Provisional Translation (as of November 2025) *

Quality of Fecal Microbiota Transplantation (FMT) Products at the Initial Development Stage (Early Consideration)

October 31, 2025
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1. Introduction

Fecal microbiota transplantation (hereinafter referred to as "FMT") is a therapy in which enteric bacteria prepared from the feces of healthy human donors, but not specifically identified bacterial strains, are transplanted into patients with the aim of improving the gut microbiota and thereby exerting the expected effect.[1)] Outside Japan, FMT products derived from human feces have already been approved. In 2022, "BIOMICTRA" and "REBYOTA" were approved in Australia and the US, respectively, and in 2023, "VOWST" was approved in the US for the indication of refractory *Clostridioides difficile* infection, which is an intestinal infection.[2-4)]

For development of FMT products, how to assess the eligibility of fecal donors, including evaluation of infectious risks, is critical for ensuring product safety. In ensuring the safety of subjects, the most important action is to sort items for selecting eligible donors, such as screening by interview, stool test, and blood test.

The objective of this Early Consideration is to present the current regulatory perspective regarding considerations on quality of FMT products at the initial development stage in view of experience at the Pharmaceuticals and Medical Devices Agency (PMDA) as well as regulatory guidelines and literature from outside Japan.[5-7)] It should be noted that the perspective presented in this Early Consideration is formulated based on knowledge available up to date and may be subject to change depending on new knowledge obtained in the future.

2. Scope of application

This Early Consideration apply to FMT products that are prepared from feces of healthy human donors and intended to be regulatory approved as drugs.

3. Eligibility of donors and donor feces

3.1 Basic policy

Because FMT products are comprised of enteric bacteria directly derived from donors without substantial processing and intended to be transplanted into patients, eligibility of human donors of feces must be assessed from a multi-angled view of safety. Interviews and tests should be appropriately used in combination to determine whether prospective donors are fully qualified.

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Physician's interview with prospective donors about health history and lifestyle is important in assessing their eligibility. Specific items in the interview should be determined with reference to the regulatory guidelines from outside Japan and interview sheets used for blood donation, etc.[5-8)]

From the viewpoint of ensuring the safety of subjects, both donors and donor feces used in FMT products should be tested for infections with pathogenic bacteria, fungi, viruses, etc. (hereinafter referred to as "pathogens"), and infection with pathogens must be ruled out. For specific pathogens to be ruled out for the presence, refer to Section 3.2.

If biological raw materials other than human feces are used in manufacture of FMT products, those raw materials need to conform to the Standards for Biological Raw Materials. As a general principle, use of biological raw materials should be avoided as much as possible. In FMT products, use of biological raw materials other than human feces should be also avoided wherever possible.

3.2 Pathogens to be ruled out

To rule out a risk of infection via a donor or donor feces, tests should be extensively performed. To ensure that no pathogens known to cause disease in humans as listed in Table 1 are detected, either donor or donor feces should be assessed by highly sensitive detection methods. Pathogen to be tested should be determined in consideration of country or region of the donor, target disease, and a risk-benefit profile of the product. If any new pathogen causing infection other than those listed in Table 1 emerges, it must be tested as well. Pathogens to be tested as well as details such as detection sensitivity and reference values of the test methods should be justified. In addition, if any of the pathogens listed in Table 1 is not tested, such omission should also be justified.

To rule out donor-mediated infection risk, blood samples should be tested for at least hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (serological test and nucleic acid amplification test), because contamination of blood-derived substances in human feces cannot be ruled out, and blood samples are favored in terms of detection sensitivity. Testing frequency should be specified taking the window period into account.[9)]

Samples to be used for tests should be collected before feces are provided for FMT products. To maximize the capability of detecting infectious diseases, tests should be performed by methods with adequate performance within an appropriate period, and periodic retests should be reasonably performed.

Figure 1 shows an example of a donor screening flow.

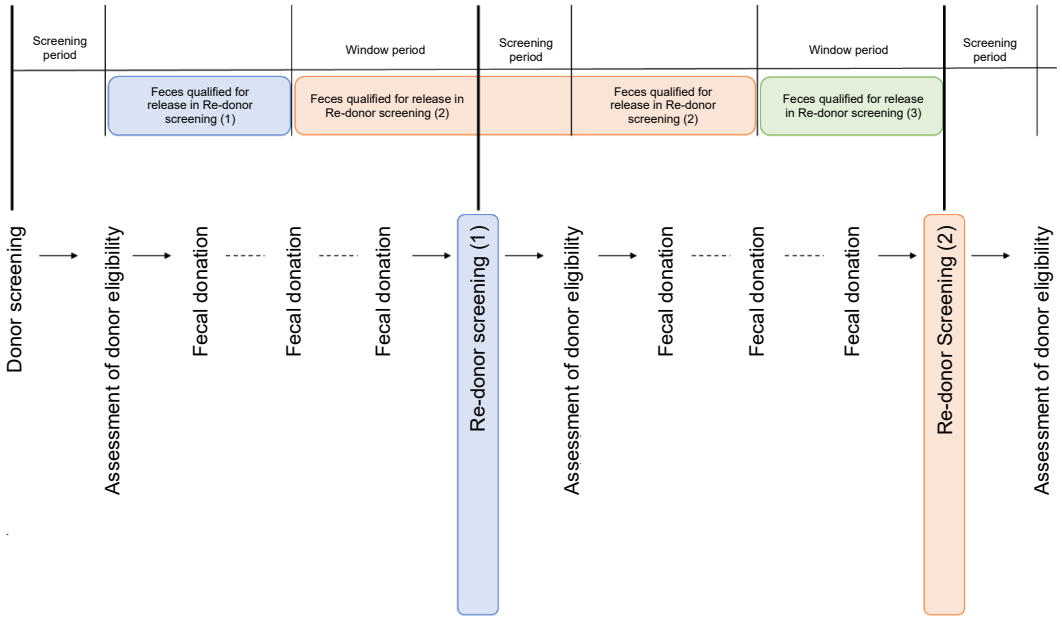

Figure 1　Donor screening flow

4.　Quality control

The composition of gut microbiota differs depending on the country or region, ethnic group, or oneself of the donor. Even from the same donor, the composition varies depending on various factors such as diet and lifestyle. Collecting data on microbiota composition of FMT products throughout the development is important from a viewpoint of ensuring efficacy and safety of FMT products. Based on gene analysis results on microbiota of FMT products, clinical trial results obtained using FMT products, changes in gut microbiota from prior to post-transplantation points in clinical trials, and publicly available information on gut microbiota related to the target disease, bacterial strains and microbiota effective in treatment of the target disease should be investigated, including their diversity. It is important to ensure that the above effective characteristics are consistently maintained within a certain range across lots of FMT products.

Separately from the tests in Section 3.2, appropriate acceptance tests for the conditions of donor feces (e.g., fecal softness and color) should be performed at the manufacturing site before use in manufacturing.

Because the active substance of FMT products is bacteria, adventitious agents brought into the manufacturing process are difficult to remove, and sterility testing is not feasible. Therefore, the manufacturing process needs to be performed in an appropriate environment and under control to prevent contamination with adventitious agents.

5.　References

1)　Points to Consider for Gut Bacterial Products Based on Microbiome Research, dated Feb

ruary 25, 2022, by the Subcommittee on Microbiome of the Science Board https://www.pmda.go.jp/files/000249812.pdf

2) AUSTRALIAN PRODUCT INFORMATION – BIOMICTRA (FAECAL MICROBIOTA TRANSPLANTATION) https://www.biomebank.com/wp-content/uploads/2022/11/BIOMICTRA-Australian-Product-Information.pdf

3) HIGHLIGHTS OF PRESCRIBING INFORMATION REBYOTA (fecal microbiota, live - jslm) suspension, for rectal use. Initial U.S. Approval: 2022 https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota

4) HIGHLIGHTS OF PRESCRIBING INFORMATION VOWST (fecal microbiota spores, live-brpk) capsules, for oral administration. Initial U.S. Approval: 2023 https://www.fda.gov/vaccines-blood-biologics/vowst

5) Health Canada. Guidance Document: Fecal Microbiota Therapy Used in the Treatment of Clostridioides difficile Infection Not Responsive to Conventional Therapies. 2022. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/regulation-fecal-microbiota-therapy-treatment-difficile-infections-2022-09-26.pdf

6) Guide to the quality and safety of TISSUES AND CELLS for human application 5th Edition. European Directorate for the Quality of Medicines & HealthCare. https://freepub.edqm.eu/publications/AUTOPUB_17/detail

7) Regulatory Considerations for Fecal Microbiota Transplantation Products. Carlson PE Jr. Cell Host Microbe. 2020; 27(2): 173-175. https://doi.org/10.1016/j.chom.2020.01.018

8) Explanation on interview items, Chapter 6 Other References, Blood Project Report 2024, Ministry of Health, Labour and Welfare https://www.mhlw.go.jp/stf/newpage_53739.html (In Japanese)

9) Infection reports and window period, Chapter 3 Safety Measures for Blood Products, Blood Project Report 2024, Ministry of Health, Labour and Welfare https://www.mhlw.go.jp/stf/newpage_53739.html (In Japanese)

Table 1 Test items for pathogens to be ruled out

Test item	
Donor feces	
Bacteria/Fungi	
Aeromonas	*Campylobacter*
Toxigenic *Clostridium difficile*	Enteroinvasive *Escherichia coli*
Enteroaggregative *Escherichia coli*	Enterotoxigenic *Escherichia coli*
Enteropathogenic *Escherichia coli*	Enterohemorrhagic *Escherichia coli* (Shiga toxin-producing *Escherichia co*li)
Shigella	*Salmonella*
Vibrio	*Vibrio cholerae*
Yersinia enterocolitica	*Plesiomonas shigelloides*
Listeria monocytogenes	*Helicobacter pylori*
Toxigenic *Staphylococcus aureus*	Vancomycin-resistant *enterococci*
Extended spectrum beta-lactamase-producing Enterobacteriaceae	Carbapenemase-producing Enterobacteriaceae
Carbapenem-resistant Enterobacteriaceae	Drug-resistant bacteria such as vancomycin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, drug-resistant *Pseudomonas aeruginosa*, and drug-resistant *Acinetobacter*
Enterotoxin-producing *Clostridium perfringens*	Microsporidia
Virus	
Norovirus	Rotavirus
Adenovirus	Astrovirus
Sapovirus	Enterovirus
Parasite	
Cryptosporidium	*Giardia lamblia*
Cyclospora	*Cystoisosporiasis*
Entamoeba histolytica	Helminths and parasite eggs
Donor blood	
Bacteria	
Treponema pallidum	*Chlamydia trachomatis*
Coxiella burnetii	*Mycobacterium tuberculosis*
Virus	
Hepatitis A virus	Hepatitis B virus
Hepatitis C virus	Hepatitis E virus

Human immunodeficiency virus	Human T-lymphotropic virus type I
Cytomegalovirus	Epstein-Barr virus
Human Parvovirus B19	
Parasite	
Toxoplasma	Echinococcus
Other samples	
SARS coronavirus 2	*Neisseria gonorrhoeae*