Australian Government
Department of Health
Therapeutic Goods Administration

ARGB Appendix 10 - Guidance on TGO 105: Standards for faecal microbiota transplant (FMT) products

Australian Regulatory Guidelines for Biologicals (ARGB)

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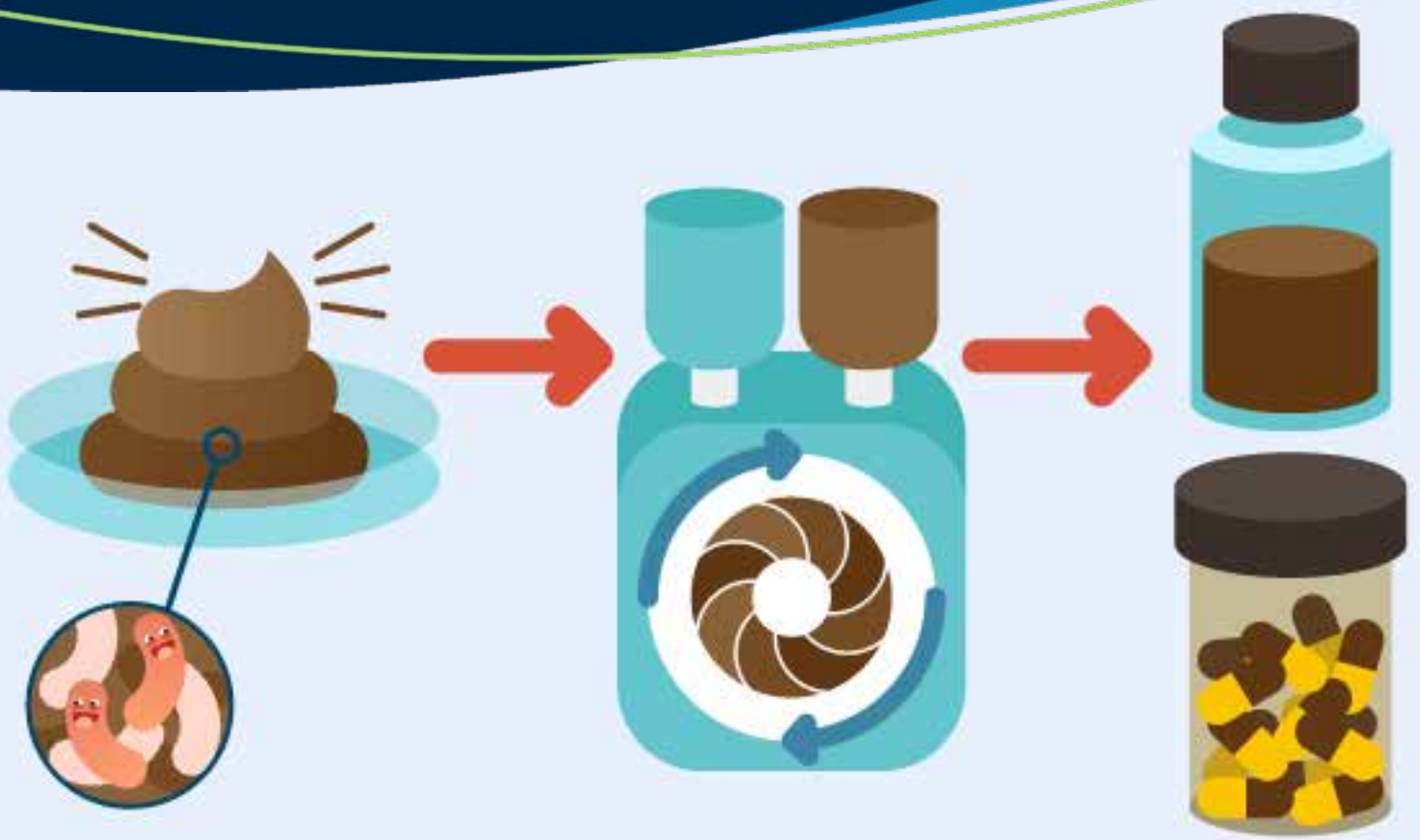
TGA Health Safety Regulation



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About this guidance

This guidance describes the requirements for manufacturers and sponsors of faecal microbial transplant (FMT) products in the Therapeutic Goods (Standards for Faecal Microbiota Transplant Products) (TGO 105) Order 2020 as prepared by the Therapeutic Goods Administration (TGA).

TGO 105 outlines the mandatory standards for FMT product providers, including all sponsors and manufacturers.

TGO 105 includes specific requirements to ensure the safety and quality of FMT products that are manufactured from both frozen and fresh stool.

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 email TGA's Biological Sciences Section (BSS): bloodandtissues@health.gov.au.

General information about TGO 105

TGO 105 specifies the minimum criteria to minimise the risk of infectious transmission during the manufacture of FMT products. Make sure you familiarise yourself with the requirements described in TGO 105, particularly:

- Division 1 – General requirements, including manufacturing
- Division 2 – Requirements relating to screening
  - General screening procedures
  - Medical and social history
  - Blood, stool and other samples – taking and testing
  - Physical assessment
- Division 3 – Requirements following collection, including microbial control procedures
- Schedule 1 – Ineligibility criteria for donor selection.

Commencement and transition periods

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**.

Review of TGO 105

TGO 105 will be reviewed regularly as changes in legislation, emerging technology, and best practice occur. Sponsors and manufacturers are encouraged to discuss with TGA any proposed changes in practice or evolving technologies that may affect, or be affected by, the requirements of TGO 105.

Send all enquires to TGA's Biological Sciences Section (BSS): bloodandtissues@health.gov.au.

Demonstrating compliance with TGO 105

As an FMT product provider, you must comply with requirements that contribute to the quality and safety of your FMT products, and that mitigate infectious disease risks.

The requirements of TGO 105 apply to all FMT products, including some additional donor screening and testing requirements for donors of stool used to manufacture fresh FMT products.

This reflects the need to mitigate higher risks associated with the use of stool from donors used in fresh FMT products that have not undergone a second round of donor screening prior to use.

Facilities supplying FMT products as Class 1 biologicals

Facilities that supply FMT products that are Class 1 biologicals will need to make an application for inclusion in the Australian Register of Therapeutic Goods (ARTG).

With this application, you are required to sign **a declaration** that processes comply with all of the requirements in TGO 105. An application and declaration must be received by TGA prior to 1 July 2021 for supply to continue after this date.

We may request supporting information from a manufacturer at any time to demonstrate compliance with specific aspects of compliance to TGO 105. No pre-market assessment of compliance is performed.

Facilities supplying FMT products as Class 2 biologicals (or greater)

Facilities that supply FMT products that are Class 2 biologicals (or greater) will need to submit a dossier to TGA demonstrating compliance with TGO 105. We will review and approve this supporting information before inclusion of the FMT product in the ARTG.

An application for inclusion in the ARTG and for a manufacturing licence must be received by TGA prior to 1 July 2021 for supply to continue after this date.

If you are planning to prepare a dossier for submission and are uncertain of requirements, we suggest you contact the Biological Sciences Section (bloodandtissues@health.gov.au) for further guidance.

Guidance on the requirements of TGO 105

Part 1 – Preliminary

Part 1 outlines preliminary requirements for TGO 105 including name, commencement, authority, definitions, standard and application (sections 1 to 6).

Part 2 – Requirements for FMT products

The requirements outlined in part 2 are designed to capture principles that ensure the quality and safety of FMT products.

These requirements are largely equivalent to Therapeutic Goods Order No. 88 - Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products (TGO 88).

Division 1 – General requirements

Section 7 – What this Division is about

This division specifies the general requirements that must be met in the manufacture of FMT products.

Section 8 – General requirements

This section ensures that facilities processing and supplying FMT products that are Class 1 biologicals, which are exempt from TGA licencing, still apply minimal principles of GMP to their facilities.

8 General requirements

(1) FMT products must only be manufactured using stool that has been collected from an accepted donor.

(2) The procedures and controls used in the manufacture of FMT products must:

  (a) be clearly defined and documented in a systematic way in the form of written policies and standard operating procedures; and

  (b) ensure that the FMT products are safe for use; and

  (c) ensure the FMT products are manufactured consistently and comply with the specifications for the products; and

  (d) be systematically reviewed and, if appropriate, modified.

(3) The procedures must ensure the traceability of stool used in the manufacture of FMT products from the collection of the stool to the supply of the products.

(4) The critical materials used in the manufacture of FMT products must not adversely affect the quality or safety of the products.

(5) The personnel involved in the manufacture of FMT products must be appropriately qualified and competent to manufacture FMT products.

(6) The test methods used in the manufacture of FMT products must be validated or verified.

(7) The equipment and reagents used in the manufacture of FMT products must be qualified.

(8) A system must be established and maintained to:

(a) handle complaints made or concerns raised by any person in relation to the manufacture of FMT products; and

(b) ensure process and quality improvement functions and activities are carried out regularly.

Manufacturing must take into account GMP principles

All manufacturers of FMT products must ensure that:

- the design and construction of the manufacturing facility is suitable to the type of processing conducted, with separation of areas for minimising mix-ups/contamination
- a documented process is in place to demonstrate that donor test results that are indicative of a disease or carrier state are reported back to that donor, where necessary.

If the manufacture of an FMT product takes place in a hospital, the facility and procedures should be designed and developed in a way that takes account the principles of GMP.

Where a facility holds a TGA manufacturing licence, compliance with the requirements outlined in this subsection are achieved through complying with the requirements of the Australian Code of GMP.

Guidance is available to assist facilities on how the Australian Code of GMP applies to the manufacture of FMT products.

For enquiries about GMP, e-mail TGA's Manufacturing Quality Branch (MQB): gmp@tga.gov.au.

Critical materials

You must ensure that critical materials used in the collection and manufacture of FMT products will not adversely affect the quality and safety of the products.

Critical materials include all supplies and reagents that come into **direct contact** with the stool during any stage of manufacture, including primary containers and collection kits.

Equipment used in the manufacturing process of FMT products that does not come into direct contact with stool is not a critical material, for example, centrifuges.

Selecting and evaluating suitable critical materials

Ensure the suitability of critical materials by reviewing:

- material specifications provided by the material supplier

OR

- testing performed by the manufacturer, to demonstrate suitability

If material specifications are not provided, or the documents do not provide sufficient evidence, you may need to perform testing on critical materials to ensure they are suitable for use and not contaminated with, or likely to introduce, bacterial or other infectious agents.

Justifying suitable critical materials

You will need to justify the suitability of all critical materials used in the collection, manufacture, storage and release of the stool and resulting FMT product.

Refer to Section 13 of TGO 88 for guidance on the level of evidence that may need to be provided to demonstrate suitability of solutions, containers, and human- and animal-derived materials.

If any of the critical materials are included in the ARTG, you:

- can cross-reference the ARTG number
- do not need to resubmit validation data for reassessment
- should include a statement justifying that the critical material is being used for the same purpose for which it is registered and that it meets the sterility requirements.

Selection and evaluation of a critical material can include documents provided by the material manufacturer or of suitability testing performed by the manufacturer. Justification of the selection and evaluation of critical material should be included in the submitted dossier.

Manufacturers need to determine what requirements are applicable to critical solutions. A filter integrity test should be performed on the filters used to sterilise solutions. It is necessary to verify that the sterilising filter is compatible with antimicrobial solutions.

Critical equipment and containers

Where equipment and containers are in direct contact with stool, they should be sterile and/or single-use. If reusable equipment and containers are used, they are subject to validated and monitored cleaning and sterilisation processes to minimise risk of cross-contamination.

Division 2 – Requirements relating to screening

Section 9 – What this Division is about

This division specifies procedures relating to screening that must be implemented in the manufacture of FMT products.

Section 10 – Proposed donors and accepted donors

This section defines a 'proposed donor' and an 'accepted donor' of stool for the manufacture of FMT products.

10 Proposed donors and accepted donors

(1) A ***proposed donor*** is a person, other than an accepted donor, from whom stool is proposed to be collected for use in the manufacture of FMT products.

(2) An ***accepted donor*** is a person:

(a) who has undertaken the screening procedures applicable to proposed donors specified in this Division; and

(b) following those procedures, has been determined to be eligible to donate stool for use in the manufacture of FMT products in accordance with this Division;

but does not include a person mentioned in subsection (3).

(3) A person ceases to be an ***accepted donor*** if the person fails to satisfy any of the screening procedures applicable to accepted donors specified in this Division.

This separation has been made to clarify when requirements apply to persons who may:

- be suitable donors

OR

- have passed screening and been/are accepted as a FMT donor.

The provisions highlight that in some circumstances, a person can cease to be an 'accepted donor' and must repeat the qualification process required of a 'proposed donor' when a significant period of time has lapsed since they were last screened, or where information has become available to suggest the donor is no longer suitable.

Section 11 – General screening procedures

This section specifies the key principles for assessing the suitability of a proposed donor to ensure there is minimal risk of transmission of infectious diseases.

11 General screening procedures

(1) Screening procedures must be implemented in relation to proposed donors and accepted donors to ensure that the quality, safety and efficacy of FMT products is acceptable.

(2) The screening procedures must include:

(a) review of medical and social history in accordance with section 12;

(b) taking of blood, stool or other samples in accordance with section 13;

(c) testing of blood, stool or other samples in accordance with section 14; and

(d) physical assessment in accordance with section 15.

Three tiers of risk minimisation

To minimise the risk of infectious disease transmission from stool donor to FMT product recipient, **3 tiers** of risk minimisation work together to provide a safety net:

- tier 1: medical and social history of a proposed donor
- tier 2: taking and testing of a proposed donor's blood, stool or other samples
- tier 3: performing a physical assessment of a proposed donor

Screening requirements for proposed donors

A summary of screening requirements for proposed donors of stool used in the manufacture of FMT products is outlined in Table 1. Please refer to the information provided in this document for more detailed guidance.

Table 1: Screening requirements for proposed donors of stool used in the manufacture of FMT products

(a) Stool donors for FMT products, other than fresh FMT products

Screening criteria	Requirement	<30 days before first stool donation	First stool donation	During Collection period	End of collection period	> 90 days of first blood sample	Ongoing screening requirements	Every 90 days
Medical and social history	Interview	Yes	No	No	No	No		Yes
	Abridged history	No	Yes	Each donation	No	No		No
Testing of stool	Microorganism detection	Yes	No	No	Yes	No		Yes
Testing of blood	NAAT and serology	Yes	No	No	Yes	No		Yes
	or serology only	Yes	No	No	No	Yes		Yes
Physical assessment	Clinical examination	Yes	No	No	No	No		Yes

(b) Stool donors for fresh FMT products

Screening criteria	Assay	<30 days before first stool donation	First stool donation	Ongoing stool donations	Ongoing screening requirements	Every 90 days
Medical and social history	Interview	Yes	No	No		Yes
	Abridged history	No	Yes	Each donation		No
Testing of stool	All specified microorganisms	Yes	Yes	No		No
	Other microorganisms	No	No	Frequency based on risk assessment		No
Testing of blood	NAAT and serology	Yes	Yes	No		Yes
Physical assessment	Clinical examination	Yes	No	No		Yes

Section 12 – Medical and social history

The requirements in this section are to assist in determining the suitability of a proposed donor of stool for the manufacture of FMT products.

12 Medical and social history of proposed donors

(1) A complete medical and social history, covering the ineligibility criteria for donor selection specified in Schedule 1 and any other relevant matters, must be obtained from a proposed donor by interview, and reviewed for the purposes of screening.

(2) The interview must be:

(a) conducted by an interviewer who is appropriately qualified; and

(b) undertaken not more than 30 days prior to the first collection of stool for use in the manufacture of FMT products; and

(c) held face to face between the proposed donor and the interviewer, to the extent that it is possible in the circumstances; and

(d) documented.

Medical and social history

You **must include questions** that capture information from proposed donors that relate to each of the ineligibility criteria for donor selection specified in schedule 1 and other relevant matters, as required by subsection 12(8).

The ineligibility criteria in schedule 1:

- reflect those where there is international consensus about risks that could impact on the quality or safety of the stool
- are minimal requirements to determine donor suitability.

Additional detailed guidance on interpretation of each of the requirements is outlined in schedule 1 of this document.

There is no mandated format of the questionnaire, but one or more questions may need to be asked to ascertain sufficient information about a donor to address each of the criteria outlined.

Donor interview process

Face-to-face interviews with proposed donors are preferable, that is, with both the interviewer and proposed donor in the same room, but if this is not possible, then videotelephony products can be used.

If a face-to-face interview is not possible or practical, you need to:

- justify alternative interview arrangements
- ensure a face-to-face physical assessment is conducted prior to, or at the time of, stool donation

This is a key risk mitigation step in screening the health of a proposed donor.

Preliminary information

You may obtain preliminary information from proposed donors, prior to the formal interview, to screen out certain high-risk donors early in the selection process.

However, for donors that progress through the screening process, the interviewer **must confirm** the donor's information and currency during the interview.

Interviewers

The interviewer must be familiar with, or trained in, the screening of donors of stool for the preparation of FMT products.

Protocols need to be in place for on-boarding new staff as interviewers, with their training designed to safeguard the health of both the donor and the recipient. The interviewer needs to understand the ineligibility criteria, record the information, and know when they can call for assistance from healthcare professionals and medical officers to interpret specific information. All procedures must be documented and staff trained accordingly.

Timing of interviews

The donor interview may be conducted in several parts, but all of the criteria outlined in schedule 1 must be covered no more than 30 days prior to stool donation.

12 Medical and social history of accepted donors

(3) The complete medical and social history must be repeated in relation to an accepted donor on an ongoing basis, such that each complete medical and social history is obtained within 90 days of the last complete medical and social history.

(4) An abridged medical and social history must be obtained, reviewed and documented, each time stool is collected for use in the manufacture of FMT products from an accepted donor, covering any relevant matters determined on the basis of a risk assessment, including one or more of the ineligibility criteria for donor selection specified in Schedule 1.

Interviews must be repeated every 90 days

For accepted donors that continue to donate or be available to donate over an extended period, the medical and social history must be collected every 90 days. All of the questions asked in the initial interview need to be repeated.

If a donor has not donated for a period of greater than 90 days, they are no longer deemed an accepted donor and must repeat the initial interview process no more than 30 days prior to a donation.

Medical and social history must be obtained and recorded for each donation

For accepted donors, certain medical and social history criteria must still be obtained and recorded at the time of each stool donation.

Medical and social history can be an abridged version of the questions asked in the full interview, but must include all criteria listed in schedule 1 that could change acutely since the initial history was obtained.

For example, questions may relate to general health and symptoms suggestive of:

- a new gastrointestinal infection (for example, diarrhoea, nausea, abdominal pain, vomiting) or an acute other infection (for example, fever, swollen lymph nodes, cough)
- the use of new medications and travel to high risk geographic regions

Cammarota et al. (2017) provides some additional guidance on questions that should be regularly asked of accepted donors.[1]

This abridged medical and social history collection does not have to be performed as an interview. For example, educational material could be given to donors about the questions they must consider prior to each donation, and the donors then provide a signed declaration that this list has been considered and accepted with each donation.

12 Review of an accepted donor

(5) Where the circumstances of an accepted donor change in relation to either the ineligibility criteria for donor selection specified in Schedule 1 or a disease or condition referred to in subsection (8), the relevant aspects of the medical and social history of the donor must be reviewed with respect to those changes before:

(a) stool collected from the accepted donor is used in the manufacture of FMT products; and

(b) FMT products that are manufactured using stool collected from the accepted donor are released for supply.

The suitability of a donor may change after they have been accepted as a donor and/or stool collected. For example, if a donor develops symptoms of an infection or becomes aware of additional medical history that may have been relevant to their suitability.

Following notification of such information, a review must occur for the suitability of:

- that donor to continue
- any stool previously collected from the donor for the manufacture of FMT products.

12 Screening requirements for allogeneic use

(6) Where a proposed donor or accepted donor meets any of the ineligibility criteria for donor selection specified in column 2 of an item in the table in Schedule 1, the donor is subject to the period of ineligibility specified in column 3 of that item in relation to the collection of stool from that donor for use in the manufacture of FMT products intended for allogeneic use.

Suitability of a proposed donor for allogeneic use

Following collection of the medical and social history of a potential donor, the suitability to donate must be assessed against the ineligibility criteria specified in Schedule 1.

For some criteria, the donor may only be ineligible for a short period of time (for example, until an active infection resolves), or may be permanently ineligible as a donor. More detailed guidance is provided in schedule 1 of this document.

[1] Box 2: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).

12 Screening requirements for autologous use

(7) Where a proposed donor or accepted donor meets any of the ineligibility criteria for donor selection specified in column 2 of an item in the table in Schedule 1, a risk assessment must be conducted as to whether the donor should be subject to the period of ineligibility specified in column 3 of that item, in relation to the collection of stool from that donor for use in the manufacture of FMT products intended for autologous use.

Conduct a risk assessment for autologous donors

Stool may be collected from an autologous donor and frozen for a period prior to reinfusion to the same patient at a later time.

This allows treating physicians to determine the extent of the medical and social history to be recorded when stool is collected for autologous use. Treating physicians are expected to conduct a risk assessment in such circumstances because there are still risks associated with the handling of infectious material and appropriate storage and labelling of stool.

12 Diseases or conditions not mentioned in Schedule 1

(8) Where a proposed donor or accepted donor has a disease or condition that may compromise the quality, safety or efficacy of FMT products manufactured using stool collected from the donor, and the disease or condition is not mentioned in the table in Schedule 1, then stool collected from that donor must not be used in the manufacture of FMT products, unless:

(a) criteria for donor selection and periods of ineligibility are applied that support and justify the quality, safety and efficacy of the FMT products for the intended use of the products, and the application of the criteria is documented; or

(b) a registered medical practitioner has agreed to, and documented the rationale for, the use of the stool in the manufacture of FMT products.

Additional factors that may compromise the quality, safety or efficacy of FMT products

There is a general requirement to consider additional clinical presentations, quality of the stool, general donor health status, and other conditions that have been associated with gut dysbiosis that may compromise the quality, safety or efficacy of FMT products. This subsection provides flexibility to implement additional criteria to those mentioned in schedule 1 that may result in rejection of a donor group based on emerging clinical evidence or a clinical determination.

Donor exclusion **must** occur wherever there is evidence of a condition or disease that may be transmissible.

Donor deferral must be considered for conditions where there is an association with gut dysbiosis, but the current level of scientific evidence to defer such donors is not yet conclusive. This includes:

- atopic disease
- chronic pain condition
- psychiatric disease
- neurological disease

- non-GI malignant disease
- developmental disorder
- chronic fatigue
- autism spectrum disorder
- attention deficit hyperactivity disorder (ADHD)

For most of these conditions, clinical judgement is also required to determine the suitability of an individual donor.

Other examples of criteria that may be applied to defer donors include a visual assessment of the donor's stool against the Bristol stool scale.[2]

Sponsors must have a list of suitable criteria that is actively monitored (annually at a minimum). This is crucial in what is a rapidly-evolving therapeutic area.

During evaluation of an application to register an FMT product in the ARTG, TGA will review and approve this list of criteria. Going forward, any changes to the list will need to be submitted to TGA as a variation to the ARTG entry for consideration and approval prior to implementation. Where a change is based on a recommendation from the Gastrointestinal Society of Australia (GESA) or Australian Consensus Working Group (CWG), the change may only need to be notified to us.

Where TGA becomes aware of a new safety or quality aspect that should be considered in the donor interview, we may contact sponsors directly and publish an update on our website. An example of this is the safety alert from the US FDA in 2019 to providers of FMT products of the need for specific donor screening questions for the risk of transmission of multidrug-resistant organisms (MDROs).[3]

12 Stool collected outside Australia

(9) Where stool is proposed to be collected outside Australia, a risk assessment must be conducted as to whether any additional matters, including additional medical and social history criteria and periods of ineligibility, need to be considered and documented in addition to the ineligibility criteria specified in Schedule 1.

The requirements outlined in TGO 105 take into consideration the unique epidemiology of donors residing permanently within Australia. These requirements may not be suitable for donors residing permanently outside of Australia.

Consider what additional social and medical history may need to be collected from donors residing permanently outside of Australia. In regions with a high MDRO risk or GI pathogen risk, it may not be appropriate to accept donors, especially if the risk relates to organisms that cannot be routinely screened.

Consensus documents published within the permanent home jurisdiction of proposed stool donors may provide insight to local epidemiological risks and appropriate donor workup.

[2] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 32: 920-924 (1997).
[3] DeFilipp Z, et al. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. *N Engl J Med*. 381: 2043-2050 (2019).

12 Upper and lower age limits

(10) Upper and lower age limits must be applied in relation to a proposed donor, having regard to the intended use of the FMT products and the extent to which the age of the proposed donor may compromise the quality, safety, or efficacy of FMT products that are manufactured using stool collected from that donor.

Apply upper and lower age limits for stool donors

Age limits **must** be set based on the potential to compromise the safety and efficacy of the FMT product.

Generally, donors should be aged between 16-60 years, as per the Australian CWG.[4] For donors aged 50+, appropriate bowel cancer screening should be completed. For donors aged 60+, additional justification should be provided as to why the donated stool is still appropriate.

Section 13 – Taking of blood, stool and other samples

This section specifies the minimum requirements for the taking of blood, stool and other samples from proposed donors.

The testing to be performed on these samples is outlined in section 14.

13 Fresh FMT products

(1) Where stool is to be collected from a person for use in the manufacture of fresh FMT products, blood samples must be taken:

(a) from the person (as a proposed donor) not more than 30 days before the first collection of stool; and

(b) from the person (as an accepted donor) at the time of the first collection of stool; and

(c) from the person (as an accepted donor) on an ongoing basis, such that each blood sample is taken within 90 days of the last blood sample.

(2) Where stool is to be collected from a person for use in the manufacture of fresh FMT products, stool samples must be taken:

(a) from the person (as a proposed donor) not more than 30 days before the first collection of stool; and

(b) from the person (as an accepted donor) at the time of the first collection of stool; and

(c) from the person (as an accepted donor) at regular intervals determined on the basis of a risk assessment.

13 FMT products other than fresh FMT products

(3) Where stool is to be collected from a person for use in the manufacture of FMT products, other than fresh FMT products, blood samples must be taken in accordance with either of the following paragraphs:

[4] Haifer C, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. *Gut* 69: 801-810 (2020).

(a) blood samples must be taken:

(i) from the person (as a proposed donor) not more than 30 days before the first collection of stool; and

(ii) from the person (as an accepted donor) on the day that, or not more than 30 days after, the collection period ends; and

(iii) from the person (as an accepted donor) on an ongoing basis, such that each blood sample is taken within 90 days of the last blood sample; or

(b) blood samples must be taken:

(i) from the person (as a proposed donor) not more than 30 days before the first collection of stool; or

(ii) from the person (as an accepted donor) not less than 90 days after the blood samples were collected in accordance with subparagraph (i); and

(iii) from the person (as an accepted donor) on an ongoing basis, such that each blood sample is taken within 90 days of the last blood sample.

(4) Where stool is to be collected from a person for use in the manufacture of FMT products, other than fresh FMT products, stool samples must be taken:

(a) from the person (as a proposed donor) not more than 30 days before the first collection of stool; and

(b) from the person (as an accepted donor) on the day that, or not more than 30 days after, the collection period ends; and

(c) from the person (as an accepted donor) on an ongoing basis, such that each stool sample is taken within 90 days of the last stool sample.

13 Other samples

(5) In addition to the samples required to be taken in accordance with this section, samples other than blood or stool samples may be taken from a proposed donor or an accepted donor where scientifically justified in the circumstances.

13 Stool samples for storage

(6) A stool sample must be taken from each stool that is collected for use in the manufacture of FMT products, and stored in accordance with subsections 14(16) and 14(17).

Blood, stool and other samples from proposed donors

The possible starting materials for FMT products are:

- stool that is collected and used in the manufacture of fresh FMT products

  AND

- stool that is frozen to allow re-testing of the donor prior to processing and use.

The risks associated with using fresh stool in the manufacture of FMT products are higher, so the sampling and testing requirements for this starting material are also higher.

Generally, samples of blood and stool are required to be taken from proposed donors, but other samples may also be taken for testing of potential organisms present in stool, for example, nasopharyngeal swabs for SARS-CoV-2.

Often samples are not taken from proposed donors until they have already passed the review of their medical and social history. Table 1 summarises the sampling requirements.

For donors of fresh stool that donate over an extended period, sampling and testing must occur at regular intervals. The onus is on the facility to justify the frequency of sampling based on a risk assessment.

Blood, stool and other samples from accepted donors

For most stool donors, repeat blood, stool and other samples must be taken and tested either:

- on the day of the last donation in a donation window (usually 2-6 weeks)

  OR

- within 3 days of this last donation, if nucleic acid amplification testing (NAAT) is performed.

If the donor is to be screened using repeat serology, the repeat blood sample must be taken > 90 days from the first sample.

Please refer to Table 1 for a summary of sampling requirements.

Blood, stool or other sample testing must be performed at least every 90 days

It is important to ensure the ongoing safety of all stool donors following the initial screening and testing.

Blood, stool or other samples must be tested at least every 90 days. Consider retesting donors more frequently if any changes are noted to a donor's medical and social history.

More frequent testing for some infectious agents may be implemented, but at a minimum all testing outlined in section 14 must be repeated within the 90-day period. This does not place any restriction on a facility imposing a stricter testing regime such as daily testing for certain infectious disease agents.

Regular stool sampling for donors of fresh FMT product, based on a risk assessment

Careful consideration should be given to the frequency of stool sampling from an accepted donor for specific stool microorganisms outlined in section 14. Generally, daily or weekly screening for those microorganisms that may appear in the stool of asymptomatic donors would be appropriate.

Collection and storage of stool samples

The primary role of retention samples is to allow 'look-back' of donor suitability should a safety issue be identified later.

Failure to store a sample or loss of a sample is a 'non-conformance' and should follow internal non-conformance procedures. This may be subject to review during GMP inspection, if applicable.

Section 14 – Testing of blood, stool and other samples

The requirements in this section reflect where there is general international consensus on the need to perform tests to lower the risk of stool donation.

Sample quality and validation of donor testing methods are critical for determining donor suitability.

14 General testing requirements

(1) Samples taken in accordance with section 13, other than stool samples taken in accordance with subsection 13(6), must be tested as soon as practicable after collection in accordance with this section, and within the claimed sample stability timeframe specified by the manufacturer of the IVD medical device or in-house IVD medical device to be used for the testing.

(2) Samples that are tested for infectious diseases must be tested using IVD medical devices or in-house IVD medical devices that:

(a) use the most appropriate methodology available for testing the samples in relation to the target organisms; and

(b) where testing is conducted in Australia—are either included in the Register or exempt from the requirement to be included in the Register, or the subject of an approval or authority under the Act; and

(c) where testing is conducted outside Australia:

(i) are approved by a relevant regulatory authority in the country in which the testing is conducted; and

(ii) are used in a facility that has been approved for such testing by a relevant regulatory authority in the country in which the testing is conducted; and

(iii) are considered acceptable by the Therapeutic Goods Administration.

(3) Where testing is conducted by a laboratory that is not under the direct control of the manufacturer of the FMT products:

(a) the testing must be conducted under a contract between the manufacturer and the laboratory; and

(b) the contract mentioned in paragraph (a) must clearly set out the responsibilities of the manufacturer and the laboratory, and include arrangements to ensure information relating to matters in this section and any other relevant details relating to the IVD medical devices or in-house IVD medical devices used for such testing can be obtained from the laboratory.

Blood, stool or other sample testing must be in accordance with test kit instructions

All sample collection and handling must be conducted in accordance with test kit instructions. Testing must also be within the timeframes stipulated in the instructions.

If sample collection and handling is not performed according to test kit instructions, validation to support the changes must be demonstrated.

Most appropriate methodology

The most appropriate methodology shall be determined and justified by the sponsor. The infectious diseases test screening protocol could be an 'in-house' test or a commercial kit and may be conducted by the sponsor or a contract laboratory. The sponsor must also consider using new testing methods, including more sensitive assays, as they become available.

Approval by a relevant regulatory authority in the country in which the testing is undertaken

For the use of kits within Australia, this means the supply and use complies with the IVD regulatory framework. This could mean that the kits are in the ARTG as Class 4 IVDs or may be accessed through the exemption for Class 4 in-house IVDs intended to be used in the screening of stool donors for the purpose of FMT product manufacture.

The current amendment exempts laboratories that develop and use these types of IVDs from the requirement to include them as devices in the ARTG. The exemption is intended to be in place for a time period that allows providers to work with TGA to establish processes that allow for data to be generated and collated that support performance as a Class 4 in-house IVD.

This data will contribute to the clinical evidence required to address some of the residual risks associated with detection of specific organisms in stool samples of donors, and their relevance to potential transmission. The proposed amendments also provide for a requirement to notify TGA so that we are aware of the devices being used for this screening purpose.

Any testing performed on additional organisms (above those specified) will also qualify as Class 4 or Class 4 in-house IVDs.

Where test methods are used beyond the level approved by the local regulatory approval, validation to support the extended use must be demonstrated.

For Class 1 biologicals manufactured within a hospital, it is the hospital that determines the suitability of test methods used and appropriate accreditation of the facility performing infectious disease testing. For sites performing testing on stool to be used in Class 2 biologicals, a TGA licence will generally be required for domestic facilities (National Association of Testing Authorities [NATA] accreditation is not sufficient).

If the test kit and methodology has current approval by the relevant regulatory authority in the country where the testing is performed, the evidence of this approval should be provided to TGA.

If unsure, sponsors are encouraged to contact TGA to ask about kit acceptability.

Testing facility

All facilities performing donor testing must be approved by the regulatory authority in the country where the testing is performed, while the sponsor must hold a TGA clearance demonstrating compliance with GMP requirements for overseas testing facilities.

Retention of records must be consistent with GMP requirements

The retention of records must be consistent with the requirements of the Australian Code of GMP.

Retention times must take into account jurisdictional or hospital policies and be consistent with Australian Code of GMP and clinical trial regulatory guidelines, where applicable.

Records can be hard copy or electronic and must be available to TGA inspectors.

Contracted testing

A contractual arrangement with any external pathology provider must be in place. The agreement must stipulate the responsibilities for each party around sample preparation and storage, and all of the relevant details relating to the IVD test kits used.

14 Blood sample testing

(4) The following tests must be conducted in relation to blood samples taken in accordance with subsection 13(1) or paragraph 13(3)(a):

(a) C-reactive protein (CRP), full blood count (FBC) and liver function tests (LFTs); and

(b) serology testing for antibodies to HIV-1 / HIV-2, HBV, HCV, HTLV-1 / HTLV-2, *Strongyloides stercoralis*, and syphilis (Treponema pallidum); and

(c) HAV testing (unless RNA testing is conducted on the stool samples); and

(d) nucleic acid amplification testing for HIV-1, HBV and HCV.

(5) The following tests must be conducted in relation to the blood samples taken in accordance with subsection 13(3)(b):

(a) C-reactive protein (CRP), full blood count (FBC) and liver function tests (LFTs); and

(b) serology testing for antibodies to HIV-1 / HIV-2, HBV, HCV, HTLV-1 / HTLV-2, *Strongyloides stercoralis*, and syphilis (Treponema pallidum); and

(c) HAV testing (unless RNA testing is conducted on the stool samples).

General blood testing

General blood tests such as CRP, FBC and LFTs are useful indicators of general health and are a requirement of most international consensus statements. However, specifications identifying acceptable levels for FMT donors (other than the standard reference ranges) do not need to be set for these results. Instead, review by a medical officer is required when considering the significance of the results on the suitability of a donor.

HIV, HBV and HCV

The requirement to perform NAAT is mandated to shorten the window period for detection of HIV, HBV and HCV infections, and to simplify the donor workup requirements. However, the ability to perform repeat serology when screening donors, instead of NAAT testing, has been provided.

Strongyloides stercoralis

Although *Strongyloides stercoralis* may be present in stool, testing for this organism in the blood is currently considered the most sensitive test.

HAV

The onus is on the sponsor to determine the most appropriate method for screening a patient for HAV. NAAT for HAV RNA in stool is the most sensitive, subject to the lowest rate of false positives, has the shortest window period, and is more relevant to the safety of stool. Otherwise, IgM anti-HAV in blood may be considered appropriate.

Additional tests to consider

Other FMT consensus statements list a number of other donor blood tests to consider, although the Australian CWG has not deemed them relevant in the Australian context.[5]

For example:

- the epidemiology for Hepatitis E does not support testing for the organism in Australia at this time
- cytomegalovirus (CMV) and Epstein-Barr virus (EBV) should be considered if treating immunocompromised patients

14 Stool sample testing

(6) Subject to subsections (7) and (8), stool samples must be tested for each of the following microorganisms:

(a) *Campylobacter* spp.;

(b) *Cryptosporidium* spp.;

(c) *Entamoeba histolytica*;

(d) *Giardia*;

(e) *Helicobacter pylori*, where stool is proposed to be collected for use in the manufacture of FMT products delivered by the upper gastrointestinal route;

(f) multidrug-resistant organisms (MDROs) including:

(i) extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*;

(ii) vancomycin-resistant *Enterococci* (VRE);

(iii) carbapenem-producing *Enterobacteriaeae* (CPE);

(iv) methicillin-resistant *Staphylococcus aureus*;

(g) norovirus;

(h) rotavirus;

(i) *Salmonella* spp.;

(j) *Shigella* spp.;

(k) toxigenic *Clostridioides difficile*;

(l) any other microorganism of clinical significance that may affect the quality or safety of the stool collected for use in the manufacture of FMT products, determined on the basis of a risk assessment.

(7) Stool samples taken in accordance with paragraph 13(2)(c) must be tested for the microorganisms mentioned in subsection (6) determined on the basis of a risk assessment, such that every microorganism is tested at least once every 90 days.

[5] Haifer C, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. *Gut* 69: 801-810 (2020).

Clinically relevant microorganisms

The microorganism list outlined in this section is largely based on current best practice and knowledge, as identified by the Australian CWG.[6] This list is also based on current knowledge around use in the treatment of recurrent or refractory *Clostridioides difficile* infection (CDI) and additional testing of stool and blood may be required for other clinical indications.

Screening of stool of potential donors is an evolving area. Therefore, the list of clinically relevant microorganisms needs to be reviewed regularly giving consideration to the need for additional testing. For example, in response to new safety alerts or events, or the emergence of new MDROs.

The term 'tested' covers any methods used to detect the presence of these agents, such as microscopy for parasites, NAAT and culture methods, or other biochemical tests for toxins.

Consideration should also be given to the frequency of stool testing, based on knowledge as to whether screening out of symptomatic donors is sufficient to control risk of acute gastrointestinal infections during an extended stool collection program. Alternatively, an aliquot from each or selected donated stools could be tested with a rapid molecular assay for specific pathogens.

Additional microorganisms of clinical significance that may affect the quality or safety of the stool

As a sponsor, manufacturer or provider of FMT products, you must maintain a list of microorganisms to actively test for, which includes:

- all of the microorganisms listed in section 14(6)

  AND

- also considers other microorganisms that could be objectionable in that they may be of clinical significance.

Principles to apply to determine if the presence of an organism should be actively tested for, include whether:

- the organism is transmissible and whether there is a reasonable association with disease in a recipient

  OR

- there is a carrier state or acute asymptomatic window (that is, no acute presentation obvious during clinical review or collection of donor medical history).

For some organisms, it may be more appropriate to exclude recipients rather than donors. For example, where the organism is very prevalent in stool but the presence is only a risk for a specific group of patients or can be readily treated (prophylactic or following onset of symptoms).

Assessment to determine risk of transmission

There is also an expectation that for any infectious risk associated with stool donation, including certain epidemiological and geographical circumstances (for example, the COVID-19 global pandemic or recent Dengue fever outbreaks in far north Queensland), a risk assessment would be performed by the FMT provider in conjunction with the testing laboratory to determine the

[6] Haifer C, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. *Gut* 69: 801-810 (2020).

most appropriate course of action. A risk assessment would produce a number of possible outcomes including:

- no additional risk mitigation by way of additional testing, but the need to clearly articulate the level of risk to the treating clinician and recipient
- introduction of an additional donor question to identify high risk donors
- reviewing the suitability of test kits available in order to detect for the presence of a specific microorganism.

Where there is potential benefit in the use of donor testing (either broadly, or more targeted testing for specific clinical situations), a more detailed analysis should be performed to review the suitability of testing platforms available and the residual risk following screening.

Assessment of test kit suitability and residual risk

A risk assessment should be conducted to determine:

- the suitability of test kits to detect a specific microorganism

  AND

- the relevance of test kits to determining stool donor suitability.

The risk assessment should include, but not be limited to, the following criteria:

- intended purpose of the test based on current validation data (for example, for a diagnostic purpose in symptomatic patients, recommended sample types do not include stool)
- limit of detection, or the sensitivity of the assay when using qualitative assays
- variable rate of detection or reproducibility of test results due to sample size, sample homogeneity, and intermittent shedding of organisms
- poor specificity or high rate of false positives due to cross reactivity
- performance limitations of the assay which restrict the interpretation of results (for example, detection limits greater than the clinically relevant dose of infectious agent, or where the chosen methodology is not the most sensitive method available)
- amount of stool used to prepare the FMT product and specific route of administration to recipients
- potential level of contamination in the FMT product
- options for risk mitigation.

Regular testing on stool samples for donors of fresh FMT product, based on a risk assessment

Careful consideration should be given to the frequency of testing on stool samples from an accepted donor for the stool microorganism outlined in section 14. Generally, daily or weekly screening for those microorganisms that may appear in the stool of asymptomatic donors would be appropriate.

14 Other sample testing

(8) The microorganisms mentioned in subsection (6) may be tested using a sample taken in accordance with subsection 13(5), where the test method is scientifically justified in the circumstances.

Testing of other samples

The use of samples other than stool or blood to test for specific microorganisms of clinical significance must be scientifically justified. For example, nasopharyngeal swabs for SARS-CoV-2, or alternative samples and test methods for detection of *H. pylori* or methicillin-resistant *Staphylococcus aureus* (MRSA).

14 Additional testing requirements

(9) Where stool is to be collected outside Australia, a risk assessment must be conducted and documented in relation to whether additional blood, stool or other samples may be needed to be tested to ensure the quality, safety and efficacy of the FMT products.

(10) Where FMT products are intended to be administered to, or applied in the treatment of, patients with increased susceptibility to infection, further testing of blood, stool and other samples must be considered in order to ensure patient safety.

Overseas donors

TGO 105 takes into account the unique epidemiology of stool donors residing permanently inside Australia and may not be suitable for workup of donors permanently residing outside of Australia.

Careful consideration should be given to additional donor and medical history that may need to be collected from overseas donors and must be justified in the context of local epidemiological risks.

Consensus documents utilised within the jurisdiction of the donors may provide insight into the most appropriate donor workup.

Patients with increased susceptibility to infection

Consider additional testing when FMT products are intended for use in patients with increased susceptibility to infection. Additional testing of blood and/or stool may be required for specific patient groups and clinical indications.

A list of additional microorganisms to be tested for patients with increased susceptibility to infection must be provided to TGA. The choice of organisms to be tested must also be justified. For example, donors of FMT material that is intended to be given to immunocompromised patients could be tested for CMV, EBV and *Listeria monocytogenes to reduce the risk of these infections in recipients.*

14 Assessment of results

(11) Where FMT products are intended for autologous use, and the testing of blood, stool or other samples in accordance with this section has resulted in repeatedly reactive results:

(a) the FMT products and stool collected for use in the manufacture of those products must be segregated and quarantined from any other stool or FMT products; and

(b) the justification for the autologous use must be documented and maintained.

(12) Where the FMT products are intended for allogeneic use, and the testing of blood, stool or other samples in accordance with this section, other than testing of blood samples in accordance with paragraphs (4)(a) and (5)(a), has resulted in a reactive result, then the stool collected for use in the manufacture of FMT products must not be used in such manufacture or, if FMT products are manufactured from the stool, the products must not be released for supply, unless:

(a) confirmatory testing of an initial reactive result in relation to such samples confirms that the result was a biological false reactive; or

(b) further testing of samples indicates that the presence of the specified microorganism has cleared.

(13) Where abnormal results are obtained from testing conducted in accordance with paragraphs (4)(a) or (5)(a), a medical practitioner must assess the potential impact on the quality, safety or efficacy of stool collected, or to be collected, for use in the manufacture of FMT products intended for allogeneic use.

Infectious disease status policy

You must have a documented policy for determining the individual infectious disease status based on test results. For example, HBV testing algorithms may be used to interpret the status of the donor.

Generally, if an accepted donor returns a reactive result for samples tested at the end of the collection period, any frozen stool of manufactured FMT product from that donor should be discarded. However, a provision has been included to allow additional testing on stool samples collected earlier in the collection window, to allow the point of infectivity for the organism to be identified. Where a negative result is obtained for samples tested earlier in the collection window, it may be appropriate an safe to use some of the collected stool in the manufacture of FMT product.

Risk assessment with autologous donors

Treating physicians can determine the extent of the medical and social history to be recorded when stool is collected for autologous use. Since there are still risks associated with handling of infectious material and appropriate storage and labelling of stool for autologous risk, there is an expectation that:

- a risk-assessment has been performed

  AND

- a decision recorded to justify the level of donor medical and social history taken.

Reactive blood and stool samples must not be used unless confirmatory tests determine suitability

Generally, if any test required by section 14 on blood and stool is reactive, stool must not be collected from the donor, or if manufactured must not be released.

However, confirmatory tests can be performed to determine if an initial 'reactive' result is true or represents a biological false positive reactive. The reason to use results from any confirmatory testing to determine donor suitability must be scientifically justified.

14 Notification and record-keeping

(14) Procedures must be implemented for notifying the proposed donor, the accepted donor, health practitioners, hospitals and other health facilities, about a test result that is indicative of a disease or carrier state at the time of the collection of the sample.

(15) Records must be maintained in relation to the following:

(a) the IVD medical device or in-house IVD medical device used for infectious disease testing;

(b) any test modifications;

(c) the results of analytical and clinical performance testing;

(d) any evaluation of, and anomalies in, the test results.

Notification about test results indicative of disease or carrier state

A process must be in place to ensure appropriate notification to the donor or appropriate health practitioners for test results that are reactive or indicative of a disease.

14 Storage of blood and stool samples

(16) Blood and stool samples collected from an accepted donor (including any serum or plasma) must be placed in long-term storage in accordance with the following conditions:

(a) blood samples must be stored at or below minus 20°C;

(b) stool samples must be stored at or below minus 70°C; and

(c) retained for a minimum of two years after the expiry date of the products.

(17) Despite paragraphs 14(16)(a) and (b), other storage specifications may be used in relation to the samples, if those specifications are validated (including in relation to temperature) or recommended by the manufacturer of the IVD medical device or in-house IVD medical device used to test the samples.

Long-term storage conditions

This subsection outlines the requirement for sample archives for blood (or the serum/plasma isolated from those blood samples) and stool samples.

All blood and stool samples of **persons accepted as donors** must be archived to allow 'look-back' of donor suitability if a safety issue is identified later.

Failure to store a sample or loss of sample is a 'non-conformance' and should follow internal non-conformance procedures. This may be subject to review during GMP inspection, if applicable.

Circumstances that may justify a failure to archive include:

- low sample volume
- breakage and loss
- any relevant testing that uses up the sample.

Where facilities choose not to maintain the archived samples on-site, contractual arrangements with an off-site facility will need to be made.

If samples are sent to pathology providers for testing

Where samples are sent to pathology providers for testing, the pathology provider will generally determine whether any of these samples are archived, as well as the conditions and duration.

However, to meet the requirements of this subsection, a contractual arrangement with the pathology provider may need to be established to ensure that the need for the samples to be archived is clear, as well as stating the storage conditions and duration.

Section 15 – Physical assessment

There is general international consensus on the need to perform a physical assessment of proposed stool donors.

15 Physical assessment

(1) A physical assessment must be conducted in relation to a proposed donor not more than 30 days before the first collection of stool for use in the manufacture of FMT products.

(2) Subsequent physical assessments must be conducted in relation to an accepted donor on an ongoing basis, such that each physical assessment is conducted within 90 days of the last physical assessment.

(3) A physical assessment must:

(a) include a clinical assessment of any physical features or characteristics that may indicate that a proposed donor or accepted donor is at risk of a communicable disease potentially transmissible by faecal microbiota transplant; and

(b) be conducted by an appropriate health practitioner.

Physical assessment by an appropriate health practitioner

Physical assessment is defined as 'a clinical inspection of an individual to determine suitability of the person to be a donor'.

An appropriate health practitioner must physically examine proposed donors to determine their general health status and ensure they do not exhibit signs or symptoms of an acute infection.

The exact nature of the assessment is not prescribed, but it must be sufficient to 'determine suitability of the person to be a donor' and appropriately documented.

Physical assessment may include, but is not limited to examining the relevance of any:

- abrasions
- lacerations and bruises / haematoma
- fractures, tattoos, piercings, scars, skin lesions, surgical incisions
- other distinguishing external feature that may be indicative of a behaviour or lifestyle or suggestive of any risk factor in relation to a relevant communicable disease.

Division 3 – Requirements following collection

Section 16 – What this Division is about

This division specifies procedures relating to microbial control that must be implemented in the manufacture of FMT products.

Section 17 – Microbial control procedures

The requirements in this section reflect where there is general international consensus on the need to ensure procedures are in place relating to microbial control in the manufacture of FMT products.

17 General requirements

(1) Microbial control procedures that are validated must be implemented in the manufacture of FMT products and must:

(a) include a strategy to minimise the proliferation of intrinsic microbial contamination and to prevent extrinsic microbial contamination of stool during the manufacture of FMT products; and

(b) specify storage, handling and transportation requirements (including in relation to temperature and duration) for stool used in the manufacture of FMT products.

17 Immediate processing of stool following collection

(2) Stool used in the manufacture of FMT products, other than fresh FMT products, must:

(a) be processed as soon as possible, and not later than 6 hours after defaecation; and

(b) during any interval to the processing mentioned in paragraph (a) including transportation of the stool—be cooled to 4□C or kept as otherwise validated by the manufacturer; and

(c) following the processing mentioned in paragraph (a)—be stored in accordance with subsection (5).

17 Processing and storage of stool used in the manufacture of fresh FMT products

(3) Stool collected from an accepted donor for use in the manufacture of fresh FMT products must be processed not later than 6 hours after defaecation:

(a) at ambient temperature (maximum 37°C); or

(b) under specifications set and validated by the manufacturer.

(4) Fresh FMT products must be administered to, or applied in the treatment of, a person:

(a) on the same day the stool is collected; or

(b) no later than 5 days after the stool is collected where the fresh FMT product is stored under conditions that will not impact the quality, safety or efficacy of those products.

17 Storage and transportation of stool and FMT products

(5) FMT products, other than fresh FMT products, and stool to be used in the manufacture of FMT products must be stored:

(a) at or below minus 70°C in a suitable cryopreservation agent for not longer than 12 months; or

(b) in accordance with justified time and temperature specifications.

(6) FMT products must be appropriately sealed within a sterile container that:

(a) prevents leakage of the FMT products from the container; or

(b) ensures that any breach of integrity of the container is evident.

(7) FMT products, other than fresh FMT products, must be transported in accordance with justified time and temperature specifications.

Processing procedures

During processing, validated processes must be in place to prevent:

- proliferation of the intrinsic microbial contamination of the stool
- extrinsic microbial contamination of the stool
- cross-contamination between stools.

Storage and transport of stool

Each sponsor must justify that the storage conditions used are appropriate to ensure quality, safety, and efficacy of the stool.

Where the stool donation does not occur at the manufacturing site, it is important that the stool be cooled during any temporary storage or during transport to the stool bank. This requirement must be communicated to stool donors and monitored.

The UK working group formed by the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) recommends that stool be transported to the FMT production site as soon

as possible after defaecation (and within 6 hours).[7] The European Directorate for the Quality of Medicines & HealthCare (EDQM) guide also recommends that fresh donor stool be processed within 6 hours of defaecation.[8] The international consensus statement states that stool should be transported to the stool bank as soon as possible after defaecation to ensure that manipulation and storage is done within 6 hours.[9]

The requirement for stool to be processed as soon as possible following defecation is not intended to imply that processing must be completed within 6 hours. The freezing of stool prior to future additional processing steps is considered a step in processing and sufficient to meet this requirement.

Storage conditions, solutions and preservation agents of FMT products

Each sponsor must justify that the storage conditions used are appropriate to ensure quality, safety, and efficacy of the finished FMT product. The addition of specific solutions and preservation agents should also be justified and validated or verified.

The EDQM guide recommends that donor stool mixed with a cryoprotectant (for example, glycerol) could be stored at minus 80°C until required for use.[10]

The UK working group recommends that donor stool stored at minus 80°C has a maximum shelf life of 6 months,[11] while the EDQM guide states a shelf life of 5-6 months and potentially even longer.[12]

However, the international consensus statement represents the most recent publication and has drawn on accumulating data out of international stool banks, and have made an informed recommendation that frozen samples should be used within one-year from donation.[13]

Some pre-clinical studies have reported loss in product viability after one year, but others have longer-term data to support even longer storage conditions. All facilities are encouraged to establish long-term stability studies, potentially including accelerated conditions, to justify any further extension to the shelf life.

The temperature and conditions during transportation and delivery must be carefully considered, but may be different from the storage conditions. Validation data should be available to demonstrate that quality and efficacy would not be impacted by any proposed transport conditions.

If there is a product return policy, for instances where a proposed clinical use is not performed or is significantly delayed, careful tracking and monitoring of the units should be in place to ensure quality of the FMT product has been maintained.

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[7] Box 4: Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[8] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 406.
[9] Box 4: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 68: 2111-2121 (2019).
[10] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 407.
[11] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[12] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 407.
[13] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 68: 2111-2121 (2019).

Schedule 1 – Ineligibility criteria for donor selection

Schedule 1 of TGO 105 describes the medical and social history that must be collected, and the potential periods of ineligibility that must be applied to a proposed donor.

Ensure you familiarise yourself with **all items listed in schedule 1** and the associated requirements.

Items 1 and 2 – Infected with certain viruses

Item	Medical and social history criteria	Period of ineligibility
1	a person who is infected with: (a) HIV-1; (b) HIV-2; (c) HTLV-1; (d) HTLV-2; or (e) syphilis	permanently ineligible
2	a person who is infected with: (a) HAV; (b) HBV; or (c) HCV	ineligible until an uninfected state is established

The ability to allow donors to be accepted after a period of ineligibility is dependent on an uninfected state of the donor being demonstrated.

HAV

For HAV, clinical illness in some persons can be prolonged and there can be a risk of relapse for up to 6 months. Virus is also excreted for months following clinical recovery. To demonstrate a proposed donor's uninfected state, the sponsor could consider the most appropriate criteria. For example, the donor should initially be deferred for over 6 months, and be anti-HAV IgM negative and/or negative by NAAT for HAV RNA.

HBV

For HBV, if a patient previously infected with HBV is Hepatitis B surface antibody positive (with or without core antibody positivity), but negative for both Hepatitis B surface antigen and HBV DNA, then they may be re-eligible to donate.

HCV

For HCV, an uninfected state can be established if an individual had undergone successful anti-viral treatment, and the individual has been shown to be to be HCV negative by polymerase chain reaction (PCR) over a period of time.

Item 3 – Recipients of viable, non-human cells or tissues

Item	Medical and social history criteria	Period of ineligibility
3	a person who has been a recipient of viable, non-human animal cells or tissues	permanently ineligible

For recipients of viable animal cells or tissue products, there is a risk of xenogeneic infections. Donors receiving such transplants should not be accepted.

Item 4 – At risk of prion disease

Item	Medical and social history criteria	Period of ineligibility
4	a person who is at risk of prion disease because the person has been, or potentially been, exposed to the putative causative agent of one of the family of pathogenic transmissible spongiform encephalopathies, including: (a) genetic (familial) exposure; (b) environmental exposure, including living in or visiting England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period of 6 months or more, at any time between 1 January 1980 and 31 December 1996; or (c) iatrogenic exposure, including receiving a transfusion or injection of blood or blood components while in England, Scotland, Wales, Northern Ireland or the Isle of Man at any time on or after 1 January 1980	permanently ineligible

Permanent deferral of a donor may need to be considered due to risk of prion disease include where:

- patients have symptoms of progressive neurological disease consistent with prion disease

  AND

- activities that could iatrogenically transfer prion disease have occurred.

Item 5 – Injected with drugs for a non-medical reason

Item	Medical and social history criteria	Period of ineligibility
5	a person who has received an injection of any substance in connection with a use that is not a therapeutic use or cosmetic use	ineligible for at least 5 years from the last injection

'Non-medical reason' refers to procedures such as recreational drug use or any procedure that is not undertaken by a registered healthcare provider in Australia.

This deferral criterion is not intended to apply to individuals who have participated in medically-supervised, registered clinical trials.

Item 6 – At increased risk due to sexual practices

Item	Medical and social history criteria	Period of ineligibility
6	a person who has engaged in sexual activity that puts the person at an increased risk of acquiring infectious diseases that could be transmitted through stool	ineligible for at least 12 months from the last sexual contact

Sexual practices that are considered to increase the risk of acquiring infectious diseases that can be transmitted in stool include, but are not limited to:

- sexual activity with a sex-worker
- sexual activity with someone who uses intravenous drugs
- having a partner who lives or lived in a high HIV-risk country
- for male donors, sexual activity with a male partner
- for female donors, sexual activity with a male partner who also has sex with men.

The donor information that informs this deferral should be determined based on risk as relevant to the nature of the product and its use.

Item 7 – At risk of acquiring a blood borne infection

Item	Medical and social history criteria	Period of ineligibility
7	a person who has been exposed to any of the following risks of acquiring a blood borne infection transmissible by stool: (a) mucosal splash with blood or other bodily fluids; (b) needle stick injury; (c) tattoo; (d) body piercing (including earring); or (e) acupuncture or dry-needling, unless performed using sterile, single-use needles	(a) where the person tests negative for HCV using nucleic acid amplification testing—ineligible for at least 4 months from exposure; or (b) in all other circumstances—ineligible for at least 6 months from exposure

A donor with exposure to the risk of acquiring a transmissible blood borne infection such as HIV, HBV and HCV must be deferred for:

- a period that allows determination of disease development

  AND

- they subsequently test negative for HIV, HBV and HCV after this period of time.

Item 8 – Recipients of human pituitary derived hormone

Item	Medical and social history criteria	Period of ineligibility
8	a person who has been a recipient of human pituitary-derived hormone	permanently ineligible

Human derived pituitary hormone is currently not available in Australia. Synthetically derived products are currently used. This permanent ineligibility does not apply to proposed donors that have received synthetically derived product.

Item 9 – Active infection, fever or infectious disease

Item	Medical and social history criteria	Period of ineligibility
9	a person who has an active infection, fever or infectious illness	ineligible for at least 2 weeks from the date of full recovery

Clinical judgement should be used to determine the relevance of the infection, fever or illness to the suitability of the stool donor. This may include a list of enteric infections.

Determination of a disease-free state should be established before a proposed donor can be allowed to donate. This may include an algorithm and testing or specified parameters to demonstrate that an infection has cleared.

Item 10 – History of gastrointestinal disorders

Item	Medical and social history criteria	Period of ineligibility
10	a person who has a history of functional gastrointestinal disorders	permanently ineligible

'Gastrointestinal disorders' refer to any condition or disease that occurs within the gastrointestinal tract.

A list of disorders should be maintained and justified.

Items 11 and 12 – History of gastrointestinal malignancy or genetic polyp condition

Item	Medical and social history criteria	Period of ineligibility
11	a person who has a history of gastrointestinal malignancy	permanently ineligible
12	a person who has a known genetic polyp condition	permanently ineligible

Careful consideration should be given to the types of malignancy and polyp conditions that should result in permanent ineligibility, or where it must be clinically assessed as to the suitability of the donor. Such a list must be maintained and justified. The risk of transmission of cancers through stool donation is generally considered low.

Examples of malignancy history that would result in a donor not being accepted, include:

- upper digestive tract malignancies such as oesophageal, stomach, pancreatic, liver, and gallbladder cancers, mucosa-associated lymphoid tissue (MALT) lymphoma, gastrointestinal stromal tumours cancers of the biliary tree including cholangiocarcinoma
- lower digestive tract malignancies such as colorectal and anal cancers, and carcinoid tumours
- genetic polyps such as hereditary mixed polyposis syndrome (HMPS), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, and juvenile polyposis syndrome (JPS).

Item 13 – History of major gastrointestinal surgery

Item	Medical and social history criteria	Period of ineligibility
13	a person who has a history of major gastrointestinal surgery	permanently ineligible

Clinical judgement should be used to determine the relevance of the surgery to the suitability of stool from a proposed donor.

Gastrointestinal surgery may include:

- abdominal surgery
- adrenalectomy
- anoplasty
- appendectomy
- colectomy
- colon resection
- colostomy
- haemorrhoidectomy
- ileostomy
- Nissen fundoplication
- polypectomy
- Roux-en-Y anastomosis
- strictureplasty
- Whipple procedures

In addition, it is likely to include colorectal surgical disorders and a range of surgeries to treat gastrointestinal problems and diseases.

Item 14 – Persons using antibiotics or immunosuppressive agents

Item	Medical and social history criteria	Period of ineligibility
14	a person using antibiotics or immunosuppressive agents	ineligible for at least 90 days from ceasing use

A list of antibiotics and immunosuppressive agents that should result in deferral or ineligibility of a proposed donor must be maintained and justified.

Some antibiotics have a more substantial and prolonged impact on gut dysposis, so donor deferral may need to be for up to 6 months. The list of medications may include:

- antibiotic classes including penicillins, tetracyclines, cephalosporins, quinolones, lincomycins, macrolides, sulphonamides, glycopeptides, aminoglycosides, and carbapenems
- immunosuppressive drugs including glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins, interferons, opioids, and TNF binding proteins
- antiprotozoals including antimalarial drugs, drugs for amebiasis, and miscellaneous antiprotozoals.

Items 15 and 16 – Symptoms of gastrointestinal illness

Item	Medical and social history criteria	Period of ineligibility
15	a person who has symptoms of a gastrointestinal illness including abdominal pain, diarrhoea, fever, nausea, vomiting, and haematochezia	ineligible for at least 30 days since last showing symptoms
16	a person who has had contact with a household member who has symptoms of a gastrointestinal illness including abdominal pain, diarrhoea, fever, nausea, vomiting, haematochezia	ineligible for at least 30 days since contact

Where a donor is allowed to resume donation following recovery or exposure to a gastrointestinal illness, careful consideration should be given to the risk of transmission through donated stool. Where the actual agent is identified, active testing for the presence of the agent may be appropriate prior to allowing the individual to be a suitable donor.

'Household contacts' refers to other individuals living in the same single residence. The risk of transmission between members in the household will depend on the characteristics of the household members, the degree of contact between them, and the household environment.

Item 17 – History of any autoimmune disease

Item	Medical and social history criteria	Period of ineligibility
17	a person who has a history of any autoimmune disease	permanently ineligible

Microbiota dysbiosis has been shown in a number of autoimmune disorders,[14] and there has been a possible case of transmission, or autoimmune disease development following FMT transplant. Further, a recent study has found that bacteria found in the small intestines of humans can travel to other organs and trigger autoimmune responses.[15]

A list must be maintained and justified of autoimmune diseases that affect the quality of the stool and should thereby result in permanent ineligibility, or where it must be clinically assessed as to the suitability of the donor.

This may include a list of autoimmune diseases with known gastrointestinal manifestations such as:

- systemic lupus erythematosus (SLE)
- rheumatoid arthritis
- Sjögren's syndrome
- Behçet's disease
- progressive systemic sclerosis

[14] De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol*. 195: 74-85 (2019).
[15] Manfredo Vieira S, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science* 359: 1156-1161 (2018).

- polyarteritis nodosa
- Kawasaki disease
- inflammatory muscle disorders
- giant cell arteritis
- Henoch-Schönlein purpura
- Takayasu arthritis
- Cogan's syndrome
- Churg-Strauss syndrome
- Wegener granulomatosis
- antiphospholipid antibody syndrome
- spondyloarthropathies.

Item 18 – Metabolic syndrome or diabetes

Item	Medical and social history criteria	Period of ineligibility
18	a person who has a metabolic syndrome or diabetes	permanently ineligible

Metabolic syndrome refers to a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which occur together more often than by chance alone. The risk factors include:

- raised blood pressure
- dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol)
- raised fasting glucose
- central adiposity.

Item 19 – BMI greater than 30 kg per m^2

Item	Medical and social history criteria	Period of ineligibility
19	a person who has a body mass index of, or greater than, 30 kg per m^2	ineligible until that person has a body mass index less than 30 kg per m^2

Consideration can be given to the impact of weight loss on restoration of a normal microbiota, with the dysbiosis observed in obese individuals only shown to normalise with maintained weight loss over a period.

Item 20 – Travel to specific areas

Item	Medical and social history criteria	Period of ineligibility
20	a person who: (a) has travelled to a country or place in Australia with a high endemic risk of travellers' diarrhoea or multidrug-resistant organisms; or (b) has had exposure to similar epidemiological situations as described in paragraph (a)	(a) ineligible for a period of time based on a risk assessment using the most up-to-date epidemiological data; or (b) where epidemiological data is not available—ineligible for at least 90 days from exposure

This deferral is intentionally broad to encompass unforeseen infectious disease risks such as an epidemic, pandemic, or other emerging or re-emerging infectious disease outbreak. It is the responsibility of the sponsor to demonstrate that a process is in place to satisfactorily monitor, assess and action epidemiological situations relevant to their products.

In the case of the COVID-19 disease pandemic, which began to spread globally in 2020, a manufacturer will need to monitor advice on the risk of infection to the safety of their product and consider how to manage the risk through deferral of donors (and potentially testing). TGA recently published advice on additional safety protections relating to COVID-19 for FMT products.

For travel-based deferrals, such as travel to a malaria-infected area, a documented procedure must be in place to record the countries where crucial infectious diseases are endemic or where there is an outbreak. The deferral may be based on a country of travel, or where an agent is endemic to a local area within that country. The World Health Organization (WHO) publishes a list of countries where specific diseases such as malaria, Zika virus, dengue fever, Ebola virus disease, West Nile Virus (WNV) are present.

Management of this requirement should be achieved through a policy for monitoring for outbreaks and notification by e-mail to TGA if interim measures are put in place. If there is a serious outbreak, but the risk to FMT products is considered to be minimal, you should notify TGA that no action is needed at this time.

Item 21 – At risk for multidrug-resistant organisms (MDROs)

Item	Medical and social history criteria	Period of ineligibility
21	a person who is at risk of being a carrier of multidrug-resistant organisms, including a person who: (a) is or has been a healthcare worker with exposure to patients in hospitals or long-term care facilities; (b) has recently been hospitalised or discharged from long-term care facilities; (c) has regularly attended or regularly attends outpatient medical or surgical clinics; (d) has recently engaged in medical tourism	ineligible until it has been demonstrated that the person is not a carrier of a multidrug-resistant organism

A person who meets the following criteria is permanently ineligible until demonstrated that the person is not a carrier of a MDRO:

- they are or have been a healthcare worker with exposure to patients in hospitals or long-term care facilities
- they have recently been hospitalised or discharged from long-term care facilities
- they regularly attend outpatient medical or surgical clinics
- they have recently engaged in medical tourism.

These questions should be asked of proposed donors, to exclude those at risk of being carriers of MDROs.

Where a proposed donor meets one of these criteria from an active or recent exposure, they should be deferred or deemed ineligible.

Where the exposure is no longer relevant, the stool must still be tested and a carrier-free status determined to allow them to be a stool donor.

Item 22 – Vaccinated with risk of transmission of the vaccine strain

Item	Medical and social history criteria	Period of ineligibility
22	a person who has been vaccinated with a live vaccine, where there is a risk of transmission of the vaccine strain	ineligible for a period of time that is consistent with defined criteria for the vaccine

A proposed FMT donor who has been vaccinated with a live vaccine, where there is a risk of transmission of the vaccine strain, must be deferred.

The length of deferral should be based on knowledge of the length of persistence of the vaccine agent, testing of the proposed donor, or based on the assessment of the risk to use of stool for transplantation.

For example, with the rotavirus vaccine there is evidence the virus can shed for up to 14 weeks following vaccination and that transmission can cause gastroenteritis. A deferral of 4-6 months may be appropriate in this situation.

Table 2 shows some typical examples of ineligibility periods applied to allogeneic use of potential donor tissue who have received a vaccine, which may also be applicable to stool donors.

Table 2: Ineligibility periods applied to the allogeneic use of potential donor tissue where donors have received a vaccine

Vaccine composition	Period of donor ineligibility prior to donation
Live attenuated bacteria or viruses, except smallpox	4 weeks
Smallpox	8 weeks
Sera of animal origin	12 weeks
Unknown	12 months

Items 23, 24 and 25 – Potential exposure to certain infections

Item	Medical and social history criteria	Period of ineligibility
23	a person who has potentially been exposed to: (a) HCV; (b) HIV-1; (c) HIV-2; (d) HTLV-1; (e) HTLV-2; or (f) syphilis	ineligible until it has been demonstrated that the person is not infected
24	a person who has potentially been exposed to HBV	ineligible until it has been demonstrated that the person is: (a) immune from HBV infection; or (b) not infected with HBV, as confirmed by a nucleic acid amplification test

This is an important 'catch-all' provision to identify donors that have potentially been exposed to such organisms but have not been tested to confirm whether transmission occurred to them or not.

Demonstration of exposure versus immunity to HBV must be determined by a testing algorithm that is informed from evidence in scientific literature or other reliable sources, as above.

For example, donors suspected of being infected with HBV who are HBsAg negative are considered 'immune' if both of the following apply:

- they have an antibody titre to HBsAg at a level greater than or equal to 10 IU/L (or 10 mIU/mL)

  AND

- HBV NAAT is negative

Donors suspected of being infected with HBV, who are HBsAg negative, are considered to be 'not exposed' if they test negative for antibodies to HBsAg and test negative by HBV NAAT.

For HBsAg negative persons who are demonstrated to be immune or never exposed, no ineligibility period applies.

Table 3 shows a summary of donor deferral criteria according to known or suspected HBV infections.

Table 3: Donor deferral criteria according to known or suspected HBV infections

Deferral criterion	How to determine infection status	Deferral outcome
If known to have HBV infection	Positive HBsAg test	Ineligible
If suspected of having an HBV infection	Symptoms of infection or close contact with infected person established at interview but negative HBsAg test and cannot establish immunity status	Ineligible
If suspected of having an HBV infection	Negative HBsAg test **AND** Positive anti-HBC test **AND** Positive anti-HBS test **AND** Negative NAAT	Immune due to natural infection previously, so no deferral required if negative NAAT result confirms no current infection
If suspected of having an HBV infection	Negative HBsAg test And Negative anti-HBc test And Positive anti-HBs test	Immune due to hepatitis B vaccination, and so no deferral required if NAAT result confirms no current infection

Item 26 – Recipient of allogeneic blood, blood components or human derived clotting factors, organs, cells or tissues

Item	Medical and social history criteria	Period of ineligibility
26	a person who has been a recipient of allogeneic blood, blood components, human derived clotting factors, organs, cells or tissues that did not conform with TGO 88	(a) where the person tests negative for HCV using nucleic acid amplification testing—ineligible for at least 4 months from receiving the allogeneic blood, blood components, human derived clotting factors, organs, cells or tissues (b) in all other circumstances—ineligible for at least 6 months from receiving the allogeneic blood, blood components, human derived clotting factors, organs, cells or tissues

If a proposed donor has received allogeneic blood, blood components or human derived clotting factors, cells or tissues, the sponsor must ensure that the product the donor received is compliant with TGO 88. Where any of these products is not in accordance with TGO 88, the proposed donor is ineligible from 6 months after receiving them.

Item 27 – Prison inmate for 72 or more consecutive hours

Item	Medical and social history criteria	Period of ineligibility
27	a person who has been imprisoned for a consecutive period of 72 hours or longer	ineligible for 12 months from the date of release from prison

There is a known relationship between imprisonment, drug use, sexually transmitted and blood-borne virus infections such as hepatitis B and C.

Item 28 – Environment where transmission of zoonotic infections is likely

Item	Medical and social history criteria	Period of ineligibility
28	a person who works or has worked with animals, in an environment where transmission of zoonotic infections is likely	ineligible for at least 90 days following exposure to the work environment

A list of professions where such exposure may occur should be determined. This would include high-level exposure to large animal herds and wildlife and other animal carers.

Item 29 – Chronic proton pump inhibitor (PPI) therapy

Item	Medical and social history criteria	Period of ineligibility
29	a person who has had chronic therapy with proton pump inhibitors	ineligible for at least 6 months from ceasing therapy

Relying on a history of functional gastrointestinal disorders is not considered sufficient to identify donor use of PPIs. The use of these medications has been found to have a significant impact on the microbiome.

Whether the use is ‘chronic’ depends on the likelihood of the treatment cycle having affected the microbiome. Current data suggests that there is not a prolonged impact on gut dysbiosis from the use of PPIs if use is ceased, unlike with the use of antibiotics.

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