis of recurrence as for the diagnosis of the first episode.[4]

Finally, there is a situation called refractory CDI, which has been recently defined in European clinical guidance[4] as CDI not responding to recommended CDI antibiotic treatment, i.e. no response after 3-5

days of therapy. Since *C. difficile* resistance to vancomycin or fidaxomicin is negligible, the persistence of diarrhoea cannot be attributed to purely microbiological failure. In fact, often in these patients the determination of the toxin in the faeces is negative. On the other hand, these cases (about 10-20 %) are catalogued as "failures" in clinical trials, but that does not mean that they do not eventually cure the infection after longer periods of observation. This situation, probably, encompasses different conditions such as persistence of diarrhoea due to dysbiosis, presence of other undiagnosed causes of diarrhoea, very early recurrences, or simple variability in response. European and North American clinical guidelines have recently been updated to incorporate recommendations related to the treatment of refractory CDI[4,8]

With these considerations, it is worth reviewing the evidence and indications of FMT in the different situations mentioned above.

1.1.1. Recurrent CDI

Recurrent CDI is considered the main use for FMT. While European treatment guidelines[4] now list fidaxomycin as the preferred agent for the treatment of initial CDI and the first recurrence of CDI when available and feasible, FMT or bezlotoxumab in addition to standard of care antibiotics are preferred for treatment of a second or further recurrence of CDI. US clinical guidelines[8, 10] also recommend the administration of FMT for second or further CDI recurrence, after standard-of-care treatment in previous episodes. The use of FMT in this scenario requires an appropriate multidisciplinary risk assessment and the clinical guidelines also call for the availability of FMT products with standardised preparation and screening.

Nevertheless, some authors have made pertinent criticisms of the available studies suggesting that there are relevant deficits in asserting the efficacy and safety of the procedure.[11]

1.1.2. Refractory CDI

While acknowledging a very low level of current evidence considering the high level of mortality associated with surgical therapy for CDI and that patients may be too ill to be candidates for surgery, European clinical guidance[4] indicate that FMT may be a rescue therapy for patients with severe complicated (or fulminant) CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible. However, it would be expected that surgical consultation is always sought, standardised and screened FMT products are readily available, the treating or consulting physicians have experience with FMT and that a careful risk assessment of the benefits and risks are made on a case-by-case basis.

US clinical guidance[8] also indicates that FMT could be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly when patients are deemed poor surgical candidates.

1.2. Use of FMT for other indications

FMT has also been investigated for the management of other conditions where disturbance of the bowel microbiota may be contributory (e.g. inflammatory bowel disease[12], hepatic encephalopathy[13], and metabolic syndrome[14]). Emerging research proposes links between the microbiome and chronic diseases. The microbiome is also being investigated in a number of conditions such as cancer, including response to immunotherapy[15] obesity[16], COPD[17] and neuropsychiatric conditions[18]. For the purpose of this document, the main focus is on the role of microbiota in bowel disorders.

1.3. Preparation of FMT

FMT products obtained from healthy donors fall into the following categories:

1.3.1. Extemporaneous preparation

Collected material that is administered fresh or after freezing and thawing with minimal processing (such as filtration or centrifugation) to patients via the upper or lower GIT (e.g. by colonoscopy or naso-duodenal tube). A mixture of undigested faecal matter and microorganisms is generally prepared on-site in healthcare facilities. Each administration may be derived from:

i. A single donor and typically from a single donation

ii. Pooled donations from the same and/or from several donors.

Whilst the donors are usually screened for infectious agents in a similar method applied to blood donors, the screening of their faecal donations for potentially pathogenic bacterial species and the methods used for this are often variable. Pooling material from multiple donors will affect traceability, may increase the risk of inadvertent transmission of infection and requires specific consideration from a regulatory perspective.

1.3.2. Manufactured

This refers to collected material that is further processed before administration to remove undigested faecal matter, leaving behind the remaining microbiological content. Such FMT products are usually prepared in dedicated facilities within research institutions or by pharmaceutical companies. In such cases, the screening of donors may be more standardised and consistent.

Further processing of these FMT products may range from:

i. Frozen or lyophilised donations presented for use in aliquots (e.g. vials or bags).

ii. Encapsulated lyophilised bacteria, with or without pre-selection of organism sub-groups by means of pre-treatment with antibacterial agents and/or specialised culture conditions. These are intended for oral administration and may be formulated within gastro-resistant capsules to prevent bactericidal activity in the stomach and upper intestine.

iii. Spores that have been harvested from faecal donations, thereby restricting the range of organisms included to species that readily sporulate. These are usually formulated within gastro-resistant capsules.

FMT products may undergo multiple manufacturing steps, like lyophilization, differential centrifugation, low energy milling, etc. It should be investigated whether manufacturing steps could change the bacterial composition or reduce viability of the bacteria. In addition, different routes of administration (enema and oral route) could lead to a different bacterial outgrowth in the gastrointestinal tract. Comparative clinical trials should show that both treatments are as efficacious and safe in a clinical setting.

Current research aims to determine which bacterial species is/are most important for competition with *C. difficile* such that product development can rely on controlled culture methodologies with consistent bacterial content rather than on variable faecal donations. Frozen FMT products from an authorised manufacturer may be preferred to extemporaneous preparations due to the diversity of bacterial mixtures from faecal donations.[19]

2. Current status and key emerging trends

2.1. Examples of known research/development in this area and any observed trends related to such work

Global research and development of products based on FMT have advanced in recent years with a number of academic researchers and pharmaceutical companies actively developing such products.

Clinical trials are ongoing in Europe and other regions and some sites involved in the production of FMT-based products have obtained Manufacturing and Importation Authorisations enabling them to produce Investigational Medicinal Products (IMPs) for clinical trials. *C. difficile* infections are the most common target in current clinical trials, with Phase 3 trials in this indication currently ongoing. As part of such studies, different routes of administration and pharmaceutical forms are being investigated (including rectal administration via enema and oral administration via capsules). In addition, efforts are being made to identify constituents that may be responsible for the activity of FMT and to optimise the quality and stability of the products. Further investigation into the mechanism of action of FMT including immunomodulatory effects is needed to inform evaluation of its efficacy.

Other potential clinical uses of FMT are also being investigated including the treatment of ulcerative colitis[20] and to address graft-versus-host disease, a common, potentially life-threatening complication of allogenic hematopoietic stem cell transplantation[21]. In general, these are not as advanced as studies in *C. difficile.*

Future developments for FMT products involve *in vivo/vitro* screening of drug candidates constructed from libraries and making use of high throughput robotics, bioinformatics, and omics technologies[22]. This will include longitudinal omics methods to better understand how the microbiome changes over time and in response to treatment[23].

2.2. Anticipated timeframe for regulatory submissions

There are a number of ongoing clinical trials for FMT and some Member States (MSs) have experience in reviewing IMPs for FMT products. FMT products have been authorised as an IMP in at least fifteen clinical trials to date on EudraCT[24]. There have been national and European scientific advice procedures, as well as requests for participation in PRIME and orphan designation but at present, it is not clear that any Marketing Authorisation Application (MAA) has been submitted in the EU.

Based on the current interest in FMT-based products and ongoing clinical trials, there is a high likelihood of additional regulatory submissions in this area with the potential for MA applications within the next 5-10 years.

3. Challenges and opportunities from a regulatory perspective

At present, there is no agreed EU position in relation to how FMT should be regulated or any published regulatory guidance specifically related to FMT. Therefore, at present there is likely to be significant variability in relation to the data and approaches taken to the regulation of FMT-based products in clinical trials and the oversight of the use of FMT in clinical practice. This has implications for the protection of the safety of patients receiving FMT and could also limit patient access to FMT. There is a need to identify and agree clear EU standards for the regulation of FMT to ensure that appropriate safeguards are in place to facilitate the use of FMT when clinically appropriate, while at the same time

preventing the inappropriate use of FMT, e.g. 'do-it-yourself' FMT or the use of FMT where there is no evidence of a clinical benefit and inadequate assurance of quality and safety.

In addition, the variability associated with FMT itself, the lack of certainty in relation to the constituents responsible for any clinical effect and the nature of the product all give rise to specific challenges relating to: donor selection and screening, traceability, the characterisation of the product, quality control and standards during production and of the final product, the control strategy, batch-to-batch consistency and safety monitoring post-administration.[22,25] A number of these challenges are discussed in the following sections.

3.1. Classification

Although there have been previous discussions at EU level, as of yet there is no agreed EU approach to the classification of FMT-based products even though they are intended to have medicinal effects related to the treatment / prevention of disease.

The classification of FMT-based products was discussed at a meeting of the competent authorities for tissues and cells in 2014.[26] During the discussion the European Commission (EC) noted that the focus of the use of human faeces for FMT is not the cells contained therein and that it did not fall within the scope of the EU Tissues & Cells legislation. However, it was noted that there was a clear mandate in the Treaty on the Functioning of the EU for future regulation of such substances in terms of their quality and safety. The EC also confirmed that as human faeces for FMT was not considered as falling within the scope of a particular quality and safety legislative framework at Union level, MSs were free to decide on an appropriate regulatory framework at national level either by creating a specific framework or by applying one of the existing legislative frameworks, including the tissues and cells quality and safety requirements. More recently, as part of an ongoing process which is expected to lead to the revision of the EU legislation on blood, tissues and cells, consideration is being given as to whether FMT should be included in relation to the scope of that legislation and if so whether this would cover only specific aspects (e.g. donation and testing) or all aspects from donation to distribution.

FMT-based products are excluded from the scope of the new Medical Devices Regulation 2017/745 as Article 6 excludes viable transplants, tissues or cells of human origin as well as viable biological material or viable organisms including living micro-organisms from the scope of the Regulation.

The lack of an agreed EU framework for the regulation of FMT has led to a situation where individual MSs have made national decisions on the approach to regulation of FMT products, resulting in different approaches and a lack of consistency in relation to the regulatory standards and associated scientific guidelines that should apply to such products.

The following table summarises the approaches taken in selected countries including some non-EU countries:

Table 1. The Regulation of FMT in selected countries: [22, 27, 28]

Country	Medicinal Product or Equivalent	Tissue and Cells (or equivalent)	Therapeutic Intervention	Classification undetermined / Case-by-Case
Australia		✔*		
Austria				✔**
Belgium		✔***		
Canada	✔			
Croatia	✔			
Czechia	✔			
Denmark				✔****
Finland			✔	
France	✔			
Germany	✔			
Ireland	✔			
Italy		✔***		
Netherlands				✔
Portugal	✔			
Spain	✔			
Sweden	✔			
UK	✔			
USA	✔			

***** In Australia most FMT products are regulated as biologicals but where a strain(s) of microorganisms, known to be present in stool, is characterized and grown from established isolates with standardised consistency, such a product may be regulated as a medicine rather than a biological.[27]

****** In Austria 'extemporaneously prepared' FMT (see section 1.3.1) could be classified as a therapeutic intervention whereas 'manufactured' FMT (see section 1.3.2) could be classified as a medicinal product or equivalent

******* Even though Directive 2004/23 itself does not apply to FMT, in Belgium and Italy FMT is covered by the national Tissues and Cells legislation.

******** In Denmark, the classification of FMT based products as a tissue or a medicinal product is considered on a case-by-case basis taking into account the degree of manipulation and whether or not an indication is claimed. FMT can be regulated as tissue for the treatment of dysbiosis (under hospital conditions) with FMT material only manufactured to enable administration e.g. filtration, formulation in bag for administration via tube or in capsules for oral administration. When an indication is claimed, the FMT is classified as a medicinal product. Any selected subpopulation of the faecal material propagated as treatment is a medicinal product.

While a number of countries consider FMT to be a medicinal product there is no agreed approach in this regard, which creates considerable difficulties in defining and implementing consistent regulatory and scientific standards and guidance to ensure the quality, safety and efficacy of FMT-based products.

3.2. Approaches and considerations to ensure the quality and safety of FMT products

Quality control is required for FMT products to provide reliable and safe treatments for patients. FMT products pose challenges concerning the ability to characterise and reproducibly manufacture products due to the variable nature of the material and the uncertainty in relation to which constituents are responsible for any clinical activity.[22] It is essential that appropriate standards to ensure quality and safety are applied throughout the process, from the selection and screening of donors, the processing and storage of the faecal material, and during administration. Patient safety may be compromised if appropriate standards are not followed. In addition, there is a need to ensure appropriate product traceability, registration of donors and patients, monitoring and follow-up concerning suspected adverse reactions.

The EDQM's Guide to Quality and Safety of Tissues and Cells for Human Use[29] includes a dedicated chapter on faecal microbiota and provides a generic quality and safety framework for healthcare professionals treating patients with these substances.

3.3. Donor selection, screening and traceability

An individual's intestinal microbiota is influenced by a number of factors including host genetic and environmental factors and other individual factors (such as diet). A donor, who is healthy at the time of donation, could have a predisposition to systemic diseases that might be predicted by the characteristics of their microbiota. Assessing a patient's microbiota is challenging as there is no current guidance on the precise location to assess as a marker, for example, the mucosal surface, lumen, faeces, or a faecal swab would have different organisms present and also varying relative abundance.[22]

Appropriate donor selection, screening and traceability are essential in ensuring the quality and safety of FMT products. Selection criteria may include the donor's demographics, Body Mass Index (BMI), and geographical origin as well as other factors. While donors are usually screened for infectious agents along the lines applied to blood donors, there is a need to implement a consistent and standardised approach to donor selection and screening.[3,25] The timing of donor and stool screening should be standardised and the list of pathogens of concern should be kept under continuous review and updated over time. Standardised questionnaires should be in place to identify and exclude potentially high-risk donors. Donor testing kits also need to be readily available and standardised to minimise the risk of shortage or inadequacies.[25]

In addition, the faecal donations need to be screened for potentially pathogenic bacterial species using appropriate, standardised methodology. Consideration also needs to be given to the regulatory oversight of stool banks where faecal donations from different donors may be combined and processed for use in unrelated patients.[25] Furthermore, sampling faeces can be challenging depending on a patients' frequency of bowel movements. The standardisation of sampling techniques needs to be laid out to be able to contrast and compare studies easily.[22]

Experience in the US has also shown the importance of robust screening and traceability relating to FMT, with FDA safety alerts highlighting the potential risk of serious adverse events.[30, 31, 32]

Therefore, specific regulatory guidance relating to donor selection and screening and traceability should be developed to facilitate a consistent approach to these important aspects.

3.4. Processing, Quality Control and Storage

FMT poses considerable challenges to conventional quality control approaches. The active constituent of FMT products is unknown, leading to poor product characterisation.[25] In addition, there is a lack of batch-to-batch consistency due to the natural origin of faecal material. Defining a control strategy for such products is challenging as standard approaches to control potency cannot be applied where the active pharmaceutical ingredient (API) is not established.

The purity and potency of organisms in FMT products are unknown, leading to a lack of uniformity and standardisation and therefore, licensure of such products is very challenging. Several species of microorganisms present in stool require extensive screening for pathogenic materials before patient administration.[22] The sensitivity of stool tests and the ability to detect pathogens present in low numbers is currently limited.[22]

For these and other reasons, it is difficult to define detailed specifications to be applied to each batch to ensure its quality, and the quality (and ultimately) the safety of FMT products (particularly those that are subject to limited processing) is heavily dependent on screening of donors and testing of samples for pathogenic bacteria. Nevertheless, there is a need to agree on a consistent approach to the quality control of FMT products.

There are also difficulties in applying some of the standard GMP requirements to FMT products linked to the nature of the product, the limited amount of processing in some cases and the sites at which these operations may be carried out (e.g. hospitals or clinics). However, it should be possible to define and agree on appropriate GMP standards to be applied when preparing FMT products including sample collection, processing and storage. For example, where FMT is extemporaneously prepared in a hospital / clinical setting the need for and scope of any processing steps should be clearly defined and should inform the implementation of appropriate GMP standards[1]. The possibility to define a set of appropriate GMP standards is reflected in the fact that some countries have issued GMP certificates to facilities involved in the production of FMT products.[33]

Steps that could be taken to minimise the risk of contamination during the manufacturing of FMT products include the minimisation of reusable equipment.[22] The British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) recommend frozen FMT products from an authorised manufacturer are preferable to fresh extemporaneous preparations[34], in recognition of the ability to apply additional manufacturing controls at dedicated manufacturing facilities.

The impact of processing and storage on the viability of FMT products needs to be considered. The conditions under which stools are processed may significantly affect viable microbial content.[35] Liquid FMT formulations can be frozen and remain efficacious, however, spores can still exist, and powdered products face issues around moisture and aerosolisation.[22] Refrigeration of such products may be necessary as they cannot withstand room temperature which could be both an inconvenience to patients and another challenge to developers in the transport and storage of FMT products.[22] Cold chain logistics and storage as well as temperature monitoring along the supply chain may be relevant to temperature-sensitive FMT products.

3.5. Administration of FMT

FMT administration can be performed through the lower gastrointestinal tract by means of a retention enema or colonoscopy, or through the upper gastrointestinal tract by means of a gastroscope or tube (nasogastric, nasoduodenal or nasojejunal tube) or through capsules that can contain the frozen or freeze-dried material.

The preferred method of administration may vary depending on the clinical situation of the patient. The route of administration will determine the volume of the FMT that can be administered to the patient.

When administering FMT the use of other medications such as antibiotics or other medicines which could interfere with the treatment needs to be carefully considered as does the fasting / fed state of the patient. Patients may need to be prepared for receipt of FMT (e.g. intestinal washing may need to be considered). If administering via a tube, it may be necessary to check by X-ray to ensure that the tube is correctly inserted. FMT administration to the lower gastrointestinal tract by colonoscopy should be used with caution and may not be safe or feasible in all patients (e.g. elderly patients).

3.6. Clinical Challenges

As noted in section 1, there is still a need for well-conducted randomised controlled trials (RCTs). Many clinical trials on FMT products are ongoing as previously referred to in section 2, however there is considerable variability in the nature of the clinical trials and their design, for example, variable inclusion/exclusion criteria; manufacturing methods; single or pooled stool donors.[22] Some studies also involve the use of oral administration instead of rectal enemas which may give rise to different bioavailability and ultimately safety and efficacy profiles.[22]

The lack of regulatory guidance on FMT products may limit patient access to suitable treatments. Unanswered questions surround the use of FMT in clinical settings such as the ability to perform adequate donor and faecal screening, the need for standardised protocols and additional long-term safety data which require additional large-scale studies to be conducted.[22]

3.7. Pharmacovigilance and post-authorisation activities

Post-approval monitoring is an important aspect of new treatments to ensure patient safety and to generate additional efficacy data. Little information is available on FMT durability and long-term side effects of FMTs are not understood, and so, patients who receive such therapy require careful monitoring for a number of years.[22] The absence of an EU regulatory framework and post-marketing surveillance for FMT products is of concern as there is no systematic review or evaluation of cumulative safety data including the reporting of adverse reactions or potentially inappropriate use.

Late post-FMT outcomes, such as the risk of late relapse of CDI or a new infection with systemic antimicrobial therapy after successful FMT, are unknown. Further, the role of anti-CDI antibiotic and/or probiotic prophylaxis needs to be addressed. Post-authorisation efficacy studies may help to understand the use of the product under real-life conditions and to define FMT's long-term effectiveness in treatment of CDI.

Rare adverse events may be attributable to FMT products as reactivation of or new-onset autoimmune and metabolic conditions have been noted in case studies in the US.[31] Particularly vulnerable populations, such as immunosuppressed patients, may be at highest risk of rare serious adverse events. The FDA issued a safety alert for FMT products, due to the potential for serious or life-threatening adverse events, likely due to the transmission of pathogenic organisms.[30] The National Institutes of Health (NIH) have funded a FMT register to allow side effect monitoring in FMT patients up to 10 years which will allow significant data collection.[22] This intervention of significant data retention is costly, and ideally, a bio-bank should be linked to be able to trace a side effect back to the specific donor.[22] The regulation of such products in the EU could enhance patient safety by similarly monitoring FMT product data. This would enable use of the existing robust pharmacovigilance structures and facilitate a systemic and consistent approach to risk management, including risk minimisation measures and additional activities including post-authorisation safety studies.

Identification of a causal relationship between FMT and a specific reported adverse event is often difficult and confounded by many FMT-, host- and comorbidity-related factors. Every effort should be made to best investigate causality.

Risk minimisation to vulnerable patients receiving FMTs is clinically vital, however the absence of an agreed framework for the regulation of FMT and an agreed systematic approach to safety and pharmacovigilance monitoring is a significant challenge that needs to be addressed.

The pharmacovigilance system could include the following activities:

1. Monitoring the transplanted patient to detect possible adverse drug reactions (ADR).
2. Management of the reporting of possible ADRs and describe in detail any severe adverse reactions.
3. Coordination, together with the research groups involved, of prospective observational studies to identify any factors that may predispose the transplanted patient.
4. Active participation in the clinical committees that are directly involved in the use of the human microbiota.
5. Establishment of strategies for the prevention and improvement of the ADRs, together with the research groups.

4. Existing regulatory preparedness

4.1 Current regulatory approaches relevant to the innovation

At present, there is no agreed EU approach in relation to the classification of FMT as reflected in Table 1 in section 3.1 above. While some MSs have decided to classify and regulate FMT as a medicinal product, some are regulating or considering regulating FMT under Tissues and Cells legislation and one MS considers FMT to be a therapeutic intervention.[22,25,26] The need for a consistent EU approach to the regulation of FMT has been highlighted by industry and by clinicians and researchers although there is disagreement in relation to the desired approach with some favouring regulation as a medicinal product and others lobbying for regulation as a transplant product.[19, 36]

There is a need to agree a consistent EU approach to the regulation and oversight of FMT to require the generation of reliable clinical safety and efficacy data for FMT products, to ensure the appropriate quality of such products, and ultimately to ensure safe and appropriate patient access. Efforts to alignment among MS should be the first step in ensuring regulatory preparedness for such products.

Due to the absence of an agreed regulatory framework, at present, there is no regulatory guidance that specifically addresses FMT-based products. Once the applicable regulatory framework has been agreed, new guidance, or updates to current guidance, can define the appropriate regulatory standards and approaches to FMT.

4.2 Existing knowledge/expertise within the regulatory network

In relation to expertise, there is likely to be sufficient expertise within the network particularly in agencies who have experience in regulating specialised medicinal products such as ATMPs and may also have responsibilities for other legislation such as blood and tissues and cells. The effective regulation of FMT is likely to require a hybrid approach addressing key issues such as donor and sample screening, traceability, as well as appropriate standards and approaches in relation to the quality, safety and efficacy of FMT-based products. Pooled expertise from within the EU regulatory network could effectively and appropriately regulate FMT products.

5. Recommendations

5.1. Suggested actions to address the challenges and opportunities

- Work with EU public funders and EU research infrastructures to explore the establishment of a microbial biobank and library that can facilitate basic research to better understand the mechanisms of action underpinning FMT efficacy and safety. This should be designed to facilitate product development and clinical trials with adequate traceability and long-term follow up.
- Consider the establishment of a working group with a mandate from HMA (NCAs), EMA and EDQM to develop a proposed EU-wide approach to the regulation of FMT initially focusing on the regulatory classification of FMT and subsequently the development of standards / guidelines. Given the increasing usage of FMT, it is important to progress these points in a timely manner and establish an EU-wide approach to ensure quality, safety and efficacy. This should include detailed consideration of existing approaches and best practices, involve all stakeholders and take account of existing stakeholder initiatives in this area.
- Engage with academic clinical research professionals to elaborate challenges, to explore potential solutions and to inform guidance by regulators and other stakeholders.
- Communicate on the usefulness and application of scientific principles and good clinical practice principles to clinical research on FMT.

5.2. Possible changes to the regulatory framework (guidance, need for new regulatory approaches)

- Following the agreement of an EU-wide approach in relation to the classification of FMT, regulatory guidance and standards for FMT will need to be developed to provide assurance in relation to quality, efficacy and safety. Aspects to be addressed would include:
  - Donor selection and screening – in particular the expectations relating to the screening of blood and faeces from donors should be addressed
  - Traceability of donors, donated material and recipients – this should address the potential pooling of material from an individual donor and from multiple donors
  - Standards to be applied during processing and storage – including manufacturing standards / GMP and expectations in relation to product control / testing
  - Different formulations and presentations: capsules, liquid, etc.
  - Expectations related to the initial administration and potential consecutive administration of FMT – this should consider the different routes of administration and their suitability for certain patients, and the impact of the use of intestinal washing and other medication before and after the administration on the FMT treatment
  - Safety monitoring following the initial and potential consecutive administration of FMT – this should be informed by a literature review in relation to the potential adverse reactions associated with FMT
- When developing guidance, explore links to the broader area of live biotherapeutic products

5.3. Need for development of additional knowledge / expertise within the regulatory network or access to such knowledge / expertise via external experts

Given the nature of FMT and the criticality of donor and material screening to safety, experts from the blood products and / or tissues and cells regulatory network could be invited to work with experts from the medicinal products regulatory network on the development of suitable regulatory guidelines and standards.

5.4. Identification of regulatory / scientific groups who should be involved in further review / actions relating to this topic

- CTFG – to consider data requirements to support CTs
- CHMP and relevant working parties such as SAWP, BWP – development of regulatory standards / guideline
- GMP/GDP Inspectors Working Group – manufacturing standards for FMT products
- EDQM – to incorporate aspects related to FMT from the EDQM's Guide to Quality and Safety of Tissues and Cells for Human Use
- HTA bodies – some of the conditions for which FMT is being use / investigated (such as recurrent CDI) are associated with high healthcare costs so consideration of the evidence required from a HTA perspective would be beneficial
- Academic clinical research professionals.

6. Annex - List of References

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