



Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Guidance 9: Therapeutic goods that contain or are produced from human blood or plasma

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TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part 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. 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 <<http://www.tga.gov.au>>.

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Introduction

This guidance provides information for sponsors and manufacturers about the regulatory requirements for [therapeutic goods](#) that contain, or are produced from, human blood or plasma (except biologicals, as defined in the [Therapeutic Goods Act 1989](#) [the Act]).

Examples of the therapeutic goods covered by this guidance are coagulation factors, immunoglobulins of human origin and albumin and in vitro fertilisation (IVF) media.

9.1 Background to the regulation of therapeutic goods containing human blood or plasma

Australia is signatory to a World Health Organization (WHO) policy that states that each country should aim to be self-sufficient with regard to the supply of goods derived from human blood.

The aim under this policy is for therapeutic goods containing human blood or plasma for supply in Australia to be manufactured from blood or plasma from Australian donors.

[The National Blood Authority \(NBA\)](#) manages the supply of these products.

The TGA uses international standards and guidelines to evaluate data on therapeutic goods that are derived from human blood or plasma to minimise the risk of transmitting infectious diseases through their use.

Sponsors are required to:

- submit a PMF to support an application to enter the therapeutic goods on the [Australian Register of Therapeutic Goods](#) (ARTG)
- update the PMF every year to ensure continued safety and quality of the therapeutic goods.

9.2 Standards and guidelines for human blood or plasma

The TGA has adopted the European Medicines Agency (EMA) guideline:

- [Guideline on plasma-derived medicinal products](#) (EMA/CHMP/BWP/706271/2010).

This guideline:

- outlines the quality and control measures expected of a medicinal product that is manufactured from human plasma
- is used as guide to assess these products.

Related information and guidance

- [Adventitious agent safety of medicines](#)

9.2.1 Medicines derived from human plasma

The plasma used as a raw material in the manufacture of medicines derived from human plasma must comply with either:

- the European Pharmacopoeia (Ph. Eur.)
- the British Pharmacopoeia ([BP](#)) monograph 'Human plasma for fractionation' (0853) which is a Standard under subs. 3(1) of the Act.

9.2.1.1 Plasma used for fractionation

In addition to the requirements of the standard monograph, the plasma used for fractionation must comply with [Therapeutic Goods Order No. 81—Blood and blood components](#) (TGO 81) and the [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) with regard to donor exclusion and screening requirements, particularly exclusion criteria for variant Creutzfeldt–Jakob disease (vCJD).

Sponsors include in Module 3 (in the PMF):

- a statement identifying the countries of origin of the plasma
- an assurance that the individual donors had not resided in the United Kingdom for a cumulative period of six months or more between 1980 and 1996, or received a blood transfusion in the United Kingdom from 1980 onwards
- an assurance that donations had been screened using nucleic acid amplification technology for human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

The United States Pharmacopeia–National Formulary (USP–NF) monograph 'Plasma protein fraction'

The United States Pharmacopeia–National Formulary (USP–NF) monograph 'Plasma protein fraction' is not a Standard because it is exempted under the [Therapeutic Goods \(Exempting monographs of pharmacopoeias\) Determination No. 1 of 2011](#), thereby excluding the USP–NF as a Standard for these products.

For this reason the Monographs of the USP–NF cannot be used for the following medicines derived from human plasma:

- Antihemophilic Factor
- Antithrombin III Human
- Cryoprecipitated Antihemophilic Factor
- Factor IX Complex
- Hepatitis B Immune Globulin
- Immune Globulin
- Pertussis Immune Globulin
- Plasma Protein Fraction
- Rabies Immune Globulin
- Rho (D) Immune Globulin
- Tetanus Immune Globulin
- Vaccinia Immune Globulin

- Varicella-Zoster Immune Globulin.

Standard for human albumin

The standard for human albumin accepted by the TGA is defined by [Therapeutic Goods Order No. 90 - Standard for human albumin](#) (TGO 90), which states that 'albumins from humans must comply with the monograph for human albumin in the BP or the Ph. Eur.'.

9.3 Plasma Master Files for human blood or plasma

The PMF is a stand-alone document that records the quality aspects of human plasma used as a raw material for the manufacture of therapeutic derivatives, including clotting factors, immunoglobulins and albumin. The PMF includes information on:

- the source of the plasma
- the location(s) where the plasma was collected
- the screening process for donors
- the tests used to screen donated blood and plasma
- the results of these testing procedures (epidemiology data).

9.3.1 When is a plasma master file required?

9.3.1.1 Applications for plasma derivative or a product containing a plasma derivative

Include a PMF as part of the product quality data in Module 3 of the [Common Technical Document](#) (CTD) format.

The PMF will be evaluated in conjunction with the other product quality data, such as virus removal/inactivation steps.

9.3.1.2 Requests to make a variation to an existing ARTG entry

The PMF is also required in some requests to make a variation to an existing ARTG entry. For example:

- If a manufacturer of a therapeutic good that includes human albumin changes the supplier of the albumin to a different manufacturer, the variation request would need to include the PMF (or a letter of access to the PMF) of the new manufacturer of the albumin as part of the Module 3 data for that application.
- If a manufacturer of a plasma-derived medicine applies to use a fractionation intermediate from an alternative manufacturer, the Module 3 data for such a variation request would need to include the PMF from the alternative manufacturer.

9.3.1.3 Data and format of the Plasma Master File

The data and format of the PMF should conform to both:

- [Annex 1 to Guideline on the scientific data requirements for a plasma master file \(PMF\) Revision 1](#) (EMEA/CHMP/BWP/3794/03 Rev 1 Annexes)
- [Guideline on epidemiological data on blood transmissible infections](#) (EMEA/CHMP/BWP/125/04).

All activities from donor recruitment and selection through to manufacturing of the first homogeneous plasma pool should be stated in the PMF and are subject to evaluation.

9.3.2 Administrative categories of plasma master files

For the purposes of administration, the TGA has grouped PMFs into two categories:

- Type I PMFs provide the information to support products registered for supply to the Australian market.
- Type II PMFs are those that are required to be submitted to the TGA under [Therapeutic Goods \(Manufacturing Principles\) Determination No. 1 of 2013 \(MP1/2013\)](#).

9.4 Plasma master files for human blood or plasma products in the ARTG (Type I)

PMFs for applications for new entries in the ARTG or requests for variations to existing ARTG entries (e.g. where a new plasma fractionator or supplier of albumin is requested) should use the CTD format. The PMF remains a stand alone document distinct from the registration/variation dossier and should be submitted to:

Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Annual updates to Plasma master files

Once a plasma derivative is included in the ARTG, or the variation to the product is approved, a condition of registration is usually applied requiring the PMF to be submitted to the TGA every year.

A PMF update must include updated epidemiology data, and information about changes in plasma collection and screening that have occurred since the last update.

The TGA reviews the PMF update to ensure the continuing quality and safety of the plasma being used in the production of the plasma derivative(s).

Provide a covering letter with the annual update stating:

- the sponsor's name
- the plasma source(s) covered by the PMF that are relevant to the Australian product
- the product(s) covered by the PMF, including the ARTG number(s)
- the period covered by the PMF.

Submit the annual updates to:

Biological Sciences Section
Office of Scientific Evaluation
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

There is no statutory timeframe for the evaluation of PMF updates; however, the TGA tries to review them within 60 working days of receipt.

Sponsors will be advised in writing of the outcome of the review and the expected date of the next update.

In lieu of submitting a PMF update for an [excipient](#), the TGA may agree for sponsors to obtain a letter from the fractionator responsible for the PMF to allow the TGA to access the latest version of the PMF on the sponsor's behalf.

9.5 Plasma master files for plasma processed in the same facility as Australian plasma (Type II)

Sponsors are required to submit a PMF for plasma that is sourced outside Australia but processed in the same facility as Australian plasma. This is prescribed by the [Therapeutic Goods \(Manufacturing Principles\) Determination No. 1 of 2013 \(MP1/2013\)](#):

A blood processing plant that processes plasma collected from donors in Australia for products that are or will be used in Australia (the Australian product) may only be used to process plasma collected from a source outside Australia if, for that source:

- a PMF, prepared in accordance with the requirements of the European Agency for the Evaluation of Medicinal Products document entitled [Guideline on the scientific data requirements for a plasma master file \(PMF\) Revision 1](#) (EMA/CHMP/BWP/3794/03 Rev 1) has been submitted to the [Secretary](#) by the licensee of the relevant blood processing plant.
- the Secretary has advised the licensee of the plant, based upon the PMF, and having taken into account the plant's processes, that the plasma from the source outside Australia is unlikely to present a risk of contamination to the Australian product with any known blood borne pathogens.

9.5.1 Manufacturers who fractionate Australian and overseas sourced plasma

Manufacturers that fractionate both Australian plasma and plasma sourced from overseas in the same facility must submit a separate PMF for plasma from each different overseas source.

Only overseas-sourced plasma with a TGA-approved PMF can be fractionated in the same facility as Australian plasma.

These requirements, together with good manufacturing practice (GMP), ensure that products that are manufactured from plasma from Australian donors do not have their safety and quality compromised if the same facility also processes plasma from donors outside Australia.

Submit PMFs to:

Office of Manufacturing Quality
Therapeutic Goods Administration

PO Box 100
WODEN ACT 2606

Approval of PMFs for plasma that is processed in the same facility as Australian plasma is usually granted for one year.

9.5.2 Annual updates

Annual updates to PMFs for plasma that is processed in the same facility as Australian plasma (Type II PMFs) are required under the [Therapeutic Goods \(Manufacturing Principles\) Determination No. 1 of 2013 \(MP1/2013\)](#).

A PMF update must include updated epidemiology data, and information about changes in plasma collection and screening that have occurred since the last update. The TGA reviews the PMF update to ensure the continuing quality and safety of the plasma being used in the production of the plasma derivative(s).

Type II PMF updates should be submitted at least three months before the approval of that PMF expires, to allow time for evaluation and resolution of any issues. Sponsors will be advised in writing of the outcome of the evaluation and whether any issues need to be addressed.

[Fees](#) apply for the submission of Type II PMFs.

9.6 Variations to plasma master files

Once a PMF has been accepted by the TGA, any changes in plasma collection and testing represent changes to the quality information that may affect product quality and safety.

Major changes to plasma collection and testing require prior approval from the TGA and should not be introduced for the first time in a PMF annual update.

Related information and guidance

- [Minor variations to registered prescription medicines: Biological medicines](#)

9.6.1 Variations that require data to be submitted to the TGA

The point at which individual plasma units are pooled into a manufacturing pool is the first homogeneous pool is a critical point in the manufacture of plasma derivatives.

- Submit any change made to the manufacture of the first homogeneous pool as a Category 3 application.
- Include approved changes in the next PMF update with reference to the TGA approval date and submission number.

The types of changes that should be reported as a Category 3 application are described in the TGA guidance [Minor variations to registered prescription medicines: Biological medicines](#), Section 4.3, Part O.

9.6.2 Variations that can be reported in an annual plasma master file update

Minor changes do not generally require prior approval or notification to the TGA but should be reported in the PMF annual update.

The types of changes that could be introduced for the first time in a PMF annual update include, but are not limited to:

- addition or removal of collection centres for a currently approved collection organisation
- change of sites for testing individual donations
- change of tests for testing individual donations provided the type and principle of the test remain unchanged.

Therapeutic Goods Administration

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