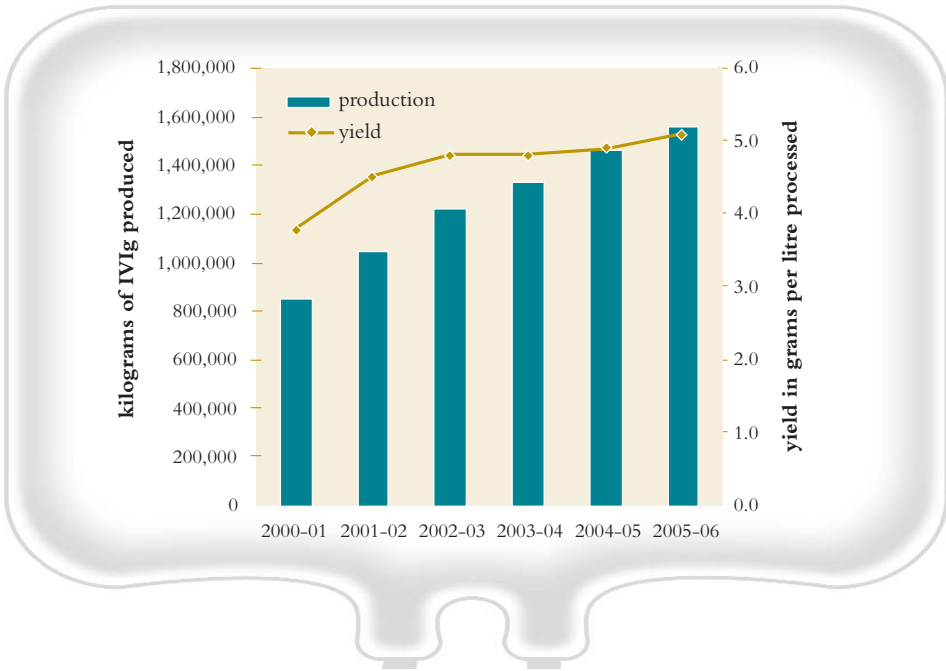
Chapter 6
Demand for plasma products in Australia

This chapter reviews usage of plasma products in Australia in recent years and then makes projections for future demand to 2015–16. It is first necessary to make a comment about plasma product production.

The quantities of individual proteins that can be isolated from a litre of plasma depend upon the amounts of those proteins in the plasma, and the rate of yield that can be achieved during the fractionation process. In Australia, plasma collection has generally been targeted towards meeting the need for the plasma product in most demand.

The relationship between the production of individual plasma products and the required inputs of starting plasma is not uniform. For some products, including intravenous immunoglobulin (IVIg) and plasma derived Factor VIII, the link is straightforward, as the quantity of product that can be harvested from a specified quantity of starting plasma is relatively constant and thus there is a definable yield: the greater the plasma input, the more product can be made. In the case of the hyperimmune immunoglobulins, however, the quantity of the specific antibody to be harvested can vary enormously between individual donations and thus across the plasma pool. A small volume of plasma containing a high level of a particular antibody can yield as much or more product than a larger volume with a low level of antibody.

Fig. 6.1 Domestic IVIg production and yield



Source: Derived from data supplied by CSL Bioplasma, 2006.

Prior to 2005, all plasma fractionated in Australia was employed in the production of immunoglobulins and Factor VIII; a small proportion of the total plasma fractionated was used in the manufacture of other products, including albumin and clotting factors (other than Factor VIII).

It was not until the late 1990s to early 2000s that supply pressures on IVIg started to emerge. The failure of supply to keep up with increasing demand was due not to a lack of production capacity but rather to a growing shortage of raw plasma. Efforts were made to address this shortfall by both increasing plasma collections (including collections made via apheresis) and improving production yields. CSL Bioplasma significantly increased its yields of IVIg during the period 2000–01 to 2005–06 (fig. 6.1).

By 2003–04, however, it appeared that cyclical shortages of IVIg were going to become commonplace, due to variability in levels of plasma collected, combined with growing demand. These two factors were together starting to impact on Australia's ability to supply sufficient IVIg from domestic sources.

In 2003–04, under the national blood arrangements, governments agreed to allow for the ongoing importation of IVIg manufactured from overseas-sourced plasma, and for imported IVIg to be used as a contingency measure at times when the domestic product was in short supply. Ongoing importations first occurred in 2003–04, and continue today at an expanding rate.

In the last decade there have also been shortages of other products. A shortage of Rh(D) immunoglobulin, requiring the importation of foreign product, has now been overcome.

The supply of domestic plasma derived Factor VIII has also been problematic. Ongoing shortages were experienced until the advent of recombinant alternatives meant that the demand for plasma derived product could be fully met. The recent upgrading of donor restrictions, however, so as to exclude from the plasma pool used in the manufacture of Factor VIII (Biostate®) all donations from people who have travelled outside Australia and New Zealand since 1980 (see below), has started to exert pressure on supply.

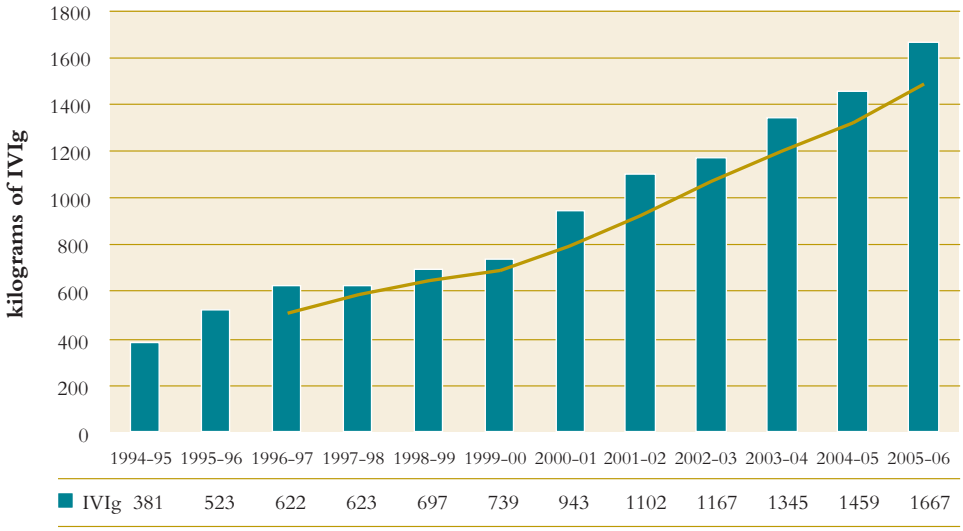
For the remaining plasma products manufactured in Australia, supply generally now meets or exceeds demand.

Production of intravenous immunoglobulin (IVIg)

Prior to 1999, CSL Bioplasma produced a 6% liquid formulation of IVIg, called Intragam®. This product was manufactured using Cohn technology. In 1999–2000, CSL introduced Intragam® P, a new, chromatographically purified 6% IVIg preparation. Intragam P offers improved specifications over those for Intragam and represents a higher yield of product from each litre of plasma processed. Improvements in IVIg yield arising from the introduction of Intragam P are reflected in the increase in quantities of IVIg issued from 1999–2000 onwards (fig. 6.2).

The compound annual growth rate for IVIg issued in Australia in the period 1994–95 to 2005–06 was 14.4%. This growth rate has been erratic, however, ranging

Fig. 6.2 Intravenous immunoglobulin issued



Source: Derived from data in: National Blood Authority, Distribution Report, June 2006, and Australian Red Cross Blood Service, issue estimates for 2005–06, June 2006. Includes a three-year moving trend line.

from as low as 0.2% in 1997–98 to as high as 37% in 1995–96, suggesting that a number of factors are influencing the supply and use of IVIg in Australia. As noted previously, the Australian rate of consumption of IVIg has been between that of North America and that of Europe, with 73 grams of product issued per 1000 head of population in 2005–06 (see table 2.1).

Clinical drivers for IVIg usage

In Australia, IVIg has been reported to have had some therapeutic value with respect to at least 70 clinical indicators. There is clear and unambiguous evidence for the clinical efficacy of IVIg in the treatment of primary immune deficiency (PID), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, and lymphoproliferative disorders (LPDs). The evidence presented in respect of a number of other indications, however, lacks rigorous clinical trial data and in fact in some cases there would appear to be little evidence-based support for the use of IVIg.

As noted above, the supply of IVIg in Australia has been restricted by the limited availability of domestic plasma, together with growing demand, and supply shortages have been reported from time to time. Some of these reported shortages, however, in at least one state, appear to be the result of restrictions on prescribing. This would suggest that usage of IVIg might have been higher had more product been available.

Nevertheless, all IVIg produced in Australia in recent years has been consumed, and since at least 2003–04 some IVIg products have been imported to provide contingency stocks, given that there has been no domestic surplus. CSL Bioplasma meanwhile has increased IVIg production and rate of yield (fig. 6.1) and in the latter half of 2006 reported large increases in prepayment inventories of IVIg.

The product shortages that occurred in Australia in the late 1990s led to a review of the use of IVIg in Australia by the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council (AHMAC).[1] The review report made a number of recommendations relating to target levels for the distribution and supply of IVIg. Clinical guidelines were revised and conditions classified into three groups, based on clear evidence with regard to patient benefit (see Chapter 5). The report also recommended that the supply of IVIg should be augmented through a combination of increasing the amount of plasma collected and importing alternative IVIg.

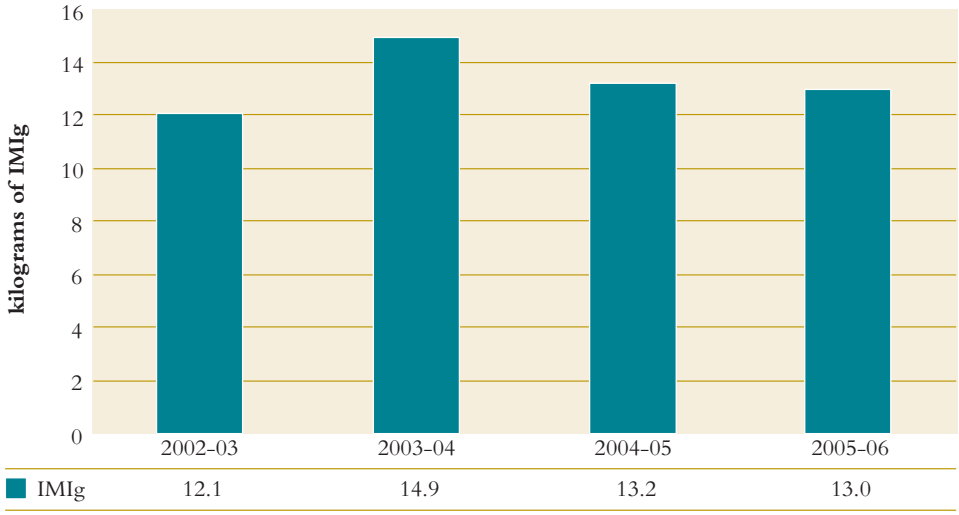
In 2004, acting on this recommendation and with the agreement of all Australian governments, the National Blood Authority (NBA) negotiated a standing offer for imported IVIg. As a result, imported product is now available to meet the supply plans of all jurisdictions, and the clinical needs of patients, on a more secure basis and at a lower price than IVIg acquired under earlier, ad hoc arrangements.

Production of intramuscular immunoglobulin (IMIg)

Issues of intramuscular (normal) immunoglobulin (IMIg) over a four-year period have been as set out in figure 6.3.

The reasons for the use of IMIg are mixed and range from management of chronic fatigue syndrome to prophylaxis for those at risk of hepatitis A, measles or poliomyelitis. A vaccine for hepatitis A is reducing the need for the use of IMIg in protecting people travelling to countries where there is a risk of contracting hepatitis A. IMIg is also used instead of treatment with IVIg in some cases where self-administration is deemed appropriate. In other countries, a subcutaneous alternative to IMIg (SCIg) is available for self-administration purposes.

Fig. 6.3 Intramuscular immunoglobulin (IMIg) issues



Source: Derived from data held by the Department of Health and Ageing.

1 Blood and Blood Products Committee, *Review of the Use and Supply of Intravenous Immunoglobulins in Australia*, Blood and Blood Products Committee, Melbourne, 2000; also available online at <http://www.nba.gov.au/PDF/ivig.pdf>.

CSL Bioplasma's sister organisation CSL Behring received FDA approval in January 2006 for a new 16% liquid, pasteurised subcutaneous immunoglobulin for use in the treatment of primary immune deficiency.[2] CSL Bioplasma is developing a similar high-yielding product for subcutaneous application.

Hyperimmune production

Hyperimmune immunoglobulin products are manufactured from plasma provided by donors who have acquired a high level of a particular type of immunoglobulin, either through accidental exposure or through deliberate immunisation. For example, individuals who have recovered from hepatitis B infection, or have been immunised against hepatitis B with a vaccine, will have high levels of immunoglobulin that will react with and neutralise the hepatitis B virus before it can inflict damage. A preparation of immunoglobulin sourced from the plasma of a blood donor with an elevated level of anti-hepatitis B immunoglobulin can be given to a non-immunised person so as to afford 'passive' protection against hepatitis B.

CSL Bioplasma manufactures a range of hyperimmune immunoglobulin products and these are listed in table 6.1.

Table 6.1 Hyperimmune immunoglobulin products manufactured in Australia by CSL Bioplasma

Product	Formulation	Package size	Use
Hepatitis B Immunoglobulin	16% liquid	100 IU, 400 IU	Prevention and treatment of hepatitis B infection
CMV Immunoglobulin	6% liquid	1.5 million IU	Prevention and treatment of cytomegalovirus (CMV) infection in bone marrow, renal, cardiac and liver transplant recipients
Tetanus Immunoglobulin	16%, 6% liquid	250 IU, 4000 IU	Prevention and treatment of tetanus infection
Zoster Immunoglobulin	16% liquid	200 IU	Prevention and treatment of chickenpox infection
Rh(D) Immunoglobulin	16% liquid	250 IU, 625 IU	Prevention of Rh(D) sensitisation in Rh(D) negative women at or below child-bearing age
Intramuscular (normal) Immunoglobulin (IMIg)	16% liquid	2 mL, 5 mL	Treatment of hypogammaglobulinaemia, multiple myeloma, leukaemia and nephrosis, and prevention of hepatitis A, measles and poliomyelitis

2 See 'Business Briefs', *International Blood/Plasma News*, vol. 24, no. 1 (August 2006), p. 2.

These products are manufactured at a small plant within the CSL facility at Broadmeadows, using the traditional Cohn process. The yields of these products are low relative to those for Intragam® P.

Hyperimmune usage

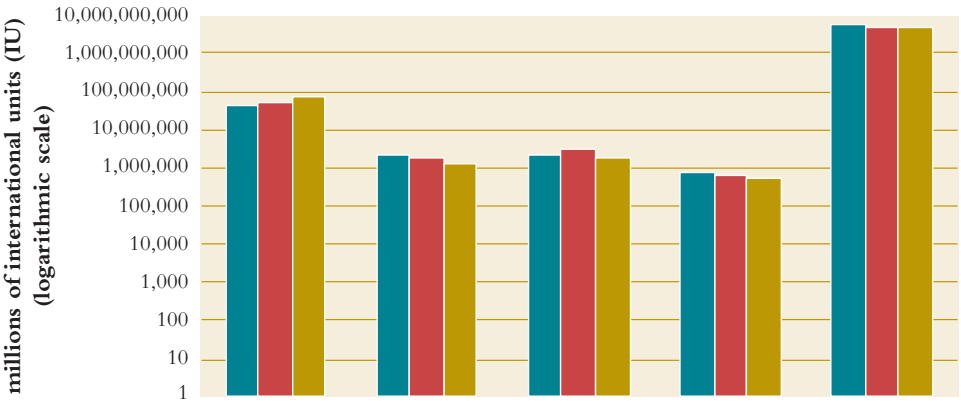
Demand for hyperimmunes has been declining for all products, with the exception of Rh(D) immunoglobulin (fig. 6.4). This trend is consistent with an overall decrease in the incidence of specific infectious diseases in Australia, and with the more widespread use of preventive measures. The growth that continues to be recorded for Rh(D) immunoglobulin can be ascribed to the newly implemented routine prophylactic use of the product by Rh(D) negative women during pregnancy. The sudden increase in the use of tetanus immunoglobulin in 2004–05 was due to the South-East Asian tsunami, in the relief efforts for which Australian medical teams played a major role.

Recent demand patterns for the various hyperimmunes are illustrated in figure 6.4.

Rh(D) immunoglobulin production

Maintaining an adequate supply of Rh(D) immunoglobulin has always been a concern in Australia, as was highlighted in 1999 when the National Health and Medical Research Council issued its *Guidelines on the Prophylactic Use of Rh D Immunoglobulin (Anti-D) in Obstetrics*. This report, updated in 2003, suggested ways to achieve best practice in the use of Anti-D, given a limited national supply. Both versions of the report also established that to meet demand for this product it would be necessary to increase collections of Rh(D) plasma, from Australia's select pool of donors, and to import Rh(D) product as an interim measure to ensure adequate supplies.

Fig. 6.4 Hyperimmune immunoglobulin issues



	Rh(D) Immunoglobulin (Incl WinRho™)	Tetanus Immunoglobulin	Hepatitis B Immunoglobulin	Zoster Immunoglobulin	CMV Immunoglobulin
2003-04	41,193,358	2,126,250	2,295,300	703,600	5,277,000,000
2004-05	50,382,750	1,897,250	2,799,100	591,800	4,438,500,000
2005-06	66,412,325	1,362,750	1,889,200	527,800	4,753,500,000

Source: Derived from data held by the Department of Health and Ageing.

These two initiatives have since been undertaken, alleviating concerns regarding supply of this product. By 2006–07, Australia will be collecting and processing enough Rh(D) plasma to return to self-sufficiency, although imported products may still be required in special clinical circumstances.

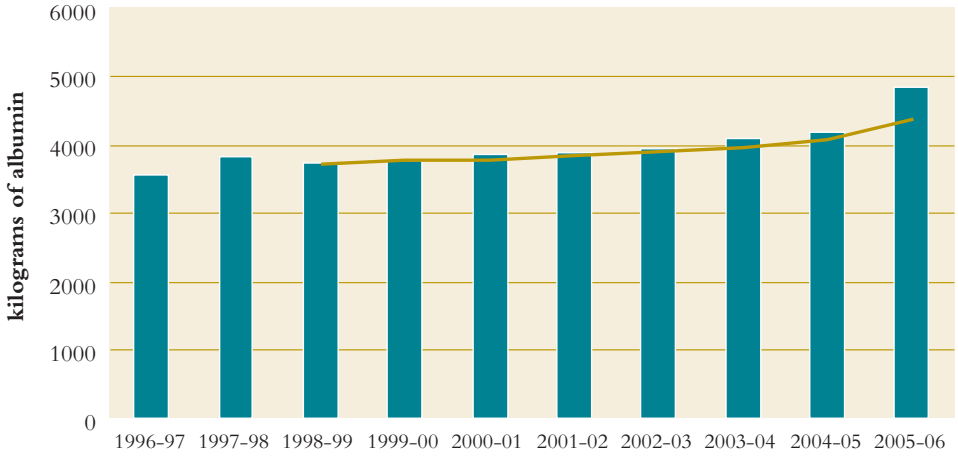
Albumin production

Albumin is the most abundant protein found in plasma. Historically, Australia has used less albumin per capita than have other developed countries. The amount of albumin issued over the period 1996–97 to 2005–06 has increased by a compound annual growth rate of 3.4%, although in the last five years this value has been higher, at 4.7% (fig. 6.5).

In contrast, the compound annual growth rate for plasma collections has been 5.4% over the same period; if all of the plasma collected had been converted into product, Australia would have accumulated a substantial excess of albumin over requirements. CSL Bioplasma was therefore instructed to limit its production of albumin from 1999–2000 onwards in order to balance supply with demand. The latest data from 2004–05 indicates that as a consequence of this policy Australia is meeting its demand for albumin by converting only about 60% of the available plasma fraction V into finished product.

Limited quantities of albumin are held at various locations around the country and this National Reserve is available at short notice should there be a sudden change in demand, created by a national or regional emergency.

Fig. 6.5 Albumin issued



Source: Derived from data held by the Department of Health and Ageing. Includes a three-year moving trend line.

Clinical drivers for albumin usage

A number of factors have affected the patterns of use of albumin in Australia and overseas. Firstly, there are various synthetic products that can be used as alternatives to albumin. Although there is considerable professional debate over the merits of these products, their availability has created more choice and hence has eroded albumin usage. In addition, these products are less expensive than albumin, and this factor is likely to have had some impact with regard to the use of albumin in Australia.

Another significant factor was the publication of the Cochrane Report in 1998.[3] This report, which suggested that mortality rates for critically ill patients treated with albumin were higher than for those treated with alternative regimens, raised the same concerns in Australia as it did overseas. The findings of this report have now been questioned, however, and a more recent trial, conducted in Australia (the SAFE study), has shown no difference in safety profile between the locally manufactured albumin product Albumex® and a saline volume expander when used in intensive care situations.[4]

Production of coagulation factors

The treatment of haemophilia A and B with Factor VIII and Factor IX respectively has traditionally been one of the primary reasons for the collection and fractionation of plasma.

While the administration of these concentrates has had an immense positive influence on the management of haemophilia, it also unwittingly resulted in the transmission of viral diseases to people with this condition. In the 1980s both HIV and hepatitis C were transmitted to recipients of Factor VIII and IX and, although the industry as a whole was quick to respond with appropriate viral-inactivation and removal procedures, many people with haemophilia became infected. As a consequence, haemophilia societies around the world mounted highly effective campaigns to replace plasma derived Factor VIII and IX with products manufactured via recombinant DNA technology.

Factor VIII usage

In August 2005, the Chief Medical Officer, Department of Health and Ageing, in a statement regarding the implementation of measures to further enhance the safety of plasma products for Australians with inherited bleeding disorders, made the following observations concerning domestically produced Factor VIII:

> A small amount of the plasma-derived Factor VIII is required for some people who cannot use recombinant clotting factors. These include patients with severe von Willebrand's disease, some patients with haemophilia who have developed inhibitors and some who have chosen to use plasma-derived products. On the basis of international experience, it is estimated that approximately 15% of Australia's total Factor VIII supply needs may need to be met with a plasma-derived product.
>
> The current plasma-derived Factor VIII (Biostate, which is supplied by CSL Limited) is suitable for meeting these residual needs and has an excellent safety

3 Cochrane Injuries Group Albumin Reviewers, 'Human Albumin Administration in Critically Ill Patients: Systematic Review of Randomised Controlled Trials', *British Medical Journal*, vol. 317, no. 7153, 25 July 1998, pp. 235–40.

4 S. Finfer, R. Bellomo, N. Boyce, J. French, J. Myburgh & R. Norton [The SAFE Study Investigators], 'A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit', *New England Journal of Medicine*, vol. 350, no. 22, 27 May 2004, pp. 2247–56.

record with no cases of transmission of pathogens. However, a risk assessment conducted by the Special Expert Committee on Transmissible Spongiform Encephalopathies (SECTSE) of the National Health and Medical Research Council (NHMRC) has found that although the theoretical risks of transmission of [variant Creutzfeldt-Jakob disease] are very small for Biostate with the current manufacturing process, these risks cannot be said to be totally negligible. Therefore it has been agreed that further precautions should be taken to reduce the already small risk as soon as practicable.

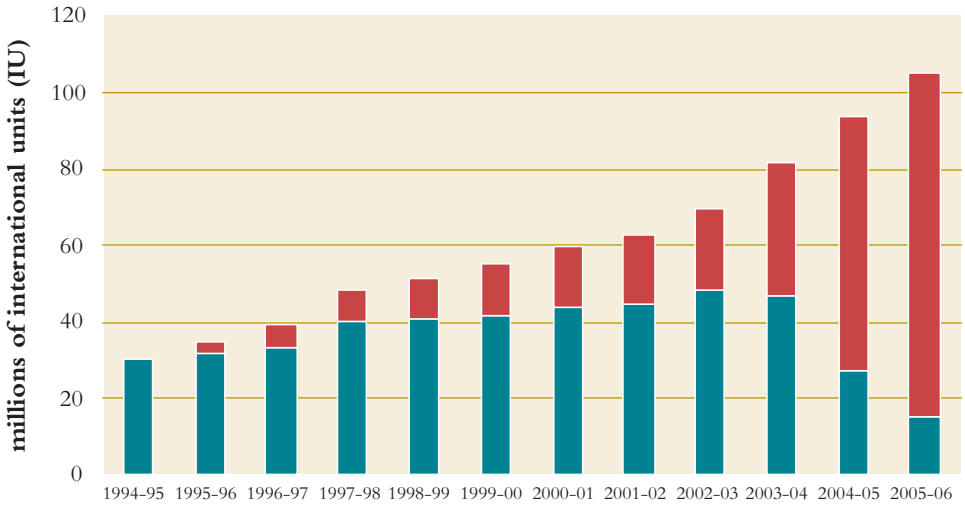
As a result the TGA, the Australian Red Cross Blood Service (ARCBS) and CSL Limited have agreed to introduce a staged series of targeted donor selection processes for Biostate manufacture.

The result of the new policy is that the ARCBS commenced collecting – specifically for the domestic production of Factor VIII – plasma from people who have not lived or travelled outside Australia or New Zealand since 1 January 1980.

The collecting of raw plasma from this selective cohort of donors effectively reduced the amount of material available for Factor VIII production to approximately 100 000 litres in 2005–06, which equates to approximately one third of total plasma collections in Australia for the year.

The introduction of recombinant Factor VIII in the early 1990s foreshadowed the potential for a negative impact on the demand for the plasma derived product. This impact was substantially delayed until 2004, however, when the Commonwealth Government made available additional funding to enable patients to transfer to the recombinant (see below).

Fig. 6.6 Factor VIII issues



	1994-95	1995-96	1996-97	1997-98	1998-99	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06
recombinant FVIII		2.8	5.8	8.3	10.7	13.2	15.9	18.5	21.1	34.8	66.6	89.3
plasma derived FVIII	30.2	31.8	33.6	40.1	41.0	41.7	43.9	44.7	48.2	46.7	27.4	15.6

Source: Derived from data held by the Department of Health and Ageing.

Figure 6.6 makes clear that the overall use of Factor VIII in Australia has increased significantly since 2003–04, with the supply of both plasma derived and recombinant Factor VIII increasing by a compound annual growth rate of 12% for the period 1994–95 to 2005–06. The use of plasma derived product, however, has decreased in direct reciprocal proportion to the growth in use of the recombinant.

There are some complex issues reflected in this chart. Firstly, up until 2003 there was a steady increase in the supply of AHF (HP), an intermediate-purity plasma derived Factor VIII product manufactured by CSL Bioplasma.

Secondly, the introduction of Biostate, the new high-purity Factor VIII product released by CSL in 2003, directly resulted in a decrease in the supply of plasma derived Factor VIII. This was a consequence of the incorporation of a second viral-inactivation step into the manufacturing process, leading to a lower overall yield.

A third key factor has been the 2003 recommendation by the Working Party of the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council that Australia should achieve a national supply target of 3.75 IU Factor VIII per head of population. The Committee further recommended that the use of recombinant Factor VIII reach a level of 85% of total Factor VIII use by 2004, and that the availability of the recombinant product be increased accordingly. The Committee also established an order of priority with respect to the use of recombinant Factor VIII by patients and proposed that once a newly diagnosed patient had commenced treatment with recombinant products, this practice should continue.

In response to these recommendations, the Commonwealth Government announced in August 2004 that additional funds would be made available to ensure that all people with haemophilia in Australia could have access to recombinant Factor VIII and recombinant Factor IX products. The dramatic impact of this decision, in terms of the amount of recombinant Factor VIII issued after this date, can be seen in figure 6.6. Approximately 85% of people with haemophilia in Australia now use recombinant Factor VIII, and from 2004 onwards demand for the plasma derived product has decreased significantly.

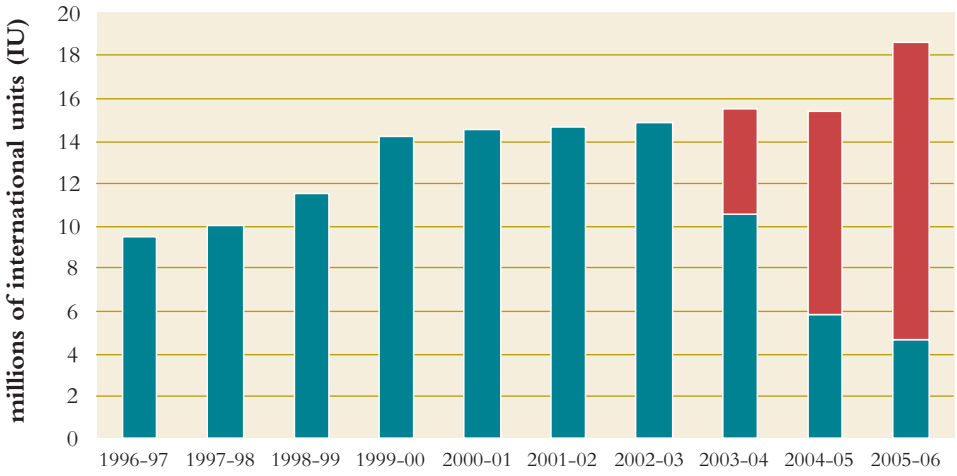
Factor IX usage

The history of Factor IX use in Australia has similarities with the use of Factor VIII, in that the introduction of a recombinant form has resulted in a substantial downturn in the usage of the plasma derived product.

Figure 6.7 illustrates the history of demand for Factor IX in Australia. Once again, the figures reflect the 2004 decision of the Commonwealth Government to fund patient use of the recombinant form.

The supply of Factor IX products in Australia has always exceeded demand, and the transition to recombinant Factor IX has been based largely on safety considerations rather than on any shortages of the plasma product. In 2004–05 Australia issued a total of 15.4 million units of Factor IX, of which 62% was recombinant product. The total issue of Factor IX for this period represents 0.8 IU of product per head of population, a figure slightly above the level recommended

Fig. 6.7 Factor IX issues



	1996-97	1997-98	1998-99	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06
recombinant FIX								4.9	9.6	14.0
plasma derived FIX	9.5	10.0	11.5	14.2	14.5	14.7	14.9	10.6	5.8	4.6

Source: Derived from data held by the Department of Health and Ageing.

in 2003 (0.7 IU of Factor IX per head of population) by the Working Party of the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council.

Clinical drivers for Factor VIII and Factor IX usage

The major drivers of demand for Factor VIII and Factor IX are related to the improvements occurring in the quality of treatment available to people with haemophilia, and to their greater life expectancy. Factors driving strong growth include:

- the longer life span of people with haemophilia, due to a reduced occurrence of cranial bleeds and other debilitating conditions
- a gain in lean body mass by people with haemophilia, resulting in a need for more product
- increased product use for people with haemophilia who have medical or surgical conditions associated with ageing (e.g. the need for a knee or hip replacement)
- increased prophylactic treatment of people with haemophilia, which typically requires about three times the amount of product used for treatment on demand
- increases in the numbers of people with haemophilia in Australia (about 25 new cases per annum), with these increases well in excess of mortality rates.

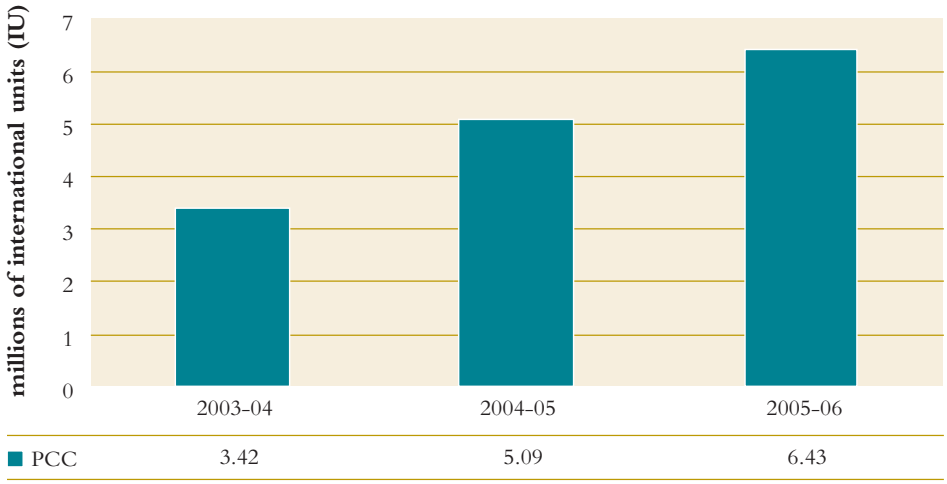
In addition to being used in the treatment of haemophilia A, Biostate® (Factor VIII) is reported as being employed outside approved indications, as a replacement therapy for patients with von Willebrand's disease.

Prothrombin complex concentrate (PCC) usage

Demand for prothrombin complex concentrate (PCC) has increased substantially over the past three years, as demonstrated in figure 6.8.

The increase in demand for PCC has been attributed to the growing use of this product for reversing the effects of warfarin therapy where excessive anticoagulation has occurred. It is likely that with the ageing of the population, and the resulting diagnosis and treatment of more cases of cardiovascular disease, the use of warfarin will continue to increase as will the use of PCC.

Fig. 6.8 Prothrombin complex concentrate (PCC) issues



	2003-04	2004-05	2005-06
PCC	3.42	5.09	6.43

Source: Derived from data held by the Department of Health and Ageing.

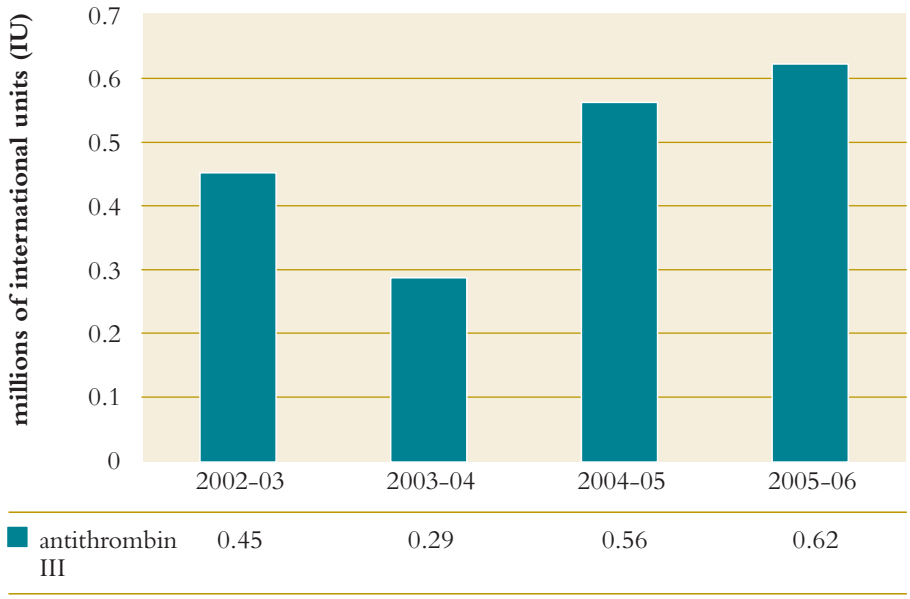
Antithrombin III usage

The Australian Red Cross Blood Service reports that recent changes in clinical practice involve antithrombin III concentrate being used 'in some jurisdictions to prevent the development of vascular thromboses due to transient AT deficiency in paediatric liver transplantation. [Antithrombin III] is also being used in the management (therapy or primary prevention) of thrombosis in acute lymphocytic leukaemia. There is also usage in adult sepsis and meningococcal infection'.[5] The ARCBS notes, however, that distribution of the product is variable and is strongly influenced by the requirements of a small number of patients.

The pattern of usage of antithrombin III over the past four years is illustrated in figure 6.9.

5 Australian Red Cross Blood Service, submission to Plasma Fractionation Review, 2006, p. 29.

Fig. 6.9 Antithrombin III issues



Source: Derived from data held by the Department of Health and Ageing.

Fractionation costs

The costs of fractionation for the main groups of plasma derived products (excluding costs associated with plasma collection) are shown in table 6.2.

It should be noted that this table excludes recombinant products. It should also be noted that in 2005–06 the tiered pricing structure (affecting minimum amounts of plasma products) was replaced with a single price structure for all quantities of individual products.

It can be seen from the table that the overall fractionation costs for plasma derived products in Australia have changed very little in the past two years. The cost of albumin, however, has decreased by some 61% over this period, principally because of the revised pricing structure. The amount of albumin supplied increased by 16% in 2005–06 (fig. 6.5).

The plasma derived coagulation factors have experienced a decrease of 42% in cost; this is due to the rapid conversion from plasma derived Factor VIII to the recombinant form.

Table 6.2 Volumes and total costs for fractionation of domestic plasma derived products and for purchase of imported plasma derived products issued under Australia's national blood arrangements, 2004–05 and 2005–06

Product	Volume 2004–05	Total cost 2004–05 A$000s	Volume 2005–06	Total cost 2005–06 A$000s	Volume change%	Value change%
Domestic products						
Albumin 20 – 10 mL	7 680	230	7 234	88	-6	-62
Albumin 20 – 100 mL	62 574	8 784	74 558	3 303	19	-62
Albumin 4 – 50 mL	6 960	228	6 877	84	-1	-63
Albumin 4 – 500 mL	144 990	17 508	165 832	7 346	14	-58
Total albumin		**26 750**		**10 821**		**-60**
Cytomegalovirus (CMV) immunoglobulin	2 362	2 368	2 758	2 838	17	20
Hepatitis B immunoglobulin – 100 IU	4 303	124	2 332	88	-46	-29
Hepatitis B immunoglobulin – 400 IU	5 922	380	4 140	357	-30	-6
Intravenous immunoglobulin (IVIg) – 50 mL	61 536	16 423	56 172	9 639	-9	-41
Intravenous immunoglobulin (IVIg) – 200 mL	97 376	53 522	99 217	68 103	2	27
Intramuscular immunoglobulin (IMIg) – 2 mL	4 129	77	4 514	122	9	58
Intramuscular immunoglobulin (IMIg) – 5 mL	14 807	451	17 236	765	16	70
Rh(D) immunoglobulin – 250 IU	20 436	442	21 318	543	4	23
Rh(D) immunoglobulin – 625 IU	56 310	2 461	80 105	5 103	42	107
Tetanus immunoglobulin – 250 IU	18 757	355	3 739	139	-80	-61
Tetanus immunoglobulin – 4000 IU	52	96	24	14	-54	-85
Zoster immunoglobulin	2 959	590	2 639	622	-11	5
Total immunoglobulins		**77 289**		**88 333**		**14**
Antithrombin III	557	618	621	717	11	16
Factor VIII	109 770	19 271	62 324	8 588	-43	-55
Factor IX	11 635	6 524	9 246	3 269	-21	-50
Prothrombin complex concentrate (PCC)	10 188	3 761	12 858	5 195	26	38
Total coagulation factors		**30 174**		**17 770**		**-41**
Total domestic products		**134 213**		**116 924**		**-13**
Imported products						
C-protein	0	0	16 000	34	0	0
Factor VII Concentrate	89 000	223	48 000	100	-46	-55
Factor Eight Inhibitor Bypass Agent (FEIBA)	251 500	717	251 500	717	0	0
Factor XI	88 400	663	1 200	9	-99	-99
Factor XIII	60 000	29	149 250	72	149	148
Intravenous immunoglobulin grams	106 296	6 072	307 770	21 703	190	257
Rh(D) immunoglobulin 1 IU	11 052 000	1 663	5 526 667	829	-50	-50
Total imported products		**9 367**		**23 464**		**150**
Total products		**143 580**		**140 388**		

Source: National Blood Authority (NBA) distribution reports, and National Supply Plan.

Projections for future use of plasma products

In addition to accounting for population growth and the ageing of the population, any predictions about the future demand for plasma products in Australia need to consider a range of factors, including:

- changing clinical needs and indications
- changes in the population's illness and disease profile, and the emergence of new illnesses and diseases
- improvements in the diagnosis of illness and disease
- development of substitutes for existing plasma products, and alternative treatments
- changing consumer and community expectations about the range of products and services provided, their safety and quality, and access to them
- availability of products
- mechanisms that moderate product demand (e.g. prescribing guidelines and authorisation processes).

Since these factors have differing influences in respect of the supply and demand profiles of individual plasma products, each major product group will be reviewed separately.

In considering future demand for plasma products, the present Review has taken account of projections provided by the National Blood Authority, the Australian Red Cross Blood Service, and CSL Limited on behalf of CSL Bioplasma. Forecasts provided to the Department of Health and Ageing by the Allen Consulting Group (ACG) have also been incorporated into the discussion that follows.

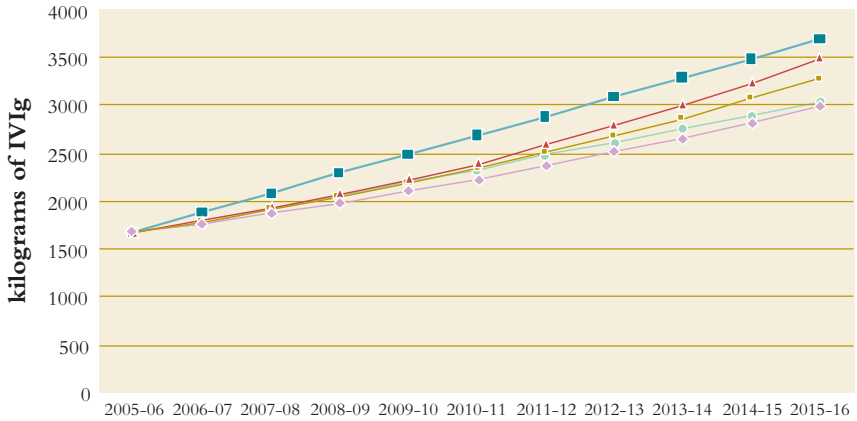
Intravenous immunoglobulin (IVIg)

For the purposes of this Review, forecasts with respect to IVIg are the most crucial of the product projections to be considered, because demand for IVIg directly sets the level of domestic starting plasma required for the production of most plasma derived products. As noted earlier, the compound annual growth rate for IVIg issued in Australia over the last decade has been 14.4%.

Figure 6.10 shows a range of possible outcomes, suggesting that Australian demand for IVIg will fall somewhere between 2985 and 3687 kilograms in the year 2015–16. The average of these two figures, 3336 kilograms, represents more than double the amount of IVIg currently being issued in Australia on an annual basis and consequently would require more than double the amount of plasma (at existing yields). If the Allen Consulting Group forecast is correct, Australia will need 686 tonnes of plasma in 2015–16, compared with 308 tonnes in 2005–06.

Options for all parties to manage better the future demand for IVIg are currently being explored by the National Blood Authority and the Commonwealth and state and territory health departments.

Fig. 6.10 Forecast demand for intravenous immunoglobulin (IVIg)



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
CSL forecast 6% pa	1667	1767	1873	1985	2105	2231	2365	2507	2657	2816	2985
ARCBS forecast 7% pa	1667	1784	1909	2042	2185	2338	2502	2677	2864	3065	3279
Allen Consulting Group forecast 7.7% pa	1667	1795	1934	2082	2243	2416	2602	2802	3018	3250	3500
NBA Scenario #1	1667	1887	2087	2287	2487	2687	2887	3087	3287	3487	3687
trend projection	1667	1767	1906	2045	2185	2324	2463	2602	2742	2881	3020

Source: Derived from data held by the Department of Health and Ageing.

The NBA through its IVIg Quality of Use Improvement Project (iQuip) is initiating three strategies to manage IVIg demand issues. These strategies are:

- gaining a greater understanding of the IVIg supply chain through the 'Track and Trace' process, which will map the current IVIg supply system and will seek to reduce inefficiencies and wastage in the system
- exploring the development of national tools for improved clinical assessment and clinical audit for the supply of IVIg, and the collection of outcome data
- improving demand modelling by better utilising existing data and by using new data to be generated by the other strategies.

The new Criteria for IVIg Use in Australia, which will succeed the AHMAC 2000 Guidelines, will aim to enhance the use of IVIg for treating patients for whom it will have a clear benefit compared with alternative therapies. In addition, as discussed in Chapter 5, some jurisdictions have instituted measures to undertake more efficient management of the treatment regime for existing IVIg recipients.

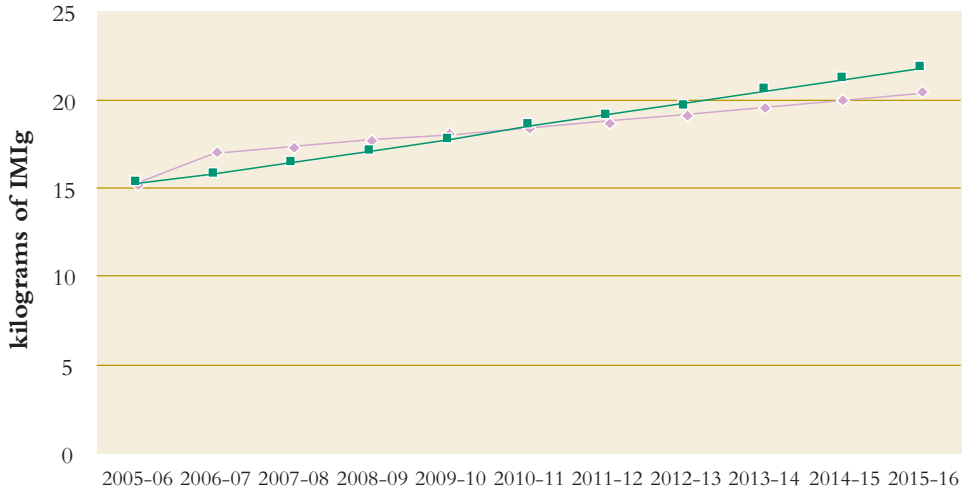
Despite the adoption of these strategies to minimise the rate of growth in demand for IVIg, and given the advice to the Review that within this time frame no synthetic substitutes are likely to emerge, Australia will need to significantly increase the quantity of plasma available for domestic fractionation, and/or import increasing quantities of finished product, and/or severely restrict growth in demand. A discussion of the prospects for increasing Australia's plasma collections may be found in Chapter 7 of this report.

Intramuscular immunoglobulin (IMIg)

The demand for IMIg out to 2015–16 is seen to reflect only moderate growth, based on trend and on anticipated population growth. The forecast presented in figure 6.11 has been provided by the Australian Red Cross Blood Service, with the trend projection calculated by the Review secretariat. The two sets of figures suggest similar outcomes. It should be noted that at some point during the forward planning period IMIg may be replaced to some extent by a subcutaneous form of normal immunoglobulin (SCIg).

Although IMIg manufacture draws on domestic raw plasma collections, the quantities involved are not material to the amount of plasma required overall for the production of plasma derived products in Australia.

Fig. 6.11 Forecast demand for intramuscular immunoglobulin (IMIg)



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
trend projection	15.23	15.8	16.5	17.1	17.8	18.5	19.2	19.8	20.5	21.2	21.8
ARCBS forecast	15.23	17.0	17.4	17.7	18.1	18.4	18.8	19.2	19.5	19.9	20.3

Source: Derived from ARCBS submission to Plasma Fractionation Review, and from data held by the Department of Health and Ageing.

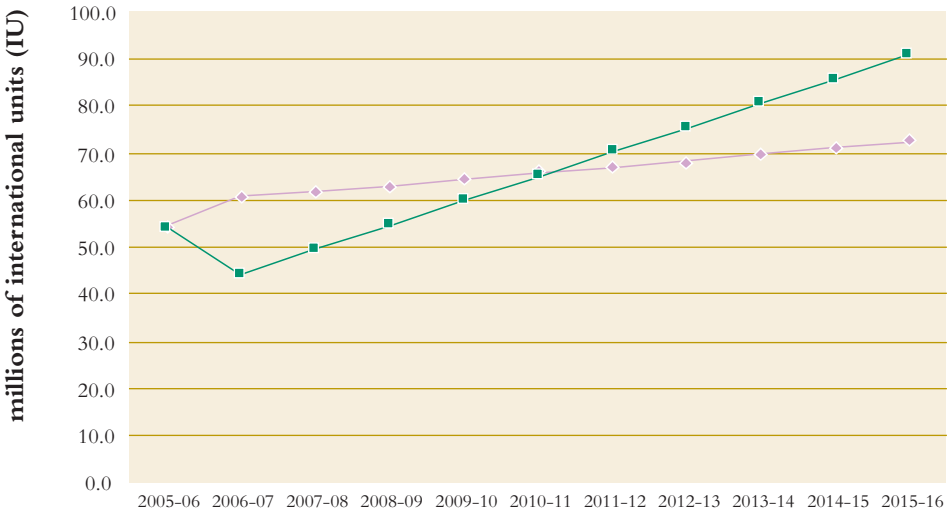
Hyperimmunes

The demand history for five of these specialised products demonstrates a slow decline in usage. The exception is Rh(D) immunoglobulin. The Australian Red Cross Blood Service indicated in its submission to the Review that recent changes in clinical practice guidelines will promote the growth in use of this product over the forward planning period.[6] From 2003 to 2005, Australia imported Rh(D) to supplement local stocks so as to meet increasing demand. Collections of the special plasma required for the production of Rh(D) have now been increased, however, leading to the prospect that, from 2006–07 onwards, Australia will be totally self-sufficient in this product.[7]

6 ARCBS, submission to Plasma Fractionation Review, p. 22. For guidelines in respect of the clinical use of Rh(D) immunoglobulin, see National Health and Medical Research Council, *Guidelines on the Prophylactic Use of Rh D Immunoglobulin (Anti-D) in Obstetrics*, Department of Health and Ageing, Canberra, 2003; also available online at <http://www.nba.gov.au/PDF/glines_anti_d.pdf>.

7 ARCBS, submission to Plasma Fractionation Review, p. 21.

Fig. 6.12 Forecast demand for Rh(D) immunoglobulin



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
ARCBS forecast	55.4	60.6	61.8	63.1	64.3	65.6	66.9	68.3	69.6	71.0	72.5
trend projection	55.4	44.2	49.4	54.6	59.8	65.0	70.1	75.3	80.5	85.7	90.9

Source: Derived from data held by the Department of Health and Ageing.

Figure 6.12 shows a calculated trend projection for Rh(D) immunoglobulin, plus an ARCBS forecast of demand.

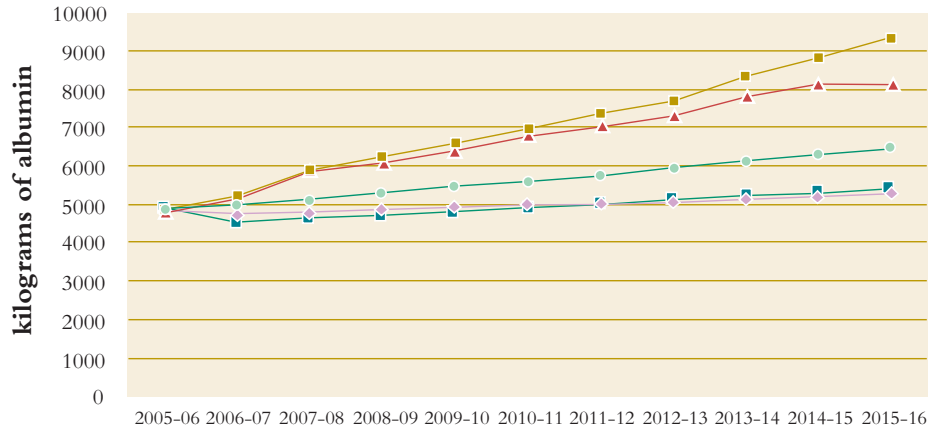
The ARCBS forecast is considered to be more reliable than the trend projection, because the strong growth in demand experienced in recent years is likely to extend to year 2006–07 but then to ease, to keep pace with anticipated changes in the birthrate. Importantly, it is deemed that the demand as forecast by the ARCBS can be met by Australia's capacity to provide sufficient special plasma.

Albumin

The demand for albumin is now increasing, due to the publication of the SAFE study in 2004. The reported increase for 2005–06 over the preceding year is 15.7%. Whether or not this single figure can be used as a predictor of expanded demand in subsequent years is difficult to assess. Figure 6.13 illustrates a range of forecasts, based on input provided to the Review by stakeholders.

The National Blood Authority bases its forecast for albumin on the fact that Australian consumption of this product has historically been approximately half of that recorded in both North America and Europe; on this basis, Australian rates of consumption would be expected to increase over time. Further, the NBA suggests that the strong year-on-year growth recorded in 2005–06 for albumin is the result of

Fig. 6.13 Forecast demand for albumin



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
trend projection	4836	4510	4608	4706	4805	4903	5001	5099	5198	5296	5394
NBA forecast	4836	5200	5900	6100	6400	6800	7050	7300	7800	8150	8150
ARCBS forecast	4836	5241	5869	6222	6595	6991	7410	7655	8326	8826	9355
CSL forecast 3% pa	4836	4981	5131	5284	5443	5606	5774	5948	6126	6310	6499
Allen Consulting Group forecast	4836	4735	4792	4849	4908	4967	5026	5086	5148	5209	5271

Source: Derived from data held by the Department of Health and Ageing.

its increased usage in cardiopulmonary bypass surgery.[8] The Australian Red Cross Blood Service supports this view and indicates that increased use in line with an increase in the treatment of coronary heart disease, and longer life spans, will see demand grow strongly in the short term and taper off in the longer term.[9]

By way of contrast, CSL Limited has suggested that growth will be limited to 3% per annum over the forward planning period.[10] At the lower end of the forecasts, the Allen Consulting Group has suggested a conservative growth rate of 2.1% per annum, decreasing to 1.1% by the end of the forecasting period.[11] This last forecast follows closely the trend projection, based on historical values, that has been calculated by the Review secretariat. The average value across all forecasts for demand in the year 2015–16 is 7319 kilograms of albumin.

Coagulation factors

The decision made by Australia in August 2004 to provide funds to allow all people with haemophilia A and B access to recombinant Factor VIII and Factor IX has to a large extent ensured a balance between supply and demand for these products. It is currently estimated that by the end of 2006 around 85% of people with haemophilia A will be receiving recombinant Factor VIII.

8 National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 23; also available online at <http://www.nba.gov.au/pubs.htm>.

9 ARCBS, submission to Plasma Fractionation Review, p. 8.

10 CSL Limited, submission to Plasma Fractionation Review, p. iv.

11 Allen Consulting Group, Actuarial, Demographic and Indemnity Insurance Issues: Consolidated Report, August 2006, p. 19.

Factor VIII

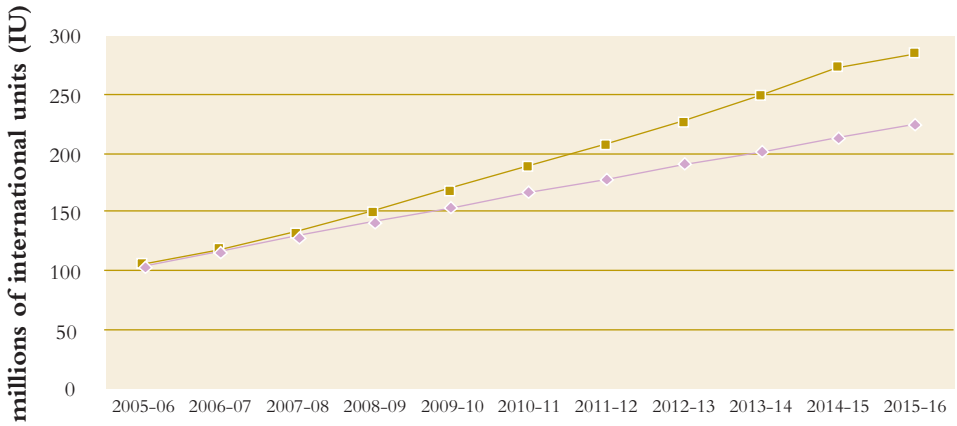
As noted earlier, there will continue to be demand for plasma derived Factor VIII for those people with haemophilia A who prefer to continue with a plasma derived product, and for use in the treatment of von Willebrand's disease. Currently, demand for therapy for this condition is not strong, as the severe form of the disease is rare.

The National Blood Authority's latest modelling with respect to demand for Factor VIII over the next decade is based on the following assumptions:

- Prophylactic product use will increase at a rate of 7.5% per capita per annum in the first three years, then at 5% for the next three years and will then remain at 2.5% for the remaining four years of the forward planning period.
- Increases in surgery for people with haemophilia will result in a 5% per annum increase in per capita product use.
- Increasing lean body mass in people with haemophilia will see an increase of 0.5% per annum in per capita product use.
- 15% of the total demand for Factor VIII will continue to be met by the plasma derived product, with the bulk of demand being met by recombinant Factor VIII.

Figure 6.14 illustrates the impact of these assumptions with respect to the total requirement for Factor VIII over the period 2005–06 to 2015–16. The average annual growth rate of the issuing of Factor VIII in Australia is predicted to be 11.6% over the next decade, with Australia predicted to be issuing 12.0 IU per head of population by 2015–16.

Fig. 6.14 **Forecast demand for Factor VIII recombinant and plasma derived combined**

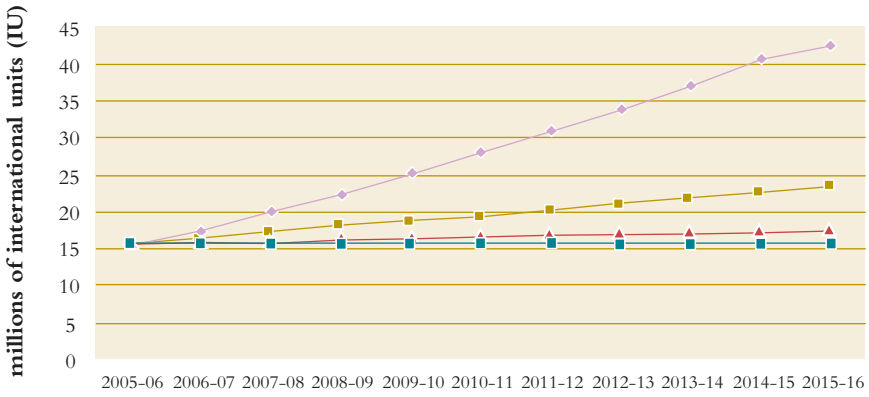


	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
trend projection	103.7	118	130	142	153	166	178	190	201	213	225
NBA forecast	103.7	116	132.2	149.5	167.8	188.3	206.4	226.3	247.9	271.6	284.1

Source: Derived from data held by the Department of Health and Ageing.

Projections by the NBA, the Australian Red Cross Blood Service, CSL Limited and the Allen Consulting Group, with respect to demand for plasma derived Factor VIII, are captured in figure 6.15.

Fig. 6.15 Forecast demand for plasma derived Factor VIII



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
NBA forecast	15.6	17.4	20	22.4	25.2	28.2	31	33.9	37.2	40.7	42.6
ARCBS forecast	15.6	16.4	17.1	17.8	18.5	19.2	20	20.8	21.6	22.5	23.4
Allen Consulting Group forecast	15.6	16	16.1	16.3	16.4	16.6	16.8	16.9	17.1	17.3	17.5
CSL forecast	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6

Source: Derived from data held by the Department of Health and Ageing.

Most of the forecasts predict either a stable level of demand, as suggested by CSL,[12] or modest growth. The average for these various forecasts indicates an annual demand for plasma derived Factor VIII of 24.75 million IU at 2015–16. (This figure is based on the assumption that plasma derived Factor VIII, for valid clinical reasons, will continue to be used by a small number of patients who fare better on the plasma derived product than on the recombinant alternative.)

The supply of plasma in Australia is discussed in detail in Chapter 7 of this report. In regard to plasma derived Factor VIII, the situation is complicated by the fact that the Therapeutic Goods Administration (TGA) requires, as an additional precautionary measure, that plasma used in the manufacture of this product must be collected from donors who have not travelled outside Australia or New Zealand since 1980. In 2005–06, this requirement reduced the starting pool of plasma available for the production of plasma derived Factor VIII to approximately 100 tonnes out of total plasma collections of 308 tonnes.

This quantity of special starting plasma was just sufficient to meet a demand of 15.58 million IU of plasma derived Factor VIII in 2005–06. If the more ambitious of the forecasts discussed here come to fruition, it follows that unless the TGA restriction is lifted (and there is currently no intention to do so), or collections of suitable domestic plasma can be increased, then Australia may need to import some plasma derived Factor VIII, sourced from overseas plasma, in future years.

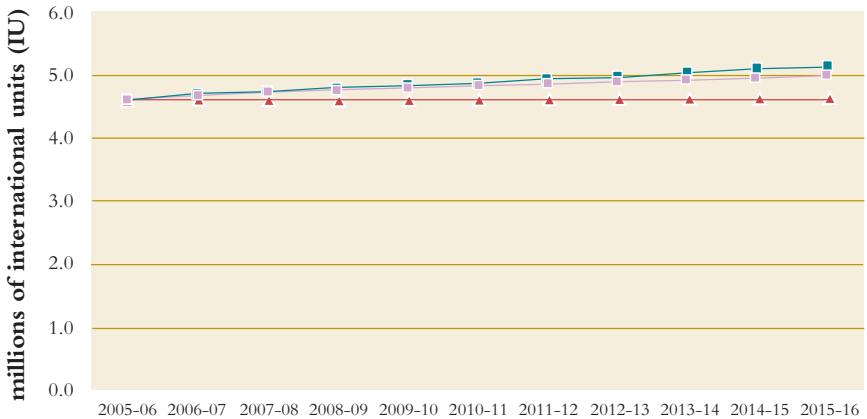
12 CSL Limited, submission to Plasma Fractionation Review, p. iv.

Factor IX

The forecasting of demand for Factor IX shares many of the characteristics of that for Factor VIII. Both product types have undergone significant market shifts following the introduction of recombinant forms.

Figure 6.16 illustrates demand forecasts for plasma derived Factor IX.

Fig. 6.16 Forecast demand for plasma derived Factor IX



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
ARCBS forecast	4.6	4.7	4.7	4.8	4.8	4.9	4.9	4.9	4.9	5.0	5.0
CSL forecast	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6
Allen Consulting Group forecast	4.6	4.7	4.7	4.8	4.8	4.9	4.9	5.0	5.0	5.1	5.1

Source: Derived from data held by the Department of Health and Ageing.

The consensus represented in this diagram suggests that plasma derived Factor IX will remain in demand throughout the forecast period and that the level of demand will be between 4.6 million and 5.1 million IU of product per annum.

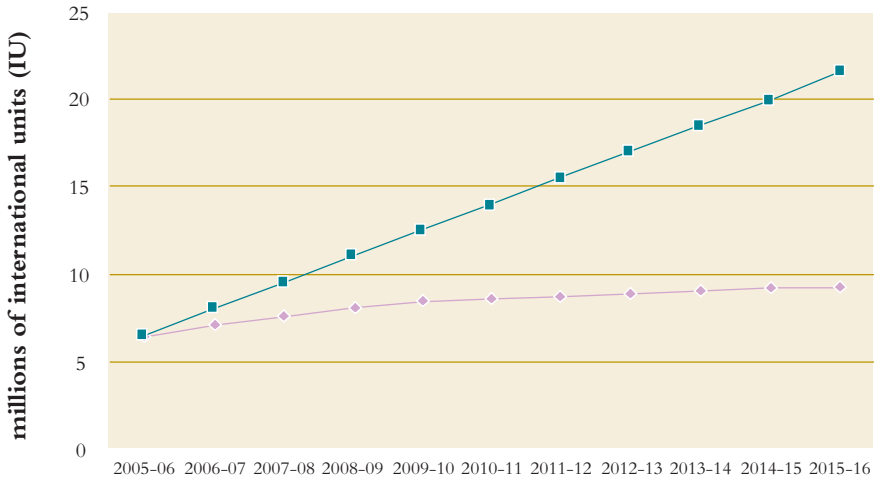
From a supply point of view, there are no restrictions in place with respect to the domestic plasma that may be used to manufacture Factor IX, and therefore demand for the product will be readily met by normal plasma collections in the foreseeable future.

Prothrombin complex concentrate (PCC)

The resurgence in demand for prothrombin complex concentrate in recent years is the result of the publication of new guidelines for the reversal of warfarin therapy.[13] While warfarin is a very useful drug in the control of cardiovascular disease, it suffers from the fact that there is a relatively narrow margin between an effective dose level and a dose level causing excessive anticoagulation in some individuals. When excessive anticoagulation occurs, PCC is used to reverse the resulting bleed.

13 See P. Campbell, L. Stevenson, C. Corke, A. Plowman & M. Mohajeri, 'Prothrombinex Use in Cardiac Surgery: Results of a 6 Month Audit', paper presented to the 38th Annual Scientific Meeting of the Australian and New Zealand Society of Blood Transfusion, Melbourne, 17–20 October 2004.

Fig. 6.17 Forecast demand for prothrombin complex concentrate (PCC)



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
trend projection	6.4	8.0	9.5	11.0	12.5	14.0	15.5	17.0	18.5	20.0	21.5
Allen Consulting Group forecast	6.4	7.1	7.6	8.1	8.4	8.6	8.7	8.9	9.0	9.1	9.3

Source: Derived from data held by the Department of Health and Ageing.

PCC is a complex of a number of blood factors and is supplied in Australia under the trade name Prothrombinex™-HT, by CSL Bioplasma. Estimates of future demand are shown in figure 6.17; the trend projection illustrated is based on historical demand.

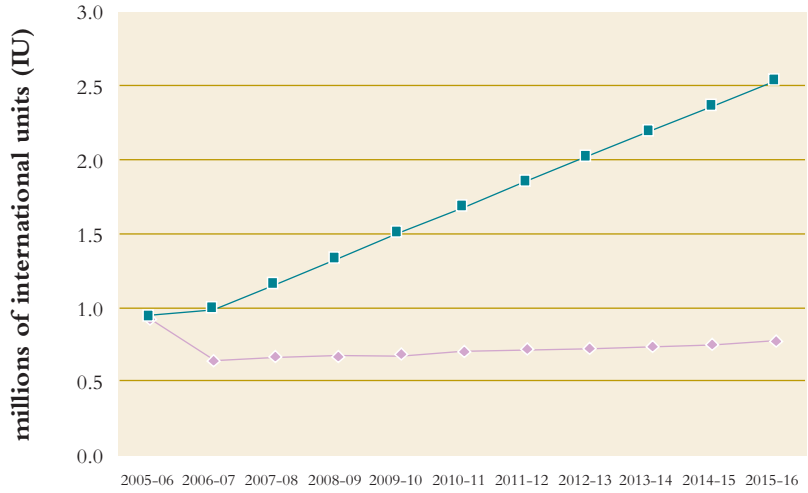
The Allen Consulting Group forecast follows approximately the 10% annual growth rate forecast by the Australian Red Cross Blood Service for the first two years of the projection;[14] thereafter the annual rate of growth tapers off to 1.4% per annum. This rate of annual increase is based on estimates of population growth, specifically in the cohort of people over 60 years of age. Those in this cohort are expected to be the primary users of PCC, as being also the group most likely to receive warfarin therapy.

Antithrombin III

Neither the Australian Red Cross Blood Service nor the Allen Consulting Group took into account the substantial jump in antithrombin III use (to 0.93 million units in 2005–06) when submitting their forecasts. Both sets of forecasts fall short of the trend projection provided in figure 6.18, and the diagram needs to be interpreted accordingly.

14 ARCBS, submission to Plasma Fractionation Review, p. 26.

Fig. 6.18 Forecast demand for antithrombin III



	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
trend projection	0.93	0.99	1.16	1.33	1.50	1.67	1.84	2.01	2.18	2.35	2.52
ARCBS and Allen Consulting Group forecast	0.93	0.64	0.66	0.67	0.68	0.70	0.71	0.72	0.74	0.75	0.77

Source: Derived from data held by the Department of Health and Ageing.

Conclusions

The two plasma derived products that experience the greatest levels of demand, IVIg and albumin, are expected to grow in demand throughout the next 10 years, to 2015–16. Demand for IVIg will drive the need for an increased supply of starting material via plasma collections.

For Australia to achieve self-sufficiency in IVIg in 2015–16, plasma collections would need to increase by 123%: from 308 tonnes in 2005–06 to 686 tonnes in 2015–16.

The demand for albumin would be comfortably accommodated within forecast levels for plasma collections required. The feasibility of substantially increasing Australia's plasma collections in the next 10 years is more extensively addressed in Chapter 7 of this report.

In the area of coagulants, all products, with the possible exception of plasma derived Factor VIII, would similarly be adequately supplied by a doubling of domestic plasma collections. Factor VIII manufacture, and therefore supply, is directly affected by the restriction of acceptable donors to those people who have not travelled outside Australia or New Zealand since 1980. Whether or not the supply of domestic plasma will match anticipated future demand for Factor VIII will depend on efforts to recruit additional suitable donors.

The other key product to rely on the adequate collection of suitable plasma is Rh(D) immunoglobulin. The National Blood Authority appears confident that domestic collections will be able to meet demand for Rh(D) from 2006–07 onwards.