The Regulation of Faecal Microbiota Transplantation (FMT)

Alyce Maksoud
Manufacturing Quality Branch
Therapeutic Goods Administration

November 2019
Overview

FMT - Why?
History of FMT
Human Intestinal Microbiome
Australian study
Is FMT a Biological
International regulation of FMT
FMT process
Donor screening
Classification of Biologicals
Pertinent Manufacturing Practice
Challenges
Questions
Faecal Microbiota Transplantation (FMT)

“All diseases begin in the gut”

The relationship between the degree of gut health and human disease processes has long been recognised.

“Let food be thy medicine”
~ Hippocrates
History of FMT

• The earliest documented administration of a faecal suspension was by the traditional Chinese doctor Ge Hong in the 4th century. He used so-called ‘yellow soup’ as a treatment for food poisoning and severe diarrhoea.  (Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? Am J Gastroenterol 2012 Nov;107(11) 1755;1755–6.)

• However, it wasn't until the 16th century that another Chinese doctor named Li Shizhen recorded a range of faecal preparations for effective treatment of GI-diseases, such as constipation, fever, vomiting and pain.

• Subsequently during World War II, African Bedouins advised German soldiers stationed in Africa to consume fresh camel faeces as a treatment for bacterial dysentery. (Lewin RA. Merde: Excursions in scientific, cultural, and socio-historical coprology. 1st ed. New York: Random House; 1999; 208.)

• Although the potential health benefits of microbes were already mentioned by Metchnikoff in 1907. It wasn't until 1958 that faecal enemas were first described for the treatment of pseudomembranous enterocolitis by Doctor Ben Eiseman, an American surgeon. (Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery 1958 Nov;44(5) (854–9).)

• Thereafter, a plethora of articles on the potential of FMT to treat recurrent CDI (rCDI) have been written.
Human microbiota

- Relative abundance of key phyla of the human microbiota composition measured by either 16S RNA or metagenomics approaches (DNA)

[The function of our microbiota: who is out there and what do they do? Frontiers in Cellular and Infection Microbiology August 2012/vol.1/art.104]
Human intestinal microbiome

- Includes bacteria, archaea (single-celled prokaryotes), viruses, fungi and parasites
  - Only 10 of more than 50 known bacterial phyla
  - *Bacteroidites, Firmicutes* ~ 90% gut microbiota
  - $10^{14}$ bacterial cells → 10 times greater than number of human cells in our body (150 times as many genes as our genome)
  - Diversity within phyla, vary widely between individuals as noted in previous slide
  - Bacteroides, Prevotella and Ruminococcus

- The gut microbiota is often referred to as “the forgotten organ”
Key finding of the first study in Australia for CDI (2011- 2016)

- Average prevalence of CDI diagnoses was 4.0 per 10,000 patient days & two major peaks observed – 4.5 diagnoses per 10,000 patient days
  - Patients with CDI diagnosis have an average length of stay of 17.7 days.
  - A patient with a principal CDI diagnosis has an average length of stay of 7.9 days
  - Other medical reason including CDI the average length of stay of 21.6 days.

- Estimated that severe CDI represents 2.2% of all CDI cases seen in Australian hospitals
  - The rate has been increasing since 2012 and
  - Proportion of severe disease that resulted in death is 0.7%

- Acquisition of CDI was directly attributable to the hospital care in 24.9% of separations assigned with a CDI diagnosis
The biologicals framework

- Biologicals incorporates a broad range of products
- Often approving a manufacturing process rather than product
- Subject to general and specific standards
- Flexibility to capture unique and emerging technologies

At present regulation of FMT material under the Biologicals framework is the applicable pathway
FMT

• **faecal microbiota transplant product** means a thing that:
  a. comprises, contains or is derived from human stool; and
  b. is for introduction into a person for a therapeutic use.

• **Definition:** Instillation of stool from a health person into a sick person to cure a certain disease

• **Rationale:** A perturbed imbalance in our intestinal microbiota (Dysbiosis) is associated with or cause disease and can be corrected with re-introduction of donor faeces. Disruption of flora is a risk factor for *C.Difficile*.

• **Routes of Administration:**
  1. Naso gastric / duodenal tube
  2. Retention enema
  3. Infused during colon / sigmoidoscopy (Brandt LJ ACG Meeting Oct. 2012)
FMT – International regulatory framework

- **FDA** - Drug and Biologic (IND Requirement) – “Enforcement discretion” and it is only for C difficile
- **Health Canada** - Oversees the use of FMT through its Biologics and Genetic Therapies Directorate & considers FMT to be an investigational new biologic drug that must be studied under an authorised clinical trial. A guidance document was published in 2016
- **European Union** - FMT not regulated in a standardised fashion
- FMT, faeces as a “combined substance” cannot be regulated under the EU Tissues and Cells Directives
- Nevertheless, a legal mandate exists for the potential future regulation of FMT
- **France** - the national agency for the Safety of Medicine and Health Products - FMT is considered a drug and release guidelines for use of FMT
- The **UK, Belgium and the Netherlands**, FMT is considered as a tissue
- **Other countries** – no regulation of FMT
- European consensus recommends implementation of FMT centres for the treatment of CDI and outlined guidelines of technical, regulatory, administrative, and laboratory requirements.
Enquiries related to FMT since 2014

11 May 2018 Proposed approach to the regulation of donation, manufacture and supply of material for Faecal Microbiota Transplantation (FMT)

10 October 2018 FMT Forum in Melbourne

Australia Consensus – Experts in the field.

Looking to an amendment to the legislation

FMT – Interpretative and technical guidance on GMP requirements
FMT

- Human stool is collected from a screened donor by defaecation
- Stool processed into an FMT product
- Provided to the recipient via enema, colonoscopy, nasoenteric tube, or orally (e.g. capsules)
- FMT products have sound clinical evidence of efficacy for the treatment of recurrent Clostridium difficile infection (CDI), an often serious bacterial infection of the gut, and emerging evidence of efficacy for treatment of ulcerative colitis (UC),
- A chronic relapsing-remitting mucosal inflammatory bowel disease (IBD).
- As you are aware from previous slides there is also increasing interest in the use of FMT products for a range of other conditions.
Donor screening

• In all cases, ensuring patient safety through carefully screening donors and following all regulations regarding donor selection.
• Only healthy donor stools should be considered in the rational selection process.
• Donors should be evaluated through assessments that exclude not only known pathogenic risk but also co-morbidities and risk factors for indications that are associated with the microbiome but where causality is unknown.
Donor screening

- Following two serious adverse events in immunocompromised individuals receiving FMT, the FDA recently implemented additional restrictions regarding screening requirements for donor stools.


- As our understanding of the risk factors related to FMT increases, donor screening criteria should be updated to reduce the likelihood of serious adverse events in patients - regardless of where donor stool is sourced and whether rational donor selection is performed.
  - For example, OpenBiome, the first public stool bank, has implemented a rigorous screening protocol to exclude donors with any of a variety of potential clinical and infectious risk factors.

Regulation of donation, manufacture and supply of FMT material

- FMT material meet the definition of a ‘biological’ under Section 32A of the Therapeutic Goods Act:
  - It comprises, contains or is derived from human cells (e.g. colonocytes) or human tissues.

- FMT material that is released fresh – within 6-hours of collection
  - poses similar risks of infectious disease transmission as for other biological material

- FMT material that is banked:
  - Single donation, or
  - multiple donations are combined & processed for use in unrelated patients
  - poses similar risks of infectious disease transmission as for other biological banks, e.g. Cardiovascular Tissue Banks.
Classification of biologicals

Biologicals are grouped into classes based on level of risk

- FMT products (in hospitals)
- Acellular skin for wound covering (tissue banks)
- Mesenchymal stem cell for treatment of graft-versus-host disease
- Demineralised bone mixed with carrier
- iPSC-derived cell therapies
- CAR T cells

Class 1
Class 2
Class 3
Class 3
Class 4
Class 4
Classification of FMT material

- Class 1 biologicals, in the case of minimally manipulated FMT products from appropriately screened donors which are 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.

- Sponsors of Class 1 biologicals will need to comply to applicable standards and have an appropriate quality management system in place.

- The sponsor will need to submit an application for the FMT product to be included in the Australian Register of Therapeutic Goods (ARTG).

- However, the manufacturer does not need to hold a Good Manufacturing Practice (GMP) licence, and does not require pre-market assessment of supporting data by TGA.
Classification of FMT material

**Class 2 biologicals**, in the case of minimally manipulated FMT products from appropriately screened donors which are manufactured in a facility that is not a hospital or manufactured and used in different hospitals or clinics. For Class 2 biologicals, these are required to be included in the ARTG and have GMP licensing for all manufacturing and testing facilities.

**Class 3 or 4 biologicals or medicines**, in the case of FMT products from appropriately screened donors which have been processed using methods that may have altered any of the biological characteristics or physiological functions of the stool. For Class 3 or 4 biologicals or medicines, these are required to be included in the ARTG and have GMP licensing for all manufacturing and testing facilities.
Regulation of donation, manufacture and supply of FMT material

- Possible changes for FMT material to address safety concerns:
  1. TGA will work to develop an appropriate FMT product Standard that will specify the minimal requirements for donor and product screening;
  2. Provide specific guidance on appropriate manufacturing practices for FMT material
  3. Transition towards all manufacture of FMT material under GMP (exemption: phase 0 or phase I clinical trials) for class II biologicals
  4. It is anticipated that the new regulatory amendments for FMT products will be implemented on 1 January 2020 with a transition period of 12 months, i.e. commencement from 1 January 2021.
  5. Information on TGA website to clarify requirements for supply & restrictions to advertising unapproved therapeutic goods
Regulation of donation, manufacture and supply of FMT material

- TGA’s job is to regulate
- The industry’s challenge is to do everything else within the TGA’s regulatory framework
- The TGA is encouraging the industry to be more focused on developing pertinent manufacturing practices for the FMT materials and processes
- The industry should not be using compliance as a primary endpoint
- The endpoint should be focused on products and processes as the primary design criteria for efficient and reliable manufacture of FMT to demonstrate that it is effective and safe
- The GMP is developed as guidelines
Challenges

• Clinical trials
  – Focus on quality aspects that relate to safety e.g. donor selection and testing, control over manufacturing,
  – What release testing should we use
  – Control and quality of critical materials

• Product registration
  – Poor product characterisation – defines the design of the manufacturing process (Quality, safe and effective)
  – Test kits not available for donor testing
Challenges (continued)

• Manufacture
  – GMP facility & Equipment that may impact on final safety of final product
  – QMS, training of personnel (The use of trained personnel to ensure consistency of process and record keeping to ensure that if there is an adverse event it is recorded.
  – Critical Materials (Traceability and required release testing)
  – Processing and QC testing