Health Canada Santé Canada

Guidance Document

Fecal Microbiota Therapy Used in the Treatment of *Clostridioides difficile* Infection Not Responsive to Conventional Therapies

Date adopted	2015-03-27
Effective date	2015-03-27
Revised date	2022-09-26

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Bactériothérapie fécale utilisée dans le traitement de l'infection à *Clostridioides difficile* qui ne répond pas aux traitements classiques

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Publication date: March 2020

Cat.: H164-287/2019E-PDF
ISBN: 978-0-660-31993-3
Pub.: 190234

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

Document Change Log			
Version	Location of change	Change made	Effective date
1	Not applicable	Initial Issuance of Document	2015/03/27
2	Not Applicable	Revisions made based on consultation period submissions	2015/08/21
3	Not applicable	Changes were made to ensure consistency between languages and to correct editorial errors.	2016/08/09
4	Page 8	Additional donor screening requirements added	2019/07/31
5	Page 8	Additional donor screening requirements added concerning SARS-CoV-2	2020/03/27
6	Page 8	Additional donor screening requirements added concerning Monkeypox Virus, *Escherichia coli* and Shigatoxin-producing *Escherichia coli*	2022/09/26

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1. Introduction

1.1 Purpose/Overview

Fecal Microbiota Therapy (FMT) refers to the transfer of bacteria and natural antibacterials obtained from the feces of a healthy individual into the gut of a patient through enema, colonoscopy or other means, with the aim of re-establishing a healthy microbial community. Although it was first described in scientific literature in the 1950s, interest in FMT has surged in recent years.

As the incidence of *Clostridioides difficile* infection (CDI) has increased over the past decade and the efficacy of traditional antibiotic therapy has declined, FMT has emerged as a therapeutic alternative, albeit one typically reserved as a last resort treatment. While the mechanisms by which it eliminates CDI remain unclear, there are a rapidly growing number of published studies on FMT, with most reporting very high cure rates, low relapse rates, and no serious adverse events.

1.2 Scope and application

The scope of this risk based interim policy regarding the Clinical Trial requirements is limited to classical FMT (fresh or frozen) used in the treatment of patients with CDI not responsive to conventional therapies and it is subject to the conditions listed in Section 2.

This interim policy does not apply to the following FMT:

- FMT that is produced from single or multiple strains of microorganisms using an in vitro culture or expansion system;
- FMT containing a novel excipient (e.g. a cryoprotectant) and at a concentration which is not normally found in gut flora and for which there is no safety data to support its application;
- FMT that is used in a comparative clinical study.

In cases where the above circumstances apply, a CTA must be submitted and authorized by Health Canada, prior to the use of the FMT.

This interim policy is limited to FMT used in the treatment of CDI. For all other indications, the use of FMT must still be conducted under a clinical trial authorized by Health Canada.

Applicants should consult with Health Canada to determine the applicability of this interim policy, if necessary.

1.3 Policy objectives

Health Canada recognizes the burden posed by CDI on Canada's health care system and on affected patients. While Health Canada considers FMT to be an investigational new biologic drug, the study of which must be done under an authorized clinical trial, the Department also recognizes the increasing role that the therapy has shown in treating patients with CDI.

There is a need to allow greater access to FMT; however, appropriate patient safeguards must still be maintained.

1.4 Policy statements

Health Canada is notifying stakeholders of its risk based, interim policy regarding the clinical trial requirements for FMT used in the treatment of patients with CDI not responsive to conventional therapies.

Research conducted to date on the treatment of CDI using FMT is very encouraging and Health Canada supports further research in this area. Current evidence supports the safety and efficacy of using FMT to treat patients with CDI unresponsive to conventional therapies.

Health Canada considers the fecal matter used in FMT to meet the definition of a "drug" under the Food and Drugs Act and, as a result, regulates FMT as a new biologic drug. The study of a new biologic drug requires a risk-benefit assessment focused on the quality, safety and efficacy of the drug as part of a clinical trial application (CTA). Since no company or individual has sought market authorizations for materials used in FMT, the therapy is considered investigational, meaning that it can only be conducted in the context of an authorized clinical trial.

As with other biological drugs derived from human sources, donor screening standards must be employed to ensure that donors are healthy and free of infectious diseases, including HIV and hepatitis. Donors must also be screened for other intestinal pathogens that could be harmful to the recipient.

To date, CDI is the only indication for which FMT has demonstrated safety and efficacy. Therefore, this is the only condition for which FMT merits consideration outside the direct regulatory provisions of an investigational clinical trial, provided that the conditions noted in this guidance document are followed.

This interim policy allows health care practitioners to treat patients suffering from CDI not responsive to conventional therapies with FMT without a clinical trial where the conditions in this guidance document are followed. A "practitioner" means a person who is entitled under the laws of a province to treat patients with a prescription drug, and is practising their profession in that province.

Effective immediately, this policy regarding the clinical trial requirements will be applied on an interim basis while the Department continues to explore future policy options for regulating FMT.

2. Guidance for implementation

Health Canada will apply a risk based interim policy regarding the clinical trials requirements for FMT used in the treatment of patients with CDI not responsive to conventional therapies. FMT can be used in the treatment of patients with CDI not responsive to conventional therapies outside the auspices of an authorized clinical trial if the following conditions are met:

i. The health care practitioner obtains informed consent from the patient or an agent acting on their behalf for the use of FMT.

ii. The feces used to prepare the FMT are obtained from a single donor known to either the patient or to a health care practitioner treating the patient. Therefore, pooled feces from multiple donors should not be used to prepare the FMT.

iii. Feces from a donor at risk of transmitting an infectious disease and/or a harmful pathogen to the recipient are not used to prepare a FMT.

iv. Donor screening is conducted with questions directed at identifying donors who may be currently or recently infected with SARS-CoV-2. The donor screening is required to include whether or not the donor has had or has symptoms suggestive of SARS-CoV-2 infections since December 1, 2019. Donor screening is to include travel history and contact with infected persons.

v. Donor screening is conducted with questions directed at identifying donors who are at high risk for monkeypox, may be currently infected with monkeypox virus, or may have been recently infected with monkeypox virus.

vi. Donors should be thoroughly screened for all relevant transmissible diseases, including HIV and hepatitis. Considerations may be given to related and co-habitating donors. Using a risk-based approach, donors should also be screened for other intestinal pathogens and infectious disease agents that could be harmful to the recipient. Donor screening may include and may not be limited to the following microorganisms and diseases:

- Monkeypox
- SARS-CoV-2
- HIV-1/2
- Hepatitis B and C
- HTLV-I/II
- syphilis
- Helicobacter pylori
- enteric pathogens [Shigella, Salmonella species, Yersinia, Campylobacter, sorbitol-negative E.coli 0157-H7, Plesiomonas, Aeromonas, shiga toxins]
- Multi-drug Resistant Organisms [at a minimum, vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta lactamase (ESBL)-producing Enterobacteriaceae, and carbapenem-resistant Enterobacteriaceae (CRE)]
- enteropathogenic *Escherichia coli* (EPEC) and Shigatoxin-producing *Escherichia coli* (STEC) by nucleic acid amplification tests (NAAT)
- Vibrio
- Listeria

- norovirus
- rotavirus
- adenovirus
- ova
- protozoa
- parasites
- malaria
- Chagas disease
- babesiosis
- Creuztfeldt-Jakob disease
- prion-related diseases from dural mater grafts
- gonorrhea
- Chlamydia
- Cancer

A combination of appropriate detection and assessment methods should be used to determine if the donor is in a good state of health at the time of stool donation for the FMT (e.g. blood and stool testing for relevant transmissible disease markers; Donor Health History/ Lifestyle Questionnaire for risk behaviours, and physical examination). Donor fecal and serological samples should be collected prior to stool donation for a FMT and be tested by a competent laboratory within an appropriate time period so as to ensure maximum detectability of an infectious disease. The extent of donor screening and periodic retesting performed should be rationalized. Donors who may transfer undesirable agents (e.g. C. difficile toxins, antibiotics, systemic immunosuppressive or biological agents, systemic antineoplastic agents and exogenous glucocorticoids, anti-diarrheal drugs, mineral oil, bismuth, magnesium, or kaolin), which can affect the safety or efficacy of the FMT or the safety of the patient, should be excluded.

vii. The health care practitioner must ensure that records are kept of both the donor and recipient and as part of a lookback/traceback program in case of disease transmission.

3. Compliance and Enforcement

The health of patients is the primary responsibility of their treating physician, the hospital, or other healthcare institution. Physicians and other healthcare professionals are responsible for their choice of the health products that they administer, sell, or prescribe to patients. Health care professionals are generally regulated by their professional bodies and/or under provincial law, although they may also have obligations under the *Food and Drugs Act* and its associated regulations.

3.1 Compliance Monitoring

Any person could become a regulated party by Health Canada if a person does something that is subject to the *Food and Drugs Act* and its associated regulations. For example, this could include manufacturing, importing, or selling health products. The regulated party is responsible for understanding the law and for maintaining compliance with the law.

3.2 Inspector Powers

Health Canada Inspectors exercise regulatory authority under Section 23 of the *Food and Drugs Act*. Designated inspectors have the authority to carry out inspections in order to assess a site's compliance with guidance documents or legislative

requirements. In such circumstances, stakeholders must cooperate with Health Canada officials to facilitate the assessment of compliance.

The Health Products and Food Branch Inspectorate (the Inspectorate) takes a risk-based approach to compliance and enforcement. When an incident of non-compliance is discovered, the Inspectorate evaluates the level of risk caused by the non-compliance and then prioritizes the incident. If action is required to address the incident, the Inspectorate will generally respond to the incident with actions that are commensurate with the level of evaluated risk.

4. Fecal Microbiota Therapy Used in the Treatment of *Clostridioides difficile* Infection Not Responsive to Conventional Therapies Notification Form

Prior to commencing use of FMT to treat patients with CDI not responsive to conventional therapies the establishment is encouraged to submit a Notification to the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) (see Appendix 1, Notification of Fecal Microbiota Therapy Used in the Treatment of *Clostridium difficile* Infection Not Responsive to Conventional Therapies Form) which will provide useful contact information to quickly communicate with all establishments should the need arise.

Completed notification forms should be sent to:

Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs
Directorate
Health Products and Food Branch
Health Canada
100 Eglantine Driveway, Tunney's Pasture
Address Locator 0601C
Tunney's Pasture,
Ottawa, Ontario
K1A 0K9

E-mail: brdd.ora@hc-sc.gc.ca
Telephone: 613-957-1722
Teletypewriter: 1-800-465-7735 (Service Canada)

5. Contact Information

Office of Regulatory Affairs

Inquiries and information requests regarding this Guidance document or the interim policy should be submitted directly to the Office of Regulatory Affairs.

Adverse Drug Reaction Reporting

Adverse drug reaction reports should be submitted directly to the Canada Vigilance Program.