



# The safety of plasma-derived products in Australia

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## Summary

**Plasma-derived products are used in Australia in a wide variety of clinical settings. The majority of these products are manufactured locally from voluntary blood donations. The preparation of plasma products is subject to rigorous safety measures, including screening blood donors, testing plasma for infectious material, and subjecting plasma to dedicated pathogen inactivation steps. The safe use of plasma derivatives requires correct storage and handling.**

Key words: coagulation, intravenous immunoglobulin, pathogen inactivation.

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## Introduction

Plasma derivatives, prepared by fractionating donated human plasma, are used in a wide range of medical conditions. Australia's national policy for these essential products is to strive for self-sufficiency. A recent review of the policy found that, while Australia has never completely produced all of its own plasma derivatives, 'Australia should be as self-sufficient as possible, and that self-sufficiency should remain an important goal'.<sup>1</sup>

## Plasma products used in Australia

Plasma-derived products can be divided into three broad categories: immunoglobulins, coagulation factors and albumin (Table 1). These are primarily used to replace missing or dysfunctional elements of the immune or coagulation systems. In the case of RhD immunoglobulin or intravenous immunoglobulin, their primary role is to modulate the immune system's responses. The uses of intravenous immunoglobulin continue to increase,<sup>2</sup> particularly as immunological bases for more conditions are revealed. Future demand for intravenous immunoglobulin may be altered by the advent of new, more targeted therapies for conditions with an autoimmune basis. The demand for coagulation factors is influenced by the availability of specific recombinant products which are not plasma-derived.

## Plasma supply

The Australian Red Cross Blood Service, under medical

oversight and operating within the principles of Good Manufacturing Practice and a licence from the Therapeutic Goods Administration (TGA), collects plasma from volunteer, non-remunerated donors.

The safety of these blood-derived products remains of utmost importance. Although Australia's blood supply is safer than it has ever been from an infectious diseases point of view, vigilance is still required against known pathogens (such as prions associated with variant Creutzfeldt-Jakob disease), currently unknown pathogens and other associated risks. The Blood Service actively monitors for new and emerging infectious threats to blood safety.

## Screening blood donors

Stringent criteria must be met before the donation of blood is permitted in Australia, and recruitment and retention of low-risk, volunteer donors is a key element in maintaining the safety of the plasma supply. Donors with temporary or indefinite ineligibility are deferred as appropriate, to minimise the risks of pathogens being present in the plasma sent for fractionation. Each donor undergoes a detailed, confidential interview and health screen.

## Collecting, testing and processing plasma

Once donor eligibility has been established, collection of whole blood or plasma (by plasmapheresis) occurs in accordance with strict safety and quality requirements. Whole blood is separated into its components (red cells, platelets and plasma) within specified time and temperature conditions to maintain plasma integrity. Bar coding of all samples and kits permits traceability at each step of the process.

All donor samples undergo pathogen screening using routine serological and nucleic acid testing (see box). Targeted serological testing may also be performed, such as malaria testing for a donor with a relevant travel history.

Nucleic acid-based amplification tests are used to directly detect viral genomes, while most serological tests rely upon detection of an immune response to infection, such as an antibody. The exquisite sensitivity of nucleic acid testing can reduce the window period for detection (from time of infection to time of detection) from 66 days to approximately 5 days for hepatitis C, and from 22 days to 9 days for HIV. Only donations with acceptable test results are released for further processing.

Table 1

**Fractionated plasma products commonly used in Australia**

Product	Indication or use	Comments*
<b>Immunoglobulins</b>		
Normal immunoglobulin		
- intravenous	Immune replacement in congenital and acquired immune deficiencies Immunomodulation in a range of haematological (e.g. immune thrombocytopenic purpura), neurological (e.g. Guillain-Barré syndrome), dermatological and other conditions (e.g. Kawasaki syndrome), usually only when other treatments have failed or are contraindicated	No alternative therapy for many patients with immune deficiency. There has been increased demand in recent years for immunomodulation, with a wide range of conditions reported to benefit from treatment with IV immunoglobulin. See 'Criteria for the clinical use of intravenous immunoglobulin in Australia', <sup>2</sup> <a href="http://www.transfusion.com.au">www.transfusion.com.au</a> , <a href="http://www.cslbioplasma.com.au">www.cslbioplasma.com.au</a> and <a href="http://www.octapharma.com">www.octapharma.com</a>
- intramuscular	For passive immunisation of contacts of cases – hepatitis A, measles, poliomyelitis and rubella	Less commonly used for these indications since vaccination programs have been expanded. See <a href="http://www.transfusion.com.au">www.transfusion.com.au</a> and <a href="http://www.cslbioplasma.com.au">www.cslbioplasma.com.au</a>
Hyperimmune immunoglobulin		
- RhD	Prevention of antenatal and postnatal RhD sensitisation in RhD negative women. Also used to prevent RhD alloimmunisation in the unlikely event of an RhD incompatible transfusion.	More information on prophylaxis in pregnancy including types of sensitising events, doses used at different stages of pregnancy and postpartum is available at <a href="http://www.transfusion.com.au">www.transfusion.com.au</a> For large doses or if IM preparation cannot be used (e.g. very large fetomaternal haemorrhage, or RhD incompatible red cell transfusion, or RhD incompatible platelet transfusion in a patient with thrombocytopenia), an IV preparation is available.
- cytomegalovirus	Prevention or treatment of cytomegalovirus infection in immunocompromised patients	See <a href="http://www.transfusion.com.au">www.transfusion.com.au</a> and <a href="http://www.cslbioplasma.com.au">www.cslbioplasma.com.au</a>
- zoster	Prevention of chickenpox or shingles in immunocompromised patients exposed to varicella zoster virus	
- tetanus	Prevention of tetanus in tetanus-prone wounds (IM formulation) or treatment of clinical tetanus (IV formulation)	
- hepatitis B	Post-exposure prophylaxis for hepatitis B where vaccination has not been given or is incomplete, including infants born to hepatitis B-positive mothers	
- others (e.g. rabies immunoglobulin)		Used rarely in Australia and only with specialist advice
<b>Coagulation factors</b>		
Prothrombin complex concentrate	Warfarin reversal and prophylaxis and treatment of bleeding in patients with single or multiple congenital or acquired deficiencies of factor II or X or multiple acquired prothrombin complex factor deficiencies requiring partial or complete reversal	Contains factor IX, II and X and low levels of factor VII. Use in accordance with guidelines. <sup>8</sup>
Factor VIII, von Willebrand factor	Prophylaxis and management of bleeding in patients with von Willebrand disorder	Contains both coagulation factor VIII and von Willebrand factor. Most patients with haemophilia A are now treated with recombinant factor VIII.
Other plasma-derived factor concentrates (e.g. factor XI, XIII, antithrombin)	These are used in very limited circumstances under the supervision of a specialist	For more information on the use of plasma-derived products for bleeding disorders, see the Australian Haemophilia Centre Directors' Organisation <a href="http://www.ahcdo.org.au">www.ahcdo.org.au</a>
<b>Albumin</b>		
Albumin 4%	For hypovolaemia associated with hypoalbuminaemia, and in therapeutic plasma exchange	Albumin and saline for volume replacement in the critically ill were found to be equally safe and effective. <sup>9</sup>
Albumin 20%	Used in shock and hypoproteinaemic states such as burns and paracentesis of ascites	The 20% formulation is hyperoncotic and fluid overload can develop rapidly
* See full URLs online with this article at <a href="http://www.australianprescriber.com">www.australianprescriber.com</a>		
IM intramuscular		
IV intravenous		

#### Box

#### Routine pathogen screening tests for blood donor samples in Australia

##### Nucleic acid tests

HIV-1

Hepatitis B (this test will be implemented in 2010)

Hepatitis C

##### Serological tests

HIV-1/2

Hepatitis B

Hepatitis C

Syphilis

Human T cell lymphoma virus I/II

Current risks of transfusion-transmitted infections from fresh blood components – red cells, platelets and plasma – collected in Australia are extremely low. These estimates are available from the Australian Red Cross Blood Service<sup>3</sup> and are updated annually.

Once pathogen screening is complete, most plasma is dispatched for manufacturing. A small percentage is retained for clinical use as fresh frozen plasma and cryoprecipitate. Transport and storage occurs at below  $-20^{\circ}\text{C}$  to retain plasma coagulation factor levels and other functional activity.

### Manufacturing plasma products

The majority of plasma-derived products used in Australia are manufactured from Australian-sourced plasma. Some products are imported, including some coagulation factors and immunoglobulins, either to supplement domestic supplies (for example, intravenous immunoglobulin) or to provide products which are not presently manufactured in Australia, such as fibrinogen concentrates. A review of Australia's plasma fractionation arrangements found that maintenance of product safety, quality and availability would be best achieved by fractionation of Australian plasma continuing locally.<sup>1</sup> Other advantages of local production were also noted, in terms of overall costs, turnaround times, management of risks to safety and availability of plasma supplies and, importantly, maintaining the confidence and support of Australian blood donors.

Plasma-derived products are typically prepared from pooled plasma, with a pool often consisting of thousands of donations. All plasma samples are uniquely identified to ensure ongoing traceability. Pooling minimises the infective risk, should the plasma pool be contaminated by a potentially infected donation. Infectious material present in one donation may be rendered below the infectious threshold by dilution in a pool of thousands of donations or may be neutralised by protective antibody present from other donations in the pool.

However, pooled plasma products are usually distributed to many patients, so infectious material not eliminated during manufacturing could potentially cause harm to many recipients. Further serological and nucleic acid testing is also performed on starting pool samples and only pools with acceptable testing results proceed to further manufacturing.

### Plasma fractionation

The fractionation process includes physical separation using precipitation and chromatography. Chromatography separates molecules from a liquid solution based on chemical and physical properties, enabling partition and purification of immunoglobulins, clotting factors and albumin from plasma.

The fractionation process also contributes to non-specific reduction of viruses and other pathogens, including prions (although variant Creutzfeldt-Jakob disease has not been identified in Australia). Each component manufactured from Australian plasma undergoes two dedicated pathogen reduction steps. These have been validated to remove or inactivate potential pathogens<sup>4</sup> and include:

- dry heat treatment ( $80^{\circ}\text{C}$  for 72 hours) or pasteurisation (vapour heat at  $60^{\circ}\text{C}$  for 10 hours)
- use of solvents and detergents
- exposure to low pH conditions
- nanofiltration.

These are performed according to approved manufacturing processes for each product. No confirmed transmissions of viruses have occurred from products used in Australia since effective dedicated pathogen inactivation and removal steps were introduced. However, non-enveloped viruses such as parvovirus B19 and hepatitis A remain a concern for some products, as current viral inactivation or removal techniques are variably effective against these.

### Quality control

The fractionation process proceeds under strict regulatory oversight in a highly controlled manufacturing environment. Cleaning and sanitation protocols prevent cross-contamination of batches. Quality control and release testing monitors interim and final products against approved plasma specifications agreed upon by the manufacturer and the TGA.

All therapeutic products used in Australia, whether manufactured locally or imported, are registered on the Australian Register of Therapeutic Goods and must meet the stringent regulatory requirements of the TGA. However, some variations between local and imported products can occur, and these may have clinical consequences. For example, the differences in intravenous immunoglobulin products, such as antibody profile, may reflect the:

- geographic locations, infectious exposures and immunity of the donor population
- plasma collection (whole blood donation, or by apheresis)
- testing performed
- manufacturing methods.

## Using fractionated plasma products

Blood products should only be prescribed with awareness of their associated harms and benefits. All plasma products used in Australia have approved product information and consumer medicine information available from the manufacturer or distributor or the TGA ([www.ebs.tga.gov.au](http://www.ebs.tga.gov.au)). Other resources are available for clinicians and patients,<sup>5,6</sup> and medical specialists and transfusion nurses at the Australian Red Cross Blood Service can provide expert advice ([www.transfusion.com.au/Contact-Us.aspx](http://www.transfusion.com.au/Contact-Us.aspx)). Ultimately, informed prescribing equates to maximal safety, efficacy and appropriate use of plasma-derived products.

## Storage and handling

Storage and transport requirements are defined for all plasma-derived products. They require storage in secure, monitored environments to ensure their safety and efficacy. Some require refrigeration, while others may be stored at controlled room temperature routinely or for short periods.

Although safety-related recalls are rare, the ability to trace each product to its final destination (transfusion to a patient) is a requirement documented in health department circulars and other regulations in a number of states.<sup>7</sup>

## Adverse reactions

Adherence to the manufacturer's guidance and institutional infusion policies, and careful monitoring of the patient during infusion, can minimise the likelihood of adverse events, or allow for early intervention should they occur.

Serious adverse reactions to plasma products are rare, but minor reactions are not uncommon. When serious reactions do occur, they should be reported promptly to the local transfusion service (hospital blood bank or issuing laboratory), and the manufacturer. Medical advice regarding reporting and management of adverse reactions is available through the manufacturer or distributor and the Australian Red Cross Blood Service.

## Recombinant products

Currently, recombinant products are used primarily for coagulation factor therapy in patients with bleeding disorders and include factor VIIa, factor VIII (haemophilia A) and factor IX (haemophilia B). They should be used in consultation with a specialist experienced in the care of these patients, such as through a haemophilia treatment centre. Complications of therapy can still occur, such as development of inhibitory antibodies in patients with haemophilia.

Recombinant activated factor VII (VIIa) is approved in Australia only for very limited indications, such as for patients with haemophilia who have inhibitory antibodies. However, there has been recent growth in 'off label' use in patients with critical bleeding in a range of settings. Evidence to support this use remains limited.

## Conclusion

The process from blood donation to administration of a fractionated blood product is lengthy and complex, with multiple checkpoints to deliver safe and effective products. As treating clinicians, it is our responsibility to ensure that they are administered correctly and for the appropriate indications.

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