Australian Government
Department of Health
Therapeutic Goods Administration

Faecal microbiota transplant (FMT) products

Interpretative and technical guidance on GMP requirements

Version 1.0, September 2020

TGA Health Safety Regulation

Contents

About this guidance

This guidance is for sponsors, manufacturers and providers of faecal microbiota transplant (FMT) products and provides information on:

- Therapeutic Goods Administration (TGA) manufacturing license requirements
- TGA interpretation and expectations for compliance with specific sections of the Australian Code of Good Manufacturing Practice (GMP) for human blood and blood components, human tissues and human cellular therapy products

Sponsors and manufacturers of FMT products are responsible for complying with the relevant legislation. Failure to comply may result in sanctions and penalties from the relevant Federal or State and Territory Government agency.

We will review and update this guidance in line with legislative changes, emerging technologies and best practice.

This information is provided for guidance only and has been developed on the basis of current knowledge of the subject matter.

It should not be relied on to address every aspect of the relevant legislation. You should seek your own independent legal advice to ensure that all of the legislative requirements are met.

If you require clarification of a particular requirement, you can e-mail TGA's Manufacturing Quality Branch (MQB): gmp@tga.gov.au.

Why FMT products are therapeutic goods

A FMT product is defined in the Therapeutic Goods Regulations 1990 as a thing that:

- comprises, contains or is derived from human stool

  AND

- is for introduction into a person for a therapeutic use

This includes fresh or frozen human stool introduced to the bowel for therapeutic use by a range of methods, including:

- rectal enema
- sigmoidoscopy
- colonoscopy
- nasogastric or nasoduodenal tube
- encapsulation to allow oral ingestion

FMT products are used to repopulate the bacterial microenvironment in a recipient's bowel with healthy microorganisms. All FMT products are regulated as biologicals.

Products that contain microbes derived from sources other than human stool are not FMT products.

Roles and responsibilities

The Australian Government Department of Health regulates FMT products through:

- Therapeutic Goods Administration (TGA)
- State and Territory health departments
- National Safety and Quality Health Service (NSQHS) standards

Therapeutic Goods Administration (TGA)

TGA administers the *Therapeutic Goods Act 1989* (the Act), the *Therapeutic Goods Regulations 1990* (the Regulations), and various Orders and Determinations, and regulates the quality, safety and efficacy of therapeutic goods as well as access to therapeutic goods that have not been approved for general use (unapproved therapeutic goods).

The TGA regulates the majority of FMT products as **biologicals**. Where the strain(s) of microorganisms known to be present in stool are characterised and grown from established isolates with standardised consistency, the TGA may instead decide to regulate these FMT products as **medicines** rather than biologicals.

What is regulated as a biological explains how we define and regulate biologicals and the types of products regulated as biologicals.

FMT product regulation provides an overview of the regulatory definition, regulatory framework and levels of regulation for FMT products.

For legislative requirements, refer to:

- *Therapeutic Goods Act 1989*
- *Therapeutic Goods Regulations 1990*

For manufacturing requirements, refer to:

- Australian code of good manufacturing practice (GMP) for human blood and blood components, human tissues and human cellular therapy products
- Therapeutic Goods (Standard for Faecal Microbiota Transplant Products) (TGO 105) Order 2020
- Therapeutic Goods Order No. 87: General requirements for the labelling of biologicals (TGO 87)
- Australian regulatory guidelines for biologicals (ARGB)

The Minister (Australian Government Department of Health) may from time to time determine written principles to be observed in the manufacture of therapeutic goods for use in humans (Section 36(1) of the *Therapeutic Goods Act 1989*).

State and Territory Health Departments

Each of Australia's States and Territories have enacted legislation on tissue and organ procurement (that were implemented mainly in the 1980s).

An example of one such requirement is the *Human Tissue Act 1982* (part II, section 8 – Consent by adult donor to removal of non-regenerative tissue):

1. A person, not being a child, may give his consent in writing to the removal from his body, at any time after the expiration of 24 hours from the time at which the consent is given, of specified non-regenerative tissue for the purpose of the transplantation of the tissue to the body of another living person.

2. A consent given under subsection (1) shall specify the time at which the consent is given.

We recommend that you contact the relevant State or Territory Department of Health to ensure your FMT manufacturing adheres to the requirements of that jurisdiction.

National Safety and Quality Health Service (NSQHS)

The NSQHS Standards were developed by the Australian Commission on Safety and Quality in Health Care, in collaboration with the Australian Government, States and Territories, private sector, clinical experts, patients and carers.

The primary aims of the NSQHS Standards are to protect the public from harm and improve the quality of health care. These Standards describe the level of care that should be provided by health services and the systems that are needed to deliver such care.

For more information, contact the Australian Commission of Safety and Quality in Health Care.

Sponsors and manufacturers of FMT products

For medicines, biologicals and other therapeutic goods, manufacture includes, but is not limited to, any of the following:

- production
- processing
- assembling
- packaging
- labelling
- storage
- sterilising
- testing
- release for supply.

Section 3 of the *Therapeutic Goods Act 1989* contains a full definition.

If you want to become involved in the manufacture of FMT products, you need to understand and comply with the regulatory requirements set out in this guidance.

- classifying your FMT product under the biologicals framework
  - biologicals are classified based on the level of risk to patients associated with their use
- including your FMT product in the ARTG
  - to supply FMT products in Australia, you will generally be required to include your product in the Australian Register of Therapeutic Goods (ARTG)
- relevant biological standards including:
  - Therapeutic Goods (Standard for Faecal Microbiota Transplant Products) (TGO 105) Order 2020
  - Therapeutic Goods Order No. 87: General requirements for the labelling of biologicals (TGO 87)
- Good Manufacturing Practice (GMP) licencing and clearance
  - in Australia, the *Therapeutic Goods Act 1989* requires, with certain exceptions, that manufacturers of therapeutic goods hold a licence or a conformity assessment certificate
- GMP principles, including those specified in the:
  - Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (Australian code of GMP)

As an FMT product sponsor, manufacturer or provider, be aware that you will also have other regulatory responsibilities including:

- product recall or hazard alert
  - the Uniform Recall Procedure for Therapeutic Goods (URPTG)
- advertising restrictions for biologicals
  - generally, you cannot advertise biologicals to the public
- biovigilance for biologicals
  - how and when to report serious and near serious adverse events
- minimising risk of exposure to Transmissible Spongiform Encephalopathies (TSE)
  - principles that aim to minimise the risk of exposure to TSEs

Regulation of FMT products

FMT product regulation provides an overview of the regulatory definition, regulatory framework, and level of regulation for FMT products.

Classifying your FMT product under the biologicals framework

To supply FMT products in Australia, you will generally be required to include your product in the Australian Register of Therapeutic Goods (ARTG).

Most FMT products are regulated as biologicals. All biologicals must be classified before they can be included in the ARTG.

FMT products regulated as Class 1 biologicals

An FMT product is a Class 1 biological if:

- it is collected under the supervision or direction, or in accordance with the requirements, of a registered medical practitioner in a State or Territory in Australia

  AND

- each later step in the manufacture of it is carried out in a hospital by, or under the supervision or direction of, the practitioner (unless the step relates to the storage or testing of the biological, in which case it may instead be carried out by a person under a contract with the hospital in a State or Territory)

  AND

- it is for use in a recipient who is a patient of the hospital with the recipient being under the clinical care of the practitioner.

FMT products regulated as Class 2 biologicals (or greater)

An FMT product is likely to be a Class 2 biological if it is:

- minimally manipulated and manufactured in a facility that is not a hospital

  OR

- manufactured in one hospital and used in other hospitals or clinics

All other FMT products will be classified as per Classification of biologicals.

FMT products regulated as unapproved therapeutic goods

Unapproved therapeutic goods are those goods not included in the ARTG, but available through the special access pathways. This includes access through:

- the Special Access Scheme (SAS)
- clinical trials, using investigational biological products in certain circumstances
  - Australian clinical trial handbook contains guidance on manufacturing experimental (unapproved) products for use in clinical trials

Including your FMT product in the ARTG

If you are **developing an FMT product**, you need to consider the classification of your product to understand the level of supporting data required to support your application for inclusion in the Australian Register of Therapeutic Goods (ARTG).

If your FMT product is a **Class 1 biological** that has to be included in the ARTG, you need to apply for inclusion of a Class 1 biological in the ARTG.

If your FMT product is a **Class 2 biological** (or greater) that has to be included in the ARTG, you need to apply for inclusion of a Class 2, 3 or 4 biological in the ARTG.

Conforming with Therapeutic Goods Orders (TGOs)

The manufacture of all FMT products **must** conform to the standards and requirements specified in TGO 89 and TGO 105.

Standards for FMT products (TGO 105)

FMT products supplied in Australia must conform to the Therapeutic Goods (Standard for Faecal Microbiota Transplant Products) (TGO 105) Order 2020. TGO 105 outlines the mandatory standards for faecal microbial transplant (FMT) products to ensure the safety and quality of FMT products that are manufactured from both frozen and fresh stool.

TGO 105 was published in August 2020 with a **commencement date** of 1 July 2021. A sponsor can move to comply with the requirements at any time, but the delayed commencement date does allow a **transition period** for sponsors to meet the requirements.

Whether TGO 105 applies to you is dependent on when FMT products are collected and released for supply:

- FMT products that are collected and released for supply prior to 1 July 2021 (or the time of elected compliance with TGO 105 and the Australian code of good manufacturing practice (GMP) for human blood and blood components, human tissues and human cellular therapy products) **are exempt from TGO 105**.
- Where an FMT product has been collected prior to 1 July 2021 but released for supply after this date, the product **must comply with TGO 105**.
- Where an FMT product is collected on or after 1 July 2021, the product **must comply with TGO 105**.

For guidance on the general and specific requirements of TGO 105, refer to ARGB Appendix 10 - Guidance on TGO 105: Standards for faecal microbiota transplant (FMT) products.

For enquires about TGO 105, email TGA's Biological Sciences Section (BSS): bloodandtissues@tga.gov.au.

General requirements for the labelling of biologicals (TGO 87)

FMT sponsors also have a similar transition period for TGO 87 to assist in compliance with the requirements for labelling and traceability.

Sponsors and manufacturers of FMT products who wish to do so may begin complying with the requirements before 1 January 2021.

For guidance on the requirements of TGO 87, refer to ARGB Appendix 9 – Guidance on TGO 87.

Manufacturing requirements

For medicines and other therapeutic goods that are not medical devices, Section 36 of the Act applies.

FMT products regulated as Class 1 biologicals

If you manufacture only FMT products classified as Class 1 biologicals, then your manufacturing facility is **exempt from requiring a TGA manufacturing licence**, but you still need to comply with biological standards, GMP principles, and Good Laboratory Practice (GLP).

Biological standards and GMP principles must be met

Whether the manufacture of FMT products takes place in a public hospital or private day care gastroenterology clinic (private hospital), you are required to comply with:

- all relevant biological standards including:
  - Therapeutic Goods (Standard for Faecal Microbiota Transplant Products) (TGO 105) Order 2020
  - General requirements for the labelling of biologicals (TGO 87)
- GMP principles

Good Laboratory Practice (GLP)

FMT products that are Class 1 biologicals, should also be designed and developed in keeping with the requirements of GLP.

GLP applies, whether the manufacture of FMT products takes place in a public hospital or private day care gastroenterology clinic (private hospital).

GLP stresses the importance of the following points:

- resources: organisation, personnel, facilities and equipment
- characterisation: test items and test systems
- rules: protocols, standard operating procedures (SOPs)
- results: raw data, final report and archives
- quality assurance: independent monitoring of manufacturing processes
- adverse event reporting.

If you require information about GLP, email the Manufacturing Quality Branch.

FMT products regulated as Class 2 biologicals (or greater)

If you manufacture FMT products classified as Class 2 biologicals, you **must**:

- hold a current TGA licence to manufacture therapeutic goods in Australia – if the manufacturer is based in Australia

  OR

- be covered by current TGA GMP certification for overseas manufacturers – if the manufacturer is based overseas.

The manufacture of FMT products that are Class 2 biologicals (or greater) **must also comply with**:

- all relevant biological standards including:
  - Standards for FMT products (TGO 105)
  - General requirements for the labelling of biologicals (TGO 87)
- Good manufacturing practice (GMP) principles, as specified in:
  - the Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (Australian code of GMP)

Manufacturing licence for Australian manufacturers

You need a TGA manufacturing licence to manufacture certain therapeutic goods for supply in or export from Australia (under the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990*).

Only Australian manufacturing sites can obtain a TGA manufacturing licence.

Applying for a biologicals manufacturing licence

Australian manufacturing licences and overseas GMP certification provides information about the process for applying for a manufacturing licence or overseas GMP certification.

Expected timeline for a biologicals manufacturing licence

On receiving an application for a manufacturing licence, we typically conduct an on-site inspection within 3 months, if the manufacturing site is ready. The time from inspection to licensing will vary depending on how quickly/effectively the manufacturing site addresses any deficiencies identified during the inspection.

For more information on the process, refer to Manufacturing inspections.

GMP certification for overseas manufacturers

For FMT products manufactured overseas, sponsors or agents acting on the sponsor's behalf, need to obtain GMP certification from TGA.

For biologicals, this can only be through a **TGA on-site inspection**. The Mutual Recognition Agreement (MRA) or Compliance Verification (CV) pathways **cannot be used for obtaining GMP certification for biologicals**.

For more information, refer to Australian manufacturing licences and overseas GMP certification.

Packing and storage companies and contract laboratories

Packaging and storage of the final FMT product is a manufacturing licencing step, unless it is in relation to a Class 1 biological. Where a manufacturer contracts out the packaging and storage activity, the contracting company will need to satisfy TGA licencing requirements.

Contract laboratories may be used for Class 2 biologicals and above, but these must also be TGA licensed for this activity.

In the case where FMT products undergo cryopreservation, packaging and release, GMP principles will apply to all steps.

Manufacturing for clinical trials

Health practitioners manufacturing FMT products for clinical trials, that are not Class 1 biologicals, are required to hold a current TGA licence to manufacture therapeutic goods in Australia and comply with GMP principles for biologicals (unless they meet the exemptions under Schedule 7 item 21 and Schedule 8 item 1 of the *Therapeutic Goods Regulations 1990*).

Australian facilities participating in the manufacture of FMT products for use in clinical trials must also hold a GMP manufacturing license issued by TGA. However, certain persons or goods are exempt from this requirement. For example, goods prepared for first time studies in humans.

The Australian clinical trial handbook contains guidance on manufacturing experimental (unapproved) products for use in clinical trials.

Import

To import FMT products into Australia for commercial supply, you must meet certain regulatory requirements set out in the Australian therapeutic goods legislation.

The products must generally:

- be included in the Australian Register of Therapeutic Goods (ARTG) before you can import them for commercial supply, unless they are the subject of an exemption, exclusion, approval or authority
- meet TGA GMP requirements unless exempt.

Overseas manufacturers can obtain GMP certification following a successful on-site inspection by the TGA or via the compliance verification pathway, if applicable. See Sponsor responsibilities related to GMP clearance and certification for more information.

A declaration of intent to supply is requested as part of the process for certification of overseas manufacturers at the application review stage, as per Australian manufacturing licences and overseas GMP certification guidance.

Export

To export FMT products from Australia for commercial supply, you must meet certain regulatory requirements set out in the Australian therapeutic goods legislation.

The products must generally:

- be included in the Australian Register of Therapeutic Goods (ARTG) before you can export them for commercial supply, unless they are the subject of an exemption, exclusion, approval or authority
- meet TGA GMP requirements unless exempt.

Where FMT products are manufactured for the export only market, the manufacturer is also required to satisfy TGA manufacturing licencing requirements.

TGA licensed manufacturers can apply for a Certificate of GMP Compliance to assist them to export biological products.

GMP principles

Different manufacturing principles apply to different kinds of biologicals:

- biologicals that comprise, contain or are derived from human cells and tissues or are specified as biologicals by the Australian Secretary to the Minister of Health must comply with the current Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (Australian code of GMP)
- biologicals that comprise or contain live animal cells, tissues or organs must comply with the PIC/S guide to GMP (the same manufacturing principles that apply to medicines), except for annexes 4, 5 and 16).

Purpose of GMP

The main purpose of GMP is always to prevent harm from occurring to the end user. It is also required that personnel be well trained.

Additional principles include ensuring the final product is:

- free from adding to the initial bioburden
- consistent in its manufacture
- well documented in its manufacture
- checked for quality more than just prior to release for supply.

GMP is typically ensured through the effective use of a quality management system.

Make sure you familiarise yourself with the GMP principles and requirements described under Australian code of GMP.

Periodic changes

GMP requirements change over time for various reasons including to:

- provide guidance for the management of new technologies
- address gaps or clarify existing compliance requirements
- manage risks identified through inspections and regulation
- facilitate continuous improvements in the way that biologicals are manufactured.

Data management and data integrity

All manufacturers of medicines, including manufacturers of biologicals, must comply with GMP relating to data management and data integrity (DMDI). TGA has specific guidance relating to data management and data integrity.

Australian code of GMP

The Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (Australian code of GMP provides minimum requirements that a manufacturer should meet to ensure that their final FMT products are consistently high in quality, from batch to batch, for their intended use.

Quality management (clauses 100 to 117)

Manufacturers are responsible for establishing, documenting, implementing and maintaining a quality system to ensure that finished FMT products are safe, are of appropriate quality, and meet TGA regulatory requirements.

The quality management system covers a broad spectrum of production processes. It allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements, and to develop and implement procedures tailored to their particular processes.

Quality management and risk management principles

Section 100 of the Australian Code of GMP makes it a mandatory requirement for manufacturers to have an operational quality management system in place to ensure that the evaluation of a risk to product quality is based on a sound, scientific basis, and that risk assessments are appropriately documented.

Annex 20 of PIC/s Guide to GMP is voluntary and provides guidance only on quality risk management tools that may be applied by a manufacturer when assessing the risk to product quality.

In addition, TGA has specific guidance relating to risk management: ARGB – Appendix 11 – Risk management.

If the manufacture of the FMT product takes place in a stand-alone manufacturing facility, the manufacture should be designed and developed in a way that takes account of the requirements of the Australian Code of GMP.

Documentation

Documentation is an essential part of all manufacturing operating processing and testing at any of the above facilities. The purpose of good documentation is to ensure that:

- there are specifications for all materials used in the various stages and methods of the manufacturing to build quality into the full process
- all have sufficient instructional detail to give directions for performing process operations at specified times in order to eliminate error through the production process
- batch documents, records and test results used in the manufacture of products have all the information necessary to demonstrate GMP compliance, and the batch released by trained (authorised) persons
- there is an audit trail of documents that records all activities that directly or indirectly impact on manufactured products.

Regulated changes and change control

Regulated changes are manufacturing changes that affect the product details as defined in the ARTG and are included as they establish the requirements for the release of biologicals in Australia. These requirements are mandatory and are outlined in the Australian regulatory guidelines for biologicals (ARGB).

In addition, the requirements within the Australian Code of GMP in relation to change control and risk assessment apply to both regulated and other changes that may impact the effectiveness of the quality system.

Change control applies to all GMP-related activities in the manufacture of therapeutic goods. Change control is included in clauses 116 and 117 of the Australian Code of GMP. This clarifies the existing expectation that change control does not just apply to qualifying activities, but to all GMP-related activities undertaken by a manufacturer and states the following:

> *Any changes to existing processes, systems, facilities, equipment, products, documents, etc. should be evaluated through a change control process. The effort and extent of change control processes should be commensurate with the nature of the change and based on risk management principles.*
>
> *All changes implemented should be verified for their effectiveness following implementation.*

Managing deviations

There are no changes to the expectations for managing deviations and corrective and preventative actions (CAPAs). However, clauses 105 to 107 provide clarity regarding the expectations for the investigation of deviations, including adequate root-cause-analysis and identification of corrective and preventative actions.

Management reviews

Management reviews in clause 112 are a basic quality system element designed to collate, evaluate and communicate details of the effectiveness of the quality system to the management group. Management reviews are particularly important in escalating concerns and enabling senior management support with the aim of resolving issues and managing risks. The results of regulatory inspections and findings, audits and other assessments or commitments are made to regulatory authorities.

The management review system should identify appropriate actions, such as:

- improvements to manufacturing processes and products
- results of self-inspections
- complaints and recalls
- results from product reviews
- capture and dissemination of knowledge.

Periodic quality reviews

Periodic quality reviews as outlined in clause 113 can include:

- a review of all materials used in the product manufacture, especially new materials
- a review of critical in-process controls and finished product results
- a review of all products that failed to meet established specifications and their investigation
- a review of all significant deviations and non-conformances, the investigations and the resultant corrective actions taken
- a review of all the changes carried out on the manufacturing processes
- a review of the resultant expiry date and stability monitoring if required
- conclusions of process performance and product quality monitoring
- any follow-up actions from previous management reviews
- a review of contractual agreements to ensure they are up to date.

Personnel (clauses 200 to 214)

The correct manufacture of FMT products relies on appropriately trained people. For this reason, there should be sufficient competent personnel to carry out all the tasks in accordance with documented procedures.

Individual responsibilities should be clearly understood by all individuals processing FMT products. Organisational chart and responsibilities of key personnel, including job descriptions, should be clearly defined.

There is a particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing activities. Senior management are accountable for ensuring appropriate resources are available to support the relevant manufacturing activities.

Necessary qualifications for staff

Necessary qualifications in clause 201 of the Australian Code of GMP means having the education, training, experience and skills, or any combination of these elements, that will ensure that staff can perform assigned duties and functions at an acceptable level.

Training requirements

Training and assessment should be carried out by persons with relevant training, qualifications and experience in the subject matter (clauses 208 to 211).

Training should be given to all personnel affected by significant change, for example when procedures or methods of manufacture change. The requirement for initial and ongoing training should be reflected in procedures, and training records should be generated and kept. This concept is not new since this is a requirement for working in a hospital, both in day care clinics and hospital-based clinics.

There are a number of people who have a direct bearing on quality outcomes. These include senior management, contractors, production staff, Quality Assurance staff and casual employees. Therefore, appropriate training and assessment should be provided and recorded (clauses 212 and 213).

Signature list

Manufacturers of FMT products need to maintain a signature list. These should include the names, signatures and initials used by individuals who complete GMP documentation. The signature list is the key reference when providing traceability between manual signatures used on documents and the individuals who completed them (clauses 213 and 214).

Premises and equipment (clauses 300 to 337)

Premises, facilities and equipment should be located, designed, constructed, adapted, maintained, and suitable for its intended purpose. The layout and design should aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid adding to the existing bioburden, the build-up of dirt, and in general, any adverse effect on the quality of FMT products.

Premises

A suitable environment depends on the location of the facility, whether it is a hospital, day care clinic, or a suitable manufacturing facility.

The premises should be adequately adapted and of sufficient size and include a potential mobile unit (clean trolley) in day care clinics. The area should be designed and maintained to suit the operation(s) to be performed.

Pest control is a requirement by hospitals or clinics. There should be records including ensuring that chemicals in use are not affecting the quality of the FMT product.

To ensure the safety of the patient, security should be in place at both hospital facilities and/or day care clinics.

Where appropriate, contingency plans should be in place for breakdowns of critical services, for example, hospital generators. For day care clinics, there may be other contingency plans in place since all processes would be affected if there was a power outage.

A designated area for processing and storage of FMT products should be designed and used to avoid mix-ups and adding to the existing bioburden.

In both hospital and day care units, there is already a GMP requirement to ensure adequate cleaning to reduce infectious disease. Additional controls may include processing in a dedicated clean area or in a biological safety cabinet.

Manufacturing operations may be performed where the manufacturer has undertaken an appropriate risk assessment of the proposed operations, considered all potential risks to product quality, and detailed instructions regarding the management of operations and associated control measures.

Manufacturers should evaluate stool that is processed and ensure that adequate control measures are in place for the manufacture of FMT products.

Dedicated premises (or BSC) are normally required where the risk associated with the material cannot be adequately controlled by operational and technical measures. However, for an effective recall, cooperation from critical material suppliers is often essential.

Air quality for the manufacture of FMT products

In all cases, it is the manufacturer's responsibility to ensure that there is a documented justification to demonstrate that the air quality is sufficient for the manufacturing areas for FMT products.

Manufacturers are required to demonstrate that the manufacturing environment for FMT products affords appropriate protection to the products and prevents contamination. Use of a risk-based approach to determine the required air quality and associated controls is based on a thorough understanding of the:

- manufacturing processes
- nature of the product handled
- risks of contamination and cross-contamination
- risks to FMT product quality.

Equipment

Manufacturing equipment for FMT products should be designed, located and maintained to suit its intended purpose. Equipment should not present any risk to the FMT products.

The equipment that comes in contact with the FMT product should be compatible with the product, should not leach harmful materials and/or infect the final product.

There should be a unique identification for the equipment in use just in case there is an adverse event and an investigation is required so is thereby traceable to all records.

There should be information on the use of equipment and its effect on the manufacture of the product and what is to be done if the equipment failed.

Cleaning of equipment should be in place along with records that equipment has been sanitised.

Where controlled temperature conditions are required (including during transport and storage of final product), there should be temperature recording devices and records kept and reviewed. This is already a requirement in certain sections of hospitals and day care clinics.

Cleaning and sanitisation

The manufacturer of the FMT product is responsible for demonstrating that the applied cleaning and sanitisation procedures for the premises and equipment are suitable for its intended purpose. This can be demonstrated by qualification, validation and monitoring studies. The extent of these studies will depend on the nature and types of products manufactured and the associated risks of cross contamination of unwanted pathogens that could potentially support the intrusion of microbial competitors that could have a pathogenic outcome for the host.

The manufacturer of the FMT product is responsible for cleaning the area so that no remaining FMT product remains from a previous manufacture.

Documentation (clauses 400 to 415)

The minimal GMP requirements to obtain a licence for low risk activities performed within an accredited hospital include a documentation system that:

- has procedures for the investigation of non-conformances
- manages changes to the process
- reports adverse events
- reviews data that may impact on the process over a specified period.

Documentation is an essential part of QA and relates to all aspects of GMP. Good documentation defines the system of information and control, minimises the risk of misinterpretation and error inherent in oral or casually written communication, and provides unambiguous procedures to follow.

All processes and associated activities in the manufacture of FMT products should be documented, and the documentation controlled.

The cost of poor quality documents is hard to measure but there is considerable time wasted through interpretation of poorly documented data, recovering from errors in data collection, and failing both internal and external audits.

Documents should be:

- designed
- prepared
- reviewed
- distributed with care.

Documents should show:

- what was done
- how it was done
- when the work is performed
- who performed the work.

Documents should also:

- define how to carry out protocol-specified activities
- include a chronological listing of any step performed as part of the manufacture of the FMT product and record all information
- include long-term storage of final records that follow hospital state and federal legislation
- be reviewed at regular intervals
- be removed when considered obsolete documents.

Control of material (clauses 500 to 512)

All materials, that may affect the quality and safety of the FMT product, should be controlled and meet defined specifications. The level of control of each material should reflect its use and potential risk to the product.

All handling of materials, such as receipt and quarantine, sampling, release, storage, and labelling, should be performed in accordance with written procedures and, where necessary, recorded.

The requirement of both hospitals and day care centres to use hospitals and/or day care clinic suppliers for manufacturing materials (e.g. containers and reagents such as saline that is sterile and within expiry) is acceptable for Class 1 biologicals. This would meet minimal requirements.

However, manufacturers of Class 2 biologicals are required to comply with section 500 of the Australian Code of GMP, TGO 88 (section 13) and TGO 105.

There should be approved quality control (QC) specifications for any manufacturing materials that may have a direct impact on the manufacture of FMT product. Material that does not conform to specifications should not be inadvertently used. It should be stored at a different location.

Subcontracting (clauses 600 to 602)

Any activity covered by the Australian Code of GMP that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings that could result in a product or operation of unsatisfactory quality. There should be a written contract between the contract giver and the contract acceptor that clearly establishes the duties of each party.

Examples of outsourced activities include, but are not limited to:

- contract manufacturing and analysis, for example donor testing laboratories, FMT testing
- maintenance and calibration services, for example BSC, generator, power, temperature monitoring equipment, pipettes if required
- providers of critical consumables, for example bottles, pipette tips, laboratory coats
- suppliers and manufacturers of raw materials, packaging materials and printed artwork
- provision of training and consulting services
- provision of transport and logistical services for products
- contract cleaning (hospital cleaning is accepted)
- clinical and general waste management services
- contract pest control services
- contract IT services.

Monitoring the contract acceptor

The contract acceptor must not subcontract any work without written authorisation from the contract giver.

For contract service providers (for example, contract calibration services), it would be appropriate for the contract giver to review the available records and data to ensure that the results or work provided meet the requirements of the contract giver's quality system and procedures.

Complaints and recalls (clauses 700 to 704)

TGA has published procedures for the uniform recall of therapeutic goods.

There may be further State or Territory regulatory requirements that are applicable, which should be checked with the relevant local authority.

There should be a procedure established, implemented and maintained for the investigation of adverse events and product complaints.

Adequate monitoring of patients over time must be maintained to detect such occurrences as late adverse effects and to also allow for an analysis of pharmaco-epidemiology and pharmaco-economics.

Collection and processing (clauses 800 to 841)

Collection

The efficacy of FMT products must be monitored by an independent organisation (for example, a competent authority) to safeguard patients and allow for evidence-based decision-making.

Collection and processing activities should be conducted in a manner that minimises both errors and risks associated with adding to the existing bioburden.

In the case of critical materials including starting material (stool), their receipt, quarantine, sampling, storage, labelling, collection, processing and release for supply should all be performed in accordance with written procedures.

The selection of stool donors and relevant screening tests including those for infectious agents in stool and blood should ensure that manufactured FMT products are suitable for the intended use. Records should include the following:

- donor consent (state and federal requirements need to be considered)
- donor questionnaire (medical history) (clause 806 of the Australian Code of GMP)
- donor medical assessment: stool and blood samples
- microbiome specific exclusion criteria
- critical materials used that are traceable to specific donations
- any other information may affect the quality of the FMT product.

Donation number or unique identifier (ID) to the stool donor should be on all products and sample containers and on all donor records. The procedure for identification labelling should be available to avoid any risk of error or mix-up.

The confidentiality of the stool donor should be maintained.

There should be information on the transport of the collection of FMT product.

Processing

FMT products should be processed in a physical area and in a manner that will prevent contact or cross-contamination with FMT products from other donors. Before processing, the work area and equipment should be cleaned and free from contamination with starting material (stool).

The process record should provide traceability and, as applicable, include:

- date, time, venue, and unique identification number(s)
- identity of staff performing critical steps
- in-process QC tests
- equipment used
- label of products prepared from one donor or multiple donors
- storage requirements (for example, room temperature, 2–8°C, -80°C)
- release specifications.

Cryopreservation

In instances of banked stool, cryopreservation records should be maintained that include the time and temperature of the process, stamp date, and time when the FMT product was placed in the freezer.

Freeze drying

Freeze drying records should be maintained that include time, temperature and vacuum pressure at each step in the cycle, along with any required specification required for release.

Storage and despatch

Storage and despatch should be performed according to documented procedures to ensure product quality and a process to control the storage of products.

Validation

Facilities, systems, equipment and processes should be tested and qualified to verify that they are operating in a valid manner. In addition, periodic evaluation should be in place to ensure ongoing effectiveness.

Quality Control (clauses 900 to 918)

FMT must be conducted with stool that meets rigorous quality standards (for example, absence of pathogens and infectious transmittable diseases) to limit the risks to the recipient.

Quality Control is concerned with sampling specifications and testing, with all necessary tests carried out according to documented procedures to ensure that the released product meets specifications.

Computers (clauses 1000 to 1017)

For Class 1 biologicals

Hospital record-keeping systems must meet the minimal requirements for the storage of electronic data.

For Class 2 biologicals (or greater)

Section 1000 of the Australian Code of GMP applies for Class 2 biologicals (or greater).

Section 1000 has been updated to provide clarification of existing requirements to ensure that computerised systems are managed appropriately, particularly in relation to data management and integrity.

In some cases, the wording of the clauses has been made less prescriptive to allow for better use of quality risk management principles in the validation and control of computerised systems.

Validation and control of computerised systems

The level, extent and formality of system control should be commensurate with the criticality of the system. Manufacturers should have a good understanding of all the systems used, along with the impact and criticality of each system. Examples of systems that should be fully validated and controlled include, but are not limited to:

- for the electronic acquisition of QC data
- to control and monitor the operation of critical utilities, facilities and equipment
- to generate, store or access electronic GMP records
- to generate, process, calculate or monitor data that forms part of the batch processing record, or batch control testing records
- electronic spreadsheets to track records or data, or to perform calculations, in the place of physical (hard-copy) records
- to perform the release of materials and release for supply of finished goods
- to track the distribution of products and/or control the reconciliation of products and materials in the case of quality defects or recalls
- to manage quality investigations and store and track investigation records, for example deviations, out of specifications, complaints and change control.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	September 2020

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #