



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Guideline for the Preparation of Technical Master Files for Blood, Blood Components and Haematopoietic Progenitor Cells

Third Edition, 2008

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. The TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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For more information about the *Guideline for the Preparation of Technical Master Files for Blood, Blood Components and Haematopoietic Progenitor Cells 2008* and Technical Master Files, or any other matter related to the regulation of blood, blood components, or haematopoietic progenitor cells please contact:

Blood and Tissues Unit
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
Department of Health and Ageing
PO Box 100
MDP 122
WODEN ACT 2606

Telephone: 02 6232 8443

Facsimile: 02 6232 8687

Website: <http://www.tga.gov.au>

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1. PURPOSE AND INTRODUCTION TO THE GUIDELINE

1.1 The purpose of the Guideline for the Preparation of Technical Master Files for Blood, Blood Components and Haematopoietic Progenitor Cells 2008 ('the Guideline') is to guide manufacturers in the development of Technical Master Files (TMF) relevant to blood, blood components and haematopoietic progenitor cells. The Guideline describes the scope and information expected in a TMF to demonstrate the safety and quality of blood, blood components and haematopoietic progenitor cells.

1.2 The purpose of a TMF is to provide information to the Secretary of the Department of Health and delegates of the Secretary in the Therapeutic Goods Administration (TGA) for review. It provides a medium for a manufacturer to demonstrate how appropriate standards for product safety and quality have been met by the organisation. The TMF should include sufficient information to indicate that blood, blood components or haematopoietic progenitor cells will be manufactured in compliance with relevant standards as specified by the TGA.

1.3 The structure of technical information in the TMF to be submitted to the TGA can either follow the Suggested Content of the Guideline or, where a specific standard is mandated, the TGA strongly recommends that manufacturers provide an overarching description of their activities as a preface to the presentation of information and data according to the structure of the relevant mandated standard. Guidance may be drawn from Section 7 of this Guideline for any supplementary depth to information.

1.4 The Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2007 (MP1/2007) made under Section 36 of the Therapeutic Goods Act 1989 ('the Act') sets out the principles for the manufacture of blood, blood components, plasma, and haematopoietic progenitor cells for use in humans. Division 2 of the Manufacturing Principles includes the requirement for manufacturers of blood, blood components and haematopoietic progenitor cells to lodge a TMF with an application for a manufacturing licence.

1.5 A TMF is:

- (a) a compilation of scientific data provided by a manufacturer which includes a description of the steps of manufacture consistent with the Guideline recommendations; and
- (b) detailed technical and scientific data or information that must satisfy the Secretary that:
 - i) the blood or blood components, manufactured using the steps of manufacture mentioned in paragraph (a) above, will meet [Therapeutic Goods Order No. 102 - Standard for Blood Components](#); or
 - ii) the haematopoietic progenitor cells derived from cord blood manufactured using the steps of manufacture mentioned in paragraph (a) will meet [Therapeutic Goods Order No. 75 - Standard for Haematopoietic Progenitor Cells derived from Cord Blood](#)

1.6 This edition of the Guideline is based on the Second Edition of *Guideline for the Preparation of Technical Master Files for Blood and Blood Components 2004* which came into effect in August 2004.

1.7 Although this version of the Guideline covers aspects of the safety and quality of manufacturing blood, blood components and haematopoietic progenitor cells, it is not intended that any restraint should be placed upon the development or introduction of new concepts or technologies. It is acknowledged that there can be acceptable alternatives conforming to the same end and retaining compliance with applicable guidelines and standards. *Applications may describe alternative methods and procedures, but these should be justified and validated to confirm relevance for inclusion in the TMF.* The manufacturer bears the ultimate responsibility for the products it manufactures.

1.8 Comments on the Guideline are invited at any stage in the life of this edition. The Guideline is available on the TGA website at <http://www.tga.gov.au>

2. RELEVANT DOCUMENTS

Many of the documents mentioned above can be obtained from the TGA website <http://www.tga.gov.au>.

3. SUBMISSION OF A TMF

3.1 A manufacturer of blood, blood components, plasma or haematopoietic progenitor cells is required to submit a relevant TMF with its application for a licence to manufacture.

3.2 Initial TMFs should be submitted together with a photocopy of the 'Application for a Licence to Manufacture Therapeutic Goods'.

3.3 TMFs (initial, variations and annual updates) should be submitted as three paper copies and an electronic version of the TMF. The electronic version should be submitted on a compact disc and forwarded with the paper copies.

3.4 The form at Attachment A should be submitted with variations and annual updates to the TMF. The form is also available via the TGA internet page.

3.5 All TMF submissions should be forwarded to:

Administration Officer, Blood and Tissues Unit
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
Department of Health and Ageing
PO Box 100
MDP 122
WODEN ACT 2606

or
delivered by courier to:

Administration Officer, Blood and Tissues Unit
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609

- 3.6 TMFs will be evaluated by the TGA to the following target timeframes:
- § 10 working days filter for acceptance/rejection to evaluate the TMF,
 - § 150 working days for a new TMF (including resubmission of an unapproved TMF),
 - § 90 working days for Annual Updates, and
 - § 45 working days for a variation to an existing TMF.

3.7 The timeframe will commence from the date of the TGA's receipt of the TMF submission or payment of the evaluation fee if applicable, whichever is later, and end with the letter from the Blood and Tissues Unit issuing a decision regarding compliance of the TMF with the requirements. The target working days are TGA working days and do not include the time taken by the manufacturer to respond to queries raised by the TGA during evaluation.

3.8 The organisation may request completion of the evaluation in a shorter timeframe which will be considered on a case by case basis.

3.9 The form for Application for a Licence to Manufacture Therapeutic Goods can be obtained from the TGA web site at <http://www.tga.gov.au/pdf/forms/manuf-forms-licence-application.pdf> or from the Office of Manufacturing Quality, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606.

3.10 It is the responsibility of the manufacturer to keep the contact details for their organisation and personnel up to date on the manufacturing and client databases in the TGA's information system.

4. EVALUATION AND APPROVAL OF A TMF

4.1 A TMF submitted as part of an Application for a Licence to Manufacture will be evaluated by the Blood and Tissues Unit of the Office of Devices, Blood and Tissues, TGA. The TMF will primarily address the safety and quality of the particular products and confirm that the products satisfy all aspects of the applicable mandatory standards and other relevant guidelines/documents. The manufacturer should ensure data and information provided in the TMF is current and any claims should be supported by data, validation reports and literature citations, particularly with areas involving new technologies.

4.2 The Office of Manufacturing Quality, TGA will conduct audits of the proposed manufacturer to assess the manufacturing process and quality system for compliance with the relevant manufacturing standard(s) as described in the Manufacturing Principles.

4.3 A licence will be issued to a manufacturer only after the TGA delegate is satisfied that the manufacturing operations including the TMF conform to the Manufacturing Principles determined under the Act.

4.4 Once a TMF has been approved by the TGA, it may not be changed without the approval of the TGA (see Section 6 *Changes to a TMF*, below).

4.5 As changes will often be made to a TMF, annual submissions of the TMF specifying the changes are required.

5. FEES

5.1 A Licence Application Fee is payable at the time of making an Application for a Licence to Manufacture. Additional fees are usually levied on an organisation for the evaluation of a TMF and for audit costs.
(Therapeutic Goods Regulations 1990, Schedule 9).
<http://www.tga.gov.au/about/fees.htm>

5.2 An evaluation fee for the TMF submission may not be levied on an organisation that can substantiate eligibility for exemption from such fees.
(*Therapeutic Goods Act 1989*, Section 59(3)).
<http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/all/search/65278038011B7DF3CA257375000D669B>

5.3 Fees are charged for TMF annual updates for those agencies not covered by Section 59(3) of the Act.

5.4 Fees are also charged for audits of manufacturers to assess compliance with the Australian Code of GMP for Blood and Tissues.

6. CHANGES TO A TMF

6.1 After a TMF has been determined to be satisfactory by the TGA delegate it represents the agreed manufacturing conditions for that product or products. As such, the manufacturing conditions and the TMF cannot be changed without notification to, or approval by, the TGA delegate. The TGA accepts that changes to the manufacturing conditions will occur from time to time.

6.2 To assist the TGA in approving changes, each submitting manufacturer is requested to include in the TMF:

- (a) a summary of changes between the previous version and the updated version, and

(b) the supportive documentation justifying the proposed change.

This documentation should include a description of the changes, a description of how the effect of these changes on product quality will be assessed, and describe how the changes will be implemented, documented and validated. The documentation should describe, but not be limited to, the procedures to be used when introducing changes to a starting material, product component, processing equipment, method of production or testing.

6.3 The TGA considers that changes fall into three categories which are listed below.

(a). Changes requiring pre approval by the TGA.

These include changes to manufacturing processes or conditions which have a significant potential to impact on the quality and safety of the product. These may include changes to infectious disease product release testing and changes to manufacturing conditions such as the introduction of new technologies or changes to manufacturing parameters.

Such changes need regulatory approval from the TGA prior to implementation.

Requests for such changes should be submitted in writing to the TGA and should include a justification for the change and supporting documentation, such as protocol(s) and validation report(s). A GMP audit may be required prior to the introduction of changes to critical steps of manufacture.

(b). Changes requiring notification to the TGA

A change requiring TGA notification is one that may have an effect on quality and/or safety of the product. These changes require notification to the TGA preferably before the change is implemented. Requests for such changes should be submitted in writing to the TGA and should include a justification. The TGA may request additional information regarding the changes such as data and validation reports.

Examples could include change to reagents used within an established assay.

(c). Changes which only require incorporation into a TMF update.

A change only requiring incorporation into the TMF is not likely to have a detectable impact on the quality or safety of the product. For example, “like- for-like” equipment replacement (e.g. replacement of one centrifuge with another centrifuge) would be unlikely to affect the manufacturing process if the change control mechanism is implemented satisfactorily.

NOTE: Manufacturers are encouraged to contact the TGA in order to seek clarification of any proposed changes.

7. SUGGESTED CONTENT OF A TMF

7.1 Purpose of the TMF

7.1.1 A TMF should contain a statement of the product's capability to comply with the relevant mandated standard as set out in the current applicable Therapeutic Goods Orders and any other measures relevant for blood, blood components or haematopoietic progenitor cells.

7.1.2 The applicant should refer to the current mandated standards that are referenced on the TGA website. Applicants are to comply with standards and guidelines for product safety, quality, efficacy, quality parameters and acceptance criteria. These standards should be identified in the TMF.

7.1.3 Data provided to the TGA should be sufficient to justify claims made in the TMF. It is essential that the manufacturer provide details of all acceptance criteria, release criteria and quality control parameters.

7.1.4 The TMF should be presented in a folder(s) or bound, on A4 papers printed on one side only, legible, paginated and include a Table of Contents, indexing and cross-referencing as applicable.

7.2 Products included in the TMF

7.2.1 Each product subject to the same standard and intended to be covered by or relevant to the Application for a Licence to Manufacture must be included in the TMF. Details of product(s), including all product sub-types that are being manufactured should be specified in the TMF as described on the Application for a Licence. Details providing an introduction to the product(s) to be manufactured, in a way which can be appreciated by a general scientific reviewer, and the rationale for use of the product and information on the manufacturer should also be provided to assist with the evaluation process.

7.2.2 A literature review including the scientific basis and background of the product should be provided. (*Cited references should be included as an annex to the TMF*).

NOTE: If in doubt, the scope of the TMF should be discussed with the TGA.

7.3 Donor selection and assessment

7.3.1 Where applicable to the product, a TMF should describe all matters relating to:

- donor selection acceptance criteria,
- deferral,
- quantity of donation,
- donation interval, and
- follow up tests after donation.

The processes used to ensure ability to donate, compatibility with the recipient (if applicable) and exclusion of the risk of disease transmission should be described.

7.3.2 Donor identification should be detailed so that all donors are positively verified at critical steps.

7.3.3 The process of referral of donors (if applicable) should be detailed to provide information relating to donor and recipient planning.

7.3.4 Re-admission criteria of a previously temporarily deferred donor should be provided (if applicable).

7.4 Donor testing

The TMF should describe the complete regimen of donor testing performed. It should cover, but need not be limited to:

7.4.1 A list of mandated and non-mandated laboratory tests, the purpose of each and their limitations.

7.4.2 Criteria for acceptance or rejection of donation and re-testing policy.

7.4.3 The relevant information which the manufacturer is required to submit in support of any exemptions sought under the *Therapeutic Goods Act 1989*.

7.5 Materials and reagents

7.5.1 A list of all materials, equipment and medical devices used in the collection and manufacturing process should be provided including respective ARTG numbers, where applicable.

7.5.2 If a material is neither registered nor listed on the ARTG, the manufacturer's name, a Certificate of Analysis for the material and the rationale for the choice of material should be provided. Evidence of compliance with the relevant monograph of the British or European Pharmacopoeia should be provided (if applicable).

7.5.3 If the material is a medicinal component it should be included on the ARTG. If the medicinal component is not entered on the ARTG, a justification for its use and a Certificate of Suitability should be provided.

7.5.4 If a material contains any components of human or animal origin, it should be tested and confirmed to be free from any potential transmissible infectious disease agent. The sources of the material and evidence of the negative status should be provided (eg screening test results).

7.6 Collection of starting material

The TMF should describe all matters relating to the starting material including but not necessarily limited to:

7.6.1 Acceptance criteria - specified parameters such as the minimum target volume to be collected, target cell dose (if applicable), donation intervals, retrieval procedures and the time interval between collection and commencement of processing of starting material should be detailed.

7.6.2 Donor treatment - for example, the administration of growth factors for the mobilisation of haematopoietic stem cells should comply with relevant medical ethical codes and should be quoted in the TMF. There should be a description of special requirements for apheresis such as a written request from the physician and written consent from the donor.

7.6.3 Collection procedures including preparation of the venepuncture site should be detailed. Any limits on the duration of the collection should be specified.

7.6.4 Details of additive/preservative solutions and the bag system (if applicable) should be outlined. Details should be provided for the starting material, intermediate products and final products including transportation requirements (if applicable).

7.6.5 Materials used in the process should be listed.

7.7 Product manufacture

7.7.1 The TMF should provide a brief outline of the manufacturing process. Where possible the TMF should use a flow chart to detail the processes involved including critical decision points.

7.7.2 The TMF should contain a description of the critical control points and key elements for each system as identified by the manufacturer. These include: preparation and acceptance criteria for starting material, tests applied to starting material to confirm freedom from infectious disease agents, tests and acceptance criteria applied to finished products and criteria for quality control of the products. The manufacturer is required to substantiate the selection of critical process controls (operational parameters and in – process tests).

7.7.3 A description of the process **validation** should include, but not be limited to:

7.7.3.1 Demonstration that the process and product meet specifications and the factors which will determine an acceptable or unacceptable result. In-process controls and tests performed on the product should be included as well as the limits of acceptance and the rationale for specifying these limits. Process validation applies to all critical process steps, examples include any step which may change the form of the product, steps which may affect product quality, and an indication if there has been prolonged storage steps.

7.7.3.2 The tests performed should assure the identity, purity, and safety of the product. Such assurances may include, but not be limited to: cell viability, cell number, microbial assessment, dose of specific cell types, product volume, and functional potency (if applicable).

7.7.3.3 Details of procedures taken to prevent contamination or cross-contamination of product should be provided (eg details of the segregation of operations and product particularly if the manufacturing area is used for the processing of different products).

7.7.3.4 Details of procedures implemented to avoid possible contamination throughout the entire process: collection, transport, quarantine, testing, manufacturing, storage, release, labelling and transfusion / transplant.

7.7.3.5 If pathogen inactivation is carried out then validation should be performed.

7.8 Product testing methods

7.8.1 Descriptions of product testing methods should be provided in the TMF and include, but not be limited to:

7.8.1.1 The provision of scientific principles with details of testing procedures and algorithms.

7.8.1.2 Test methods for transfusion-transmitted infections. A list of testing kits and reagents should be included in an appendix. Tests and test kits used by the testing laboratory should be verified for the purpose for which they will be used.

7.8.1.3 The internal procedure for out of specification test results.

7.8.1.4 Any additional tests that may be necessary under certain circumstances to increase safety for susceptible recipients (eg tests for CMV) if applicable.

7.8.1.5 The use and requirements for nucleic acid amplification technology (NAT) testing).

7.9 Labelling

7.9.1 The TMF should include the details of labelling procedures that ensure labels have been validated for their in-process (eg collection bags) or final product use. Information contained in the labelling must comply with the relevant standards.

7.9.2 A description of the labelling of viral positive samples should be detailed. The description should include the procedures for the containment and labelling of products from donors confirmed to be positive for infectious agents (if applicable) and arrangements for the quarantine storage of non-conformant product.

7.10 Storage, stability, shelf life and transportation

7.10.1 Storage conditions should be provided for all relevant products detailed in the TMF. Where applicable, details of validation tests performed to establish product viability post storage should be provided together with the generated data.

7.10.2 Storage methodology for products intended for transplantation should be provided. This should include, but not be limited to, choice of cryoprotectant, method of cryopreservation, and the storage and testing of cryopreserved product, pre- and post-storage.

7.10.3 Storage conditions and management of non-conforming and contaminated (viral/microbiological), products should be detailed.

7.10.4 Description of validated protocols used to ensure the recommended storage temperature is maintained during transportation and over the proposed storage period. The anticipated extremes of ambient temperature of transport should be detailed.

7.10.5 Demonstration of product stability and end of storage specifications should be provided.

7.10.6 Procedures for disposal of unused product and the handling of expired products should be detailed.

7.11 Product release

7.11.1 The methods and specifications selected to determine acceptability of product for release should be substantiated.

7.11.2 If test results are not available until after product release, the TMF should include an explanation of why product is released before results are available, together with a justification and indicate the length of time until results are obtained. Details of the procedure in place specifying action plans for notification to the authorised physician and the patient of any significant abnormal post-release result should be included.

7.11.3 Procedures for handling returned product and, if applicable, acceptance criteria should be detailed.

7.12 Clinical indications/clinical outcomes/adverse reactions

7.12.1 The clinical indication for use of the product should be provided.

7.12.2 Relevant clinical practice guidelines on the use of the product(s) should be specified.

7.12.3 There should be a procedure to obtain post product release data following the transplant or transfusion of product. Examples may include, but not be limited to, engraftment data or any adverse reaction of the donor or recipient following transplant or transfusion.

7.12.4 Details on the procedures for monitoring an adverse reaction should be provided (if applicable).

7.13 Relevant appendices

Relevant Appendices that may be included:

- A list of validation reports,
- Standard Operating Procedures relevant to the manufacturing and quality assurance requirements,
- A list of full references,
- A list of equipment and materiel specifications used in the manufacturing steps,
- Glossary and terminology,
- Label register (including mock up labels),
- Any other relevant data or information.

Appendix A



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

TMF Submission Form

For the Attention of

Administration Officer
Blood and Tissues Unit
Office of Devices Blood and Tissues
Therapeutic Goods Administration
PO BOX 100 WODEN ACT 2606

<<**PRODUCT NAME**>> **TMF**
<<Name of Manufacturer/Applicant>>
<<Address of Manufacturer/Applicant>>

Authorised Person: << Name of person submitting form and contact re evaluation>>]

Reference:

Request for TMF evaluation:

Initial submission	
Annual update	
Variation (needs TGA pre-approval)	
Notification (Information only, incorporate in next TMF annual update)	

Manufacturing sites affected	
Target commencement date	
Documentation provided and/or TMF amendments	

Further Information (short summary):

.....
.....
(Signature of Authorised Person
dd/mm/yyyy)

(Date

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

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www.tga.gov.au

Reference/Publication #