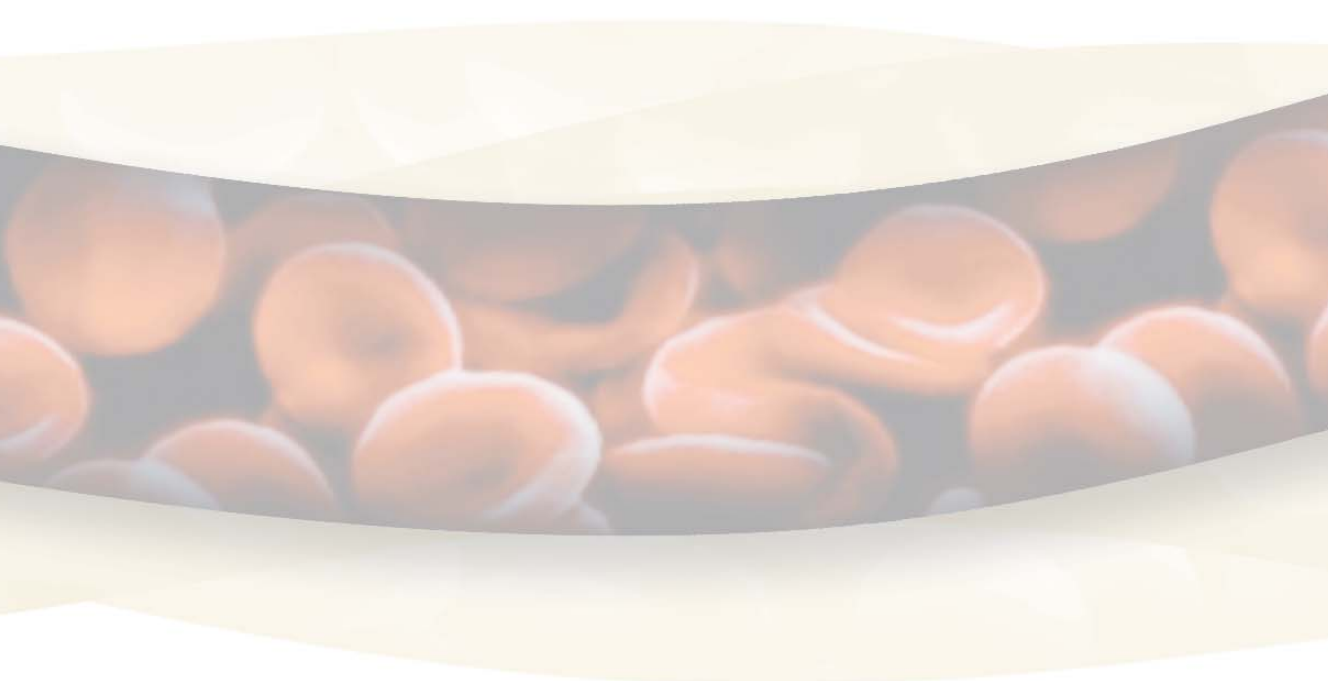




Review of Australia's Plasma Fractionation Arrangements



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Australian Government

Review of Australia's Plasma Fractionation Arrangements

13 December 2006

The Hon Tony Abbott MP
Minister for Health and Ageing
Parliament House
CANBERRA ACT 2600

Dear Minister

I am pleased to submit, on behalf of the Committee, the report of the Review of Australia's Plasma Fractionation Arrangements.

Australia now has an enviable system for the provision of safe, high-quality blood and plasma products to the Australian community. Australian voluntary donors play a vital role in this achievement.

We cannot take it for granted that the present situation will continue without strong action on the part of the Australian community and the Commonwealth, state and territory governments. Accordingly, the Committee has made a series of recommendations for action. These are designed to ensure that future arrangements (a) provide the highest standards of safety, quality and efficacy in respect of plasma products fractionated for use in Australia, (b) assure security of supply, and (c) offer the best possible value for money for Australia.

The Review Committee thanks all those individuals, organisations and companies who have contributed information and views that have enhanced the Committee's understanding of the relevant issues and have contributed to our deliberations. We are grateful for the professional support of the Secretariat, under the excellent leadership of Yael Cass.

I commend the report to you.

Yours sincerely

A handwritten signature in black ink that reads 'Philip Flood'.

Philip Flood AO
Chairman

Plasma Fractionation Review Committee

Mr Philip Flood AO – Chairman

Philip Flood is a former Secretary of the Department of Foreign Affairs and Trade and former High Commissioner to the United Kingdom. He was also Ambassador to Indonesia, Director-General of the Office of National Assessments, Director-General of AusAID, and Chief Executive for Special Trade Negotiations. He was Chair of the Australia Indonesia Institute from 2001 to 2004. He is a board member of CARE Australia, Deputy Chairman of Asialink and a member of the Foreign Affairs Council. Mr Flood headed the Inquiry into Immigration Detention Centre Procedures, which reported to the Australian Government in February 2001, and the Inquiry into Australian Intelligence Agencies, which reported in July 2004.

Mr Peter Wills AC – Deputy Chairman

Peter Wills is the founder and Chairman of CRI, one of Australia's leading property and infrastructure companies. He is notable for his contribution to the support of medical research in Australia. He was Director (1990–93) and Chairman (1993–2001) of the Garvan Institute of Medical Research, as well as Chairman (1990–93) and subsequently Director (1993–2001) of the Garvan Research Foundation. Mr Wills chaired the Health and Medical Research Strategic Review ('the Wills Review') and its Implementation Committee (1998–2000). More recently he has been Strategic Adviser to the Investment Review of Health and Medical Research (2003–04). Mr Wills is a past member of the Biotechnology Consultative Group (1999–2001) and the Prime Minister's Science, Engineering and Innovation Council (2001–02) and a former Chairman of the Australian Research Council (2001–02). He is a Fellow of the Australian Institute of Management, a Fellow of the Company Directors' Association and a Trustee and Member of the Board of Governors of the Committee for Economic Development of Australia (CEDA).

Sir Peter Lawler OBE

Sir Peter Lawler had a distinguished career in the Australian Public Service spanning over 42 years. He joined the Department of Post-War Reconstruction as an economics graduate in 1944 and undertook postgraduate training in several European cities while posted to the British Cabinet Office in 1952–53. Sir Peter's later appointments included Deputy Secretary of the Prime Minister's Department / Department of the Prime Minister and Cabinet (1964–72), Secretary of the Department of the Special Minister of State (1972–75) and Secretary of the Department of Administrative Services (1975–83). From 1983 to 1986 he was Australian Ambassador to Ireland and the Holy See. Sir Peter was knighted in 1981 and in 1986 received the Papal honour of Knight Grand Cross of the Order of Pius IX.

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The Review Committee (top row, left to right) Professor Graeme Ryan AC, Ms Yael Cass (Review Secretariat), Mr Peter Wills AC (Deputy Chairman), Associate Professor Kevin A. Rickard AM, (seated) Sir Peter Lawler OBE and the Chairman of the Committee, Mr Philip Flood AO.

Professor Graeme Ryan AC

Professor Graeme Ryan, a pathologist, is Director of Research Strategy at the Alfred Hospital, Melbourne, and Chairman of the Royal Victorian Eye and Ear Hospital Board of Directors. His other current appointments include Governor of the Ian Potter Foundation, Professor Emeritus at the University of Melbourne and Chairman of the NHMRC Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC). His previous positions include Dean of the Faculty of Medicine, Dentistry and Health Sciences at the University of Melbourne (1986–95) and Chief of Clinical Services and Member of the Board of Directors, Inner and Eastern Health Care Network (1996–2000). Professor Ryan has also served as a board member of numerous medical research institutes and community organisations. He is the author of some 150 published articles and book chapters.

Associate Professor Kevin A. Rickard AM

Professor Kevin A. Rickard AM, RFD, FRCP (Lond), FRACP, FRCP (Edin), was haematologist at Sydney's Royal Prince Alfred Hospital (RPAH) for 36 years, relinquishing this position in 2005. He was Director of the RPAH Haemophilia Centre and the Thrombosis and Haemostasis Unit within the Institute of Haematology. He is Associate Professor of Medicine at the University of Sydney, Consultant Emeritus to RPAH and Consultant Emeritus in Haematology and Transfusion Medicine to the Australian Defence Force. As Surgeon Captain RANR he has been Consultant in Pathology to the Surgeon General ADF and Consultant in Haematology to the Royal Australian Navy. In addition he has had a longstanding association with the World Federation of Hemophilia, holding a number of positions, including Vice President Developing World and Chairman of the Federation's worldwide network of International Haemophilia Training Centres. He is a Past President of the Haematology Society of Australia New Zealand and also a Past President of the Australia New Zealand Society of Blood Transfusion.

Executive summary

This is the first and final report of the Review of Australia's Plasma Fractionation Arrangements.

The Review has involved a comprehensive analysis of Australia's current arrangements for the collection of blood plasma from Australian donors and for the separation of this plasma as the basis for a range of therapeutic products designated for use within the Australian health care system.

Global context

The global plasma fractionation industry, together with individual countries' national arrangements for the supply of blood and blood products to meet domestic need, contributes very significantly to the health care of many millions of people around the world.

The value of the global market for plasma derived products, together with alternative products manufactured via recombinant DNA technology, is currently assessed at approximately US\$10.5 billion. The world market for plasma products grew by 5% between 2003 and 2005 and is forecast to expand by a further 11.5% in the period 2005–08.

The past two decades have seen dramatic changes within the global industry, the result primarily of mergers and acquisitions, the development of recombinant alternatives for existing plasma products, and increasing levels of regulation with respect to product safety.

The United States is the only country in the world that is totally self-sufficient in whole blood and in the full range of plasma products. Some 70% of the plasma collected globally is collected in the United States. In other countries, arrangements for the collection of plasma, and for its subsequent fractionation, reflect domestic demand together with various economic, demographic and historical factors.

Over the decade 2006–16, global demand for intravenous immunoglobulin (IVIg), commercially the most important of the plasma derivatives, is expected to increase by 65%. Additional clinical uses for IVIg, changes in clinical practice, or entry by the product into new markets, could generate even greater demand. Projections suggest that worldwide demand for albumin, another key plasma product, will experience more modest growth over the same period, increasing by 15%.

Australia's arrangements

Australia's national arrangements with respect to the supply of fresh blood and of fractionated plasma products are unique and are not replicated in any other country.

Crucial to these arrangements is the contribution made by Australian donors. The many individuals who voluntarily donate blood or plasma on an ongoing basis

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contribute a gift of immeasurable value to the health and wellbeing of their fellow Australians. Indeed it is difficult to conceive of a more altruistic form of community service than the regular donating of blood or plasma – where the gift may well be that of life itself. Over 400 000 people in Australia receive a blood product each year, and it is estimated that more than 50% of Australians will require blood or a blood product during their lifetime.

Also playing a vital role in Australia's arrangements for the supply of plasma derived products is the Australian Red Cross Blood Service (ARCBS), an operating division of the Australian Red Cross Society. The ARCBS is currently responsible for all collections of Australian blood and plasma, with plasma being sourced both from whole blood donations (recovered plasma) and from donors directly, via the process of plasmapheresis (source plasma). In its capacity as a humanitarian organisation of long and distinguished standing, the Australian Red Cross is held in high regard by Australians, and the association between the ARCBS and the national blood supply system is therefore likely to engender donor confidence, and confidence within the broader community, for years to come.

Plasma collected by the ARCBS from Australian donors is fractionated by CSL Bioplasma, a business unit of CSL Limited, at its plant at Broadmeadows, Victoria. Founded in 1916 as the Commonwealth Serum Laboratories, CSL has played a major role in the delivery of health care for nearly a century. In addition to fractionating Australia's plasma supply, CSL conducts leading-edge medical research and has for many years produced vaccines and other pharmaceutical products in quantities sufficient to enable Australia's health system to respond quickly and effectively to emerging public health crises. CSL's Broadmeadows plant is the only facility of its kind in Australia with the technology and expertise necessary for the efficient fractionation of the quantities of plasma collected by the ARCBS from Australian donors.

The National Blood Authority (NBA), a federal agency, manages the national blood supply system on behalf of Australian governments, monitoring demand for blood and blood products, managing procurement arrangements with product suppliers, and undertaking annual supply planning and budgeting. In its short period of existence the NBA has been conspicuously successful in ensuring greater value for governments.

The strong regulatory environment within which plasma products are manufactured and distributed in Australia is managed and monitored by the Therapeutic Goods Administration (TGA), an arm of the Commonwealth Department of Health and Ageing, to ensure that plasma derivatives are subject to the highest standards of regulation applicable to therapeutic goods.

The close oversight of CSL Bioplasma in its capacity as Australia's national fractionator, and of the ARCBS as the agency charged with collecting blood and plasma nationwide – together with the longstanding commitment by both organisations to health care in Australia, and the exceptional generosity of Australia's many voluntary blood and plasma donors – are the factors that combine to create the unique, world-class system that today governs the supply of plasma products to the Australian community.

The total cost of funding Australia's national blood arrangements for 2006–07 is estimated at A\$650.7 million.

Australian demand, present and future

While the great majority of plasma products provided to the Australian community are manufactured in Australia, from domestically sourced plasma, the importance of ensuring a secure and adequate supply of plasma derivatives, sufficient to meet the needs of all Australian patients, currently necessitates arrangements for the importation of some fractionated products.

Importation becomes necessary where clinical demand exceeds the quantities of a particular product that can be produced within Australia from available Australian plasma, or where a required product is low-volume and is not manufactured from available Australian plasma by CSL Bioplasma. All suppliers of plasma products for use in Australia operate under agreements that ensure security of supply, as well as reserve stockholdings.

The critical factor in forecasts concerning future demand for plasma products in Australia is the projected demand for intravenous immunoglobulin (IVIg). Over the past decade, demand for IVIg in Australia has been increasing at an annual rate of 14%, a growth rate much steeper than that for the supply of starting plasma available for fractionation. Since 2003–04, therefore, in order to meet the needs of Australian patients, the domestic IVIg supply has been supplemented with imported IVIg products.

Forecasts provided to the Review indicate that by 2015–16 the level of demand for IVIg in Australia will be between 2985 and 3687 kilograms of product per annum. The average of these two figures, 3336 kilograms, represents more than double the amount of IVIg currently being issued.

At present rates of product yield, this increase in demand for IVIg would mean that the amount of raw plasma collected from Australian donors in ten years' time must be more than double the amount of plasma collected today. If the forecast provided to the Review by the Allen Consulting Group (ACG) proves accurate (the ACG forecast anticipates a 7.7% annual growth in demand for IVIg), Australia will require 686 tonnes of starting plasma in 2015–16, compared with 308 tonnes in 2005–06, an increase of 123% for the decade.

It is clear, therefore, that a key issue – perhaps *the* key issue – in relation to Australia's current plasma fractionation arrangements is that the volume of plasma collected in this country must greatly increase if future demand for plasma derivatives, especially IVIg, is to be met primarily by products fractionated from Australian plasma.

While Australia has never been totally self-sufficient in respect of all plasma products, the Review is of the opinion that Australia should be as self-sufficient as possible and that self-sufficiency should remain an important national objective.

Donation trends to date, however, do not offer any certainty that Australia's donor pool can be increased to the levels necessary for providing the quantity of domestic plasma needed in order to meet projected demand.

Assessment of alternative fractionation arrangements

The Review has closely examined fractionation arrangements in the United States and in Europe, and has given close consideration to possible alternative arrangements for Australia.

The Review has determined that if Australian plasma were to be fractionated overseas, rather than at a locally based fractionation plant, there would be a need for substantial initial

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expenditure, extensive transitional planning, contingency plans, risk mitigation plans, and investment associated with registration and other compliance and approval processes.

There would also be significant additional ongoing costs associated with the overseas manufacture of plasma products for use in Australia. Some of these costs (e.g. for the transportation of Australian plasma to an overseas fractionation facility; for the return of finished plasma products to Australia; and for cold storage and warehousing) would be borne by the offshore fractionator and would be reflected in its pricing structures.

Major costs arising from the offshore fractionation of all Australian plasma would include a one-off 'transition cost', of approximately A\$75 million. This would enable either the collection (if feasible) of sufficient additional domestic plasma to cover the 60-day withholding period if required (and the period required for sea transport) and scheduled processing time, or the one-off purchase of the same quantity of imported finished product. The National Reserve would thus have to be increased by an additional six months' stockholding, over and above the present inventory target of three months' supply of plasma products.

Moreover, on the basis that an offshore fractionator's yield of IVIg would most likely be less than the yield realised by CSL Bioplasma, projections indicate that overseas fractionation could result in additional annual purchasing costs for starting plasma.

It is also evident that overseas fractionation would see a doubling in lead time 'vein to vein' (i.e. the period that elapses between a donation of plasma and its clinical use, in the form of a finished plasma product).

Finally, there are potentially major risks associated with the offshore fractionation of Australian plasma. Although the scenarios envisaged carry a low probability of occurrence, their consequences would be costly and highly disruptive. For example, the loss of a 20-foot reefer container of plasma would mean a serious interruption to the supply of plasma products in Australia and would necessitate the acquisition of a compensatory quantity of overseas-sourced plasma, or of the equivalent in finished products fractionated from overseas-sourced plasma.

Community expectations

Across the broad range of local submissions received by the Review, concern about the possibility of change to Australia's current blood arrangements was almost universal. Maintaining the existing integrity of these arrangements, together with the reliability and high levels of safety that they represent, is seen by the majority of stakeholders to be of vital importance.

Another key issue in terms of community expectations is that CSL Limited's Broadmeadows and Parkville plants are widely regarded as iconic establishments within the biotechnology sector, not only in terms of technology and R&D, but also of the employment opportunities offered by both facilities.

Key conclusions

- If Australia is to be self-sufficient in the plasma required for the production of IVIg, then, given projected demand over the next ten years, a dramatic increase in domestic plasma collections by the Australian Red Cross Blood Service will be necessary. Achieving this increase will require of all Australian governments vigorous review and reform of current domestic plasma collection arrangements.

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- In any event, Australia will need to maintain imports of plasma derived product in order to meet domestic demand. If the increases in plasma collections projected by the ARCBS are not met, then the requirements for imported products will increase considerably.
- Overseas fractionation of Australian plasma would involve significant transitional costs and, because of yield considerations, there would be the potential for an ongoing shortfall in the supply of IVIg and other plasma derived products. The consequent need to source these products via imports would have implications for the national self-sufficiency policy.
- There are potential supply chain risks involved in overseas fractionation of Australian plasma. While some of the risk scenarios are of low probability, their consequences would be expensive and disruptive. Addressing these risks would require either an impost on the National Reserve of plasma products or an added call on existing standing offers for imported product.
- Any supply to Australia of plasma products from overseas fractionators would require significant lead times and investment in registration and other approval processes. If registration of products were to be a prerequisite to tendering for the supply of plasma products to Australia, not all overseas fractionators would be likely to want to incur the costs of registration in the absence of a supply contract. If, on the other hand, product registration were to be required only after a tender contract had been agreed, then a lead time of at least two years would be needed for registration and approval processes.
- When the transitional costs, the risks, and the indeterminate yield ratios of overseas fractionation are considered against the national self-sufficiency objective, and when account is taken of the national strategic importance of CSL's plant at Broadmeadows, then overseas fractionation of Australian plasma is not an advantageous option for Australia.

Recommendations

1. Ministers should note the Review's conclusion that overseas fractionation of Australian plasma is not an advantageous option for Australia. Ministers should also note the substantial regulatory and other changes, as set out in this report, that would be necessary in the event it were desired to alter present arrangements and invite overseas manufacturers to tender for the fractionation of Australian plasma.
2. In view of the prospect of substantial shortfalls between projected demand for plasma products in Australia, and domestic plasma collected by the Australian Red Cross Blood Service, urgent action must be taken to increase plasma collection rates. There needs to be a vigorous and creative campaign, led by Commonwealth, state and territory governments, to energise the community in favour of blood donation.
3. The Commonwealth, state and territory governments should safeguard the security of supply of plasma products for Australians by importing plasma products to address any shortfall and risks in supply of domestically manufactured products. Procurement of imported plasma products should be undertaken by an international competitive tender process, which could include provision for tiered pricing related to the volume of specific products required. This may also facilitate benchmarking by the National Blood Authority of domestically manufactured plasma products against prices for imported plasma products, in order to further the objective of value for money in future contract negotiations, consistent with other policies. Existing contracting, risk management and mitigation strategies for Australia's plasma fractionation arrangements should be reviewed

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by the Australian Health Ministers' Conference in consultation with relevant parties and, where appropriate, upgraded in line with world's best practice.

4. The ARCBS needs to enhance innovation in its marketing efforts and customer service strategies in order to recruit donors from a broader cross section of the Australian community and to retain existing donors. In particular, there is a need for new strategies for encouraging more young Australians and members of ethnic communities to donate blood. The ARCBS will need additional funding support from governments to develop and implement such strategies. In the future, consideration may need to be given as to whether travel costs incurred by blood donors and plasma donors should be reimbursed or permitted to be treated as an allowable taxation offset; taxation offset for costs incurred as a direct consequence of blood or plasma donation would be a powerful statement of the importance attached by Government to the voluntary donation of blood.
5. The present annual planning and budgeting framework for plasma supply should be reviewed, with a view to moving to a four- to five-year business planning cycle. The current annual planning cycle is not consistent with best practice in strategic planning and can limit capacity for ensuring operational efficiency.
6. Uniform provisions concerning the age at which a person is eligible to donate blood should be introduced by all state and territory governments. A uniform approach along the lines of the system operating in South Australia would be in the best interests of collections by the ARCBS.
7. There should be greater consistency between states and territories in the application of revised national guidelines for IVIg usage.
8. The Therapeutic Goods Administration regulatory base should be revised to provide explicitly for the conduct of unannounced audits of overseas manufacturers. The new arrangements should be supported and confirmed through either Mutual Recognition Agreements or provisions in contracts with manufacturers. Consideration should be given to negotiating amendment of the Australia–EC/EFTA MRAs, to enable joint inspections of manufacturers of high risk medicines (including plasma products) by the TGA and designated EC/EFTA GMP inspectorates, where appropriate. Consideration should be given to amending the Therapeutic Goods Regulations to ensure that fees may be imposed on Australian product sponsors to cover the costs of GMP auditing of overseas manufacturing sites.
9. The Australian Health Ministers' Conference should continue to monitor and assess industry developments, with the aim of ensuring that the range of Australian plasma derived products remains appropriate to clinical requirements.
10. Australia should maintain its reservation regarding the procurement of blood fractionation services under the Australia–United States Free Trade Agreement. The reservation exempts the procurement of plasma fractionation services from the government procurement provisions in Chapter 15 of the Agreement. The CSL Act should also be maintained.

Introduction

On 17 February 2006 the Minister for Health and Ageing, the Hon. Tony Abbott MP, announced a review of Australia's plasma fractionation arrangements:

Under the Australia–United States Free Trade Agreement, the Australian Government has committed to undertake a review of its arrangements for the supply of plasma fractionation services for plasma collected in Australia.

The Review will focus on the provision of plasma fractionation services following the collection of plasma donated in Australia, on a voluntary basis, to meet Australian demand for plasma derived products.

The Terms of Reference for this Review are to:

- (1) Examine the projected demand for plasma products over the next ten years and the relationship between demand trends and the requirements on supply of plasma fractionation services.
- (2) Identify appropriate requirements to be met by producers of plasma products or suppliers of plasma fractionation services to ensure the safety, quality and efficacy of such products or services. These requirements shall not create unnecessary obstacles to trade.
- (3) Identify issues arising as a result of any increase in competition for the provision of plasma fractionation services for Australia and indicate how these issues could best be dealt with through future procurement arrangements.
- (4) Assess issues under (3) above against the following evaluation criteria: safety, quality, efficacy, security of supply and the potential impact on expenditure under the National Blood Agreement.

In its work the Review will:

- be consistent with the policy of providing plasma products to patients free of charge;
- be consistent with the policy of recognising the role of Australia's regulator, the Therapeutic Goods Administration, in regulating the safety, quality and efficacy of plasma products;
- be consistent with the policy objectives and aims of the National Blood Agreement; and
- engage in public consultation to assist with the conduct of work under the Terms of Reference.

The Review will report to the Minister for Health and Ageing by 1 January 2007.

The Minister appointed Mr Philip Flood AO, former Secretary of the Department of Foreign Affairs and Trade and former Australian High Commissioner to the United Kingdom, as Chairman of the Review Committee. Also appointed to the Committee were Mr Peter Wills AC (Deputy Chairman), Sir Peter Lawler OBE, Professor Graeme Ryan AC, and Associate Professor Kevin A. Rickard AM.

Provisions of Australia–United States Free Trade Agreement (AUSFTA) in relation to Australia's plasma fractionation arrangements

Under the Australia–United States Free Trade Agreement (AUSFTA), the Commonwealth Government agreed to:

- undertake a review of its arrangements for the supply of plasma fractionation services, with this review to be concluded no later than 1 January 2007
- (after completion of the Review) recommend to the state and territory governments that future arrangements for the supply of plasma fractionation services be implemented in accordance with tender processes consistent with Chapter 15 ('Government Procurement') of the AUSFTA.

The AUSFTA requires that, if all Australian state and territory governments are in agreement with the aforementioned recommendation, the Commonwealth Government shall withdraw the reservation in the AUSFTA that currently exempts the procurement of plasma fractionation services from the government procurement provisions in Chapter 15 of the Agreement.

These obligations are set out in an Exchange of Letters forming part of the AUSFTA (see Annex A at conclusion of this report).¹ The Letters also confirm Australia's right to:

- require any producer of blood plasma products or supplier of blood fractionation services to fulfil requirements necessary for ensuring the safety, quality and efficacy of plasma products
- require that blood plasma products for use in Australia be derived from blood plasma collected in Australia.

Conduct of the Review

The Review has been conducted with a view to informing Australia's plasma fractionation arrangements well into the future. At the same time, the Review has been concerned with ensuring that all safeguards remain in place to protect the safety, quality, efficacy, and security of supply, of blood and blood products for Australia.

The Review has assessed the existing arrangements, and alternatives, with respect to products fractionated from plasma collected from voluntary, non-remunerated Australian donors and destined for use in Australia. The possible implications of changes to current tendering processes have also been considered.

The Review Committee has undertaken a number of consultation activities in order to give all interested parties an opportunity to express their views.

Written submissions, from within Australia and from overseas, were received from a range of professional associations, consumer groups, patient support groups, pharmaceutical companies, industry organisations, federal, state and territory government agencies, and interested members of the public. (A complete list of individuals and organisations that provided submissions is included at Annex B.)

¹ A facsimile of the original signed correspondence can be found at <http://www.dfat.gov.au/trade/negotiations/us_fta/final-text/index.html>.

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At meetings in Canberra and in state capitals, members of the Review Committee consulted with representatives of stakeholder groups. Committee members and Secretariat staff also visited regulatory agencies, agencies with relevant procurement and policy-making responsibilities, industry organisations and private enterprises, in North America and Europe. The views of all state and territory governments were sought, and Australia's regional neighbours with an interest in the Review's terms of reference were invited to contribute their views to the Committee. (A list of persons consulted is provided at Annex C.)

So that the Review had the benefit of specialised and independent advice on the implications of the current plasma fractionation arrangements and on possible options for increasing competition, the Department of Health and Ageing engaged expert opinion with respect to legal considerations and the clinical and scientific environment, and international business environment, surrounding plasma fractionation. The National Blood Authority and the Therapeutic Goods Administration provided valuable input to the Review. Advice from other Commonwealth government agencies, including the Department of Foreign Affairs and Trade, was also obtained.

A team in the Acute Care Division of the Department of Health and Ageing provided Secretariat support to the Review Committee (see Annex E).

National Blood Agreement

The Review took into account the policy objectives and aims of the National Blood Agreement of 1 July 2003, to which the Australian Government and all state and territory governments are party. These objectives and aims are summarised as follows in the Agreement:

1. The primary policy objectives for the Australian blood sector are:
 - (a) to provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services in Australia; and
 - (b) to promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.
2. In pursuing the primary policy objectives, the Parties will have regard to the following secondary policy aims:
 - (a) to meet international obligations and standards;
 - (b) to maintain reliance on voluntary, non-remunerated donations of whole blood and plasma;
 - (c) to promote national self-sufficiency;
 - (d) to provide products to patients free of charge and based on clinical need and appropriate clinical practice;
 - (e) to promote optimal safety and quality in the supply, management and use of products, including through uniform national standards;
 - (f) to make best use of available resources, and to give financial and performance accountability for the use of resources by all entities involved in the Australian blood sector;

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- (g) to undertake national information gathering, monitoring of new developments, reporting and research in relation to the Australian blood sector;
- (h) to maintain flexibility and capacity to respond in a timely manner to changing circumstances and needs;
- (i) to ensure public support and confidence in the Australian blood sector; and
- (j) to work towards optimal access to blood products and blood related products across the nation, ensuring that patients continue to access the blood products and blood related products their clinicians determine will best meet their needs so far as practicable in accordance with national best practice based on clinical guidelines. This clause does not preclude States and Territories from altering the range of blood products and blood related products that are prescribed and received in their jurisdiction.²



Donating blood is Lisa Wilkinson, co-host of Channel 7's Weekend Sunrise. Photo courtesy of ARCBS.

² *National Blood Agreement*, National Blood Authority, Canberra, 2003, p. 2, http://www.nba.gov.au/PDF/national_blood_agreement.pdf. The full text of the Agreement may be accessed at this URL.

Chapter 1

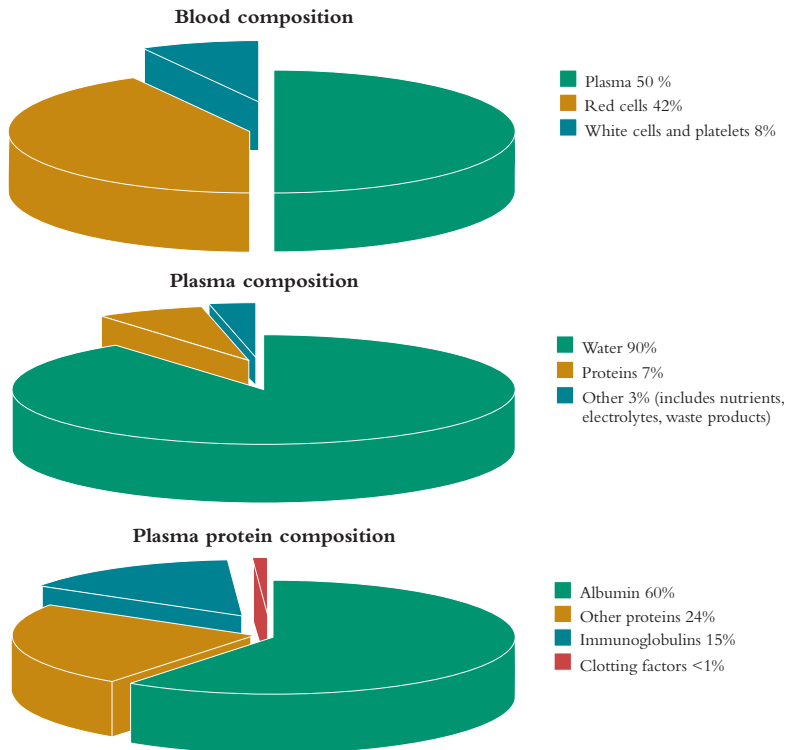
Plasma and its applications in medicine

Throughout human history, blood has been imbued with many different cultural, religious and social meanings. Its use in medicine, however, is relatively recent. Scientific discoveries in the early part of the twentieth century made possible the collection, preservation and transfusion of blood and blood components. These developments revolutionised medical practice and have saved countless lives. Over 400 000 Australians receive a blood product each year, and more than 50% of Australians will require blood or a blood product in their lifetime.¹

Composition of blood

Blood is a liquid, contained within blood vessels. Its major functions are to supply nutrients (such as oxygen, glucose, vitamins and minerals) to other tissues, to transport waste products (such as carbon dioxide and lactic acid), to protect the body

Fig. 1.1 The constituents of blood, plasma, and plasma proteins



Source: Adapted from information in: World Federation of Hemophilia, *Contract Fractionation*, Facts and Figures, no. 5, rev. edn, World Federation of Hemophilia, Montreal, 2004, p. 2; also available online at http://www.wfh.org/2/docs/Publications/Treatment_Products/Monographs/FF-5_English_Fractionation.pdf.

¹ These estimates, provided by the Australian Red Cross Blood Service, relate to the full range of blood and blood-related products, including fresh blood products, plasma products, blood-derived diagnostic products used in laboratory testing, and products that use human albumin as a stabiliser (e.g. some recombinant products and vaccines).

from invasion by foreign organisms and to recognise and reject foreign tissues. Blood also functions as a regulator of body temperature. The cellular components of blood are red blood cells, white blood cells, and platelets.

Red blood cells (erythrocytes), which are cells without nuclei, contain the protein haemoglobin. Haemoglobin carries oxygen, in the form of oxyhaemoglobin, from the lungs to the tissues, and is also partly responsible for the transport of carbon dioxide, produced by metabolic activity, from the tissues to the lungs, where the CO₂ is breathed out.

White blood cells (leucocytes) protect against bacterial and viral infections and mediate immune responses.

Platelets (thrombocytes) are non-nucleated blood cell fragments that maintain the integrity of the blood vessel wall by adhering to sites of injury and aggregating to form a haemostatic plug. The surface and the interior of the haemostatic plug allow the interaction of coagulation factors; this process results in the formation of a fibrin clot, which consolidates the platelet plug.

Plasma is the straw-coloured liquid in which red blood cells, white blood cells, and platelets are suspended. Plasma contains a large number of biologically critical proteins, which have multiple physiological functions. The separation of plasma into its constituent proteins for medical use is called fractionation.

Figure 1.1 identifies the components of blood, plasma, and plasma proteins. It is important to note that the proportions indicated vary to some extent, and should not be regarded as constant values.

Plasma collection methods

Plasma is collected from donors by either of two methods: whole blood donation or apheresis. Plasma that is obtained by separation from whole blood donations is referred to as recovered plasma. Plasma collected via apheresis is referred to as source plasma.

The most common form of plasma collection by apheresis is plasmapheresis, which is a procedure whereby the donor's blood is extracted from the body and centrifuged in a closed and sterile system, so that the plasma in the blood is separated from the cells. The cells are then immediately returned to the body. The plasma is collected into sterile containers and subsequently fractionated.

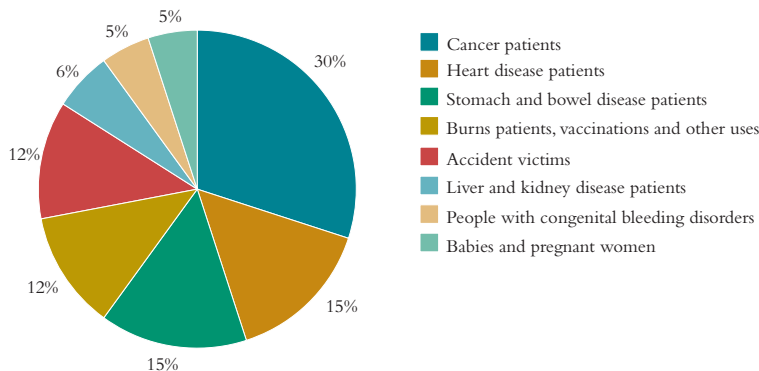
Approximately 650 millilitres of plasma per donation can be obtained using plasmapheresis, compared to approximately 250 millilitres of plasma from a whole blood donation.

The primary reason for the use of other forms of apheresis is to separate platelets for transfusion, or stem cells for bone marrow transplantation.² In these procedures, particularly the former, plasma is collected as a secondary product.

Figure 1.2 identifies the areas in which donated blood is used. The percentages shown account both for fresh blood products and for plasma derived products.

² Stem cells can also be harvested from bone marrow, although at the present time these cells are more commonly harvested from blood.

Fig. 1.2 The various patient categories for whom donated blood is used



Source: Adapted from information in: Australian Red Cross Blood Service, *How Donated Blood Is Used*, Australian Red Cross Blood Service, 2006, <http://www.arcbs.redcross.org.au/Donor/aboutblood/howused.asp>.

Comparative aspects of plasma collection methods

Plasmapheresis donations can be made more frequently than whole blood donations, because in plasmapheresis the donor's red cells are returned and anaemia caused by red cell loss is largely avoided. Under Australian Red Cross Blood Service (ARCBS) procedures as set by Australia's national medicines regulatory agency, the Therapeutic Goods Administration (TGA), plasmapheresis donations can be made as often as every three weeks, whereas the minimum interval between donations of whole blood is 12 weeks.

Although plasmapheresis allows the collection of plasma from donors in larger amounts, and more frequently, an important point with respect to plasma fractionation is that source plasma provides lower overall yields of plasma proteins than does recovered plasma, mainly because of the shorter intervals between plasmapheresis donations – these intervals do not allow time for full recovery of the lost protein components of donors' plasma.

In addition, compared with whole blood donation the plasmapheresis process is a lengthier one. It normally takes approximately 45 minutes, to which must be added waiting time, time for the donor to rest after donating, and travel time to and from the office or home; for many plasmapheresis donors, the total time involved is between two and two and a half hours. From a donor's perspective, the process may be perceived as more taxing than whole blood donation.

Plasmapheresis also imposes extra costs, including those for staffing.

Plasma products

Plasma products can be grouped into three major categories:

- **Albumin:** Albumin is a low-molecular-weight protein that is essential for the maintenance of blood volume and thus for the stability of the circulation. Loss of albumin, through injury such as severe burns, may result in the collapse of the circulation. In some forms of kidney disease, there is loss of albumin via the urine, and severe liver disease can result in a failure to synthesise albumin. In all three

conditions, water and electrolytes exit from the circulation into tissues, causing swelling. Large blood or plasma losses following traumatic injury (including burns) or extensive surgery can result in hypotension (low blood pressure). Replacement albumin may be required in these various circumstances.

- **Immunoglobulins:** Immunoglobulins are proteins that provide protection against infection and modulate the immune system. Immunoglobulin products contain antibodies – complex protein substances that are a key component of the immune system. Hyperimmune immunoglobulins are plasma products that contain a high concentration of specific antibodies capable of combatting particular infections or antigens (substances that cause the formation of antibodies).
- **Clotting factors** (also termed ‘coagulation factors’³): Clotting factors are proteins that when activated function as enzymes, leading to the production of thrombin and then fibrin, which together with platelets prevent loss of blood after vessel injury. Clotting factor concentrates are used to treat haemophilia and other conditions that require treatment to promote normal control of bleeding.

Other plasma derivatives include wound-healing products (fibrin sealants) and human alpha-1 antitrypsin, which is used in pulmonary disease therapy.

Recombinant products

Recombinant clotting factors are not produced by fractionating plasma. Instead, they are made using recombinant technology (genetic engineering) in a laboratory environment. Recombinant products are made by isolating a human clotting factor gene and inserting it into non-human cells, which are then grown in cell culture. The clotting factor produced by these cells is harvested from the fluid in which the cell culture is suspended. Although the risk of contamination cannot be completely ruled out, recombinant products are considered to be safer than their plasma derived counterparts.

Most of the recombinant products that are currently commercially available, however, are first- and second-generation products, and the cell cultures in which they are grown contain small amounts of human or animal plasma proteins. In addition, in first-generation recombinants human albumin is used as the stabiliser in the final product. Third-generation recombinants, which have no human or animal cell content (meaning that the risk of contamination is even lower), are now becoming commercially available.

While recombinants are largely supplanting plasma derived Factors VII, VIII and IX, in Australia there is a continuing residual level of demand for the plasma derived factors.

A brief history of plasma fractionation and of arrangements in Australia

The effective use of blood transfusions in clinical care dates from the early twentieth century, following the publication in 1901 of Dr Karl Landsteiner’s identification of the main blood groups. Prior to that time, there were no efficacious treatments available for people with blood disorders such as haemophilia, a condition whose prevalence within the royal families of Europe has been well documented (see story on next page).

3 The term ‘coagulation factors’ encompasses products that either promote clotting or extend clotting times.

Queen Victoria's haemophilia: The Australian connection

Queen Victoria was a carrier of haemophilia. Her youngest son, Prince Leopold (1853–1884), had a severe form of the condition, while two of the Queen's daughters were also carriers of the haemophilia gene.*

It has been suggested that Prince Leopold had aspirations to be the governor of the colony of Victoria. Some historians have proposed that it was the British prime minister, Benjamin Disraeli, who recommended to the Queen that she send the Prince to Australia on a royal visit in 1867–68, on the grounds that the warmer climate would be beneficial for his health. The Queen, however, did not wish to be parted from Prince Leopold. Instead she chose to send her second son, Prince Alfred, on what would prove to be an incident-filled visit to Australia.



Prince Alfred in the full dress uniform of an admiral in the Royal Navy

As a 24-year-old captain in the Royal Navy, Prince Alfred sailed for Australia in command of the wooden steam frigate HMS Galatea, arriving in Adelaide on 31 October 1867. Several months later in Sydney, on the afternoon of 12 March 1868, he attended a picnic with many of the city's dignitaries, including the Governor of New South Wales and the Chancellor of the University of Sydney. During the course of this picnic, to the horror of the assembled crowd, Prince Alfred was fired upon and was wounded in the chest. The would-be assassin, Henry James O'Farrell, a Fenian sympathiser, was immediately arrested, and some six weeks later was found guilty of attempted murder and hanged at Darlinghurst Gaol. The Prince eventually made a full recovery.

The people of Sydney were so appalled by the attack that, following a public meeting at Sydney Town Hall, they collected £30 000 in an effort to make some reparation to the Queen. It was the Prince's wish that these moneys be used to create a hospital. With the approval of the Senate of the University of Sydney, a new teaching hospital was founded on university land. Prince Alfred Hospital (later Royal Prince Alfred Hospital) would open on 25 September 1882.

In Melbourne there was also a strong public reaction to the shooting of the Prince. Moneys were again collected from the public and these donations, combined with a Victorian government grant, were used to establish the Alfred Hospital in Prahran. Prince Alfred laid the foundation stone of the new hospital on 6 March 1869. He eventually sailed from Australia the following month.

Had Prince Leopold been involved in an incident similar to that suffered by his brother during the royal visit to Australia, the wound might well have been fatal, because of the amount of bleeding that would have ensued. At the time, there were no plasma products available, and blood transfusions would not become a viable clinical option until after the discovery of blood groups in 1901.

* Through Princess Alice and Princess Beatrice, haemophilia was transmitted to the family of the Tsar of Russia and to the Spanish royal family. It could even be argued that the condition played a role in the origins of the Russian Revolution of 1917 and the Spanish Civil War of 1936–39. The influence of Rasputin on the Romanovs in Russia was directly related to haemophilia: that of the Tsar and Tsarina's only son, Prince Alexei. There has been speculation that the illness led to severe strain within the Russian royal family, enabling Rasputin to gain influence over them and thus ultimately contributing to the downfall of the once-powerful Romanov dynasty. The abdication of King Alfonso XIII in Spain was also related to haemophilia. In both cases the repercussions were profound and far-reaching.

Review of Australia's Plasma Fractionation Arrangements

As transfusion science developed, groups of blood donors were recruited and blood banks were established in many countries during the 1920s and 1930s.

The need for albumin for the treatment of battlefield casualties in World War II provided the impetus for the large-scale separation of plasma proteins, as fractionated products are concentrated into a small volume and can be better preserved and more readily transported than fresh plasma.

In the early 1940s a team at Harvard Medical School, led by Dr Edwin Cohn and with support from the United States National Research Council, pioneered the fractionation of human plasma using cold-ethanol techniques. Once full-scale production for the war effort commenced, several US companies became involved in fractionation. A similar project to develop fractionation techniques was initiated in Britain during the war years; after the war, fractionation plants commenced operations in many countries in the developed world.

In Australia, the Red Cross and the then Commonwealth Serum Laboratories (now CSL Limited) took a keen interest in these advances. The Red Cross found that CSL had the basic equipment and expertise to develop a fractionation plant. Following representations to the federal government by the Red Cross, seeking funding for CSL to enable it to establish fractionation facilities, Cabinet gave approval in 1949. CSL commenced production of fractionated products in 1953.⁴

The Commonwealth Serum Laboratories were founded in 1916. Originally a federal government entity, CSL has undergone a number of organisational changes during its history, culminating in its privatisation as a listed public company in 1994. Since then it has built up considerable overseas interests, and the CSL Group of companies together operate as a major global fractionator.

The organisation's original function was to produce vaccines for treating illnesses such as diphtheria, tetanus, typhoid fever, cholera, whooping cough and influenza. While CSL continues to develop and produce vaccines, plasma fractionation has become a major component of its Australian operations.

Since fractionation commenced in Australia, the Australian Red Cross has collected plasma and supplied it to CSL for fractionation. Collections are today made by the Australian Red Cross Blood Service, which is an operating division of the Australian Red Cross Society.

Australia's first organised blood transfusion service was established by the Red Cross in Victoria in 1929, with similar services subsequently being established in the other states and territories. These Red Cross Blood Transfusion Services were largely autonomous and were funded predominantly by state and territory governments. In 1995, the Commonwealth Review of the Australian Blood and Blood Product System (the McKay Wells Review) identified the need for a single, integrated blood supply agency in Australia, in the interests of enhancing the safety, efficiency and adequacy of supply of blood and blood products. In 1996, the separate state and territory blood services combined to form the ARCBS.

The Review of the Australian Blood Banking and Plasma Product Sector (the Stephen Review), which was completed in 2001, recommended the establishment of an authority to provide national management and oversight of Australia's blood system. As part of the

⁴ See Alfred Brogan, *Committed to Saving Lives: A History of the Commonwealth Serum Laboratories*, Hyland House, South Yarra, Vic., 1990, chapter 10.

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introduction of national blood arrangements following the Stephen Review, the National Blood Authority (NBA) came into operation in 2003.⁵ Until this time, fractionation services in Australia had been funded entirely by the Commonwealth.

The formation of the NBA saw funding and service delivery arrangements with suppliers consolidated into a unified approach. The NBA manages funding arrangements in relation to the ARCBS, as well as CSL Limited and other blood product suppliers, and coordinates the supply of blood and plasma products on behalf of Australia's federal, state and territory governments. Under the national blood arrangements, funding for the provision of plasma products to meet Australia's needs is now cost shared, on a 63%/37% basis, between the Commonwealth and the state and territory governments respectively.

In Australia, the safety, quality and efficacy of plasma products throughout the collection, manufacturing and supply chain are regulated by the Therapeutic Goods Administration. There is an inherent risk that infectious agents will be transmitted through plasma products, due to the biological origin of the material used in their manufacture. The TGA has stringent regulations in place to minimise this risk. The regulations govern donor selection policies; the testing of donations; procedures to inactivate or remove pathogens during the manufacturing of plasma products; processes and procedures for maintaining the integrity of plasma and finished plasma products throughout all transportation, distribution and storage phases; and the auditing of the manufacturing process.

The key drivers of demand for fractionation services have changed over time as new plasma products have become commercially available and alternative therapies have emerged for some conditions. The product in most demand initially was albumin, but the pattern of demand began to change in the late 1960s, after researchers in the United States pioneered a concentrated form of Factor VIII – which had a clotting power one hundred times greater than that of plasma – for the treatment of haemophilia A. Demand for intravenous immunoglobulin (IVIg) increased rapidly during the 1990s and 2000s, and now accounts for the bulk of worldwide demand for plasma products (see Chapter 2).

Plasma products available in Australia

Table 1.1 lists the plasma derived products currently provided to Australian consumers under Australia's national blood arrangements. It should be noted that a number of other plasma products (including alternatives to the products identified in this table) have been approved by the Therapeutic Goods Administration for use in Australia but are not provided under the national blood arrangements.

All of the products that CSL Limited manufactures in Australia, through its CSL Bioplasma business unit, are fractionated using plasma collected by the Australian Red Cross Blood Service from voluntary, non-remunerated donors.

The ARCBS retains some plasma for use in acute care settings and in the preparation of fresh frozen plasma (FFP) and cryoprecipitate. FFP is used to treat patients who develop clotting problems after trauma or liver transplantation. Cryoprecipitate is prepared from FFP and contains the blood clotting substances fibrinogen, Factor XIII, von Willebrand factor, fibronectin and Factor VIII. The product is used in surgery, for patients with

Table 1.1 Plasma products currently available in Australia

Product group	Produced by CSL in Australia	Imported plasma products
Albumin	<ul style="list-style-type: none"> Albumex® 4 Albumex® 20 	
Immunoglobulins	<ul style="list-style-type: none"> Intragam® P (intravenous immunoglobulin (IVIg)) Normal Immunoglobulin (intramuscular immunoglobulin (IMIg)) 	<ul style="list-style-type: none"> Octagam® Sandoglobulin®
Hyperimmunes (specific immunoglobulins)	<ul style="list-style-type: none"> CMV Immunoglobulin Hepatitis B Immunoglobulin Rh(D) Immunoglobulin Tetanus Immunoglobulin IM Tetanus Immunoglobulin IV Zoster Immunoglobulin 	<ul style="list-style-type: none"> WinRho SDF™*
Coagulation factors	<ul style="list-style-type: none"> Biostat® MonoFIX®-VF (Factor IX concentrate) Prothrombinex™-HT (Factor IX complex concentrate) Thrombotrol®-VF (antithrombin III concentrate) 	<ul style="list-style-type: none"> Ceprotrin®(protein C concentrate) Factor VII concentrate Factor XI concentrates FEIBAVH® Inhibitor Treatment Fibrogammin P® (Factor XIII concentrate)

* WinRho SDF™, an alternative product to Rh(D) Immunoglobulin, is manufactured in Canada by Cangene; Baxter is the Australian distributor. The regular importation of WinRho to Australia is no longer necessary, because a shortage of Australian Rh(D) hyperimmune plasma was overcome in early 2006. WinRho remains listed, however, on the National Supply Plan for blood products, and a small level of demand in Australia remains because the product can be administered intravenously when clinically appropriate, unlike the domestically produced Rh(D) Immunoglobulin.

particular clotting factor deficiencies; in cardiac surgery where there is persistent post-operative bleeding; in the intensive care setting when there is massive blood loss, or overwhelming infections with persistent bleeding; and in liver transplants. However, cryoprecipitate, a single-donor product, is not virally inactivated.

The National Blood Authority, acting on behalf of all Australian governments, has a contract with CSL Limited for the manufacture of products from Australian plasma. This contract, the Plasma Products Agreement (PPA), is a five-year agreement (from 1 January 2005 to 31 December 2009).

As far as is practicable, Australia uses products fractionated from plasma collected in this country. It is also necessary, however, to import quantities of a number of products, either because they are not manufactured in Australia, or to supplement domestically sourced supplies. The NBA has contractual arrangements with suppliers of these imported blood products (referred to as Defined Blood Products), which

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include the plasma derivatives listed in the right-hand column of table 1.1, together with the following recombinant products, which are also manufactured overseas:

- Novoseven® (second-generation recombinant Factor VIIa, produced by Novo Nordisk)
- Recombinate® (first-generation recombinant Factor VIII, produced by Baxter)
- Advate® (third-generation recombinant Factor VIII, produced by Baxter)
- ReFacto® (second-generation recombinant Factor VIII, produced by Wyeth)
- Benefix® (second-generation recombinant Factor IX, produced by Wyeth)

All products – local and imported – that are provided to Australian consumers under Australia's national blood arrangements are provided free of charge to recipients.⁶

Recent developments in plasma products

A number of plasma derivatives are currently not provided under Australia's national blood arrangements. Generally these products have become commercially available relatively recently. They include subcutaneous immunoglobulin (SCIg), alpha-1 antitrypsin, C1 esterase inhibitor, and fibrin sealants.

Immunoglobulins, as noted above, are generally used by people suffering from immunodeficiency syndromes and autoimmune disorders. Traditionally there have been two forms of immunoglobulin: intravenous immunoglobulin (IVIg) and intramuscular (normal) immunoglobulin (IMIg). IVIg infusions are delivered directly into the vein, usually in a hospital clinic but sometimes in the patient's home. This process takes approximately two to four hours and it is usual for an individual with chronic immune deficiency to receive a dose of IVIg once every month.

Although some existing immunoglobulin products have been used subcutaneously, there is now a move towards products specifically formulated for subcutaneous injection. These involve slowly infusing the antibody preparation directly under the skin, and the injections can be self-administered using a special pump. Infusions are usually required at least once a week, as only 10–15 millilitres can be infused into any one site at a given time; a 10 millilitre SCIg infusion can be delivered in half an hour.⁷

While there is growing demand for IVIg in Australia, SCIg has not yet become a significant driver of demand for plasma products, although it is increasingly being used in Europe as an alternative to IVIg. A specific SCIg preparation is not currently available in Australia.

Alpha-1 antitrypsin is used for chronic replacement therapy for patients with congenital alpha-1 antitrypsin deficiency together with clinically demonstrable panacinar emphysema, which is a chronic lung condition ('panacinar' refers to the involvement of all the lobes of the lung in a uniform manner). Alpha-1 antitrypsin deficiency is a rare disorder, affecting about 200 patients in Australia. Alpha-1 antitrypsin is available in Australia through the Special Access Scheme. This program,

6 Any potential additions to the plasma products listed on the National Supply Plan would need to undergo an evidence-based evaluation process (as specified in Schedule 4 of the National Blood Agreement), prior to consideration of their inclusion.

7 See Australasian Society of Clinical Immunology and Allergy, *About Immunoglobulin Replacement Therapy*, Information Bulletins, Australasian Society of Clinical Immunology and Allergy, Balgowlah, NSW, 2006, <http://www.medeserv.com.au/ascia/aer/infobulletins/immuno_replacement.html>.

operating under the auspices of the Therapeutic Goods Administration, allows individual patients to access therapeutic goods that have not been approved for and included on the Australian Register of Therapeutic Goods (ARTG). Applications are assessed on a case-by-case basis.⁸

C1 esterase inhibitor, used to treat C1 esterase inhibitor deficiency (also known as hereditary angioneurotic oedema (HANE)), is also available in Australia via the Special Access Scheme. HANE is caused by low levels of the plasma protein C1 inhibitor (C1-INH). Acute episodes can result in respiratory difficulties, with severe and even fatal consequences.

Fibrin sealants, used primarily in surgery – to control bleeding, seal wounds and promote healing – are being utilised increasingly, particularly in neurosurgery and vascular surgery. Fibrin sealants are particularly advantageous for patients with abnormal haemostasis. Prepared from a combination of fibrinogen (from human plasma) and thrombin (from bovine sources or human plasma), these products also contain Factor XIII (fibrin-stabilising factor), which cross-links the fibrin strands so as to promote wound healing.

In Australia, the fibrin sealant Tisseel®, manufactured by Baxter, is included on the ARTG. Hospitals are required to purchase Tisseel out of their operating budgets. Tisseel is also on the Prostheses List, administered by the Department of Health and Ageing. This register lists the prostheses and human tissue products that attract private health fund benefits, and the amount of benefit to be paid.

Hospitals sometimes constitute fibrin sealants from cryoprecipitate (supplied by the Australian Red Cross Blood Service), which contains fibrinogen: pharmaceutical-grade thrombin is appropriately added to the cryoprecipitate, generally in the context of emergency or major surgical procedures. The blood components used for constituting fibrin sealants in hospitals are subject to regulation by the TGA.

As alternatives to fibrin sealants and platelet gels, synthetic surgical glues provide a new therapy in the field of haemostatic sealants used in surgery to control microvascular bleeding.

Clinical indications for plasma products

Outlined below are the therapeutic uses for each of the plasma derived products currently provided under Australia's national blood arrangements. These products are manufactured in Australia by CSL unless otherwise stated.

Albumin products

Albumex® 4

The function of Albumex 4 (4% albumin solution) is to increase plasma volume.

Albumex 4 may be used when blood volume is low (hypovolaemia), during heart–lung bypass surgery, and in plasma exchange. Hypovolaemia can also occur during shock, after heart–lung bypass surgery, and in patients with multiple organ failure or leaky small blood vessels.

⁸ For further information on the Special Access Scheme, see Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods via the Special Access Scheme*, Therapeutic Goods Administration, Canberra, 2004; also available online at <<http://www.tga.gov.au/docs/pdf/unapproved/sas.pdf>>.

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Albumex® 20

The main function of Albumex 20 (20% albumin solution) is to retain fluid in the bloodstream and to carry biochemical products to the appropriate sites in the body so that they can perform their specific functions.⁹

Albumex 20 may be used when the quantity of protein in the blood is low in an acutely ill patient; for resuscitation of patients in shock due to acute loss of blood or plasma; in the treatment of extensive burns or respiratory distress syndrome; in haemodialysis (for renal failure); in plasma exchange; and for patients with venoocclusive disease resulting from complications of bone marrow transplantation.

Immunoglobulins

Intravenous Immunoglobulin (IVIg)

In general terms, IVIg is a successful clinical strategy for the replacement of immunoglobulins in patients with congenital or acquired immunodeficiency syndromes who are subject to frequent and/or severe infections. IVIg is also used in other situations where there is an increased risk of infection, for example following solid organ or bone marrow transplantation, in surgery, or in the treatment of trauma or burns.

The other major use of IVIg is for immunomodulation in patients with autoimmune disorders of neurological, haematological, dermatological or immunological origin. IVIg is also used as an immunomodulant in solid organ (e.g. kidney) transplants when there is a high risk of rejection of the donor organ, or if acute rejection occurs.

Three IVIg products are provided under Australia's national blood arrangements:

Intragam® P

Intragam P is CSL Limited's Australian-sourced liquid-form IVIg product.

Octagam®

Octagam is an overseas-sourced IVIg product in liquid form, imported in order to supplement supplies of IVIg sourced from Australian-collected plasma. Octagam is manufactured and supplied by Octapharma.

Sandoglobulin®

Sandoglobulin is an overseas-sourced IVIg product in powder form, which CSL Limited supplies, under an arrangement separate to the Plasma Products Agreement, in order to supplement Australia's IVIg stocks. Sandoglobulin is manufactured by CSL Behring, a business unit of CSL Limited.

Normal Immunoglobulin (NIG)

Normal Immunoglobulin (intramuscular immunoglobulin (NIG)) is used to prevent infection by viruses such as poliomyelitis, hepatitis A and measles, in those coming into contact with a source of infection (e.g. family members), or where there is an outbreak of the disease.

⁹ Various natural products of metabolism (e.g. bilirubin) circulate as a complex of metabolite and albumin. Many drugs used for the treatment of disease circulate in the same way – as a complex of the drug and albumin.

CMV Immunoglobulin

CMV Immunoglobulin is used to provide protection against cytomegalovirus (CMV) infection in specific transplant patients and may also help in the treatment of CMV infection. CMV Immunoglobulin donors are selected on the basis that their plasma contains high levels of antibody specific to this virus.

Hepatitis B Immunoglobulin

Hepatitis B Immunoglobulin is used to prevent hepatitis B infection in persons who come into contact with blood or other material suspected of being infected with this disease. This product is also routinely given at birth, 2, 4 and 6 months of age and can be given at other ages for people who have not previously been vaccinated.

Rh(D) Immunoglobulin

Rh(D) Immunoglobulin is given to women who have an Rh(D) negative blood group, in the following circumstances: the product is administered to all Rh(D) negative women during pregnancy, and again after the birth of an Rh(D) positive baby, to prevent a mother generating antibodies to the Rh(D) on the red blood cells of a baby in a future pregnancy. Rh(D) Immunoglobulin is also used when an Rh(D) negative woman of child-bearing age is exposed to Rh(D) positive blood, and in particular is routinely used after termination of pregnancy in Rh(D) negative women.

If a pregnant woman is Rh(D) negative and her baby is Rh(D) positive, the baby's blood is incompatible with that of the mother, and this could cause rhesus haemolytic disease in the baby. This condition is known as Haemolytic Disease of the Newborn (HDN), a form of anaemia requiring exchange transfusions in order to lower levels of bilirubin, which is a breakdown product of haemoglobin. Bilirubin has the potential to cause deafness and mental retardation in an affected infant. In severe cases, HDN can cause severe anaemia, leading to death *in utero* (hydrops fetalis). The antibodies in Rh(D) Immunoglobulin can prevent HDN due to Rh incompatibility.

Tetanus Immunoglobulin IM

Tetanus Immunoglobulin IM, a preparation for intramuscular administration, is used for the prevention of tetanus in persons who have not been immunised within the recommended period and who have suffered an injury that could expose them to the tetanus bacteria.

Tetanus Immunoglobulin IV

Tetanus Immunoglobulin IV is a preparation used in the treatment of tetanus infection and administered intravenously.

Zoster Immunoglobulin

Zoster Immunoglobulin is used for the prevention of chickenpox and shingles in people who are susceptible to virus infection and who come into contact with an infected person. This product is administered in particular to those whose ability to fight infection is weakened, such as people with leukaemia and patients who have had bone marrow transplantation.

Plasma derived coagulant products

Biostat[®]

Biostat is a dried preparation that contains purified and concentrated human Factor VIII, a protein that is essential for normal blood clotting and that circulates in a bound form in plasma, with von Willebrand factor. Factor VIII deficiency is the cause of haemophilia A. Biostat, which contains von Willebrand factor as well as Factor VIII, is administered to people with haemophilia A and to people with the bleeding disorder known as von Willebrand's disease (vWD). It is important to note that Biostat is the only blood product currently available in Australia for the treatment of vWD, which is estimated to affect up to 1% of the population, although mild forms of the condition are by far the most common. Only a minority of people diagnosed with vWD will therefore require treatment with Biostat, but those with the disorder may be administered this product when undergoing surgical or dental procedures.

MonoFix[®]-VF

MonoFIX-VF is a dried preparation containing purified and concentrated Factor IX, a protein essential for normal blood clotting. MonoFIX is used to treat people with haemophilia B (Christmas disease), a bleeding disorder resulting from reduced levels of Factor IX. This product has now been largely replaced by recombinant Factor IX.

Prothrombinex[™]-HT

Prothrombinex-HT is a dried preparation of proteins essential for normal blood clotting. The product mainly contains concentrated Factor IX, together with Factor II and Factor X – proteins that belong to a grouping referred to as human prothrombin complex.

Prothrombinex-HT is used for the prevention and treatment of bleeding in patients with low levels of Factor IX, Factor II or Factor X and is now the recommended clinical strategy when reversal of oral anticoagulant therapy is required as a matter of some urgency.¹⁰

Thrombotrol[®]-VF

Thrombotrol-VF is a dried preparation that contains the protein antithrombin III in a concentrated form. Antithrombin III, normally present in the blood, prevents the extension of blood clots beyond sites of injury.

Thrombotrol-VF may be administered, as a preventive measure, when persons with an inherited deficiency of antithrombin III are pregnant or are about to undergo childbirth or surgery. Such patients may be at risk of a spontaneous thrombosis (blood clot) or a pulmonary embolism (a blood clot that stops blood circulating through the lungs). The risk of these conditions increases with age, and in association with surgery, pregnancy and childbirth.

Ceprotrin[®]

Ceprotrin (protein C concentrate) is used to treat congenital deficiency of protein C, a substance that regulates coagulation and prevents abnormal clot formation (thrombosis). Severe congenital protein C deficiency causes life-threatening blood clotting complications. Ceprotrin, which is manufactured and supplied by Baxter, may also have an important role in the treatment of meningococcal septicaemia, where protein C concentrate may be limb- and life-saving.

Factor VII Concentrate

Factor VII Concentrate is administered to treat Factor VII deficiency, a rare congenital bleeding disorder characterised by spontaneous bleeding episodes in severely affected individuals, and by bleeding following trauma or surgery in mildly affected patients. Factor VII Concentrate is manufactured and supplied by Baxter. This product has been largely replaced by recombinant Factor VIIa (Novoseven®). Novoseven has proved very effective in treating people with haemophilia who have inhibitors and is also a valuable haemostatic agent for use in managing extensive surgical or obstetric bleeding.

Factor XI Concentrates

Factor XI deficiency, also known as haemophilia C, affects about one in 100 000 people and, unlike haemophilia A and B, affects both males and females. CSL Limited supplies BPL Factor XI and Hemoleven®.

Feiba VH® Inhibitor Treatment

FEIBA (Factor Eight Inhibitor Bypass Agent) VH is used in the treatment of bleeding episodes (including those occurring as a result of surgical interventions) experienced by people with haemophilia A or B who have Factor VIII or Factor IX inhibitors respectively.¹¹ Patients with these serious complications of haemophilia can now also be treated quite effectively with recombinant Factor VIIa (Novoseven®). FEIBA VH is manufactured and supplied by Baxter.

Fibrogammin P®

Fibrogammin P (Factor XIII concentrate) is used to treat inherited Factor XIII deficiency. Factor XIII deficiency is a very rare bleeding disorder with an incidence of one case per 2–5 million population, and affecting both males and females. Severe forms of this disorder may cause bleeding from the umbilical stump or cerebral haemorrhage in the newborn, as well as other forms of bleeding. Fibrogammin P is supplied to the Australian market by CSL Limited.

Blood product usage in Australia

While some plasma products are administered only to people with specific conditions, such as severe bleeding disorders, there are other products – for example, albumin and some of the immunoglobulin products associated with the treatment or prevention of particular diseases – that are extensively used in hospitals (e.g. in surgery, childbirth or intensive care). It can therefore be said that everyone is a potential recipient of plasma products.

It has been estimated that in this country there are approximately 5000 people with chronic or inherited conditions who are long-term users of plasma derived products. Some 125 000 Australians use plasma products each year (see table 1.2), and nearly one in three Australians will use a plasma product in his or her lifetime. In addition, as many as 300 000 people receive fresh blood products in Australia each year. As noted earlier, all blood products provided under Australia's national blood arrangements are issued free of charge to recipients.

¹¹ Inhibitors are antibodies that recognise clotting factors administered in factor replacement therapy as 'foreign', and attack and neutralise the Factor VIII or Factor IX that has been introduced to the body. The procedure of administering high doses of clotting factors to 'swamp' these inhibitors is known as tolerisation.

Review of Australia's Plasma Fractionation Arrangements

Table 1.2 Plasma product use in Australia, 2005–06

Plasma derived product	Use	Est. number of patients*
Rh(D) immunoglobulin	Rh negative pregnancy	74 722
IMIg	Prevention of infections	18 200
Albumin	Burns, shock	13 476
Hyperimmune immunoglobulins	Prophylaxis for specific diseases	11 330
IVIg	Immunodeficiency	5 937
Prothrombin complex concentrate	Multiple factor deficiency	2 143
Factor VIII	Haemophilia A; von Willebrand's disease	320
Factor IX	Haemophilia B	25
Antithrombin III	Antithrombin III deficiency	21
Total		126 174

Source: Estimates of patient numbers provided by the Australian Red Cross Blood Service.

* The estimates relate to CSL Limited products produced in Australia. In addition, a number of patients receive imported IVIg, either exclusively or in combination with Intragam® P, and a very small number receive other imported plasma derived products.

Expenditure in Australia in 2005–06 under the national blood arrangements, for all blood products, including plasma derivatives, is detailed in table 1.3.

Table 1.3 Purchase of blood and blood-related products in 2005–06, by supplier

Supplier	Products purchased	Amounts (A\$ millions)
CSL Limited	Plasma products <ul style="list-style-type: none"> • albumin products • immunoglobulin products (including IVIg and hyperimmune products) • plasma derived clotting factors Diagnostic reagent products <ul style="list-style-type: none"> • blood grouping sera • reagent red cell products Defined Blood Products <ul style="list-style-type: none"> • Rh(D) immunoglobulin • Factors XI and XIII • IVIg Standing Offer Management of National Reserve	136.77

Review of Australia's Plasma Fractionation Arrangements

Table 1.3 Purchase of blood and blood-related products in 2005–06, by supplier (cont.)

Supplier	Products purchased	Amounts (A\$ millions)
Australian Red Cross Blood Service	Fresh blood products <ul style="list-style-type: none"> • whole blood • red blood cells • platelets • clinical fresh frozen plasma • cryoprecipitate • buffy coat (white cells) • plasma for fractionation 	297.7
Baxter Healthcare Pty Ltd	Defined Blood Products <ul style="list-style-type: none"> • recombinant Factor VIII • protein C • Factor VII concentrate • Factor Eight Inhibitor Bypass Agent (FEIBA) 	68.47
Wyeth Australia Pty Ltd	Defined Blood Products <ul style="list-style-type: none"> • recombinant Factor IX 	15.87
Novo Nordisk Pharmaceuticals Pty Ltd	Defined Blood Products <ul style="list-style-type: none"> • recombinant Factor VIIa 	23.57
Octapharma Pty Ltd	Defined Blood Products <ul style="list-style-type: none"> • IVIg Standing Offer 	21.98
DiaMed Australia Pty Ltd	Diagnostic reagent products <ul style="list-style-type: none"> • blood grouping sera • reagent red cell products 	0.84
Ortho-Clinical Diagnostics (a Johnson & Johnson Company)	Diagnostic reagent products <ul style="list-style-type: none"> • blood grouping sera • reagent red cell products 	0.17
Australian Laboratory Services Pty Ltd	Diagnostic reagent products <ul style="list-style-type: none"> • blood grouping sera • reagent red cell products 	0.03
Total purchases of blood and blood products		565.40

Source: National Blood Authority, *Annual Report 2005–06*, National Blood Authority, Canberra, 2006, pp. 29–30.

Note: All amounts exclude GST.

Review of Australia's Plasma Fractionation Arrangements

Table 1.4 lists the unit prices of the preparations supplied by CSL Limited under the Plasma Products Agreement; in terms of volume and expenditure, these account for the bulk of plasma products available in Australia. The role of the Australian Red Cross Blood Service as Australia's collector of plasma for fractionation is funded separately, under the arrangements between the NBA and the ARCBS, and the plasma product prices recorded in table 1.4 therefore do not reflect the costs associated with plasma collection and delivery to the fractionator.

Table 1.4 Prices of plasma products supplied by CSL Limited, 2005

Product	Unit size	Final price (A\$, excl. GST)	Final price (A\$, incl. GST)
Albumex® 20	10 mL	12.17	13.39
Albumex® 20	100 mL	44.30	48.73
Albumex® 4	50 mL	12.17	13.39
Albumex® 4	500 mL	44.30	48.73
Intragam® P	50 mL	171.60	188.76
Intragam® P	200 mL	686.40	755.04
Biostate®	250 IU	137.80	151.58
MonoFIX®-VF	500 IU	353.60	388.96
Prothrombinex™-HT	500 IU	404.04	444.44
Thrombotrol®-VF	1000 IU	1154.40	1269.84
CMV Immunoglobulin	30 mL	1029.11	1132.02
Hepatitis B Immunoglobulin	100 IU	37.61	41.37
Hepatitis B Immunoglobulin	400 IU	86.11	94.72
Normal Immunoglobulin	2 mL	27.09	29.80
Normal Immunoglobulin	5 mL	44.40	48.84
Rh(D) Immunoglobulin	250 IU	25.48	28.03
Rh(D) Immunoglobulin	625 IU	63.70	70.07
Tetanus Immunoglobulin IM	250 IU	37.18	40.90
Tetanus Immunoglobulin IV	4000 IU	594.88	654.37
Zoster Immunoglobulin	200 IU	235.87	259.46

Source: *Plasma Products Agreement* [edited version for publication on NBA website], National Blood Authority, Canberra, 2004, p. 92, <<http://www.nba.gov.au/PDF/PPA%20for%20web.pdf>>.

Note: Prices specified are subject to indexation at the rate of 1.75% per annum, with indexation taking effect on 1 July 2006 and on the first day of each financial year thereafter for the duration of the Agreement.

Review of Australia's Plasma Fractionation Arrangements

Australia's total annual consumption of and expenditure on plasma products under the national blood arrangements is monitored at the jurisdictional level and, as indicated in table 1.2, numbers of recipients can be estimated. Yet, it is difficult – because of the degree of variation on a case-by-case basis – to derive a meaningful 'average' or 'typical' quantity, or cost, with respect to a product used to treat individual patients with a specific medical condition. Furthermore, while some patients with chronic or inherited disorders require ongoing treatment with a plasma product, certain hyperimmune products may be administered on a single occasion in a person's lifetime.

Table 1.5 Estimated use of and expenditure by Governments on CSL Limited plasma products in Australia, 2005–06

Plasma derived product	Use	Est. number of patients*	% of total plasma product recipients	Est. cost to govts for fractionated products supplied by CSL (A\$)†	Amount per product as % of total expenditure	Average est. cost per patient per annum (A\$)‡
Rh(D) immunoglobulin	Rh negative pregnancy	74 722	59.22	5 474 123	4.51	73
IMIg	Prevention of infections	18 200	14.42	752 921	0.62	41
Albumin	Burns, shock	13 476	10.68	10 504 698	8.66	780
Hyperimmune immunoglobulins	Prophylaxis for specific diseases	11 330	8.98	3 971 502	3.27	351
IVIg	Immunodeficiency	5 937	4.71	81 959 763	67.55	13 805
Prothrombin complex concentrate	Multiple factor deficiency	2 143	1.70	5 380 601	4.43	2 511
Factor VIII	Haemophilia A; von Willebrand's disease	320	0.25	8 748 922	7.21	27 340
Factor IX	Haemophilia B	25	0.02	3 462 098	2.85	138 484
Antithrombin III	Antithrombin III deficiency	21	0.02	1 070 129	0.88	50 959
Totals		126 174	100.00	121 324 757	100.00	962

* Estimates of patient numbers provided by the Australian Red Cross Blood Service.

† Adapted from data on expenditure held by the Department of Health and Ageing. These figures for expenditure by Australian governments on the supply of fractionated products do not represent the overall amount of funding provided to CSL Limited in 2005–06, as the cost of managing reserve products is not included.

‡ These are per capita averages only and *do not* reflect actual clinical usage and costs. The case studies later in this chapter provide more information on the variables associated with clinical use of plasma products.

Review of Australia's Plasma Fractionation Arrangements

It is possible to generate in the first instance an extremely general figure for average overall expenditure on plasma products per patient per annum: a figure in the order of A\$1000 is derived from the ratio of annual expenditure on products supplied under the PPA (approximately A\$120 million), to the number of recipients of plasma products (approximately 125 000).

In considering these figures, it is again important to note that actual clinical use is very specific to the physical and medical circumstances of individual patients. For example, the treatment regime for a person with a clotting factor deficiency is dependent on several variables, including:

- dosage – corresponding either to the person's age and weight (for patients who have not reached physical maturity) or to the person's plasma volume (for adults)
- severity of condition (severe, moderate or mild)
- severity and nature of bleeding
- any surgical procedures that the patient undergoes
- frequency of treatment (whether on a regular basis, for prophylaxis, or intermittent – prophylactic treatment for haemophilia A and B typically requires about three times the amount of product as is used in treatment on demand, and can cost in the order of A\$100 000–\$150 000 per patient per annum; there are long-term savings, however, in regard to joint sequelae).

Attempts to obtain an average cost per person per annum are further complicated in the case of IVIg by the many clinical indications for which a product may be a beneficial therapy. There are varying regimes for IVIg, in terms of frequency and strength of dosage, as well as duration of treatment, with these factors also depending on individual patient circumstances and variations in clinical practice (see Case Studies below).

The price of a product, moreover, does not give the complete picture of expenditure on treatment, particularly when hospitalisation is required. While some preparations are self-administered, others are provided in hospital or in same-day clinical care settings, with resulting implications for the costs of an episode of care. (These costs, aside from the costs of plasma products, are outside the scope of the national blood arrangements.) Co-morbidities (medical conditions requiring simultaneous treatment) must also be considered: for example, albumin tends to be administered in conjunction with other therapies and medical procedures. For these reasons, an attempt to assess the full cost of treatments in which plasma products are used becomes problematic.

It is likely that these difficulties are the reason that assessments of per capita consumption of products (assessments that often include comparisons between Australia's health systems and comparable systems overseas), and not of the cost of individual treatment episodes, tend to be used in planning and forecasting exercises with respect to the provision of blood and plasma products.

Case studies

Estimated costs associated with the following case scenarios reflect only the price of the plasma product prescribed (excluding costs of plasma collection by the Australian Red Cross Blood Service) and do not account for other costs, such as the full cost of hospitalisation, the financial impact of time away from work, impact on family, and costs arising from adverse outcomes (e.g. central venous line infections).

Indirect cost savings ensuing from treatment are difficult to quantify but can include savings associated with a reduction in acute hospital admissions and a reduction in disease-related side effects. Increased quality of life, as a result of treatment, can mean social benefits both for patients and for their families.

Case study 1

Immunomodulatory therapy: Adult Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

IVIg is used for many conditions where the aim of therapy is to prevent the immune system from damaging important parts of the body in patients with the so-called autoimmune conditions. People tend to consider autoimmune conditions in terms of the area of the body most affected, but the underlying problem lies with the balance of the immune system, so that the most sensible treatments are those directed at the immune system itself. This is why IVIg, which is an immunomodulator (an agent that augments or diminishes immune responses), is used to treat a collection of diverse conditions that do not appear at first glance to be related to one another.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is one of the key autoimmune conditions. In this disorder, there is a sustained autoimmune attack on the myelin sheath surrounding the nerves, resulting in abnormal sensation and in motor weakness. The outcome for the patient may be great disability but the manifestations can vary greatly from one person to another, and for any particular individual may fluctuate with time. Neurologists caring for CIDP patients need to design their therapies according to patients' individual needs.

IVIg may be very effective at blocking an autoimmune attack on nerves, but therapy may have to be sustained for many months or even for years.

Clinical scenario

Janet is a 42-year-old lawyer and the mother of two children. Four weeks after a moderate viral infection of the upper respiratory tract, she develops numbness, burning in the limbs and difficulty walking, but she recovers without treatment.

Several weeks later a further attack occurs. Janet's symptoms become so severe that she is unable to walk and requires assistance with showering. She is referred to a neurologist, who carries out nerve conduction and cerebral spinal fluid studies, takes X-rays and performs a nerve biopsy. Findings are suggestive of CIDP.

The neurologist prescribes IVIg (Intragam® P), to commence at 0.4 g/kg for five consecutive days, followed by an initial maintenance strategy of one infusion at 0.4 g/kg per month for three months. Janet weighs 65 kilograms.

Janet experiences prompt improvement in her symptoms and she is able to return to work. In the week before her second IVIg treatment, however, her symptoms worsen

Dose requirements and cost

	Initial treatment	Current maintenance	Proposed maintenance
Dose	0.4 g/kg x 65 kg = 26 g per dose for 5 consecutive days	0.4 g/kg x 65 kg = 26 g per dose – 12 doses per year	0.4 g/kg x 65 kg = 26 g per dose – 17 doses per year
Volume	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g
Cost	2 x \$755.04 plus 1 x \$188.76 = \$1698.84 per daily dose Total (5 doses) = \$8494.20*	2 x \$755.04 plus 1 x \$188.76 = \$1698.84 per monthly dose Total (12 doses) = \$20 386.08*	2 x \$755.04 plus 1 x \$188.76 = \$1698.84 per three- weekly dose Total (17 doses) = \$28 880.28*

Initial treatment plus current maintenance treatment = \$28 880.28 per annum

Initial treatment plus proposed maintenance treatment = \$37 374.48 per annum

* Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

once again. Her neurologist recommends continuation of the maintenance infusions, but at a frequency of once every three weeks.

Qualifier: The individual dosage for IVIg depends on a patient's responsiveness to the therapy, and the dose could potentially be increased during the course of treatment.

Case study 2

Replacement therapy

Primary immune deficiency (PID)

Common variable immunodeficiency (CVID)

There are more than 150 different types of primary immunodeficiencies. These are disorders where an individual is born with defects in the immune system that prevent normal defence against infection. Primary immunodeficiencies range in severity from rare, fatal diseases in childhood to relatively common disorders of adulthood, all of which are characterised by the failure of normal antibody responses. Typically, adult patients develop severe and recurrent bacterial infections of the lungs and sinuses, which over time lead to chronic lung damage and bronchiectasis.

Immunoglobulins function as antibodies. Therefore IVIg gives doctors the opportunity to prevent infections and long-term damage in these patients. The disease termed 'common variable immunodeficiency' (CVID) is the single largest user of IVIg in Australia. Treatment, which is continued monthly and is lifelong, is impressively effective, returning many patients to normal lives.

Dose requirements and cost

Current maintenance	
Dose	0.4 g/kg x 80 kg = 32 g per dose – 12 doses per year
Volume	Treatment dose: 3 x 12 g bottle = 36 g
Cost	3 x \$755.04 = \$2265.12 per monthly dose*
Maintenance treatment = \$27 181.44 per annum	

*Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

Clinical scenario

Clyde is a 37-year-old bus driver. From the age of nine he experienced recurrent episodes of middle ear infection, requiring grommets. Throughout his high school years he was, in his own words, 'constantly' on antibiotics for ear, and sinus, infections, and he has had two operations to clear his sinuses. At age 17 he developed severe pneumonia, requiring admission to intensive care, but he recovered with the aid of antibiotics. By age 21 he was coughing up infected phlegm every day, and by his early thirties was experiencing shortness of breath when climbing stairs. He has started to have long absences from work.

A respiratory physician detects early bronchiectasis via a CT scan of Clyde's chest, and measures antibody levels in his blood. When these are found to be low, Clyde is referred to an immunologist, who is able to confirm a profound defect in antibody production, consistent with CVID. IVIg (Intragam P) is commenced immediately. Within two months of beginning this therapy, Clyde is free of infections for the first time he can remember. More gradually, his breathing returns to normal, although he remains at risk of pneumonia, due to the chronic scarring in his lungs.

Clyde, who weighs 80 kilograms, begins treatment with an IVIg dose of 0.4 g/kg, or 32 g, per month by infusion.

Case study 3

Immunomodulatory therapy: Paediatric Kawasaki disease

Kawasaki disease is an uncommon illness that occurs mainly in preschool-aged children. The incidence of the disease is 15 per 100 000 children (US figures). It occurs more frequently in the Japanese population. Although rare, Kawasaki disease tends to occur with seasonal peaks.¹² Its cause is currently not known but it is thought to be a severe abnormal immune response to infection. The result is inflammation of blood vessels (vasculitis), all over the body. When vasculitis affects important organs such as the heart, severe complications and death may follow. There is no simple diagnostic test for this condition, but the clinical challenge is to identify patients early (as Kawasaki disease may easily be confused with other illnesses, including simple viral infections), and to intervene quickly with IVIg to prevent

12 The 2004–05 and 2005–06 annual reports of the Australian Institute of Health and Welfare did not report on the incidence of Kawasaki disease in Australia, and it is therefore difficult to determine incidence with any accuracy.

Dose requirements and cost

Current maintenance	
Dose	2 g/kg x 20 kg = 40 g
Volume	3 x 12 g bottle and 1 x 3 g bottle = 39 g
Cost	3 x \$755.04 plus 1 x \$188.76 = \$2453.88*
Total IVIg treatment cost = \$2453.88	

* Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

cardiovascular and other complications. The timely use of IVIg can also reduce the length of hospitalisation required.

IVIg therapy is particularly useful in the paediatric age group, for two main reasons: first, with the body size of the patient so much smaller, the doses required are much less than those needed in order to achieve the same effect in adults; and second, alternative immunosuppressive therapies may have very undesirable long-term side effects in young people. The treatment of Kawasaki disease provides an excellent example of how IVIg is used in paediatrics.

Clinical scenario

Jonathon is a four-year-old boy who presents to hospital with high fever, rash, swollen lymph glands, cherry-red lips and eyes, and redness and swelling of the hands. A diagnosis of Kawasaki disease is made and Jonathon, who weighs 20 kilograms, is prescribed aspirin and IVIg 2 g/kg (Intragam P) as a single dose over 12 hours.

Case study 4

Clotting factor deficiency

Von Willebrand's disease (vWD)

Von Willebrand's disease (vWD) is an inherited autosomal dominant disorder characterised by a deficiency of von Willebrand factor, a highly complex plasma protein. The functions of von Willebrand factor are to enable the adherence of platelets to areas of blood vessel wall damage and to carry the anti-haemophilic clotting factor Factor VIII.

Von Willebrand's disease may affect as many as 1% of the population, but in the great majority of cases is very mild, and is frequently diagnosed only after severe trauma or major surgery. There are three types of vWD: types I, II and III. Type III is the rarest but most severe form of the condition. The disease affects both sexes, and in contrast to haemophilia has more clinical consequences in females than in males.

The fractionated plasma product Biostat® contains both von Willebrand factor and Factor VIII, and is used for the treatment of bleeding episodes in severe cases of vWD. It is to be noted that recombinant Factor VIII is not effective in treating vWD as the recombinant form does not contain von Willebrand factor.

Dose requirements and cost

Current maintenance	
Dose	30 units Factor VIII/kg x 50 kg = 1500 units per dose for first 3 days of monthly menstrual period
Volume	Treatment dose: 6 x 250 unit vial = 1500 units
Cost	6 x \$151.58 = \$909.48 per daily dose* 3 x \$909.48 = \$2728.44 per monthly dose*
Maintenance treatment = \$32 741.28 per annum	

*Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

Clinical scenario

A 12-year-old girl, Sarah, is referred by her general practitioner to a gynaecologist because of heavy and irregular menstruation. There is a family history of menorrhagia, and of hysterectomy for menorrhagia in young relatives. Sarah has had frequent nosebleeds and bruises easily. Her gynaecologist suspects a congenital bleeding disorder, and orders blood investigations, which establish the diagnosis of severe vWD, type I.

Sarah and her parents are given the choice of hormone replacement therapy to suppress her periods, or infusions of Biostate at the beginning of and during menstruation. The family are very concerned about the side effects of hormone replacement therapy and choose treatment with Biostate.

Sarah is referred to a clinical haematologist, who is to decide on the frequency and dose of Biostate. The haematologist finds that in addition to vWD she has iron deficiency anaemia, due to her severe blood losses, and prescribes treatment with oral iron tablets to correct the iron deficiency. At the visit to the haematologist, Sarah weighs 50 kilograms.

The haematologist arranges for infusions of Biostate, in a dose of 30 units of Factor VIII/kg (a total dose of 1500 units of Factor VIII) each day for the first three days of the patient's menstrual period. The dose calculation is based on the Factor VIII content of Biostate, since it is known that the amount of von Willebrand factor closely parallels that of Factor VIII in the product. (The ratio of von Willebrand factor to ristocetin co-factor is 2:1.)¹³ In addition, the haematologist prescribes an antifibrinolytic oral medication, to enhance the bleeding control effect of Biostate.

There are a variety of ways of measuring responses to Biostate therapy. Perhaps the most common is to measure a patient's levels of Factor VIII after therapy. Clinical response may also be used as a measure of success of therapy. If, in the present case, abnormal bleeding were to persist, the dose of Biostate could be increased incrementally, to as much as 60 units of Factor VIII/kg.

¹³ Biostate product information.

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The patient will continue her treatment with Biostate into early adult life or until she becomes sexually active, at which time her treatment could change to hormone replacement therapy, boosted, if required, by occasional Biostate infusions.

In conclusion, under Australia's national blood arrangements three main types of plasma products – albumin, immunoglobulins and clotting factors – are provided to Australian patients. These products are used to treat or prevent a diverse spectrum of conditions, with varying levels of incidence. Administration of plasma products takes place in various clinical care settings.

Intravenous immunoglobulin (IVIg), in particular, is notable for its association with a very broad range of clinical indicators, across immunological, neurological, haematological and transplant situations. IVIg is by far the main driver of demand for plasma products in Australia and worldwide. On the other hand, there are a number of products that are used solely for the treatment of single, specific conditions. In terms of the treatment of individual recipients with a given product, there are considerable variations in usage patterns, dosage and frequency of dosage administration.

These issues present challenges from the point of view of managing plasma product supply and predicting demand. Demand and supply trends will be addressed at length in subsequent chapters.

Chapter 2

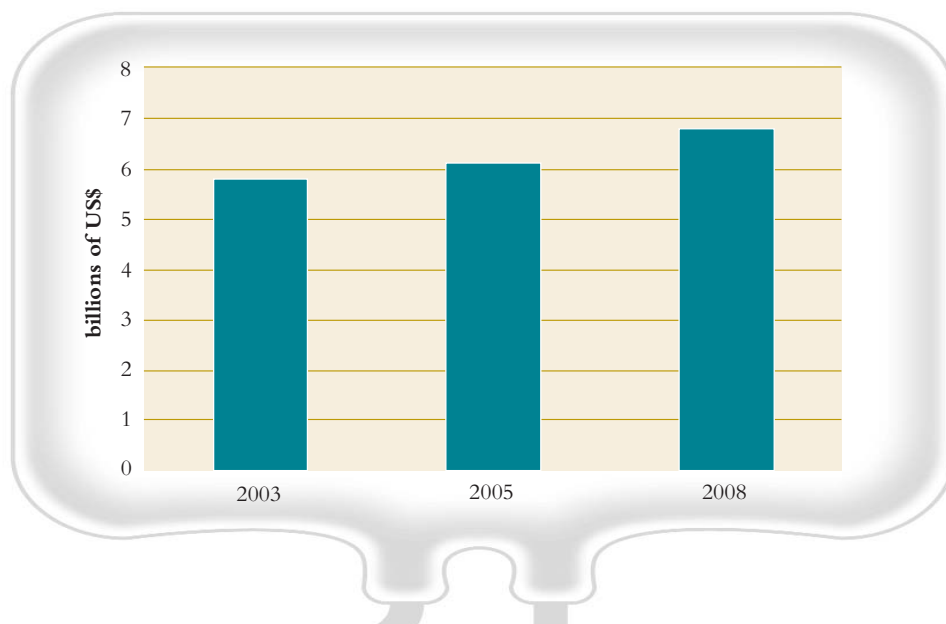
Global demand for plasma products

The global plasma market exceeds US\$6.9 billion and is both very dynamic and highly complex. The market overall is driven by the United States and Europe, specifically with respect to intravenous immunoglobulin (IVIg), but China, Brazil and other countries are major drivers for products such as albumin and plasma derived Factor VIII.

The market for plasma products grew by about 5% between 2003 and 2005 and is forecast to increase by a further 11.5% between 2005 and 2008 (fig. 2.1).

Products expected to experience significant growth in the immediate future are IVIg, alpha-1 antitrypsin, fibrin sealants, and minor coagulant products. In March 2006, Mr Jan Bult, President of the Plasma Protein Therapeutics Association, made the following points to the annual International Plasma Protein Congress in Prague: demand for IVIg is growing globally at 3–5% per annum; once-large albumin inventories have been depleted; plasma derived Factor VIII is being used to a greater extent in the treatment of people who have developed inhibitors in response to recombinant products; demand for von Willebrand factor is increasing strongly; and in the past two years in the United States there has been a 25% increase in demand for treatment of people with emphysema and alpha-1 antitrypsin deficiency.¹

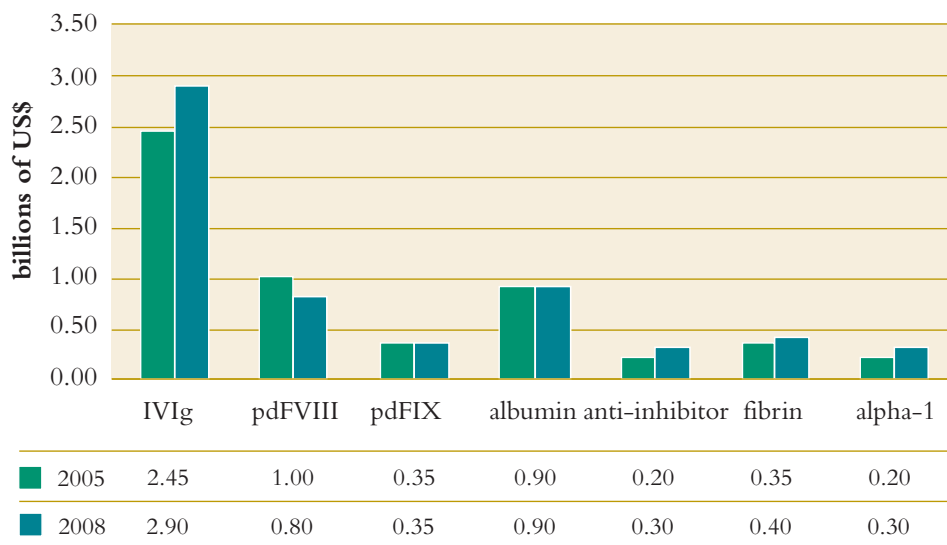
Fig. 2.1 Projection of global sales of plasma products



Source: Derived from Marketing Research Bureau data, and from data in Baxter Healthcare Pty Ltd submission to Plasma Fractionation Review, 2006.

¹ Jan Bult, 'Market and Industry Developments', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

Fig. 2.2 Global demand for plasma derived products, 2005 and 2008



Source: Derived from Marketing Research Bureau data, 2005.

Research undertaken by consultants engaged for the Review indicates that albumin sales are forecast to remain static in the period 2005–08, while sales of plasma derived Factor VIII and Factor IX will decline in favour of sales of recombinant alternatives (fig. 2.2).

IVIg has been for some time the high-growth product within the plasma derived product sector, at both a global and an individual country level.

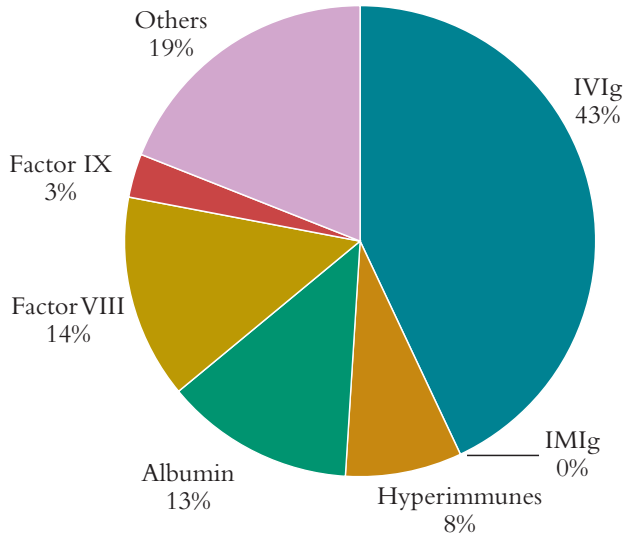
At the global level, this trend continues for IVIg because other contenders (i.e. albumin and clotting factors) have been subject to marketplace changes that have limited their expansion. In the case of albumin, there has been debate about the relative merits of this product when compared with alternatives such as normal saline. Only after the publication in 2004 of scientific evidence that reaffirmed albumin’s value as a therapeutic agent in trauma care, have sales begun to recover.² China in particular is importing increasing quantities of albumin.

In the area of clotting factors, recombinant technology has diminished the potential for plasma derived products to lead global market growth. There seems little prospect, however, that a recombinant IVIg will be available in the foreseeable future to challenge the market leadership position of plasma derived IVIg.

Figure 2.3 shows the estimated shares of the global market held by the various plasma products in 2005–06.

2 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. This study is widely referred to as the SAFE Report.

Fig. 2.3 Global plasma products market, by product share (US\$6.933 bn)



Source: Adapted from Marketing Research Bureau data supplied October 2006.

The demand for and supply of plasma derived products is closely bound up with global fractionation capacity, which is influenced not only by demand and supply factors, but also by the economic and regulatory environment.

In the late 1990s and early 2000s, the fractionation industry in the United States was subjected to a number of regulatory interventions, leading to the temporary closure of some plants. The resulting downturn in product supply led directly to price inflation, followed by a period of reinvestment undertaken with a view to increasing production.

This series of factors culminated in over-capacity and a downward price spiral, compounded by the increasing market impact of recombinant products (see Chapter 3).

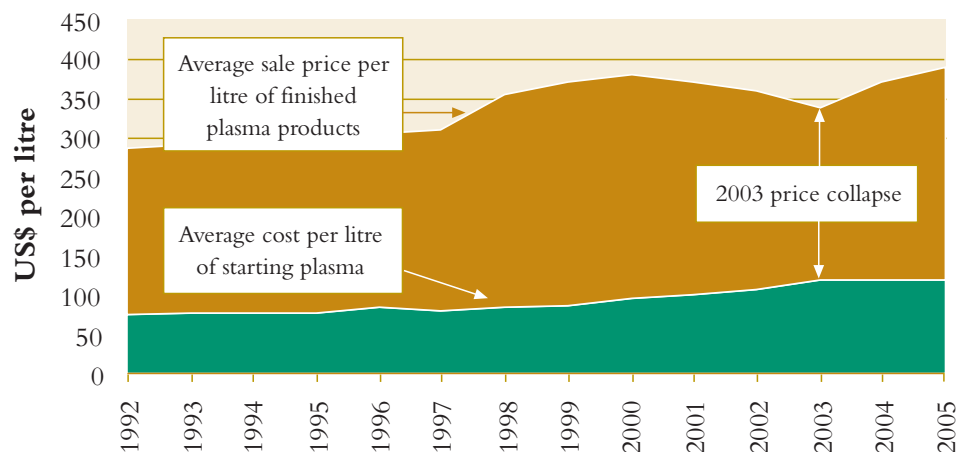
By 2004, the US market had come back into balance, with this shift leading to steadily increasing prices and renewed demand pressures.

Figure 2.4 shows the impact of these various events upon the average global cost per litre of starting plasma and, more significantly, upon the variation in the average global price per litre of finished plasma products.

The fluctuations in the world's largest market caused flow-on effects globally, opening the way for a series of rationalisations and takeovers. The result has been a global industry that is fundamentally different from the industry as it existed in earlier periods.

The effects of these various events can be seen in figures 2.5–2.8, which map historical volumes and trend projections for individual plasma products.

Fig. 2.4 Starting plasma cost per litre and sales per litre



Source: Derived from data in: Jan Bult, 'Market and Industry Developments', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

Projected demand for principal plasma products

Intravenous immunoglobulin (IVIg)

A projected trend out to the year 2016, with respect to the global demand for intravenous immunoglobulin, is set out in figure 2.5. The trend is based on historical demand figures dating from 2000 onwards and suggests an increase in demand of 5.1 tonnes annually for the period 2006–16.

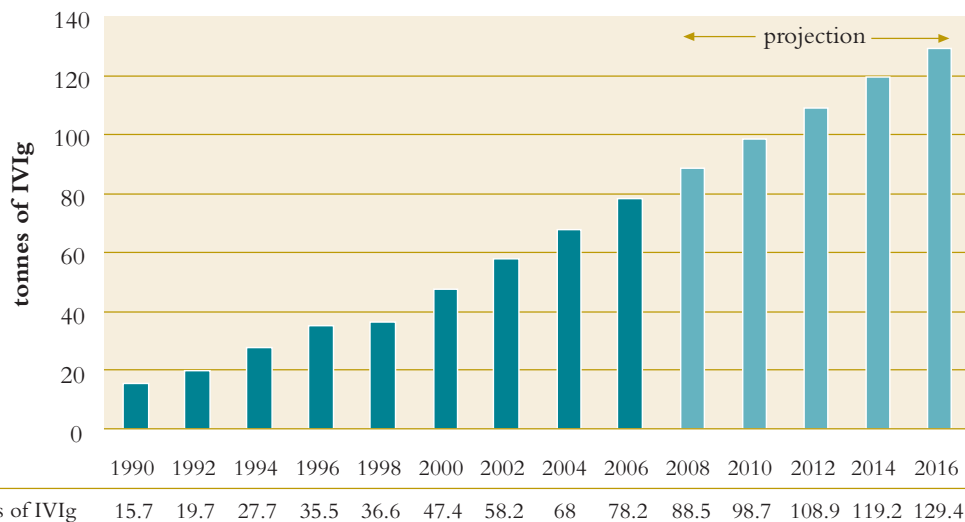
The projected trend takes account only of factors that are already embedded in the historical figures. The use of IVIg for new indications, changes in clinical practice, or the expansion of use into new markets, could generate demand beyond the levels projected here. It is important to note that there is no international consensus on expected growth rates for IVIg.³

As table 2.1 indicates, rates of IVIg consumption across the various markets are by no means uniform.

The reasons for the substantial differences in consumption rates between countries are not clear, but relate to differences in clinical practice, the presence or absence of price signals at prescriber level, and/or funding levels for health services.

³ See National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 25; also available online at <<http://www.nba.gov.au/pubs.htm>>.

Fig. 2.5 Intravenous immunoglobulin (IVIg) actual global consumption and projection



Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

Table 2.1 International usage rates for IVIg, 2005

Country/province	Usage rate (g/1000 population)
Quebec	126
United States	105
Canada	92
Sweden	81
Australia	73
Austria	67
Belgium	67
France	47
New Zealand	46
Italy	40
United Kingdom	39
Germany	38
Netherlands	35
Japan	28
China	3

Source: National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 24; also available online at <<http://www.nba.gov.au/pubs.htm>>.

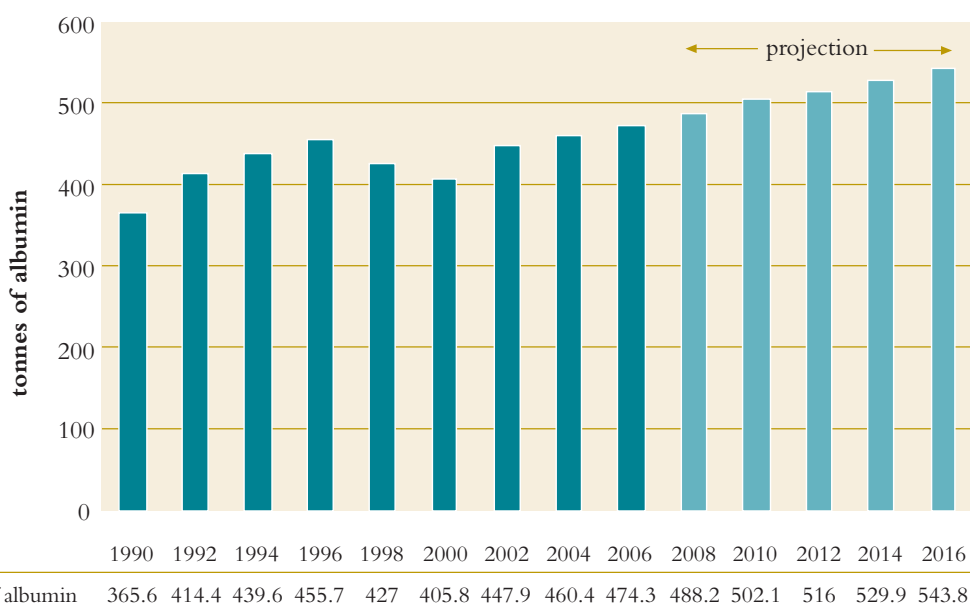
Albumin

The use of albumin globally has in recent years been significantly influenced by two reports. The Cochrane Report, published in 1998, suggested that the product may be associated with higher levels of mortality when compared with alternatives such as glucose or saline.⁴ This finding caused a material decline in albumin usage. The publication in 2004 of the SAFE Report, which concluded that albumin was as safe as alternatives and could be used with confidence,⁵ stimulated a recovery in albumin sales.

Figure 2.6 shows that the level of demand for albumin has not been increasing at the same rate post-2004. In the development of the forward trend projection, all figures prior to those for 2004 have been excluded, so as to remove the effects of the demand decline and subsequent recovery.

It is possible that the global demand trend for albumin will become steeper as developed and developing countries increase clinical usage. As noted earlier, China, in particular, is importing increasing quantities of albumin.

Fig. 2.6 Albumin actual global consumption and projection



Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

4 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.

5 See note 2 above.

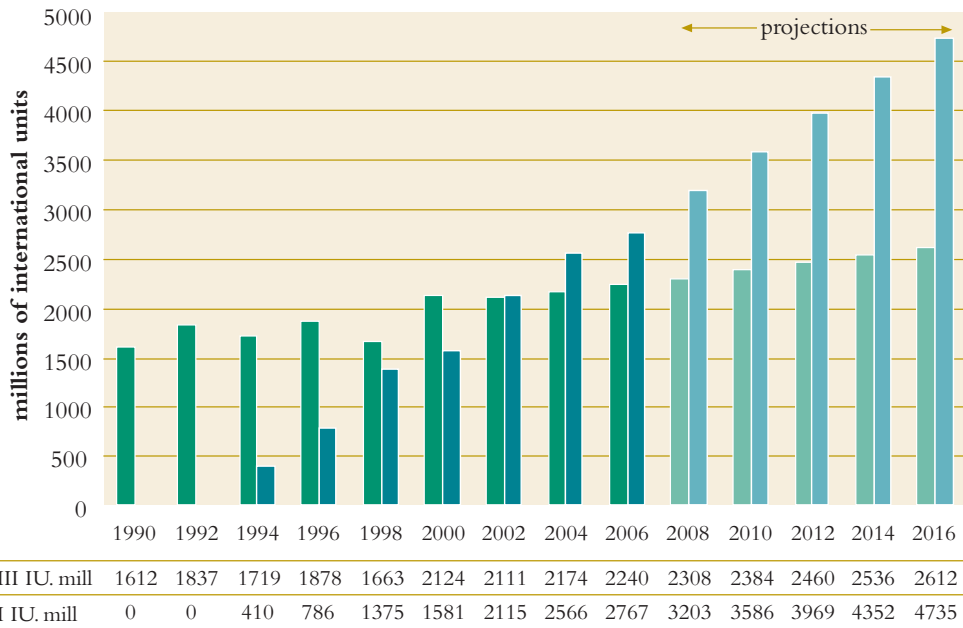
Factor VIII

From the late 1960s to the mid 1990s, plasma derived Factor VIII was the driving product for plasma fractionators. In the early 1990s, however, recombinant forms of the product started to become available in developed markets. The market dynamics that ensued are indicated in figure 2.7.

Contrary to some expectations, demand for plasma derived Factor VIII has continued to grow (albeit at a slower rate than the recombinant form). There are a number of factors at work, including different countries’ varying rates of conversion from plasma derived to recombinant products, differing clinical practices and preferences, and the emergence of immune tolerance and inhibitor issues for some patients treated with the recombinant form.

The trend projection for plasma derived Factor VIII shows an annual growth expectation of approximately 75 million units per year from 2008 onwards. At the same time, the demand for the recombinant form is projected to increase by approximately 400 million units annually from 2008.

Fig. 2.7 Plasma derived and recombinant Factor VIII actual global consumption and projections



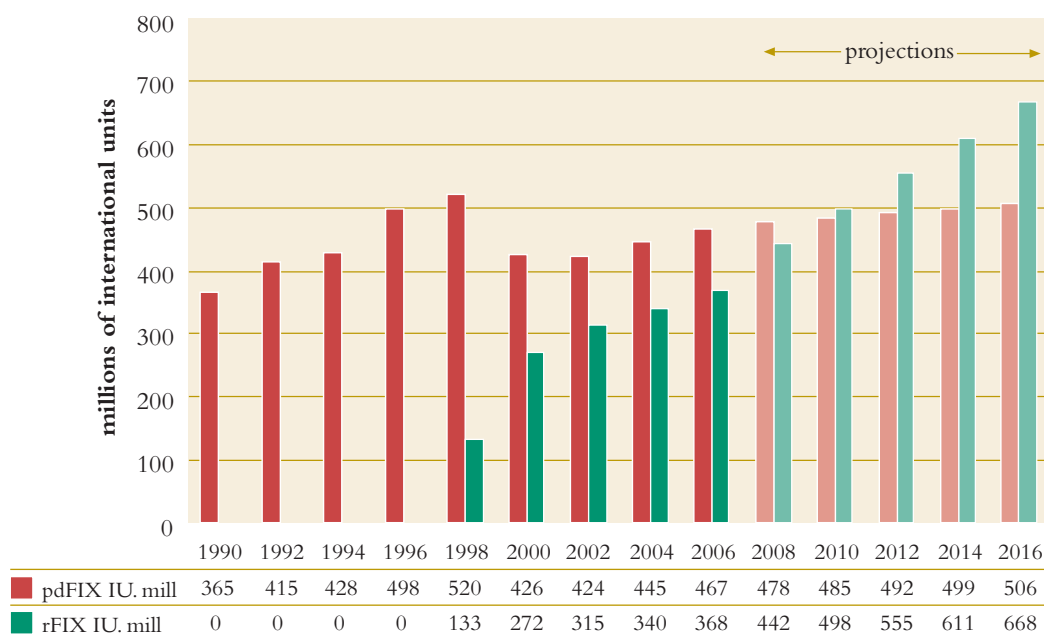
Source: Derived from data in: Patrick Robert, ‘Market Statistics and Trends’, paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

Factor IX

By 2002, demand for recombinant Factor IX had similarities with that for recombinant Factor VIII. The patterns of subsequent change, however, as seen in figure 2.8, are quite different.

The introduction of recombinant Factor IX followed the introduction of recombinant Factor VIII by approximately four years. It is not expected that demand for the recombinant form of Factor IX will exceed that for the plasma derived form until 2010. However, while demand for plasma derived Factor IX is expected to increase marginally, by approximately 7 million units per year, from 2008 onwards, demand for the recombinant analogue is likely to increase by approximately 57 million units annually from 2008.

Fig. 2.8 Plasma derived and recombinant Factor IX actual global consumption and projections



Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

Demand for other plasma derived products

Intramuscular (normal) immunoglobulin (IMiG)

Global use of intramuscular immunoglobulin (IMiG) has been affected by the advent of hepatitis A vaccines. The future demand for IMiG is uncertain, because of emerging factors such as the increased propensity, given its suitability for self-administration, to use this immunoglobulin as an alternative to IViG (a positive factor); the increasing use of subcutaneous immunoglobulin (SCiG), instead of IMiG, in self-administration regimes (a negative factor); and the increasing use of hepatitis A vaccines (a negative factor).

Hyperimmune immunoglobulins

Hyperimmune immunoglobulins are highly specialised products for use in the control of specific infectious diseases and in the treatment of, and prophylaxis with regard to, anti-D in pregnancy. Apart from demand for Rh(D) immunoglobulin, the global requirement for hyperimmunes is at a comparatively low level, as the incidence of diseases such as tetanus and cytomegalovirus infection has become less pronounced in developed countries. Relatively few manufacturers are involved in the production of these low-volume, high-value products, which depend on the collection of starting plasma from small cohorts of donors with specific antibody profiles.

Factor XI, Factor XIII and Factor Eight Inhibitor Bypass Agent (FEIBA)

Factor XI, Factor XIII and Factor Eight Inhibitor Bypass Agent (FEIBA) are used to treat relatively rare bleeding disorders. The small global demand is met by the few manufacturers, predominantly not-for-profit fractionators, that produce Factor XI and Factor XIII, and by the one commercial fractionator that produces FEIBA.

Alpha-1 antitrypsin

Alpha-1 antitrypsin is a relatively new product of plasma fractionation and is being used increasingly to treat chronic respiratory disease. Demand is presently concentrated in the United States. It is expected, however, that demand will spread, and that usage levels will increase in future years.

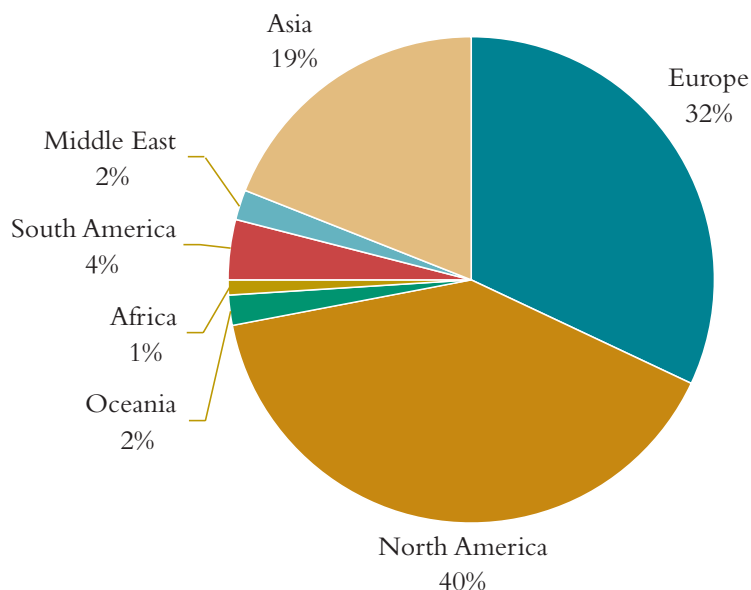
Fibrin sealants

Demand for fibrin sealants, which are used in place of suturing to seal surgical and other wounds, is largely concentrated in the United States.

Demand by region

The demand for plasma derived products (and indeed for recombinant alternatives) is centred on North America and Europe. Figure 2.9, a diagram developed from Marketing Research Bureau data, shows the shares of the total global market accorded to each of seven regions, on the basis of the value of product acquired.

Fig. 2.9 Global plasma products market, by region (US\$6.933 bn)



Source: Derived from Marketing Research Bureau data supplied October 2006.

Global supply

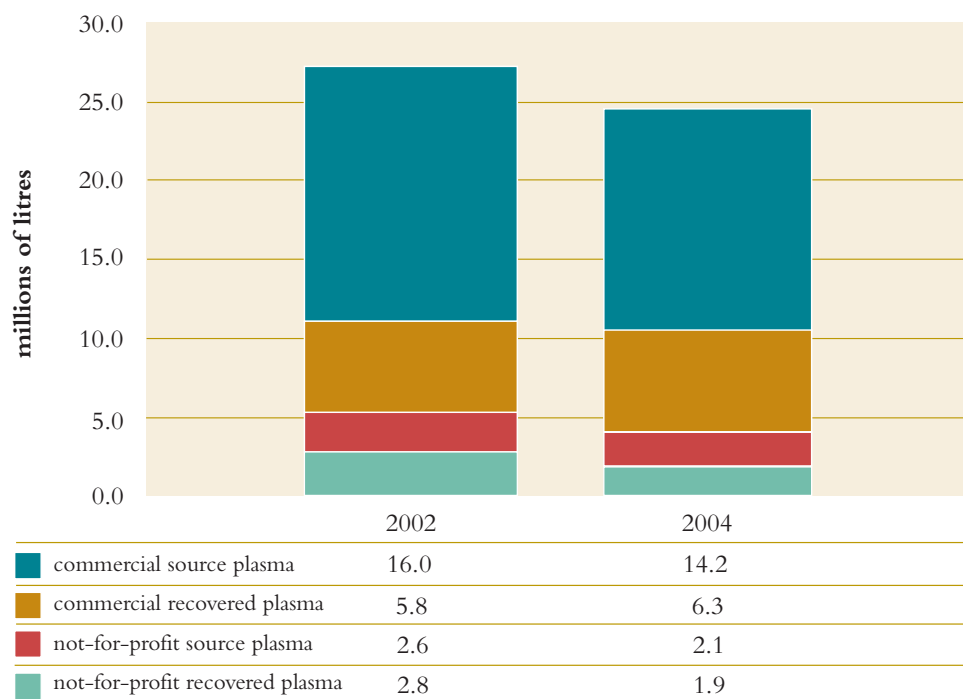
In 2004, the commercial plasma fractionation sector processed 20.5 million litres of plasma, comprising 14.2 million litres of source plasma and 6.3 million litres of recovered plasma. In 2002, the quantities were: 21.8 million litres in total, and 16.0 million litres and 5.8 million litres respectively for source and recovered plasma.

The not-for-profit sector fractionated 4.0 million litres of plasma, comprising 2.1 million litres of source plasma and 1.9 million litres of recovered plasma, in 2004. The figures for 2002 were: 5.4 million litres in total, and 2.6 million litres and 2.8 million litres for source and recovered plasma respectively (fig. 2.10).

The decline in throughput shown here for the period 2002–04 is consistent with the industry rationalisation discussed earlier. Given these circumstances, the question must arise as to how demand for IVIg (which draws on 100% of all fractionated plasma) was met over this period, when there was a reduced throughput of starting plasma. The answer is that steadily improving yields were being achieved, as a result of less wastage, increased batch sizes, and technological improvements in the area of processing. These three factors have contributed to a leaner, more efficient, global industry, which is producing more IVIg from less plasma.

The average capacity of individual fractionation plants worldwide has increased in recent years as a consequence of industry consolidation. Table 2.2 illustrates this point.

Fig. 2.10 Volume of plasma fractionated by commercial and not-for-profit sectors, 2002 and 2004



Source: Derived from data in: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, Marketing Research Bureau, Orange, CT, 2005, p. 9.

Table 2.2 Average capacity of plasma fractionation plants, 1987 and 2005

Region	Average plant capacity 1987 – '000 litres	Average plant capacity 2005 – '000 litres
Europe	162	500
North America	570	1144
Rest of world	116	333
Global average	192	475

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 8.

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Table 2.3 provides recent figures for the distribution of worldwide fractionation capacity, by region.

Table 2.3 Worldwide fractionation capacity, by region, 2005

Region	Total volume in millions of litres	% share of global capacity
Europe	14.0	41
North America	10.3	31
Asia	7.3	22
Rest of world	2.1	6

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 8.

During the period 1987 to 2004, as a consequence of industry rationalisation, fractionation capacity steadily moved from the not-for-profit sector to the commercial sector, as shown in table 2.4.

Table 2.4 Relative fractionation capacity of commercial and not-for-profit sectors, 1987, 2002 and 2004

Status	1987	2002	2004
Commercial	68%	75%	81%
Not-for-profit	32%	25%	19%

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 9.

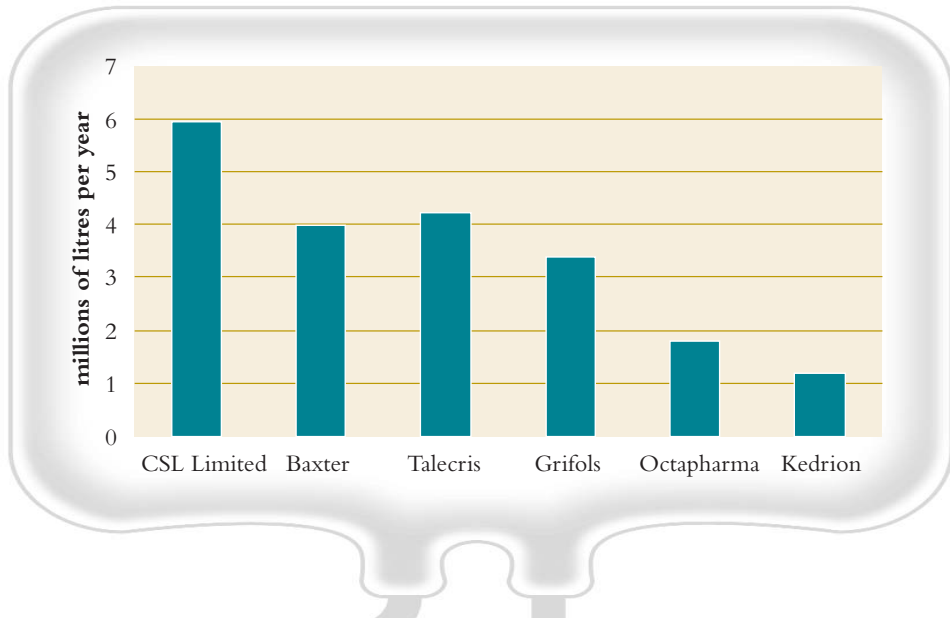
Global production capacity is now largely concentrated in six companies, which together account for 63% of world capacity (fig. 2.11).⁶

In conjunction with shifts in market demand, there have also been significant shifts in the numbers of fractionators producing individual products. Products less attractive in commercial terms are being phased out and replaced by products with a more secure commercial future (table 2.5).

Table 2.6 identifies the amounts of starting plasma required for the production of varying amounts of IVIg, given different rates of fractionation yield. If requirements with respect to the quantities of raw plasma necessary for the manufacture of IVIg can be met, then most other plasma derived products will be adequately resourced in terms of starting plasma (with the exception of hyperimmunes, which require specialised pools of starting plasma).

⁶ See Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, Marketing Research Bureau, Orange, CT, 2005, p. 10.

Fig. 2.11 Capacity of major fractionators



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

Table 2.5 Numbers of plants producing various plasma products, 2002 and 2005

Plasma derived product	Number of plants producing in 2002	Number of plants producing in 2005
Albumin	73	66
IVIg	43	47
IMIg	32	38
Hyperimmunes	36	36
Factor VIII	38	34
Factor IX	29	28
Antithrombin III	12	14
Fibrin sealants	0	10
Other products	31	22

Source: Derived from data in: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 11.

By applying the global trend projection for IVIg consumption, as provided at figure 2.5, to the data in this table, it is possible to calculate an approximation of the amount of raw plasma that would be required, going forward, for each of the four rates of yield (table 2.7).

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Table 2.6 Levels of starting plasma required for production of various quantities of IVIg

Input of starting plasma in litres x 1000 (tonnes)	300	500	700	900	1100
Rate of IVIg yield per litre	IVIg yield in tonnes	IVIg yield in tonnes	IVIg yield in tonnes	IVIg yield in tonnes	IVIg yield in tonnes
4.0 g/L	1.2	2	2.8	3.6	4.4
4.5 g/L	1.35	2.25	3.15	4.05	4.95
5.0 g/L	1.5	2.5	3.5	4.5	5.5
5.5 g/L	1.65	2.75	3.85	4.95	6.05

Source: Secretariat calculations.

Table 2.7 Actual and projected demand for IVIg, varying according to rate of yield, 2000–16

Year	Global demand for IVIg (actual and estimated) in tonnes	Plasma supply requirement in litres x 1000 at 4.0 g/L yield	Plasma supply requirement in litres x 1000 at 4.5 g/L yield	Plasma supply requirement in litres x 1000 at 5.0 g/L yield	Plasma supply requirement in litres x 1000 at 5.5 g/L yield
2000	47.4	11 850	10 533	9 840	8 618
2002	58.2	14 550	12 933	11 640	10 582
2004	68.0	17 000	15 111	13 600	12 364
2006	78.2	19 550	17 378	15 640	14 218
2008	88.5	22 125	19 667	17 700	16 091
2010	98.7	24 675	21 933	19 740	17 945
2012	108.9	27 225	24 200	21 780	19 800
2014	119.2	29 800	26 489	23 840	21 673
2016	129.4	32 350	28 756	25 880	23 527

Source: Secretariat calculations.

These figures demonstrate the importance of yield in circumstances where IVIg demand is increasing at rates that are challenging the ability of the global plasma collection system to provide sufficient starting plasma.

The amount of starting plasma available at a global level is a function of collection practices in individual countries, and these vary considerably. Collection rates are influenced by a range of factors, including population size and levels of growth, demographics, collection methods employed (e.g. plasmapheresis), cultural considerations, the remuneration or non-remuneration of donors, and whether collecting agencies are commercial or not-for-profit.

Chapter 3

The world fractionation industry

The combined global market for plasma derived products and recombinant clotting factor alternatives is valued at US\$10.5 billion. The market segment for plasma derivatives is estimated at US\$6.9 billion, and the segment for recombinant blood products at US\$3.6 billion.¹ Intravenous immunoglobulin (IVIg) accounts for over 40% of worldwide demand for plasma products.

The global plasma fractionation industry has grown over the past 40 years into a multi-billion-dollar sector. The global industry consists of a small number of high-capacity commercial fractionators with extensive multinational operations, and a large number of medium to small fractionators, which have lower outputs and exist primarily to serve national markets. Aside from the growth in the scale of the industry, there has been an increasing sophistication in the processes that ensure the safety and quality of products; a greater use of chromatography in fractionation technologies; a concentration of the industry into fewer hands; and shifts in the patterns of clinical usage for the various plasma-fractionated products.

The key drivers of demand for fractionation services have also changed over time as new plasma products have become commercially available and new indications for the use of plasma products have been identified and adopted.

Originally albumin was the leading plasma product but its market position changed from the late 1960s onwards, when concentrated Factor VIII became widely available for the treatment of people with haemophilia A. As noted above, IVIg has now emerged as the driving product, as a result of new clinical uses being explored and wider usage following.

The plasma products market in the United States is the largest in the world, and developments there significantly influence the global market. In the mid 1990s, there was quite a different landscape in the US plasma products industry, when compared with that of today. The range of products was also quite different, as recombinant products were yet to achieve dominance in the market for clotting factors: Recombinate® (recombinant Factor VIII), produced by Baxter, was licensed by the FDA in 1992, and Benefix® (recombinant Factor IX), produced by Wyeth, was licensed in 1997.

Global capacity and production

Global plasma fractionation capacity in 2005 was estimated to be 33.7 million litres per annum, down by 1.5 million litres from 2002. The number of fractionation plants worldwide fell from 80 to 71 between 2002 and 2005. The average capacity of individual plants, however, rose in response to industry concentration. For example, average plant capacity in North America now stands at a little over 1.1 million litres, up from 570 000 litres in 1987 (see Chapter 2, table 2.2).

¹ Marketing Research Bureau data supplied October 2006.

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The commercial fractionation sector is over four times the size of the not-for-profit sector. The commercial sector provides 27.3 million litres capacity (81% of the global total), while the not-for-profit fractionators provide 6.4 million litres capacity (19% of total capacity) (see Chapter 2, table 2.4). Over the last 20 years the commercial proportion of the industry has been increasing. Between 2002 and 2005 the total capacity of the commercial sector increased marginally (by 0.5%), while that of the not-for-profit sector fell substantially (by 24.3%).

In considering capacity, it is important to note that the throughput of a fractionation plant will vary, depending on the products being manufactured and the technologies employed. In broad terms, it is accepted that chromatography is capable of producing higher yields and greater purity of product than is Cohn technology, and therefore there is an increasing use of chromatographic finishing steps in production cycles based on Cohn primary extraction. Throughput at a large-capacity plant may be optimised where there is specialisation in a particular product or group of products (e.g. IVIg or clotting factors). It is not possible, however, to estimate total theoretical plant capacities, as it is not feasible to make accurate provision for the impact of regular plant maintenance shutdowns.

Some increase in global capacity is forecast through to 2008, when, it is estimated, total theoretical capacity will be 35 million litres, with 30 million litres of plasma actually being processed, giving a capacity utilisation rate of 85%. While according to this scenario the percentage of total unused global capacity is going to fall, there will still be some 5 million litres of theoretical capacity remaining in 2008.

Between 2002 and 2005 the quantity of plasma being fractionated globally fell by 9.9%, from 27.2 million litres to 24.5 million litres. The volume of source plasma fractionated globally fell from 18.6 million litres to 16.3 million litres (representing a 12.5% reduction in the volume of the plasma starting pool). The amount of recovered plasma fractionated worldwide fell from 8.6 million litres to 8.2 million litres (a 4.4% reduction). As noted above, global plasma fractionation capacity for 2005 was an estimated 33.7 million litres, meaning that fractionators had an estimated 9 million litres of unused processing capacity in that year. The reduction in plant throughput was to some extent offset, however, by lower production losses, resulting from improved yields and the processing of larger batches of starting plasma.

Table 3.1 provides a view of the world's leading plasma fractionators, their total theoretical capacities, their total throughputs in 2005, and the capacity utilisation rates achieved. (Global fractionators are profiled more extensively in Annex D.)

Industry consolidation

In the last ten years a number of pressures on the plasma fractionation industry have led to plant closures, a phase of mergers, takeovers and product acquisitions, and concerted efforts by firms to rationalise operations. The capital intensity of the industry, arising from high infrastructure costs and fixed manufacturing costs, together with the financial exposure of fractionators to the vagaries of supply and demand, are key factors that have driven consolidation and change.

Table 3.1 World's largest plasma fractionators, by annual capacity, 2005

Fractionator	Headquarters	Capacity - '000 litres	2005 Production - '000 litres	Utilisation (%)
CSL Limited	Australia	5950	5050	84.9
Talecris	United States	4100	2710	66.1
Baxter	United States	4000	3400	85.0
Grifols	Spain	3400	1768	52.0
Octapharma	Switzerland	1800	1600	88.9
Kedrion	Italy	1200	1050	87.5
Chengdu Inst.	China	800	350	43.8
Japan Red Cross*	Japan	800	525	65.6
LFB*	France	800	650	81.3
Shanghai Blood Inst.*	China	800	600	75.0
BPL*	United Kingdom	750	400	53.3
Sanquin*†	Netherlands	800	425	53.1

Source: Derived from Marketing Research Bureau data, 2006.

* Not-for-profit.

† If the proposed joint initiative between Sanquin and Biotest proceeds, the resultant entity would have a capacity of around 1 million litres, ranking it seventh on the list, by capacity (after Kedrion).

In the late 1990s in the United States, a series of events brought about by temporary plant closures, following FDA intervention, resulted in extensive rationalisation in both the US domestic fractionation industry and the global industry. In 1997, in the wake of a recall of Centeon's albumin product, the FDA required the temporary closure of the plant then owned by Centeon at Kankakee, Illinois (this plant is now owned by CSL Limited). In 1999 the Alpha Therapeutic Corporation plant in Los Angeles (now owned by Grifols) was temporarily closed. The shortages that resulted from these disruptions, particularly in respect of IVIg supply, brought about higher prices in the open US market, spurring commercial fractionators to increase plasma collections as well as output of finished products.

Between 2000 and 2003, however, once the Kankakee and Los Angeles plants had recommenced production, there was an oversupply of products, which led to dramatic price falls and, in turn, to a 30% reduction in gross operating margins. Due to fixed costs representing a high proportion of the total costs of fractionation, this translated into a significant net profit downturn for the industry, resulting in another round of rationalisation.

Review of Australia's Plasma Fractionation Arrangements

Falls in revenue coincided with declining demand both for plasma derived clotting factors (in favour of recombinant products) and for albumin (due to existing perceptions, subsequently discounted, regarding the relative safety and efficacy of albumin when compared with alternative therapies).²

One estimate has the net revenue per litre of plasma products (with the cost of plasma collection excluded from the analysis) dropping from an all-time high of about US\$220 per litre in 1999 to just over US\$100 per litre in 2003.³

In addition to being exposed to financial impacts attributable to market dynamics, manufacturers in the United States have been required, as a result of increased FDA scrutiny, to:

- spend approximately US\$1 billion, over and above normal maintenance costs, to upgrade facilities so as to meet new regulatory requirements
- expand quality control and quality assurance functions
- phase out low-purity products and abandon development programs for products that would not have met new viral-inactivation standards.

These three factors contributed to the diminished revenue per litre of product, and increased operating expenses and capital expenditure, resulting in a higher break-even volume for individual facilities.⁴

Industry rationalisation has changed the global corporate picture. CSL Limited, having previously acquired the Swiss Red Cross fractionator, ZLB, in July 2000 and 47 US plasma collection centres (out of 56) from Nabi in July 2001, purchased the plasma products business of Aventis Behring in 2003. Octapharma acquired the plasma products business of the Swedish-based manufacturer Biovitrum in 2002. In late 2002 Baxter acquired the alpha-1 antitrypsin product Aralast™, 42 plasma collection centres and a testing laboratory from Alpha Therapeutic Corporation (Mitsubishi Pharma), and in 2003 Grifols purchased Alpha's Los Angeles fractionation plant and the company's operations in key Asian markets. Bayer sold its plasma products division to a consortium of investors in 2005 and the business is now known as Talecris Biotherapeutics. The American Red Cross (ARC) left the plasma products market in 2005.

Baxter subsequently closed 26 of its own plasma collection centres and 38 collection centres acquired from Mitsubishi Pharma, as well as a 600 000 litre-capacity fractionation plant at Rochester, Michigan. The rationalisation involved an initial loss of 2500 positions worldwide.⁵

CSL's economies included the closure of 35 collection centres in the United States, a reduction in plasma collections by 1 million litres, and a reduction in plant throughput by 1.1 million litres. ZLB Behring (now known as CSL Behring) closed its Vienna plant and moved production to Marburg in Germany.

2 See 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.

3 See J. Curling & C. Bryant, 'The Plasma Fractionation Industry: New Opportunities to Move Forward?', *BioProcess International*, vol. 3, no. 3, March 2005, p. 20.

4 See Aethena Global, *The Four Stages of Recovery: Shock – Consolidation – Aftershock – Growth*, The Ground Rounds: Insights and Intelligence for Healthcare, Healthios, Northbrook, Ill., [2005], p. 2, <<http://www.healthios.com/institute/Grand%20Rounds%20Plasma%20Therapeutics.pdf>>.

5 Baxter staff retrenchments increased to 4000, or 8% of the company's global workforce, in 2004.

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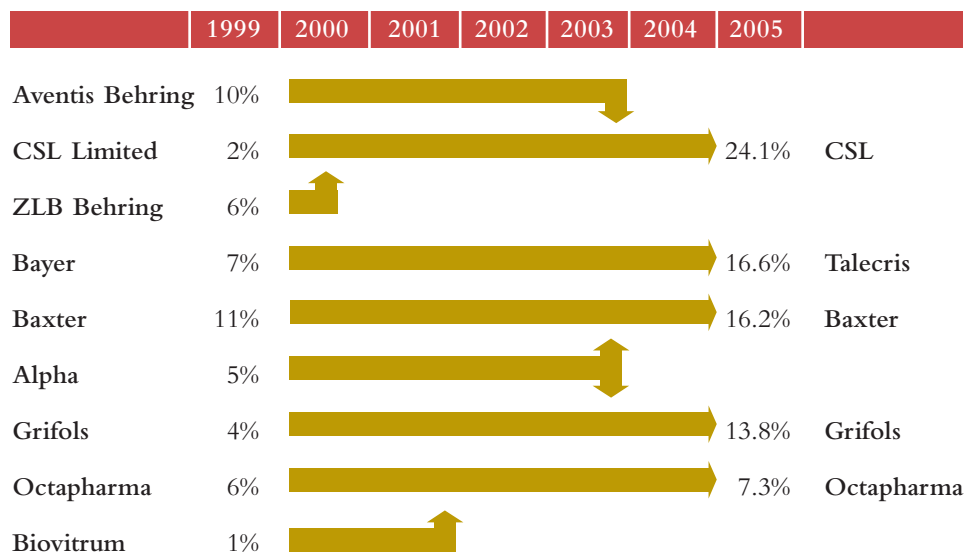
Table 3.2 Key transactions in the plasma therapeutics industry, 1997–2005

Date	Enterprise	Venture
Jan 1997	Baxter	Purchases Immuno International AG
Jan 1999	Octapharma	Purchases Aventis Behring plant at Lingolsheim, France
Jan 2000	Baxter	US\$150 million upgrade to its plasma facilities at Glendale and Vienna
Jul 2000	CSL Limited	Purchases assets of ZLB, to form ZLB Bioplasma AG
Feb 2001	Baxter	Purchases Sera-Tec Biologicals
Jul 2001	ZLB Bioplasma	Purchases 47 plasma collection centres and laboratory facilities operated by Nabi in the United States
Mar 2002	Grifols	Purchases SeraCare's 45 plasmapheresis centres
Jul 2002	Octapharma	Purchases Biovitrum's plasma products business (Sweden)
Dec 2002	Baxter	Purchases Aralast™ and 42 plasma collection centres from Alpha Therapeutic Corporation (Mitsubishi Pharma)
Jan 2003	Octapharma	Purchases Probifasa SA (Mexico)
Mar 2003	Baxter	Acquires European distribution rights for WinRho™ (Cangene)
Jul 2003	Grifols	Purchases Alpha Therapeutic Corporation plant, Los Angeles, and Japanese trading entities
Dec 2003	CSL Limited	Purchases Aventis Behring's plasma products business
Jan 2004	Cangene	Announces expansion of fractionation facility
Aug 2004	Sanquin	Enters into manufacturing agreement with Finnish Red Cross with respect to plasma collected in Finland
Mar 2005	Baxter	Enters into new long-term supply agreement with American Red Cross and terminates manufacturing agreement
Mar 2005	Baxter	Acquires US distribution rights for WinRho (Cangene)
Apr 2005	Talecris	Forms as a result of acquisition of Bayer plasma products business
May 2005	CSL/ZLB Behring	Manufacturing agreement with ARC expires
Nov 2005	Octapharma	Enters into management contract to operate plasma fractionation plant owned by NSTOB, the blood transfusion service founded by the German Red Cross

Source: Derived from information in: Aethena Global, *The Four Stages of Recovery: Shock – Consolidation – Aftershock – Growth*, The Ground Rounds: Insights and Intelligence for Healthcare, Healthios, Northbrook, Ill., [2005], p. 5, <<http://www.healthios.com/institute/Grand%20Rounds%20Plasma%20Therapeutics.pdf>>.

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Fig. 3.1 Plasma fractionators: mergers and acquisitions, 1999–2005. The percentages represent share of global fractionation capacity.



Source: Adapted from Baxter, with Marketing Research Bureau 2005 data incorporated.

News reports of plans by Grifols and Talecris to list on the share market appeared in early 2006.⁶ Negotiations for the merging of the production activities of Sanquin and Biotest, a small German commercial fractionator, were announced in May 2006.⁷

The most significant expansion activities within the plasma fractionation industry for the period 1997–2005 are identified in table 3.2; outcomes in terms of increased share of global fractionation capacity are detailed in figure 3.1.

The announcement by Sanquin and Biotest that opportunities for cooperation are being explored is a demonstration that the boundaries between the not-for-profit and commercial sectors are becoming increasingly blurred. Some not-for-profit organisations have the capacity to sell surplus products to support financial viability. Others look to securing toll fractionation agreements as a means of increasing capacity utilisation and contributing to fixed operating costs.

Key fractionators

CSL Bioplasma represents a unique case, in that its domestic operations in Australia retain historical elements in terms of market focus and product range. The CSL Bioplasma plant at Broadmeadows, Victoria, was originally designed to provide an ongoing domestic fractionation capacity for the benefit of Australia. The intention was to operate a state-of-the-art facility, capable of meeting all of Australia's growing requirements for fractionated products, using domestic plasma. Initially conceived as a

⁶ See 'New Blood on CSL's Block', *Australian Financial Review*, 10 April 2006, p. 18.

⁷ See Biotest, *AD-Hoc-Announcement §15 WpHG: Biotest and Sanquin Plan a Strategic Alliance in Plasma Products*, media release, 3 May 2006, Biotest, Frankfurt, <http://www.biotest.de/ww/en/pub/folder_ag/news/03_05_2006_biotest_and_sanquin.htm>.

not-for-profit undertaking, the Broadmeadows plant now forms part of a major international fractionation business – but fulfils a role that has fundamentally not changed. The plant is still dedicated to meeting the needs of the Australian community as a first priority, although it now also provides toll fractionation services for smaller neighbouring regional markets. This role contrasts with that of CSL Behring, which operates as a large multinational player and depends on the supply of plasma obtained from paid donors in the United States and from paid and unpaid donors in Europe.

Baxter is a large and well-respected, multi-divisional, multinational corporation engaged in the manufacture of products for supply to the global health care market. Baxter has a global presence and approximately 47 000 employees, and the company's products are used in over 100 countries.

Talecris Biotherapeutics is a new company, formed in 2005 as a result of the acquisition of Bayer HealthCare Biological Products Division's US plasma operations, based in North Carolina, and the Precision Pharma Services fractionation plant, located on Long Island, New York. The corporate vision of Talecris is to be recognised as a global leader in the development and delivery of premium protein therapies. In 2005 Talecris had the second-largest fractionation capacity in the world.

Grifols is a privately owned plasma fractionation company headquartered in Barcelona, Spain. With a production capacity of 3.4 million litres annually, Grifols is one of the five largest global fractionators. The company maintains fractionation plants in Spain and in the United States.

Octapharma is a privately owned company headquartered in Switzerland and is one of the largest privately owned plasma product suppliers in the world. Since its founding in 1983, Octapharma has become one of the key players in the global plasma products market. With sales offices and representation in over 70 countries, Octapharma competes successfully against much larger, publicly listed corporates and has a stated objective to be the fifth-largest fractionator globally.

Operational factors

Plasma collection

There are two distinctly different avenues for the procurement of starting plasma: one based on the collection of voluntary, non-remunerated donations of whole blood and plasma, and the other based largely on the collection of plasma by apheresis, from paid donors. The fractionation firms with large-scale manufacturing operations in the United States and Europe acquire the bulk of their starting plasma requirements from paid donors. The obtaining of starting plasma is estimated to represent 40% of total plasma fractionation costs.⁸ Collection costs include payments and other forms of reimbursement to donors, the cost of equipment and consumables, plus staffing and operating costs at collection centres. The open market price for starting plasma varies substantially (US\$80–\$135 per litre), depending on where plasma is collected and the method of collection used.⁹

8 See National Blood Authority, *NBA Supply Arrangements for Blood Products and Services*, National Blood Authority, Canberra, 2006, <<http://www.nba.gov.au/CONTRACTS/supplier.htm>>; and Curling & Bryant, p. 19.

9 See National Blood Authority, *NBA Supply Arrangements for Blood Products and Services*, <<http://www.nba.gov.au/CONTRACTS/supplier.htm>>.

Upkeep of fractionation plants

The difficulties and high capital cost associated with constructing and licensing a greenfield fractionation plant discourage this means of building capacity. Instead, fractionators undertake continual investment to improve and upgrade existing plants, in order to increase capacity, to improve the safety, quality and yield of products and to meet regulatory requirements. Companies do not enjoy the luxury of manufacturing from fully depreciated plants, as reinvestment is a constant process in the industry.

Range of products manufactured

Although fractionators seek to maximise product range as well as yield, no manufacturer presently produces the complete range of available plasma derived products.¹⁰ Production of hyperimmune immunoglobulins is particularly specialised. CSL Bioplasma currently produces and supplies all of Australia's requirements for hyperimmunes, using a small dedicated Cohn plant at the Broadmeadows facility. No other single manufacturer produces all of the hyperimmune products required for the Australian market. Hyperimmune manufacturing is low-volume, high-value and of limited commercial interest to most fractionators. Hence smaller, more specialised organisations, such as Cangene, Nabi and not-for-profit fractionators, tend to produce these products.

Comparison of plasma therapeutics sector and pharmaceuticals industry

Compared with the costs associated with pharmaceutical production, the fixed cost structures encountered by plasma fractionators are of a high order. Relatively high costs are imposed on fractionators by the need to comply with increasingly rigorous regulatory requirements. These involve ever more complex manufacturing processes, which, in turn, require continuing and additional regulatory oversight.

Cost pressures have created an incentive for fractionators to make full use of their available starting plasma by deriving from it the maximum number of saleable products. Fractionators usually manufacture IVIg, albumin and Factor VIII, plus a number of other plasma derived products, the aim being to spread the fixed cost burden across a broad product range. A manufacturer will face difficulties if, because its product range is narrow, it cannot maximise return from each litre of plasma, through the realisation of competitive in-market prices. Furthermore, fractionators have an interest in achieving maximum throughput in plants in order to optimise efficiency and to generate an acceptable return on capital expenditure. Manufacturers may resort to marginal pricing for toll fractionation assignments so as to soak up any under-utilised plant capacity.

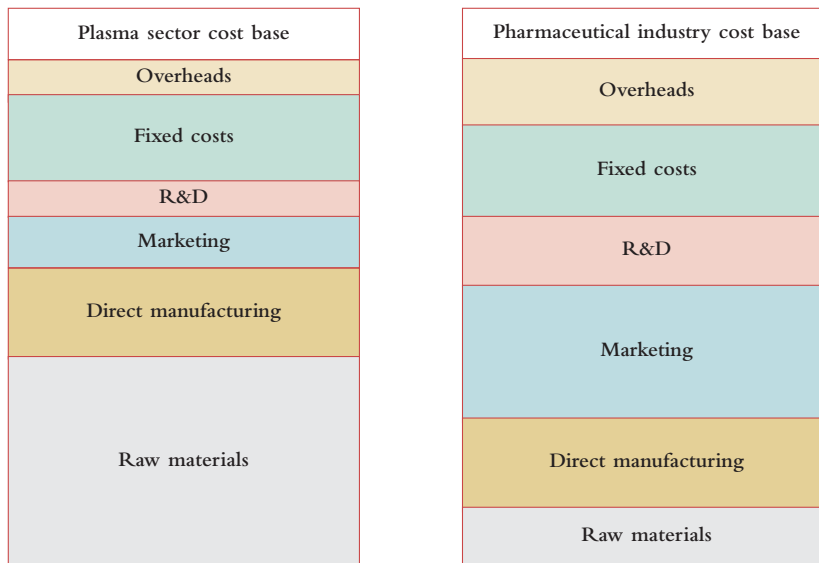
In addition to the high fixed cost structures affecting fractionators, there are other significant differences in cost structure between the plasma therapeutics sector and the pharmaceutical industry:

- 40–45% of the total cost of producing plasma therapeutics is accounted for by the cost of raw materials, whereas raw materials make up only 10% of the total cost of producing pharmaceuticals. The costs of plasma collection and testing are reflected in the open market prices for plasma, which, as noted earlier, vary between US\$80 and US\$135 per litre.

- Production lead times are longer for plasma products, the manufacturing process is generally more complex, and there is more intense regulatory surveillance.
- Patient populations for plasma derived products are small but the average cost of treatment may be substantial in dollar terms.

Figure 3.2, based on a Plasma Protein Therapeutics Association presentation at the International Plasma Protein Congress held in Prague in March 2006, contrasts the cost structures of the pharmaceutical industry and the plasma fractionation sector.

Fig. 3.2 Cost comparison for plasma sector and pharmaceutical industry



Source: Derived from data in: Jan Bult, 'Market and Industry Developments', paper presented to the International Plasma Protein Congress, Prague, 7-8 March 2006.

Plasma fractionation today

A broad distinction can be made between fractionation plants that serve large, global markets, and plants that serve the needs of national markets. The former generally focus on throughput volume and specialise in a relatively small number of products. The latter generally focus on an expanded product range so as to meet the majority of the needs of a single domestic or regional market.

Among the larger fractionators that operate several facilities, there is a trend towards plant specialisation, as distinct from the production of a comprehensive range of plasma derivatives at all plants. Plant specialisation means that individual plants are dedicated to the manufacture of one particular product or group of products. Economies of scale can be realised by specialising in this way, despite additional logistical costs. Baxter and CSL Behring are examples of global fractionators that transport fractionation intermediaries (components of plasma separated during the manufacturing process) between plants that specialise in the manufacture of one product or group of related products.

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By contrast, some global fractionators maintain a network of smaller-capacity plants and manufacture a full suite of products at each of them. The rationale for this arrangement is to ensure continuity of supply of all products, even if one plant must cease production for any reason. This model is employed by Octapharma, governing production at its three European plants. The company's view is that this paradigm provides a greater level of flexibility than the specialised plant model, and permits an ongoing process of developing efficiency gains through an internal competitive environment.

CSL Bioplasma also operates according to a stand-alone model, whereby the one plant manufactures a complete product range and undertakes all stages of production, from primary extraction right through to the finished product. CSL describes this model as 'tailored self-sufficiency'.¹¹ In the case of interruption to supply, CSL Bioplasma would rely on its sister organisation, CSL Behring, to fill any gaps in supply.

Manufacturing models for plasma fractionation

Trends with respect to manufacturing models within the global plasma products market are very much driven by country-specific objectives. Increasingly Europe is opening up to greater movement of starting plasma and finished plasma products across national borders, although nation-specific regulations remain in place. Due to factors such as increasing harmonisation of regulation, advances in logistics and communications, and economic pressures, some smaller countries have moved from a national fractionation model to toll fractionation. The list of countries relying on toll fractionation includes Belgium, Canada, Denmark, Finland, Hong Kong, Malaysia, New Zealand, Norway, Poland and Singapore. Brazil is an example of a large developing country that has attempted to build a domestic fractionation capacity in recent years but has failed, due to technical difficulties encountered. Brazil now relies on offshore toll fractionation, while seeking to reorganise for future domestic production.

As standards of medical diagnosis and care continue to rise, many developing countries are experiencing increased demand for plasma derived products and for recombinants. The high costs involved in securing these products, however, mean that there cannot be unlimited access to them. Economic capacity thus influences the procurement as well as the extent of clinical usage of plasma products, resulting in sub-optimal treatment for many patients in developing nations.¹²

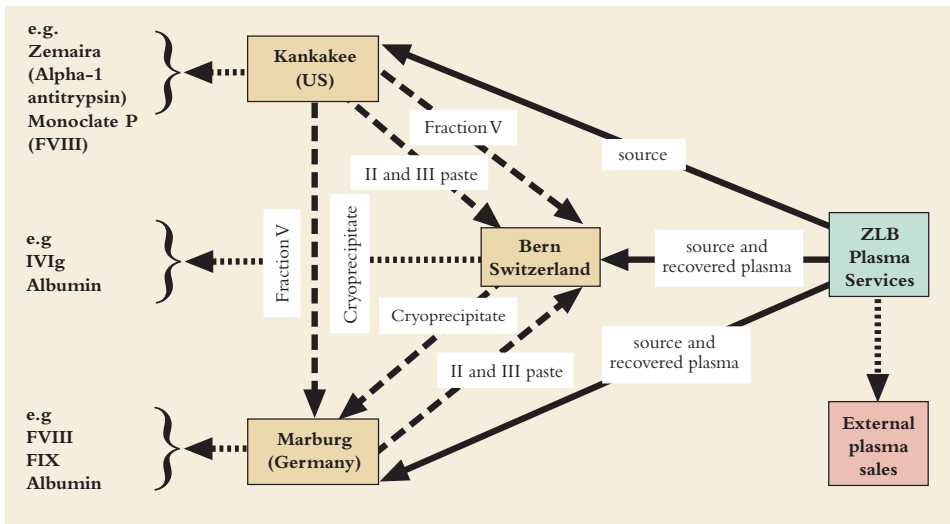
In order to meet different countries' requirements for plasma derived products, the industry has become organised along lines that reflect marketplace needs. Countries with developed economies are the big consumers of plasma products, and this factor has encouraged the emergence of large-scale fractionation capacity in the United States and Europe. Developing economies and markets draw their product requirements either from the larger-scale fractionators or from small-scale domestic fractionators.

Large-scale, multiple-site fractionators fall into one of two categories, according to the manufacturing model preferred. The 'centres of excellence' model, as illustrated in figure 3.3, is employed in various forms by CSL Behring and by Baxter.

¹¹ CSL Limited, submission to Plasma Fractionation Review, 2006, p. 20.

¹² See A. Farrugia, 'Safety and Supply of Haemophilia Products: Worldwide Perspectives', *Haemophilia*, vol. 10, no. 4, July 2004, pp. 327–33.

Fig. 3.3 Centres of excellence model



Source: CSL Limited, presentation to Plasma Fractionation Review Committee, July 2006.

The diagram describes the flow of plasma raw material and intermediaries between plants that specialise in the production of particular products (e.g. immunoglobulins, clotting factors or specialty products). Plasma that has been collected by a collection service is delivered, either as source plasma or as both source and recovered plasma, to multiple plants for primary extraction. Each plant then retains the intermediaries relevant to its specialisation and passes the remaining intermediaries on to other plants, as appropriate to their individual specialisations, for final processing to finished product stage.

According to CSL Limited, the 'centres of excellence' in its network undertake the following R & D activities:

- Marburg: 'development of coagulation therapies, along with critical care and speciality products'
- Bern: 'immunoglobulins, production methods and safety standards'
- Melbourne: 'development of state-of-the-art purification technologies for plasma products'
- Kankakee: 'continuous improvement of our Alpha-1-Proteinase Inhibitor (Alpha-1-PI) product'.¹³

A multi-centre model would not be readily adaptable to Australia's relatively small fractionation needs and it is for this reason that CSL Bioplasma sits outside the 'centres of excellence' paradigm.

Another model is represented by Sanquin (Netherlands), Laboratoire Français du Fractionnement et des Biotechnologies (LFB) (France), and Bio Products

¹³ CSL, *Research & Development*, CSL, Melbourne, 2006, <http://www.csl.com.au/R_+_D.asp>.

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Laboratory (BPL) (United Kingdom). These not-for-profit fractionators are primarily structured to supply domestic markets. Sanquin is a benevolent foundation that is mandated by the Netherlands Government to provide all blood services for the Netherlands community. LFB and BPL are predominantly state-owned bodies, operating under the auspices of the ministries of health in France and the United Kingdom respectively.

In countries where there is an open market for finished plasma products, the not-for-profit sector is finding it increasingly difficult to compete with the larger commercial-scale operations. The result has been a blurring of the boundaries between commercial fractionation and not-for-profit fractionation, with not-for-profit fractionators increasingly being driven into commercial activities, including toll fractionation and exporting, in order to survive financially.

Sanquin is undertaking toll fractionation for Belgium and Finland and is looking to form a joint venture with the small German commercial fractionator Biotest, in order to upscale fractionation capacity. The operations of BPL are under review by the British Government, but in any case BPL is looking to export markets in developing countries to provide half of its revenue stream. LFB is already engaged in toll fractionation for four other countries, and is seeking to add to its portfolio of toll fractionation clients so as to increase the organisation's international franchise and absorb its under-utilised capacity.

It is important to note that throughout Europe the market for plasma derived products is open. This means that hospitals or their proxies are free to purchase any brand of product that is registered for marketing. In Australia, by contrast, domestically manufactured products must be used as a first priority, and imported product is supplied only as a contingency in the event of shortages.

Three large companies dominate the US market: CSL Behring, Baxter Biosciences and Talecris. CSL Behring and Baxter Biosciences operate under the 'centres of excellence' model and provide products to the US market that are either manufactured domestically or imported from Europe. Talecris, which operates under the stand-alone model, only markets products that are manufactured domestically. Talecris also toll fractionates for Canada.

Countries outside the United States and Europe acquire plasma products by various means. China and Japan have domestic fractionation capacity but are finding it necessary to import some products. Russia is currently constructing a domestic fractionation facility. Brazil, as noted previously, has attempted to operate a domestic facility but more recently has been dependent on toll fractionation and imported products. Most other countries rely on products marketed by the large- to medium-sized global manufacturers, which include Grifols (Spain and the United States) and Kedrion (Italy).

The World Health Organization has estimated that 15% of the world's population consume 91% of the world's output of pharmaceuticals (by value),¹⁴ and plasma products are no exception to this pattern: usage levels in any given country broadly correspond to that country's standard of living. It will be of interest to see if rapidly growing economies such as China and India, as part of a greater investment in their health systems, choose to concentrate on domestic collection and fractionation of

plasma, or instead purchase growing quantities of plasma derived products on the open global market. Rapid increases in demand could well bring about pronounced shortages and price increases (particularly with respect to IVIg, the demand for which is continuing to grow strongly).

Differences from country to country in terms of patterns of clinical care, health care financing by government, and industrial infrastructure, have led to the development of differing national models for the supply of plasma derived products. These models may be summarised as follows.

Self-sufficiency models

For some time there has been a widespread view that governments have a responsibility to their own citizens, and to citizens of other countries, to use domestically sourced blood and blood products as much as possible. This viewpoint was articulated in a 1975 World Health Assembly (WHA) resolution, WHA28.72, to which Australia is a signatory. The resolution, driven by concerns regarding the exploitation of developing countries by commercial interests, and the consequent potential for trade in infected blood products, exhorts member states of the WHA:

- (1) to promote the development of national blood services based on voluntary nonremunerated donation of blood;
- (2) to enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and of recipients of blood and blood products.¹⁵

Policies such as these have been widely regarded as promoting public confidence in the blood systems of countries that adopt them. This confidence is critical to ensuring the sustainability of national blood systems, which rely on community goodwill and on the motivation of individuals to donate. Perceptions about safety and security of supply, together with concerns that voluntarily donated blood should not be used for commercial gain, have perpetuated the tenets of the WHA resolution.

Since the resolution was adopted, the plasma products industry has become increasingly globalised and subject to increasingly stringent regulatory regimes. These have been implemented with respect to donor eligibility as well as testing and viral inactivation, permitting international movement of products that are safe and efficacious. However, for reasons relating to security of supply, together with ethical and humanitarian considerations, there is a prevailing view that countries should avoid making disproportionate demands on the blood systems of other countries.

National health systems strive to attain degrees of self-sufficiency that suit their particular economic and policy objectives. Governments in several European countries and elsewhere, including Japan and Australia, have established, or have supported the building of, domestic fractionation infrastructure. The resulting national fractionation plants are comparatively small and do not offer the same economies of scale as the large commercial plants, which are located primarily in the United States and throughout Europe. As noted

¹⁵ World Health Organization, *Twenty-Eighth World Health Assembly, Geneva, 13–30 May 1975: WHA28.72 Utilization and Supply of Human Blood and Blood Products*, World Health Organization, Geneva, 1975, <<http://www.who.int/bloodsafety/en/WHA28.72.pdf>>.

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earlier, some national fractionators, among them CSL Bioplasma, Sanquin and LFB, accommodate toll fractionation customers so as to better utilise capacity and to alleviate high fixed cost burdens.

Toll fractionation models

Due to the substantial financial resources and technical expertise required for the establishment and maintenance of a domestic fractionation industry, a number of smaller developed nations have elected to rely on toll fractionation arrangements, sometimes referred to as contract fractionation. Under these schemes, an entity (typically a government agency or a blood collection organisation) enters into a contract with an external fractionator, for the fractionation of plasma collected in the originating country. Products manufactured from this plasma are then returned to the originating country (some toll fractionation contracts may specify that the fractionator is free to sell any excess products not required by the country from whose plasma they have been manufactured).

Toll fractionation arrangements operating today include those for:

- Belgium (Sanquin)
- Canada (Talecris)
- Denmark (CSL Behring)
- Finland (Sanquin)
- Malaysia, Singapore and Hong Kong (CSL Bioplasma)
- New Zealand (CSL Bioplasma)
- Norway (Octapharma)
- Poland (Baxter).

For many years the American Red Cross had a toll fractionation arrangement with Baxter, whereby plasma collected by the ARC was processed by Baxter and returned as finished product, but this arrangement was discontinued in 2005 when the ARC exited the plasma products market in the United States. (Today Baxter purchases starting plasma from the ARC for fractionation.)

The advantages of toll fractionation for a country entering into such an arrangement include the assurance of an adequate supply, at constant prices, of products that would otherwise need to be purchased on the open global market. There are, however, dimensions to a toll fractionation arrangement that do not apply to domestic fractionation. These include regulatory oversight requirements specific to contract fractionation, longer lines of supply, and the need for additional steps to ensure continuity of supply from an external fractionator.¹⁶ Toll fractionation agreements typically specify minimum standards of performance, including yield.

Commercial models

In the United States, a system whereby voluntary, non-remunerated donors donate whole blood for the not-for-profit provision of fresh blood products coexists with a system whereby remunerated donors provide apheresis plasma (source plasma) for fractionation. In the commercial plasma supply sector, which relies heavily on the

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collection of source plasma from remunerated donors, there are three main groups involved: collection agencies, brokers, and fractionators (some of which operate their own collection centres). The collection agencies and brokers sell plasma obtained via apheresis to fractionators in the United States and overseas. Brokers also purchase and market recovered plasma, collected from voluntary donors attending whole-blood collection centres. Fractionators market finished plasma products either directly to user institutions or through collective purchasing agencies. There are supply-driven variations in the prices of products, but buyers have a wider choice of brands than in other national markets, where choice of brand may be limited by availability, which can in turn be determined by supply policy.

The US commercial plasma products market is thus characterised by multiple suppliers and numerous purchasing agencies, in an environment in which public sector agencies do not play a dominant role with respect to the procurement of plasma fractionation services. Vertical integration is also a feature of the US industry, with some fractionators maintaining substantial plasma collection networks.

In other countries (such as Australia), finished plasma products may be sourced on the open global market, but only when they are needed to supplement domestically sourced product supply. Nations with neither a domestic fractionation capacity, nor a toll fractionation arrangement in place, obtain all of their plasma products on the open global market.

With an output that exceeds domestic requirements, the United States is the leading exporter of plasma derived products. Reliance on products purchased on the open market, however, can expose purchasers to the risks of scarcity of supply and price fluctuations (for instance when demand outstrips supply or when there are disruptions in supply as a result of regulatory sanctions). The product recalls and plant closures that affected US production during the late 1990s caused serious price increases and product shortages – particularly in respect of IVIg – both domestically and in export markets that depended on US supply.

While many countries are self-sufficient in fresh blood products, only the United States is self-sufficient in plasma for fractionation. The US system of remunerated plasma collections delivers more starting plasma than is required to meet the domestic need for finished products: just over one third of the plasma collected is used domestically, and the remainder is available for export as starting plasma, plasma intermediaries, and finished product.

With the United States accounting for approximately 70% of the plasma collected globally, a significant number of countries draw in part on US-sourced plasma or finished plasma products.

The United States exports significant quantities of plasma to Europe, where total collections are insufficient to meet both domestic demand and external demand for finished products.

Canada is an example of a country that draws substantially on US plasma products, while at the same time using finished products manufactured from plasma collected within its own borders and fractionated under the terms of a toll fractionation arrangement.

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A further model is represented by the fractionation arrangements of the Irish Republic: the Swiss-based company Octapharma, acting on behalf of Ireland, purchases plasma on the US and German open markets and then fractionates it into products for consumption in the Republic.

The British Government maintains a network of plasma collection sites in the United States so as to be able to meet UK domestic requirements (all domestic plasma in the United Kingdom is currently discarded, due to risks associated with variant Creutzfeldt-Jakob disease (vCJD)).

The risks of blood-borne transmission of infectious agents were not fully comprehended until the emergence of HIV/AIDS and hepatitis C in the early 1980s. Attention was then focused on the safety, quality and efficacy of blood and blood products, triggering changes in donor selection processes, in testing regimens, and in fractionation procedures (which now include multiple viral-elimination steps). The potential risk of transmission of vCJD through plasma products is a more recent concern.

At the same time, developments in production technologies, communications and transportation have led to increased globalisation of the fractionation industry. The use of electronic monitoring devices and bar coding systems, and improved logistics, mean that it has become feasible for starting material, finished products and even plasma intermediaries to be transported over long distances without significant risk to product integrity. There has also been an increased harmonisation of regulatory standards from country to country, and greater levels of liaison among industry participants, to ensure that the international movement of plasma products takes place safely and securely.

Chapter 4

How other countries meet their needs

This chapter describes the systems in place for plasma collection, fractionation, and the supply of finished plasma products, in a diverse range of countries – the United States, Canada, the United Kingdom, France, the Netherlands, Norway, the Czech Republic and New Zealand – and provides a brief commentary on systems operating in other countries and regions. The key dimensions along which these various systems differ relate to the ways in which they are financed, to historical factors, and to economic considerations and market size.

Developed markets, including the United States, several European countries, Australia and Japan, are characterised by self-sufficiency models, the adoption of which reflects two principal factors:

- In these markets, there is a high per capita consumption of plasma products, particularly immunoglobulins, albumin and Factor VIII. Because plasma products are life saving for many patients, health care providers place a premium not only on safety but on security and reliability of supply. Self-sufficiency under a single jurisdictional regulator helps to ensure that these criteria are met.
- Plasma is a valuable by-product of whole blood, so it is logical that these countries have established local fractionation facilities in order to make full use of this resource.

Middle-income countries generally use less immunoglobulin and Factor VIII per head of population, but still collect whole blood for use in medical treatments. Again the value of the plasma in the whole blood collected provides a strong incentive for the development of fractionation facilities. Middle-income countries generally aspire to self-sufficiency, and many have programs in place to construct domestic fractionation facilities (although some governments are evaluating toll fractionation options). The aspiration to achieve self-sufficiency is underpinned by evolving medical practice in these countries. Over time, the demand for plasma derivatives will increase, and with it the need to ensure a safe and secure supply of blood and blood products into the future.

Per capita use of plasma products in the world's poorer economies is low by comparison with usage levels in middle-income and developed markets and is confined to the small proportion of the population able to pay for health services. Many developing countries cannot afford plasma collection or fractionation infrastructure, and rely instead on imported products.

The remainder of this chapter will focus on the blood systems operating in individual countries.

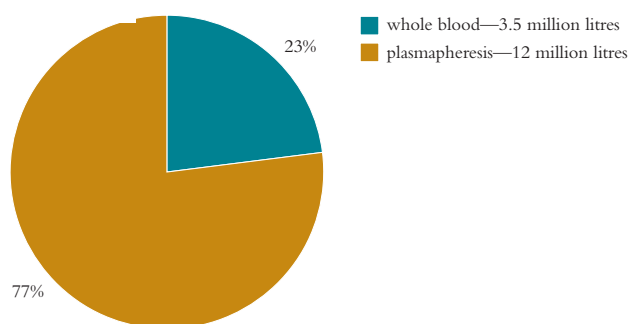
United States

The United States relies on a totally commercialised blood system, whereby starting plasma and finished plasma products, as well as fresh blood products, are traded according to the mechanisms of an open market structure. For 2005, the total US wholesale blood and blood components market was valued at US\$3.2 billion.¹

Collection

US plasma is sourced in two ways: from whole blood collected from non-remunerated donors, and via plasmapheresis (in the latter case, donors attend commercial collection centres and receive remuneration). The bulk of the plasma collected in the United States is provided by paid donors: for the year 2005, it is estimated that plasma derived from whole blood amounted to 3.5 million litres, while 12 million litres of plasma was obtained via plasmapheresis (fig. 4.1).

Fig. 4.1 US plasma collections 2005



Source: BCC Research.

Fractionation

Some plasma fractionators in the United States are structured to collect plasma on their own behalf; others purchase plasma from independent commercial collection centres and the American Red Cross; others do both. Plasma separated from whole blood is typically sold to fractionators by brokers.

CSL Behring and Baxter operate their own collection sites and also acquire raw plasma on the open market. By contrast, the Swiss-based fractionator Octapharma, to the extent that it uses starting plasma collected in the United States, relies on product purchased on the US domestic market (this plasma is then exported to Europe for fractionation).

Finished plasma products are provided to the US domestic market by both domestic and foreign fractionators. The US market accounts for nearly 37% of the global consumption, by value, of plasma products and is therefore the focus market for all global-scale fractionators, with the exception of Kedrion, which focuses on Europe and on export markets in developing countries.²

Procurement

The supply channels for plasma products in the United States are governed to an extent by the therapeutic use for which a product is designated and by its method of administration (i.e. self-administration, or administration in a clinical setting).

¹ BCC Research.

² See Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, Marketing Research Bureau, Orange, CT, 2005.

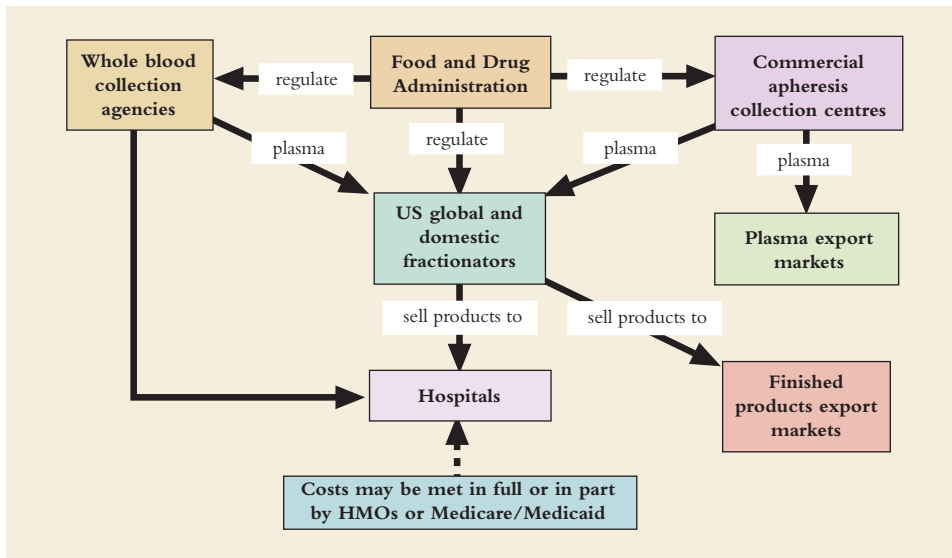
In the case of plasma products administered to patients on an in-patient or day patient basis, procurement by hospitals is either via tender arrangements whereby tenders are issued by hospital buying groups or agencies, or via direct dealings between individual hospitals and manufacturers. Prices are set by negotiation, and manufacturers do not publish price lists or pricing offers. Factors that can influence price include volume of product ordered, availability of stock, a customer’s frequency of purchase and/or brand loyalty, and market competition. Marketing, which encompasses customer service and product support, is seen to be an important aspect of manufacturers’ activities.

Certain plasma products prescribed by physicians (e.g. subcutaneous immunoglobulin and Factor VIII) are self-administered by some patients. In such cases, the product is supplied through either a hospital pharmacy or a retail pharmacy.

Financial support for patients being treated with therapeutic plasma products is typically via Health Maintenance Organizations (HMOs), which provide private or company-sponsored medical insurance, or, for the economically disadvantaged, via Medicare/Medicaid government-sponsored and supported schemes. In most instances, however, a financial contribution by the patient is necessary.

The United States is the only country in the world that is totally self-sufficient in fresh blood products, plasma, and plasma derivatives. Nevertheless, America’s Blood Centers, a network of not-for-profit blood collection facilities, has warned of an approaching crisis in the supply of whole blood, with demand for fresh blood products already facing shortages.³ No such shortages exist with respect to plasma, although the unrelenting increase in domestic use of intravenous immunoglobulin (IVIg) suggests that in future years there may be a reduction in the quantities of plasma products available for export from the United States.

Fig. 4.2 The blood supply system in the United States



3 America’s Blood Centers, *Blood Banking Community Issues National Appeal*, media release, 12 January 2004, America’s Blood Centers, Washington, DC, p. 1, <http://www.americasblood.org/download/releases/pr_040112_shortage.pdf>.

Canada

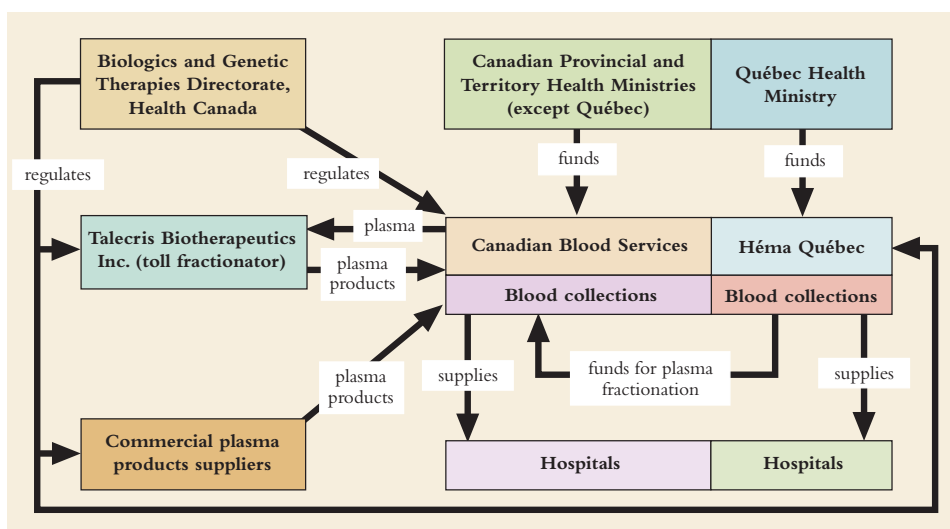
Collection

Canadian Blood Services (CBS) is an incorporated not-for-profit charitable organisation that operates at arm's length from government. Established in 1998, following the merger of the Canadian Red Cross Blood Program and the Canadian Blood Agency (the government agency that formerly funded Canada's blood supply system), CBS is responsible for collecting fresh blood and blood components in Canada, and for supplying blood and blood products to all hospitals and health care facilities in the country (apart from those in Québec). CBS is thus the monopoly provider of blood and blood products to Canadian hospitals.

The volume of whole blood collected by CBS has increased every year since 1998. Similarly, since 1998 there has been a slight increase in the size of Canada's plasma starting pool. In 2004–05 the Canadian plasma starting pool for fractionation was 193 tonnes (approximately 193 000 litres), all derived from recovered plasma. Source plasma from plasmapheresis was used as fresh frozen plasma for transfusion.

Canada's starting plasma is fractionated to produce two products, IVIg and albumin. In 2005, 75% of Canadian demand for albumin, together with 24% of the demand for IVIg, was met by domestic plasma. The Canadian Plasma Protein Products Strategic Plan, developed between September 2003 and June 2004, established the framework for Canada to achieve a sustainable balance between products derived from Canadian plasma and those sourced from commercial suppliers. The Canadian Deputy Health Ministers' forum has confirmed as a three-to five-year goal for Canada the achievement of 40% sufficiency target in IVIg fractionated from domestic plasma.

Fig. 4.3 The blood supply system in Canada



The CBS plasma collection business plan is based on the sourcing of Canada's domestic plasma starting pool from recovered plasma, the implementation of the buffy coat method of platelet production (which results in improved plasma yields), and increases in plasmapheresis collections.

Fractionation and procurement

In 2005, 25% of the albumin supplied by CBS to Canadian hospitals and health care facilities, together with 76% of the IVIg supplied, and approximately 28 other plasma and recombinant products, were produced by US suppliers.

CBS has a toll fractionation contract with the US-based company Talecris for the remaining proportion of albumin and IVIg. Plasma collected in Canada is consolidated into three-tonne shipments and transported by truck to Talecris for fractionation.

Finished plasma products, both from Talecris and from other suppliers, are delivered to the CBS fractionated product warehouse in Ottawa.

Products are then transported from the CBS warehouse to each of the 14 distribution centres that deliver plasma derivatives and other blood products to Canada's hospitals and health care facilities.

United Kingdom

In the United Kingdom, the supply of blood and blood products has been overshadowed for the past two decades by the incidence of bovine spongiform encephalopathy (BSE) in cattle, and of the related variant Creutzfeldt-Jakob disease (vCJD) in humans. There have been three cases where vCJD appears to have been transmitted by fresh blood transfusion, although no transmissions via plasma products have been reported to date. The incidence of vCJD has had, and continues to have, a profound influence on the UK blood sector.

Collection and fractionation

Blood collection in the United Kingdom is undertaken by the National Blood Service (NBS), which operates under the umbrella of the National Health Service (NHS). The NBS operates from 30 centralised blood establishments; these are integrated with regional NHS Trusts, which maintain a total of 2000 mobile collection sites throughout the country.

While fresh blood products are supplied directly to UK hospitals by the blood establishments, all plasma collected is discarded, because of continuing concern regarding potential vCJD transmission (given the lengthy period prior to the onset of symptoms of this disease).

In place of domestic plasma collections, the United Kingdom relies on a wholly UK Government-owned network of plasmapheresis centres located in the United States. These centres collect plasma from paid donors and then on-sell it, at full cost recovery prices, to the British domestic fractionator, Bio Products Laboratory (BPL). This is a competitive arrangement, under which BPL must pay market prices in order to secure its raw plasma requirements.

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The UK’s US-based plasmapheresis centres operate on a full cost recovery basis, and plasma collected by the centres but not purchased by BPL is sold on the open market.

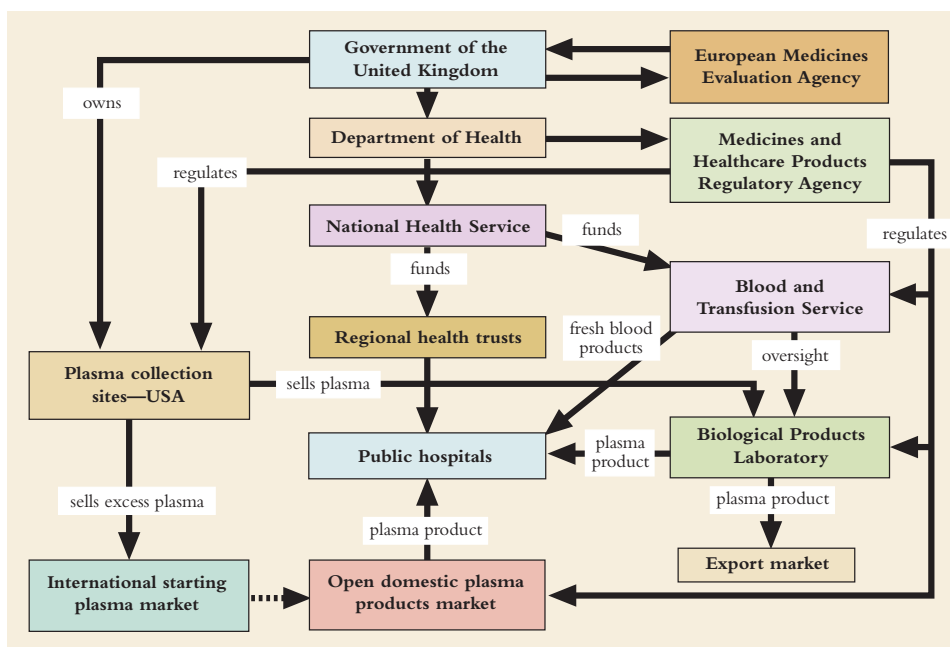
Procurement

The UK plasma products market is open to all fractionators with products registered for sale in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency. NHS Trust hospitals are free to purchase any UK-registered plasma product.

BPL, which is an NHS Blood and Transplant entity, provides a range of products to the domestic markets in England and Wales, as well as to 43 international markets (predominantly in developing countries). Exports account for 50% of BPL’s turnover.

BPL receives an undisclosed annual subsidy of millions of pounds, which, given the organisation’s £60 million turnover, cannot continue indefinitely. NHS Blood and Transplant is seeking international partners for BPL for a joint venture; further supply contracts; or a possible sale. Without change to BPL’s current structure, there is a real risk of closure.⁴

Fig. 4.4 The blood supply system in the United Kingdom



⁴ See Nicholas Timmins, 'Revamp Planned to Revive Outdated Transfusion Service', *Financial Times*, 7 July 2006, p. 4.

France

Collection

In France, the national transfusion service and national plasma fractionation arrangements are separated by law. The national transfusion service, the *Établissement Français du Sang* (EFS), operates 18 blood collection centres across France, and these in turn provide 154 collection points.

The EFS supplies fresh blood products directly to hospitals and collects plasma for fractionation by the domestic fractionator, the *Laboratoire Français du Fractionnement et des Biotechnologies* (LFB). The ratio of recovered plasma to source plasma is 88:12.

There are 1.4 million blood donors in France, whose national population is 60 million.

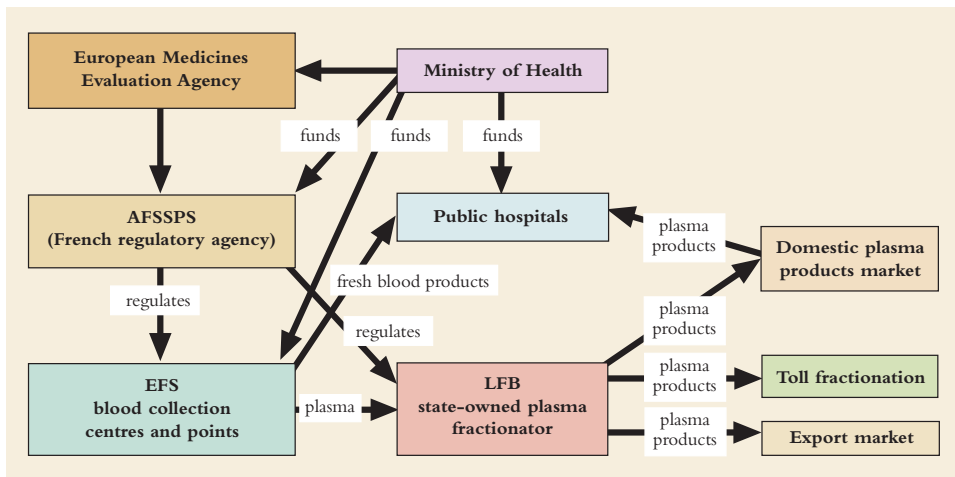
Fractionation and procurement

The *Laboratoire Français du Fractionnement et des Biotechnologies*, which is a majority state-owned company, enjoys the exclusive right to fractionate French plasma, and sells finished plasma products on the domestic market. There is no requirement, however, for French hospitals to purchase LFB product – they are free to acquire any brand of plasma derivative registered for sale in France.

In addition to fractionating French plasma, the LFB undertakes toll fractionation for other not-for-profit entities, in Belgium, Luxembourg, Brazil and Morocco. The LFB also sells finished plasma products on international markets, deriving 50% of its income in this way.

Regulation of the blood sector in France is delivered by the *Agence Française de Sécurité Sanitaire des Produits de Santé* (AFSSAPS). This agency operates under the broad guidelines promulgated by the *European Medicines Agency* (EMA).

Fig. 4.5 The blood supply system in France



The Netherlands

Collection

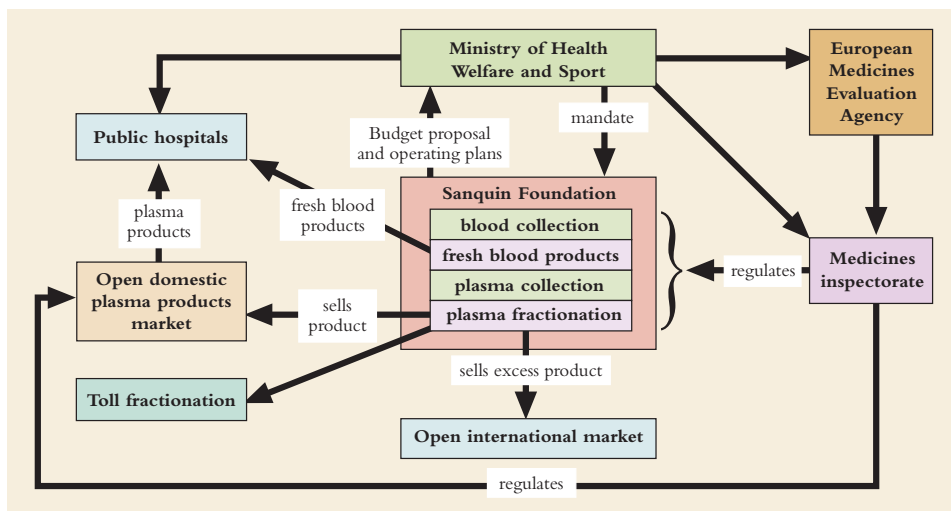
The blood system model adopted by the Netherlands comprises just two principal stakeholders: the Minister for Health, Welfare and Sport and Sanquin, a not-for-profit foundation.

The country’s national blood policy framework is set by the Ministry for Health, Welfare and Sport, while Sanquin provides all blood services, including whole blood collection, the supply of fresh blood products, plasma collection, and fractionation. The basis for the operations of the blood sector in the Netherlands is established in the Blood Supply Act (1998) (under review).

Under this Act, Sanquin provides the Minister with an annual budget and operating plan each year, and in return the Minister provides Sanquin with a mandate to deliver all blood services in the Netherlands in the ensuing 12 months. When issuing this mandate, the Ministry sets the prices at which Sanquin is to provide fresh blood products to hospitals over this period.

As a not-for-profit organisation, Sanquin is expected to run a break-even operation, or one that is marginally profitable. The foundation’s annual budget proposal to the Netherlands Government identifies the costs projected for Sanquin, together with the revenues it plans to generate from the provision of fresh blood products to hospitals and from the sale of plasma derived products on the open market. Sanquin also earns revenue from toll fractionation undertaken on behalf of both Belgium and Finland. Any profits made by Sanquin are retained in the business.

Fig. 4.6 The blood supply system in the Netherlands



Sanquin maintains a staff of 3162, the majority of whom are employed in collection activities. There are four regional blood banks in the Netherlands, and these centres operate a total of 300 collection sites, including mobile units.

The Netherlands is self-sufficient in fresh blood products (Sanquin supplies 123 public hospitals, including eight teaching hospitals), and is nominally self-sufficient in plasma derived products.

There are 503 000 active blood donors in the Netherlands, which has a total population of 17 million, and approximately 310 000 litres of plasma is collected each year. This quantity represents a collection rate somewhat higher than that in Australia, where approximately the same volume of plasma is collected from a population of 20 million.

Fractionation and procurement

Under the Netherlands Blood Supply Act, all domestically sourced plasma is retained by Sanquin, primarily for use in the manufacture of plasma products for domestic consumption. If Sanquin can demonstrate an excess, over domestic demand, in terms of plasma intermediaries or finished products, then such excess may be sold to another not-for-profit entity or (if this is not possible) on the open international market.

In the Netherlands, there is an open domestic market in respect of plasma derived products. Hospitals are free to purchase preferred brands and have no obligation to acquire Sanquin products, although the majority do so.

Norway

The defining characteristic of the Norwegian blood supply system is that it relies on toll fractionation for the provision of plasma derived products for domestic consumption.

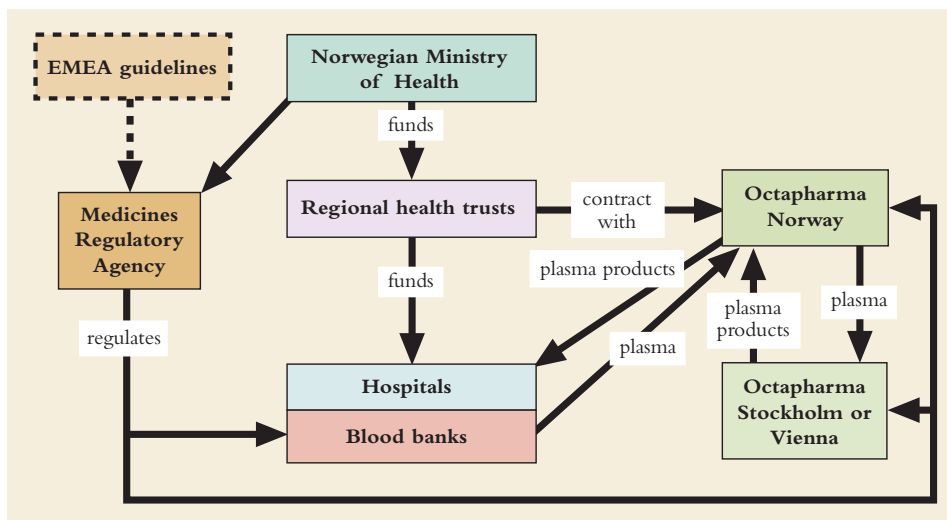
Collection

Norway's blood system is structured on a decentralised rather than a national model, reflecting historical cultural differences between geographic regions. The country's five health regions control the specialist services of the public hospitals within their jurisdictions, with all hospitals operating their own blood banks. Each of Norway's 85 public hospitals is also a discrete 'economic enterprise' under the direct oversight of the Minister for Health. Ninety-five per cent of the Norwegian population use public hospital services, which are provided free of charge to patients.

Plasma is collected by Norway's hospital blood banks, with collections annually averaging 50 tonnes (approximately 50 000 litres), from a population of 4.5 million. Forty tonnes of the plasma collected is earmarked for fractionation by Octapharma Norway, while the remaining 10 tonnes is used in the production of Octaplas®, a fresh frozen plasma replacement product, which is returned to Norway by Octapharma, for use in Norwegian hospitals.

There is currently some concern in Norway about the fact that the country's whole blood collections are increasingly under stress because of a growing demand for fresh blood products.

Fig. 4.7 The blood supply system in Norway



Fractionation and procurement

The quantities of Norwegian plasma that are designated for fractionation are transported by Octapharma Norway and consolidated into batch-size shipments for on-forwarding to an Octapharma fractionation plant in either Stockholm or Vienna. These toll fractionation arrangements are secured under a contract, based on fee-for-service, between Octapharma Norway and the South East Health Region (Helse Øst), acting on behalf of the country's four other health regions.

Octapharma has been providing fractionated products for Norway since 1988. All finished plasma products manufactured by the company from Norwegian plasma are returned to Norway, except those that are surplus to domestic requirements. Octapharma has the right to sell these excess products on the open market, but also maintains a central stock of plasma derivatives for distribution to Norwegian hospitals on demand.

Hospitals are not required to use plasma derived products manufactured by Octapharma from Norwegian plasma. If other brands are preferred, however, no additional Ministry funding is provided for their purchase.

Norway is not a member of the EU but does adhere closely to European Medicines Agency (EMA) guidelines regarding the regulation of blood and plasma collections and the manufacture of plasma derived products.

The Czech Republic

Collection

Blood collection in the Czech Republic is a function of blood banks attached to public hospitals; there is a network of 80 blood collection centres throughout the country. The Czech blood banks provide fresh blood products directly to their host hospitals, recovering plasma as a by-product of the processing of whole blood. Plasma is then sold to commercial fractionators, including Baxter Healthcare, Grifols and Octapharma, with hospitals retaining all revenue from their plasma sales.

Not all plasma can be sold, however. The fractionators purchasing plasma from Czech hospitals will deal only with those that have it available in quantities sufficient to constitute commercially viable batches. Plasma that cannot be sold to fractionators is discarded.

The Czech Republic collects approximately 80 tonnes (approximately 80 000 litres) of plasma per annum, from a population of 10 million (approximately half the rate of donation achieved in Australia).

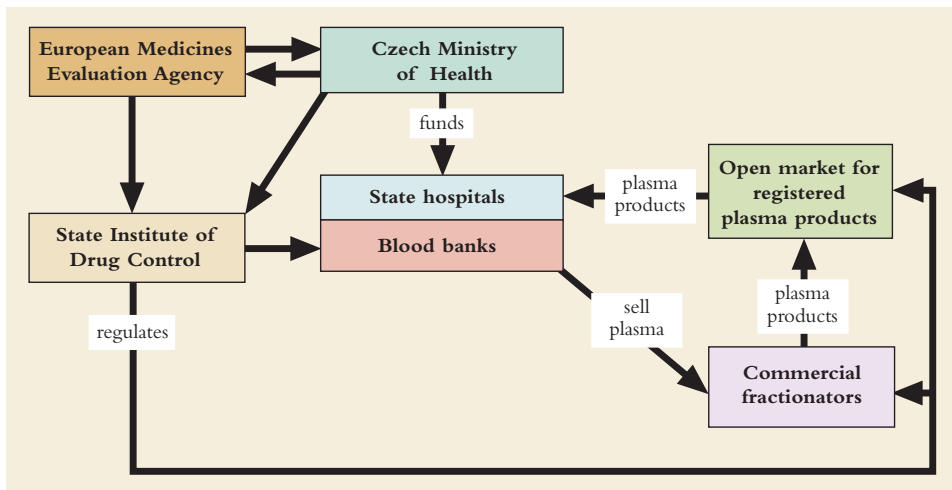
Fractionation

In 1996 the Czech Republic abandoned plans to build its own domestic fractionation plant, in favour of allowing hospitals to acquire plasma derived products from the open global market.

Procurement

The Czech Republic Ministry of Health funds the country's public hospital system, thus providing the means by which hospitals can acquire plasma derived products.

Fig. 4.8 The blood supply system in the Czech Republic



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The Ministry also publishes a price guide for plasma products, based on government funding allocations, although hospitals are free to acquire any brand of product available on the open global market (as long as all products purchased have either European or Czech registration).

The regulation of the Czech Republic's blood system is overseen by the State Institute for Drug Control, which applies Good Manufacturing Practice (GMP) and related standards, as per European Medicines Agency (EMA) guidelines and the EU Blood Directive, while also maintaining additional requirements specific to the Czech environment.

The Institute for Drug Control reports a high level of cooperation with other EU countries. For example, inspectorates from Austria and Spain are free to conduct audits of Czech blood banks from which plasma for fractionation is exported to these countries.

The Czech Republic has not issued a policy statement concerning self-sufficiency in respect of plasma products, but the EU has made recommendations in this regard and Czech authorities maintain a record of plasma exports and finished product imports, in order to calculate the degree of self-sufficiency being achieved. For the present, there is a notional excess of plasma output over procurements of plasma derivatives, because of marketplace price pressures affecting finished plasma products.

New Zealand

Collection

All blood collection services in New Zealand are the responsibility of the New Zealand Blood Service (NZBS), an entity operating under the auspices of the New Zealand Ministry of Health.

Providing a 'vein-to-vein' service for New Zealand health care consumers, the NZBS collects blood, manufactures fresh blood products, provides these products to hospitals, collects plasma, contracts for plasma to be fractionated offshore under a toll fractionation arrangement, and distributes plasma derived products to hospitals. The NZBS operates under a 'not-for-loss', or cost recovery, arrangement, which involves charging hospitals prices for delivered products that are sufficient to offset the operating costs of the Service.

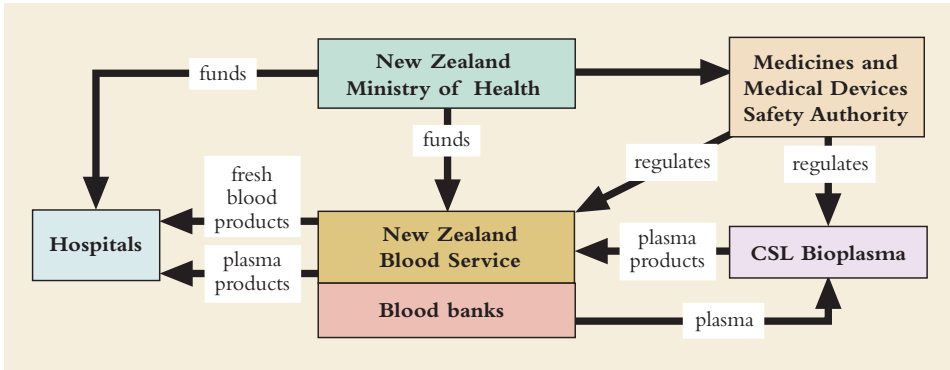
New Zealand is self-sufficient in fresh blood products and in plasma derivatives, with the exception of Rh(D) immunoglobulin. The NZBS is developing a three- to five-year strategic plan around its intention to maintain this self-sufficiency.

New Zealand collects approximately 38.5 tonnes (38 500 litres) of plasma per annum for fractionation, from a population of 4.5 million.

Fractionation and procurement

Plasma collected by the NZBS is provided to CSL Bioplasma for fractionation into a range of plasma derived products.

Fig. 4.9 The blood supply system in New Zealand



New Zealand has examined alternative options but has determined that the most cost-efficient approach is to continue its existing toll fractionation arrangements with CSL Bioplasma.

Other countries and regions

Russia

Russia currently imports the plasma derived products used in its hospitals, but has been developing a self-sufficiency strategy for several years. In early 2006, having decided to build a 600 000 litre fractionation facility, the Russian Government entered into a contract with Kedrion for a transfer of its fractionation technology.

Asia

A wide variety of arrangements with respect to plasma collection, fractionation, and domestic supply of plasma products, operate in Asia. Some Asian countries import all of their domestic requirements, while others try to maintain self-sufficiency but need to import finished products, and/or plasma intermediaries, to meet local demand.

- **China** has targeted self-sufficiency as an objective, has 30 domestic fractionators, and is closed to imports of all plasma products except albumin, the demand for which cannot be satisfied domestically. China does not fund widespread haemophilia care.
- **Japan** has four domestic fractionators, and their output is almost entirely designated for consumption within the Japanese health care system. Japan also imports some specialty products, and products for which the level of demand is such that it cannot be met domestically. The Japanese Blood Law explicitly stipulates self-sufficiency as an objective, meaning that products fractionated in Japan, from Japanese plasma, are likely to replace imports over time.
- **South Korea** has two domestic fractionators, is self-sufficient in plasma products, and is largely closed to imports (although it does import some specialty products and plasma fraction V, which is used for the manufacture of albumin).

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- **Taiwan** currently imports plasma derivatives for domestic use, but has recently introduced a blood law enshrining the principle of self-sufficiency in respect of plasma products, and the Taiwanese Government has announced its intention to construct a local fractionation facility.
- **India** has one domestic fractionator, although other parties have expressed interest in building further fractionation facilities. Demand for plasma products in India is, however, very low by the standards of more developed economies, and imports still constitute a significant share of the market.
- **Hong Kong, Malaysia and Singapore** all aim for self-sufficiency via toll fractionation, but currently also import plasma derivatives manufactured by commercial fractionators; these products are mainly for use in private hospitals.
- In other Asian nations, there is low demand for plasma derivatives. Some countries (Sri Lanka, Indonesia, Thailand and the Philippines) have signalled their intention to adopt toll fractionation arrangements, but are currently dependent on imports of commercial product.

Latin America

- **Brazil** has a strong national commitment to the treatment of haemophilia and as a result represents the largest plasma products market in South America. Currently importing significant quantities of commercially manufactured plasma derived Factor VIII, Brazil plans to move towards self-sufficiency and has established a national authority, Hemobras, to this end. Hemobras has called for expressions of interest with regard to the construction of a Brazilian fractionation facility. Brazil commenced toll fractionation in 2000 via open tender.
- **Argentina** has one small fractionation facility, with the majority of domestic demand for plasma derivatives being met by commercially fractionated imported product.
- **Mexico** imports commercially manufactured plasma products for domestic consumption, but is considering the construction of a local plant, to be used for toll fractionation.
- Other South and Central American nations use relatively small quantities of plasma derivatives, and demand is satisfied by imports of commercial product.

Eastern Europe

- **Hungary** has a fractionation facility of significant capacity.
- **Poland** aims for self-sufficiency through toll fractionation.
- Several other Eastern European countries have small fractionation facilities, but they do not operate on a commercial scale. In these countries, domestic requirements for plasma products are met primarily through imports.

Middle East

Demand for plasma products in the Middle East is focused mainly on albumin, Factor VIII and Factor IX.

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- **Israel** has two fractionation plants; these supply about half of the country's needs, with the remainder of domestic requirements being met by commercially manufactured imported product.
- **Egypt** at one time had a small fractionation facility, and a new plant is said to be under construction. In the past, Egypt has made moves towards implementing toll fractionation arrangements, but currently relies on imports.
- **Iran**, having operated a fractionation facility in the past, has reportedly entered into a contract for the construction of a new plant. Iran is also in the process of commencing toll fractionation.
- **Saudi Arabia** has for many years had plans for constructing its own fractionation facility, but the project is yet to take concrete shape.
- Other countries in the Middle East rely on imports for their plasma product supplies.

Africa

Throughout most of Africa, demand for plasma derived products is negligible. The major market for plasma derivatives is South Africa, which has a fractionation plant with the capacity to supply most of the country's requirements. Elsewhere in Africa, there are few to no sales of plasma products and no infrastructure for plasma collection and fractionation.

Chapter 5

Arrangements for production and distribution in Australia

Australia's arrangements for the funding and supply of plasma derived products are governed by the National Blood Agreement (2003). This agreement between the Commonwealth and the states and territories covers the supply of a broad range of blood products, blood-related products and blood-related services, to meet the clinical needs of Australian patients.¹

Australia's national blood arrangements represent a coordinated national approach to policy setting, governance, and management (fig. 5.1). Where other areas of the Australian health sector may be characterised by a division of roles and responsibilities between the federal and state and territory governments, or by bilaterally agreed joint funding agreements, the National Blood Agreement has established for the Australian blood sector a mechanism for joint funding, oversight and policy setting.

In accordance with the blood sector reforms embodied in this Agreement, the National Blood Authority (NBA) manages Australia's procurement arrangements with suppliers of blood products, coordinating supply on behalf of all Australian governments.

The Australian Red Cross Blood Service (ARCBS), Australia's national blood service, collects plasma from voluntary, non-remunerated donors. The ARCBS then provides plasma to CSL Limited, for fractionation at CSL's Australian plant. The plasma supplied to CSL is fractionated into a range of products designated for clinical use in this country; these are provided to recipients free of charge.

Under the Plasma Products Agreement (PPA) between CSL Limited and the NBA,² CSL is contracted to produce a comprehensive range of plasma products to meet Australia's needs. The PPA is a five-year contract, for the period 1 January 2005 to 31 December 2009.

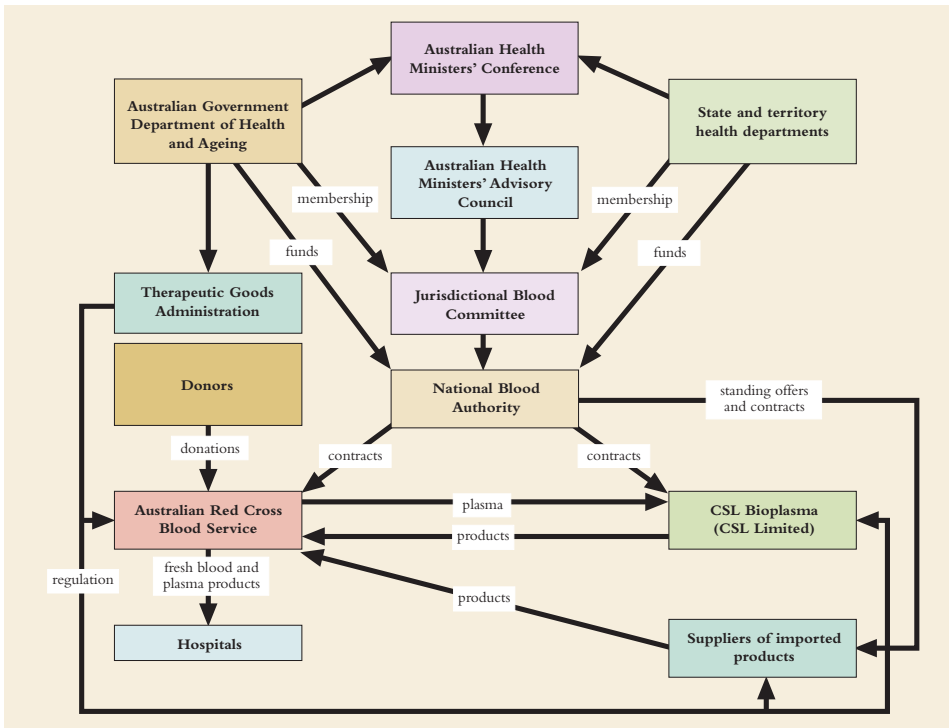
In line with the National Blood Agreement, and its aim of promoting national self-sufficiency in blood and blood products (the objectives and aims specified in the Agreement are outlined in the Introduction to this report), imported plasma products are supplied in Australia only when domestically fractionated plasma products cannot meet clinical demand, or in the event of supply chain risks.³ In addition, certain low-volume products are imported either because limited demand makes it uneconomic for CSL to produce them or because the technology used in their manufacture is not available in Australia.

1 *National Blood Agreement*, National Blood Authority, Canberra, 2003, p. 2, <http://www.nba.gov.au/PDF/national_blood_agreement.pdf>.

2 *Plasma Products Agreement* [edited version for publication on NBA website], National Blood Authority, Canberra, 2004, <<http://www.nba.gov.au/PDF/PPA%20for%20web.pdf>>.

3 See Australian Health Ministers' Conference, *AHMC Policy Statement on National Self-Sufficiency in the Supply of Blood and Blood Products*, National Blood Authority, Canberra, 2006, <http://www.nba.gov.au/articles/article_20060419_01.htm>.

Fig. 5.1 Australia’s national blood arrangements



Source: Developed by the Department of Health and Ageing.

Note: The Australian Red Cross Blood Service (ARCBS) is an operating division of the Australian Red Cross Society.

The National Blood Agreement

In 2001, the Review of the Australian Blood Banking and Plasma Product Sector (the Stephen Review) recommended that Australia’s federal, state and territory governments enter into an agreement to establish a national approach to the oversight and management of Australia’s blood supply system.⁴ In 2003, adopting the recommendations of the Stephen Review, the Commonwealth, state and territory governments signed the National Blood Agreement.

The key features of the National Blood Agreement are:

- (a) national agreement on the objectives of Governments for the Australian blood sector;
- (b) a primary policy setting and governance role for Commonwealth, State and Territory Health Ministers, supported by a Jurisdictional Blood Committee of senior officials;
- (c) a National Blood Authority, to manage the national blood supply;
- (d) joint funding of the national blood supply by the Commonwealth and the states and territories; and
- (e) a nationally agreed framework for the management of safety and quality issues within the Australian blood sector.⁵

⁴ *Review of the Australian Blood Banking and Plasma Product Sector*, Commonwealth of Australia, Canberra, 2001; also available online at <<http://www.nba.gov.au/PDF/report.pdf>>.

⁵ *National Blood Agreement*, p. 1, <http://www.nba.gov.au/PDF/national_blood_agreement.pdf>.

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The present Review of existing and alternative arrangements for the fractionation of plasma collected in Australia will not change the objectives and aims for the Australian blood sector as set out in the National Blood Agreement.

Under the terms of the Agreement, the Commonwealth provides 63% of the funding for Australia's national blood arrangements, and the remaining 37% is provided by the state and territory governments, according to their relative demand for blood and blood products.

The Australian Health Ministers' Conference (AHMC), a committee comprising all nine Australian health ministers, has responsibility for the oversight and management of the Australian blood sector.

Australia's nine jurisdictions are similarly represented on the Jurisdictional Blood Committee (JBC), a subcommittee of the Australian Health Ministers' Advisory Council (AHMAC). The JBC oversees the National Blood Authority on behalf of the health ministers, and the JBC members represent jurisdictional positions on issues relating to policy, demand, supply planning, product distribution, funding, and the assessment of emerging products, services and technologies. The JBC is responsible for providing advice and support to AHMC on these matters.

As signatories to the National Blood Agreement, Australia's Commonwealth, state and territory governments are responsible for:

- establishing the policy framework for, and specific policies relating to, the national blood supply system
- overseeing the NBA's management of the national blood supply system
- developing and implementing best-practice systems within each state and territory health system, so as to promote efficient use and minimal wastage of blood and blood products
- providing information to the NBA in relation to demand for blood and blood products
- managing issues associated with the supply of blood and blood products to health care providers, and with the use of blood and blood products in clinical settings.

Issues relating to safety and quality within the blood sector are a focus of the National Blood Agreement. The Agreement makes it clear that addressing these issues is a collaborative exercise that is dependent on the cooperation of a number of parties, with the Therapeutic Goods Administration (TGA) having responsibility for regulating product safety and production standards. The key roles of the JBC with respect to safety and quality are, firstly, to seek evidence-based advice on the safety, quality, efficacy and cost-effectiveness of existing or proposed blood products and blood-related products, services or other activities; and, secondly, to arrange for the preparation of evidence-based guidelines promoting the safe, efficient and effective collection, distribution, storage and use of blood and blood products.

Schedule 4 of the National Blood Agreement, which sets out the 'Process for Initiation, Evaluation and Implementation of National Blood Supply Change Proposals', acknowledges the role of appropriate evidence-based evaluation and advice in

supporting decisions about changes to products or services funded under the national blood arrangements.⁶

Proposals regarding changes to blood products or blood-related services are initially considered by the JBC. The JBC is entitled to request evidence-based evaluations, advice or information, from relevant bodies, on a range of issues – including safety, efficacy and cost-effectiveness – in order to reach a finding on whether it should recommend that a proposal receive funding. The proposal is then referred to AHMC for a decision.

Under the national blood arrangements, a National Supply Plan and Budget is agreed on an annual basis by AHMC. The budget approved by AHMC for 2006–07 provides funding of A\$650.7 million, which includes contributions of A\$10.6 million for the operations of the NBA. The proposed expenditure for the supply of blood and blood products in 2006–07 is A\$626.01 million, an increase of 10.6% on total expenditure in 2005–06.⁷ This figure includes: funding for the Australian Red Cross Blood Service to provide fresh blood products, to collect plasma for fractionation, and to manage distribution and support services (A\$297.7 million); and contracts with suppliers of domestically manufactured plasma products, and imported plasma products and recombinant products, supplied under the national blood arrangements.

When a decision taken by the JBC would affect a jurisdiction in terms of material effects on clinical care and outcomes, or material financial implications, or would materially restrict supply or alter the range of products available, then that jurisdiction must agree to the proposed change. In the event that a decision has financial implications for jurisdictions, those potentially affected must seek agreement from their respective financial authorities. Only upon such agreement can the National Supply Plan and Budget be approved by AHMC.

The role of the National Blood Authority (NBA)

The National Blood Authority is a statutory agency established under the *National Blood Authority Act 2003* (Cwlth). Essentially the purpose of the NBA is to manage the national blood supply system, on behalf of all Australian governments and in accordance with the objectives and aims of the National Blood Agreement. The NBA is therefore central to Australia's national blood arrangements.

The roles of the NBA, as stipulated in the National Blood Agreement, may be broadly grouped into the following functions:

- monitoring demand for blood and blood-related products and undertaking annual supply planning, production planning and budgeting, for approval by governments
- managing the national blood supply so as to ensure that there is an adequate supply of blood products to meet patients' needs, as determined by clinical practice
- negotiating and managing contracts with suppliers of blood, blood products and blood services
- developing the national price list for blood products
- information gathering, and advising relevant parties on developments in the blood sector in Australia and internationally

⁶ *National Blood Agreement*, pp. 27–9, <http://www.nba.gov.au/PDF/national_blood_agreement.pdf>.

⁷ See National Blood Authority, *Annual Report 2005–06*, National Blood Authority, Canberra, 2006.

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- establishing contingency and risk mitigation measures in relation to the national blood supply.

Among the contracts between the Commonwealth and suppliers of blood products are the Plasma Products Agreement with CSL Limited, and contracts with suppliers of other plasma derived blood products and recombinants. The products purchased through contracts with suppliers are listed in the National Supply Plan.

The NBA notifies the Australian Red Cross Blood Service annually of the volume of plasma to be supplied to CSL for fractionation. Under the terms of the PPA, the NBA must give CSL the Annual Supply Estimate for a particular financial year by no later than the preceding 30 November. Although these forecasts are not binding on the NBA, it is required under the terms of the PPA to purchase 95% of the plasma products produced in accordance with the Confirmed Quarterly Requirements that the NBA furnishes to CSL six months in advance of each quarter.

The ARCBS and suppliers alike, including CSL, assert that these short-term forecasting arrangements do not provide a reasonable opportunity for strategic business or capital investment planning.

Contracts with blood product suppliers include requirements that they maintain reserve holdings of products in order to ensure that timely and adequate supplies are available to meet clinical need.

A further important role of the NBA is in developing and promoting demand management strategies. Some increase in demand for blood products is inevitable, as a consequence of demographics and the changing nature of clinical practice, but measures to optimise the appropriate use of plasma products are desirable, and are in keeping with the aims of the National Blood Agreement. Following the commissioning of research, and consultations with stakeholders, the NBA has issued evidence-based guidelines for the clinical use of Factor VIII and Factor IX (both plasma derived and recombinant), and is currently also supporting the development by the Jurisdictional Blood Committee of revised criteria for the use of intravenous immunoglobulin (IVIg).

The NBA has a number of responsibilities with regard to safety and quality. It imposes contractual obligations on suppliers, whereby they are required to meet safety and quality standards. It also has a role in information gathering, in working with other bodies on issues of safety and quality, and in providing information and advice to the JBC. In addition, as directed by the JBC, the NBA must arrange evidence-based assessments of blood products and services, and the development of strategies to promote the safe, efficient and effective collection of blood and distribution, storage and use of blood and blood products.

The NBA administers the National Managed Fund, which was established to manage the product liability risks associated with all blood products provided and distributed by the ARCBS. The Australian Government, all state and territory governments and Australian Red Cross pay an annual contribution to this fund, which came into effect on 1 July 2000 to cover potential liabilities arising from blood-borne disease

transmission subsequent to that date. (State and territory governments have separate arrangements in place to cover liability claims made against the ARCBS before that date.) To date, no claims have been made against the National Managed Fund.

Contracts with other suppliers require them to maintain product liability insurance.

The role of the Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration, an arm of the Australian Government Department of Health and Ageing, is responsible for regulating with respect to the safety, quality and efficacy of blood, blood components and plasma derivatives in Australia, under the *Therapeutic Goods Act 1989* (Cwlth). The TGA requires that domestically sourced and imported plasma products must meet the same standards for registration in Australia.⁸

The TGA sets comprehensive and stringent regulatory requirements to ensure safety and quality throughout the supply and manufacturing chain for plasma products. The role of the TGA in monitoring compliance with these standards is particularly crucial, given the serious consequences that would arise from the transmission of an infectious agent through plasma products. The TGA regulates the activities of both the Australian Red Cross Blood Service and CSL Limited at all stages of collection, supply, and the manufacturing process.

In due course, the regulation of plasma derived products will transfer to the Australia New Zealand Therapeutic Products Authority, which will replace the TGA and its New Zealand equivalent, Medsafe. It is understood that, if required, both Australia and New Zealand will continue to be able to impose country-specific requirements with regard to regulations affecting blood, blood components and plasma derivatives.

The regulatory framework concerned with the safety, quality and efficacy of plasma products is addressed comprehensively in Chapter 8 of this report.

Quality assurance for laboratory testing and for tests within the blood sector

Quality assurance for serodiagnostic and nucleic acid screening test kits used to detect blood-borne viruses is provided by the National Serology Reference Laboratory, Australia (NRL); these kits are regulated to the highest level in Australia. Besides evaluating test kits and monitoring their ongoing, in-use performance, NRL provides various other services to the blood sector. These include the verification of testing protocols for blood services, for plasma fractionation services, and also for diagnostic and therapeutic testing programs.

The founding purpose of the NRL, which was established in 1985 in response to the emergence of HIV and the availability of HIV test kits, was to evaluate the quality of these test kits and monitor the integrity of their ongoing performance. The NRL now quality assures all Good Manufacturing Practice (GMP)-licensed facilities, to ensure that kits for the detection of blood-borne viruses are functioning to specifications. The NRL also operates quality assurance programs for all laboratories, in order to ensure the ongoing quality of test kits during their use; adjudicates on results in problematic samples; conducts targeted research; and leads training and

⁸ For further information on the regulation of blood and blood products by the TGA, see Therapeutic Goods Administration, *Blood & Tissues Regulation*, Therapeutic Goods Administration, Canberra, 2006, <<http://www.tga.gov.au/bt/index.htm>>.

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education endeavours designed to secure laboratory best practice and quality. The NRL provides information to the Therapeutic Goods Administration on the integrity of test kits, both prior to their registration and during their use.

Funded primarily through the Australian Government Department of Health and Ageing, the NRL is located at St Vincent's Institute in Melbourne.

The role of the Australian Red Cross Blood Service (ARCBS)

The Australian Red Cross Blood Service, Australia's national, not-for-profit blood service, is an operating division of the Australian Red Cross Society, which is constituted under Royal Charter. The ARCBS is active in all states and territories, operating 119 collection centres, including mobile facilities. All sites collect whole blood donations, and a selection of the larger facilities also collect source plasma via plasmapheresis. The ARCBS processes and separates whole blood donations into: red blood cells, platelets and plasma. The fresh blood products and some of the plasma are supplied directly to hospitals and clinicians. The bulk of the plasma collected is sent to CSL's Broadmeadows (Melbourne) plant for fractionation (see below). In 2005–06 the ARCBS supplied 308 tonnes of plasma to CSL.⁹

Approximately 500 000 Australians donate whole blood and plasma every year. These donors play a vital role in Australia's blood system. In 2005–06 the number of whole blood donors was 479 251, and the number of donors of source plasma, via apheresis, was 33 738. With many donors donating more than once a year, the total number of collections in 2005–06 was 1 111 154. Over the past five years, the number of collections per annum has increased from 965 821 in 1999–2000 to the current levels, representing an average annual increment of approximately 3%.

The average rate of growth in collections of plasma destined for fractionation between 2000–01 and 2005–06 was 4.6% per annum. Factors influencing the supply of starting plasma for fractionation, and donor recruitment and retention issues, are discussed in Chapter 7.

In addition to collecting whole blood and plasma from the general pool of donors, the ARCBS identifies and collects plasma from donors who have a high level of antibodies to particular pathogens. Plasma obtained from these donors is used in the manufacture of hyperimmune products.

In line with Therapeutic Goods Administration requirements, the ARCBS applies testing procedures to monitor the safety of the blood and blood components that are collected. Every donation is screened for the presence of certain viral markers (e.g. for HIV, hepatitis B and hepatitis C). Guidelines are in place to prevent donations from persons with known risk factors for, or behaviours that could increase the risk of, blood-borne infection.

Plasma for fractionation is delivered to CSL's Broadmeadows plant from eight ARCBS locations around Australia (table 5.1). Transportation is the responsibility of the ARCBS, and refrigerated road and air transport is used.

Table 5.1 Transport frequencies for shipments of plasma from ARCBS facilities to CSL

Vic.	NSW	Tas.	Qld	WA	NT	SA
Daily	Weekly	Weekly	Fortnightly	2 x week	2 x week	2–3 x week

Plasma is transported at or below -20° to -25°C . Individual donations, each with a small sample for testing attached, are shipped in cartons containing up to 17 apheresis donations or 33 donations of recovered plasma. A consignment disk verifies the donations that are contained in each plasma consignment.

Finished plasma products are generally shipped from the CSL fractionation plant to the ARCBS, which then carries responsibility for distribution (as it does for fresh blood products), through its business units in cooperation with hospitals, pathology laboratories and clinicians. There are two exceptions: intramuscular (normal) immunoglobulin (IMiG) is distributed in some states directly from local CSL facilities, with or without the ARCBS playing a role in ordering; and the 4000 IU IV tetanus product is shipped direct from CSL to customers.

The ARCBS undertakes the distribution of specific imported plasma products such as the IViG products Sandoglobulin® and Octagam®. Other plasma derived and recombinant products are distributed by suppliers to health care providers, under arrangements that vary across states and territories.

A supply agreement between the Australian Red Cross Society and CSL Limited covers their relationship with respect to the supply and delivery of plasma and the manufacture and distribution of plasma products. The agreement addresses, for example:

- the types and quantities of plasma to be supplied and delivered by the ARCBS to CSL
- the types and quantities of products to be manufactured by CSL from plasma supplied by the ARCBS
- the minimum and maximum batch sizes required for the manufacture of products
- the delivery of products (e.g. delivery dates, proposed contents of consignments)
- the supply and delivery of plasma
- the manufacture, yield, packaging, labelling and distribution of plasma products
- risk management and quality audits of both parties
- measures for addressing noncompliance under the Therapeutic Goods Act 1989, and related remedial action
- the establishment and maintenance of a national reserve of plasma products
- the development of new products by CSL from plasma supplied by the ARCBS
- the agreement of a five-year forecast
- the provision of services and support to end users of plasma products.

The role of CSL Limited

CSL Limited, through its CSL Bioplasma business unit, is the sole manufacturer of products fractionated from Australian plasma. Production takes place at the company's fractionation plant at Broadmeadows, Melbourne, which replaced an older facility at Parkville and has been fully operational since 1995. In accordance with Therapeutic Goods Administration regulation, CSL conducts a number of procedures to ensure the safety and quality of its finished plasma products. Plasma received from the Australian Red Cross Blood Service is retested by CSL. The tests include nucleic acid amplification testing for both HIV and hepatitis C. Purification and viral-inactivation measures are undertaken during the manufacturing process. Strict segregation, cleaning and sterilisation practices are observed, to prevent cross-contamination from plasma from overseas sources. Systems are in place to trace plasma from donor to recipient.

Under the Plasma Products Agreement, CSL Limited is subject to performance guarantees and to other contract performance requirements, relating to contingency supplies, efficiency gains and risk sharing, and financial penalties for non-performance. The PPA stipulates key performance measures and other mechanisms that allow the National Blood Authority to monitor, and if necessary influence, performance under the contract.¹⁰

CSL Limited maintains the National Reserve of plasma products for the NBA, under a contractual arrangement separate to the PPA. Products in the National Reserve are held at CSL sites at several locations across Australia. These products can be made available at very short notice to mitigate any shortfalls in supply, or in the event of an emergency requiring extraordinary quantities of plasma derivatives.

In addition to supplying the Australian market, CSL Bioplasma's Broadmeadows plant carries out toll fractionation of plasma for New Zealand, Malaysia, Singapore and Hong Kong.

Legislative obligations of CSL

In 1994 CSL became a public company limited by shares and taken to be registered under the *Companies Act 1981* (Cwlth). At this time, certain legislative obligations were imposed upon CSL Limited, to ensure that the company, as the sole supplier in Australia of plasma products manufactured from Australian-donated plasma, would act in the national interest. Part 3A of the *Commonwealth Serum Laboratories Act 1961* (CSL Act) sets out the requisite national interest safeguards with regard to CSL's articles of association, on and from the day of privatisation. These legislative provisions represent requirements considered necessary for the protection of the national interest when CSL ceased to be a public authority but continued to process Australian-donated plasma.

In summary, the national interest provisions of the CSL Act:

- Provide that CSL Limited is to remain Australian-controlled. For example, the Act requires that CSL's articles of association include limits on foreign control. In particular, no significant foreign shareholders may vote in circumstances where

one third of the company's directors are being appointed, replaced or removed at any one time. CSL is also required to maintain a register of foreign-held voting shares and must provide this register, or a copy thereof, to the Minister if requested to do so by the Minister, in writing.

- Require CSL, when manufacturing plasma products from Australian-donated plasma, to produce those products in Australia.
- Prohibit CSL from disposing of its manufacturing facility at Broadmeadows, which may not be sold or encumbered without Ministerial permission.
- Provide for court orders where the Commonwealth can show that CSL is breaching, or threatening to breach, a contractual obligation.

If a tender process for the supply of plasma products manufactured from Australian-donated plasma were introduced, there would be a need, in light of the existing obligations placed on CSL, for the tender process to include express provisions to ensure consistent treatment of all tenderers.

The clinical setting

The delivery of plasma derived products to patients completes the manufacture and distribution cycle for plasma products in Australia. A discussion of product delivery necessarily involves a consideration of the roles and perspectives of organisations and individuals involved in the administration and use of plasma derivatives: hospitals; jurisdiction-specific bodies responsible for managing the supply of plasma products; professional bodies and user groups; and recipients of plasma products and patient support/advocacy groups.

Access to plasma products

The process by which a patient accesses plasma derived products involves, in very broad terms, a clinician ordering a product from the Australian Red Cross Blood Service. In the case of certain products in short supply, the transfusion medicine specialist at the ARCBS makes a decision on whether the product should be provided in the quantity in which it has been requested. In most jurisdictions, the ARCBS shares its 'gatekeeper' role. At the time an order is placed, the ARCBS transfusion medicine specialist may raise concerns with the treating doctor, and perhaps with other clinicians, about the product ordered, the dose/s requested, or the reason for the order. At a later stage, review of treatment decisions takes place, particularly through blood and IVIg user groups, comprising representatives of the ARCBS and of state and territory governments, clinicians, and patients. Similar decision-making processes inform the use of both domestically sourced and imported plasma products.

The state and territory governments, the ARCBS and clinician groups monitor appropriate use of plasma products in terms of prescriber behaviour (but do not have data on responses to treatment).

There are blood user groups in most jurisdictions in Australia; these groups may comprise representatives of the ARCBS, hospitals, clinicians, public and private pathology services involved in the distribution of blood products, and major medical

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colleges. Some user groups are associated with individual hospitals, others with entire health systems.

In New South Wales, Victoria, Queensland and South Australia, IVIg user groups provide advice on the distribution and use of IVIg in their respective states (as of late 2006, Western Australia was proposing to formally establish an IVIg Reference Group). These groups include clinicians from specialty areas such as immunology and neurology, consumer representatives, patients and representatives of the ARCBS and/or the state or territory department of health. Some of the groups are managed by the ARCBS office in their state, while others are committees of health departments.

The chairs of the IVIg user groups are invited to national forums on IVIg held by the National Blood Authority. On these occasions, the states and territories where there is no user group nominate as their representative a government official with an appropriate policy portfolio.

Access to intravenous immunoglobulin (IVIg)

The carefully constructed arrangements for access to plasma products in Australia reflect the fine balance between supply and demand for these products, in particular for IVIg, which is the greatest driver of demand for plasma in this country and internationally. IVIg currently accounts for close to two-thirds of Australia's expenditure on plasma products, with consumption, and therefore expenditure, continuing to increase significantly. Consequently, across the blood sector there is a strong interest in ensuring that IVIg and other plasma products are being used effectively and appropriately in clinical settings. There is also an ethical obligation in this regard, given that the source material for these products is freely donated by members of the public.

In Australia, the distribution of IVIg within the state and territory health systems is generally determined with reference to the review of IVIg usage that was carried out by the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council and released in June 2000.¹¹ There are over 70 clinical indicators for which IVIg has been reported as having some benefit. These are grouped in the AHMAC report as:

Category 1: Indications for which there is now convincing evidence of benefit.

Category 2: Indications for which currently there is inconclusive evidence of benefit.

Category 3: Conditions for which there is convincing evidence that IVIG has no benefit.¹²

There are various estimates of the proportions of IVIg used in respect of each of these categories. According to Australian Red Cross Blood Service data presented in 2004, the 19 conditions grouped as Category 1 by AHMAC accounted for 98% of the IVIg issued by the ARCBS. Because of the increasing demand for IVIg and because the current guidelines date to 2000, the Jurisdictional Blood Committee, through a specially created IVIg Working Party with secretariat support from the

11 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>>.

12 *ibid.*, p. 2. Where use of IVIg for Category 3 indications is approved, it is often as a 'last resort' in life-threatening circumstances when other therapies have not been effective.

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National Blood Authority, is developing revised criteria. These are expected to be available in 2007.

All jurisdictions are affected by the high cost of and high demand for IVIg. Arrangements for the supply of IVIg vary by jurisdiction. Queensland, for example, has a relatively high per capita usage rate for IVIg by comparison with usage rates in other Australian states and territories, and therefore has an added impetus for promoting the appropriate use of the product. Queensland Health has instituted an IVIg Working Group, chaired by the Clinical Adviser (Haematologist) to the Queensland Blood Management Program, to provide clinical advice on IVIg therapy. One of the Working Group's responsibilities is to review all applications for AHMAC Category 2 IVIg indications, before the product can be provided to patients whose conditions fall within this category.

New South Wales also has relatively strict guidelines. It is understood that until recently the use of IVIg was approved for the treatment of a narrower range of conditions than those encompassed by AHMAC Category 1, with this range being expanded to reflect the national guidelines in 2006. In addition, price signals in respect of IVIg are imposed on the state's Area Health Services.

At the Royal Adelaide Hospital and other major hospitals in South Australia, a patient's treating clinician does not order IVIg directly from the ARCBS transfusion medicine specialist, but instead discusses the indication for IVIg with a senior haematologist at the hospital or with a state IVIg specialist. If it is agreed that IVIg treatment is appropriate, the haematologist or a transfusion medicine scientist at the hospital contacts the ARCBS and arranges for the supply and delivery of IVIg. The involvement of a hospital haematologist or a state IVIg specialist provides a formal mechanism for gathering information on patient outcomes following the administration of IVIg (or indeed on patient outcomes where a decision has been made not to use IVIg). For example, a patient's treating doctor may provide the haematologist with copies of notes relevant to the progress of the treatment protocol.

The SA IVIg User Group, which includes clinicians, ARCBS representatives and SA Department of Health officers, reports to the ARCBS and the Department. The User Group provides a forum for discussing and achieving consensus on policies and protocols for IVIg use, and plays an important role in ensuring that the product is used appropriately and in containing or minimising inappropriate use. When a clinician makes a request to commence IVIg therapy for a patient with a condition that falls outside the indications covered by AHMAC Category 1, and in cases that otherwise represent non-routine usage, the IVIg User Group considers and discusses de-identified information about the case. The User Group will then make a decision on whether to recommend the use of IVIg in the circumstances, whether other therapies should be used instead, or whether a time-limited trial of IVIg is indicated.

An additional measure that has been introduced in South Australia to support clinicians in the appropriate use of IVIg is the establishment of an IVIg Clinical Management Program. Under this program, a clinical nurse consultant, based in the public sector and funded by the SA Department of Health, takes an active role in the review of individual patients' treatment regimes, in consultation with treating doctors. The program represents a collaborative approach, drawing upon the resources

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of the Department of Health and the ARCBS and upon guidance from clinician members of the SA IVIg User Group.

The variations in authorisation procedures for the usage of plasma products in Australia reflect local clinical practices and relationships, health care delivery systems, the sizes of the populations served (and hence the numbers of patients needing IVIg), and the numbers of clinicians involved in making requests for the product.

At times, shortages of IVIg can occur. This is particularly true of domestically sourced product, due to factors such as variations in volumes of starting plasma and the time lag necessarily involved in responding to increased demand (given that the production process takes approximately three months). There may also be localised shortfalls, arising from variations in demand or from differing jurisdictional mechanisms for managing the provision of plasma products, notably IVIg, to end users. Issues of concern to health professionals and consumer groups, in relation, for example, to changes to dosage regimens, may stem from localised shortages or policies for authorisation of use.

As an example of how a health system manages IVIg shortages, the policy in Western Australia is that no patient will be transferred from one IVIg brand to another unless there is a clinical reason to do so. Decisions to use imported brands are therefore made with reference to clinical indications, also taking into account whether a treatment regimen is expected to be short-, medium- or long-term. Patients who have a poor response to Intragam® P may be treated with an imported brand to determine whether they receive greater benefit from it. A patient for whom there are improved outcomes as a result of using an imported brand will continue on it if he or she is being treated with IVIg in the longer term.

Hospital transfusion committees

Policies and procedures relating to the use of plasma products in accordance with best-practice guidelines, are developed through collaboration between hospitals, health departments at the jurisdictional level, the Australian Red Cross Blood Service, health care providers and clinician groups. Hospital transfusion committees, although not in place at all major hospitals, have an important role in overseeing transfusion practices and in promoting the safe and appropriate use of blood and blood products. Hospital-based policy is a strong institutional tool for promoting the safe and appropriate administration of blood, plasma and other biologicals.

Professional bodies

The range of professional bodies associated with the Australian blood sector is broad and diverse, and many of these groups provided submissions to the Review or were consulted during the review process (see Annexes B and C). The use of plasma products is of particular significance within the medical specialties of haematology, immunology, neurology, nephrology and intensive care.

Clinicians have the determining role in deciding the day-to-day treatment that patients receive, and key concerns for treating doctors include product safety and timely access to adequate doses. Variations in clinical practice reflect the evidence base available as a guide to decisions about prescribing. This evidence base is determined by knowledge, in the form of a growing body of clinical studies and anecdotal reports, and is overlaid with clinicians' and patients' preferences or

perceptions about risks and outcomes. In the case of some conditions for which IVIg in particular seems efficacious, the evidence base is currently limited.

Clinical haematologists, generally Fellows of the Royal College of Pathologists of Australasia and Royal Australasian College of Physicians, and represented by the Haematology Society of Australia and New Zealand (HSANZ), are the physicians usually responsible for the prescription of plasma derived products to patients with bleeding disorders and to many patients with immune deficiencies. Haematologists are responsible for the supervision of haematology laboratories in teaching hospitals and in major regional hospitals and manage hospital transfusion services, which coordinate the storage and supply of plasma products for the majority of Australian patients. Some members of HSANZ are also involved in the collection of plasma through the Australian Red Cross Blood Service.

The Australian Haemophilia Centre Directors' Organisation (AHCDO) is the peak medical body for haemophilia and related bleeding disorders in Australia, and its members are the medical directors of this country's 16 Haemophilia Treatment Centres. As well as providing medical advice to governments and health services, AHCDO maintains the Australian Bleeding Disorders Registry (ABDR). The ABDR was established to track the prevalence of bleeding disorders, and the treatment outcomes for people with bleeding disorders. It has been expanded to incorporate data on usage of treatment products, including plasma and recombinant therapy.¹³

Professional organisations also have a key role in carrying out studies relating to the efficacy of plasma products. The Australia and New Zealand Intensive Care Society, for example, organised the clinical trials for the Saline versus Albumin Fluid Evaluation (SAFE) study, published in 2004.¹⁴

Patient support and advocacy groups

A number of organisations exist to represent the interests of people with medical conditions that are treated with plasma products. The Haemophilia Foundation of Australia (HFA) and its associate organisations at the state and territory level represent people with bleeding disorders. There are also nationwide and state-based organisations representing people who are diagnosed with conditions for which IVIg is a therapy, such as primary immune deficiencies, Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy. Consumer representatives on IVIg User Groups may be drawn from these organisations. Other groups with an interest in the plasma products sector are those concerned with illnesses that in the past have been transmitted through the blood supply, most notably HIV/AIDS and hepatitis C.

In light of the inherent risks associated with blood products, product safety is a key concern for many of these groups. Large numbers of recipients of plasma products – most significantly, people with bleeding disorders – contracted HIV in the early 1980s, and hepatitis C during the 1980s and early 1990s, as a result of receiving

13 Not all New South Wales data is reported on the ABDR, and details of people with haemophilia who receive care outside the Haemophilia Treatment Centre network (e.g. from private practitioners) are not recorded on the register.

14 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. The SAFE study showed that the all-cause 28-day mortality rate for critically ill patients was no different for patients treated with albumin, when compared with patients treated with saline. These findings contrasted with those of the 1998 Cochrane Report, which had suggested that the mortality rate for critically ill patients given albumin was higher than for those given alternative treatments.

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contaminated plasma products derived from plasma collected from voluntary, non-remunerated Australian donors and manufactured in Australia.

The enduring consequences of the transmission of HIV and hepatitis C through plasma products, combined with the subsequent emergence of potential threats to the safety of these products (e.g. variant Creutzfeldt-Jakob disease (vCJD)), mean that the safety of plasma derivatives is a fundamental concern across the spectrum of plasma product recipients, but is of particular significance from the perspective of the haemophilia community. While most people with bleeding disorders now receive recombinant products, people with von Willebrand's disease will continue to require treatment with a plasma derived product such as Biostate® to replace von Willebrand factor. Treatment with plasma derived clotting factors can also be required for other clinical reasons, such as 'tolerising' regimens for people with haemophilia and inhibitors.¹⁵

The adequate supply of plasma products is a major concern of patient support groups, as it is for clinicians. Historically there were chronic shortages of plasma derived clotting factors in Australia until recombinants were introduced, and shortages of IVIg (see above) have been experienced in recent years. In general, it can be said that groups representing recipients of plasma products consider that strong controls and accountability in relation to safety, as well as ensuring adequacy of supply, are paramount.

Naturally there are differences in perspective among people with particular medical conditions. For example, some patients may have concerns about the risks involved in transferring from a plasma product with which they are familiar to an alternative, even if the evidence base does not suggest any increased likelihood of adverse outcomes.

Humanitarian aid is an important part of the advocacy efforts of haemophilia support groups. The World Federation of Hemophilia (WFH) and its member organisations (including HFA) advocate strongly for improved access to clotting factor replacement therapies in developing countries. The WFH has estimated that 25% of the world's haemophilia community receive adequate treatment. The remaining 75% are either inadequately treated or undiagnosed altogether.

Summary

The current arrangements for plasma products in Australia were developed to meet Australian needs, and are unique. These arrangements reflect many factors, including Australia's geographical isolation, demographics, community attitudes, clinical practices, and expectations about the supply, quality, safety and efficacy of products.

¹⁵ Inhibitors are antibodies that recognise clotting factors administered in factor replacement therapy as 'foreign' and attack and neutralise the Factor VIII or Factor IX that has been introduced to the body. The procedure of administering high doses of clotting factors to 'swamp' these inhibitors is known as tolerisation.

Chapter 6

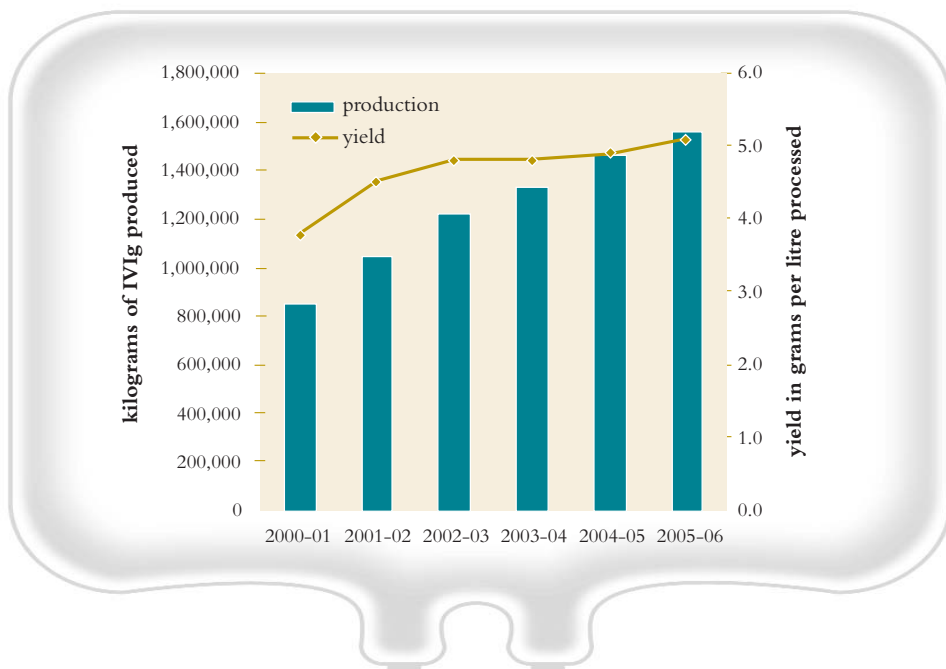
Demand for plasma products in Australia

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.

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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.

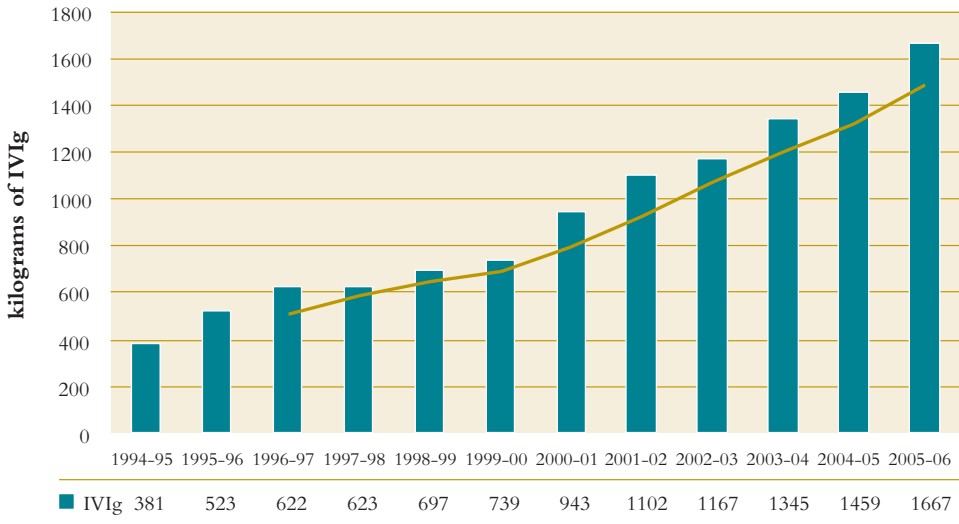
For the remaining plasma products manufactured in Australia, supply generally now meets or exceeds demand.

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.

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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.

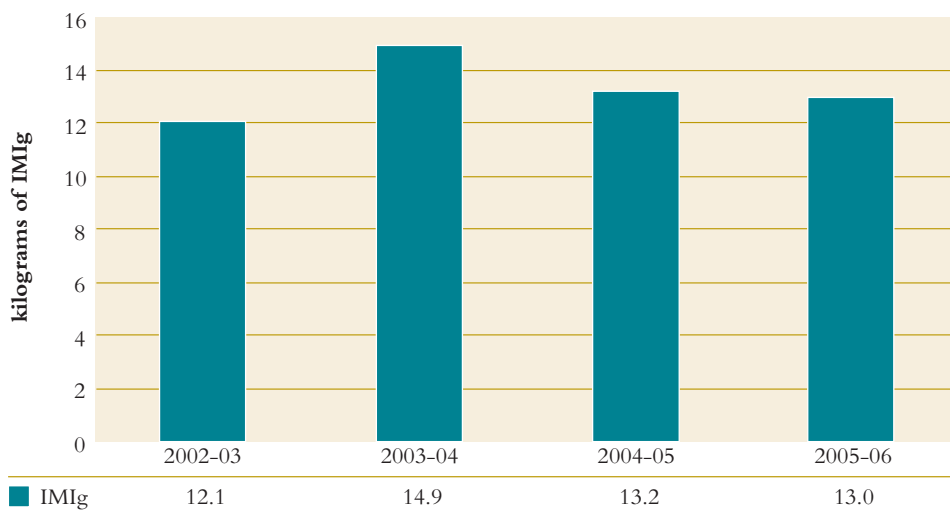
In 2004, acting on this recommendation and with the agreement of all Australian governments, the National Blood Authority (NBA) negotiated a standing offer for imported IVIg. As a result, imported product is now available to meet the supply plans of all jurisdictions, and the clinical needs of patients, 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.

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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

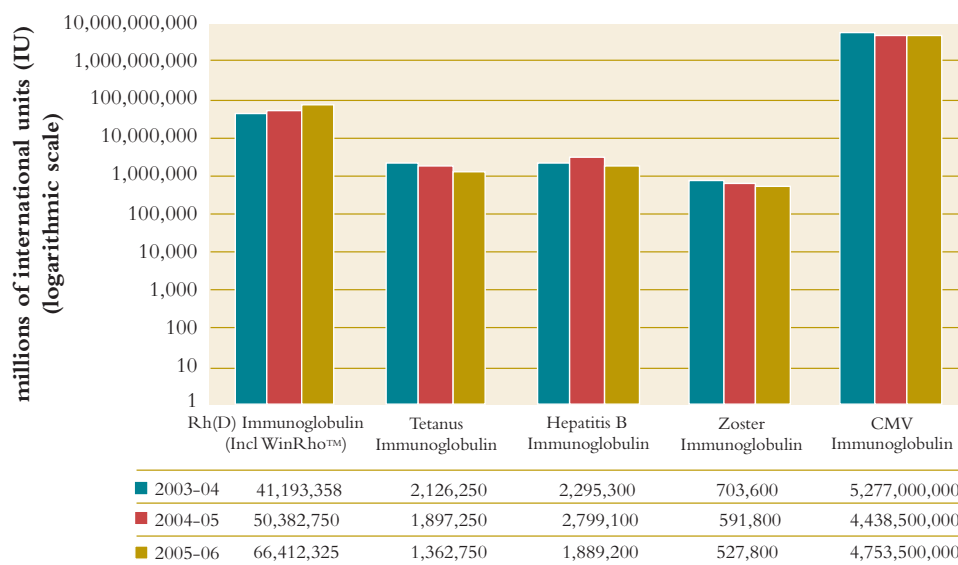
Demand for hyperimmunes has been declining for all products, with the exception of Rh(D) immunoglobulin (fig. 6.4). This trend is consistent with an overall decrease in the incidence of specific infectious diseases in Australia, and with the more widespread use of preventive measures. The growth that 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



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.

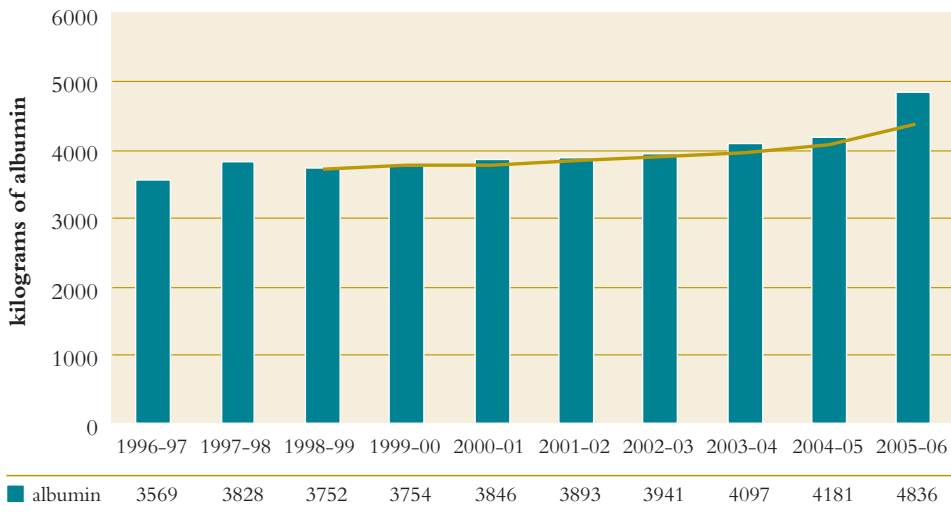
Albumin production

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.

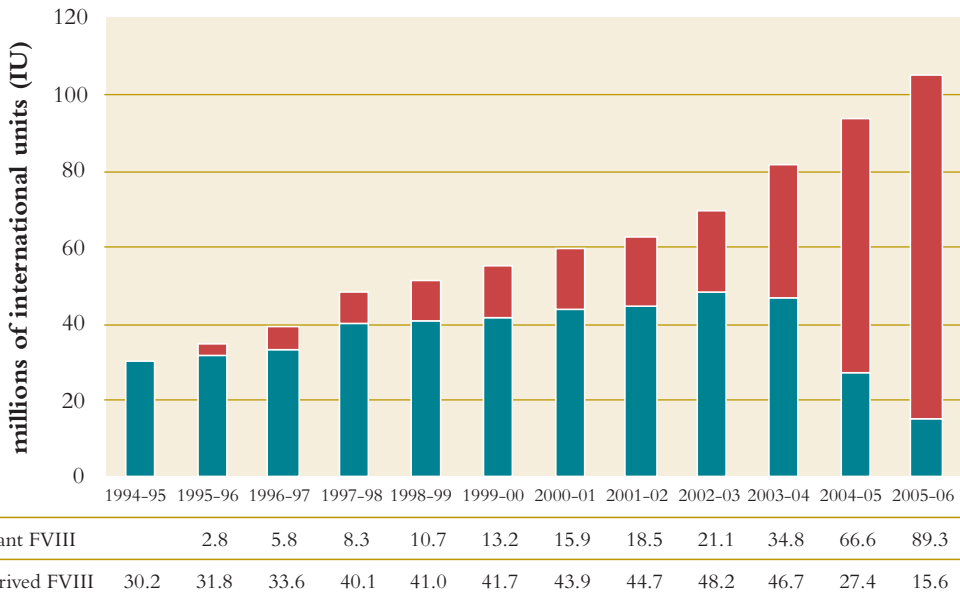
As a result the TGA, the Australian Red Cross Blood Service (ARCBS) and CSL Limited have agreed to introduce a staged series of targeted donor selection processes for Biostate manufacture.

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



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

Review of Australia's Plasma Fractionation Arrangements

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.

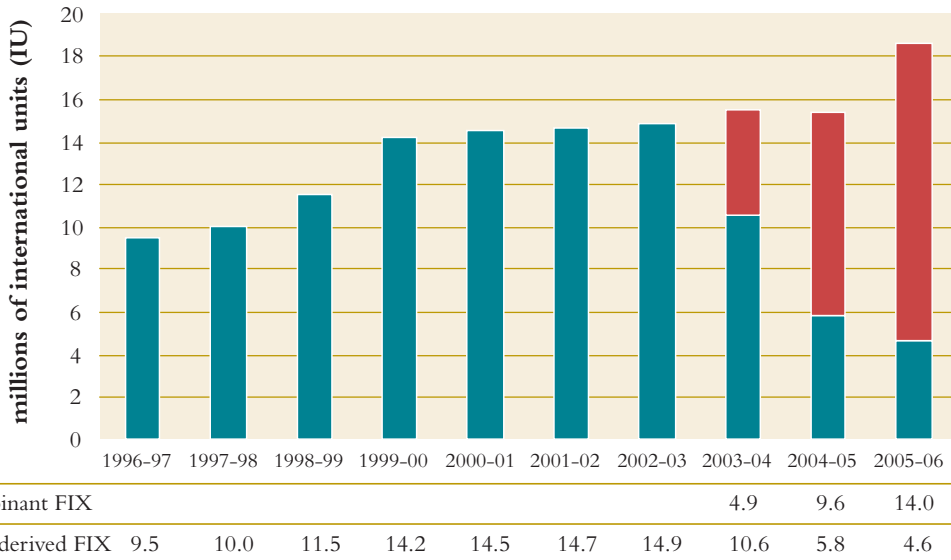
Factor IX usage

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



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.

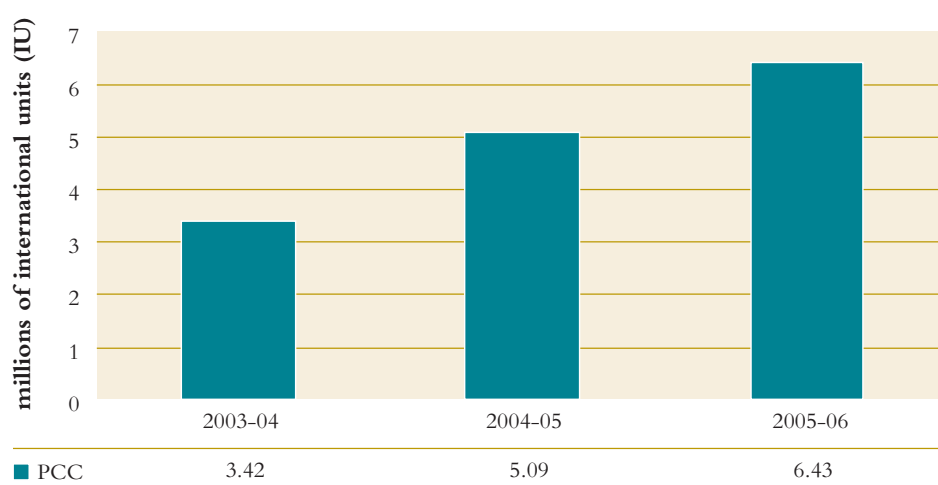
In addition to being used in the treatment of haemophilia A, Biostate® (Factor VIII) is reported as being employed outside approved indications, as a replacement therapy for patients with von Willebrand’s disease.

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



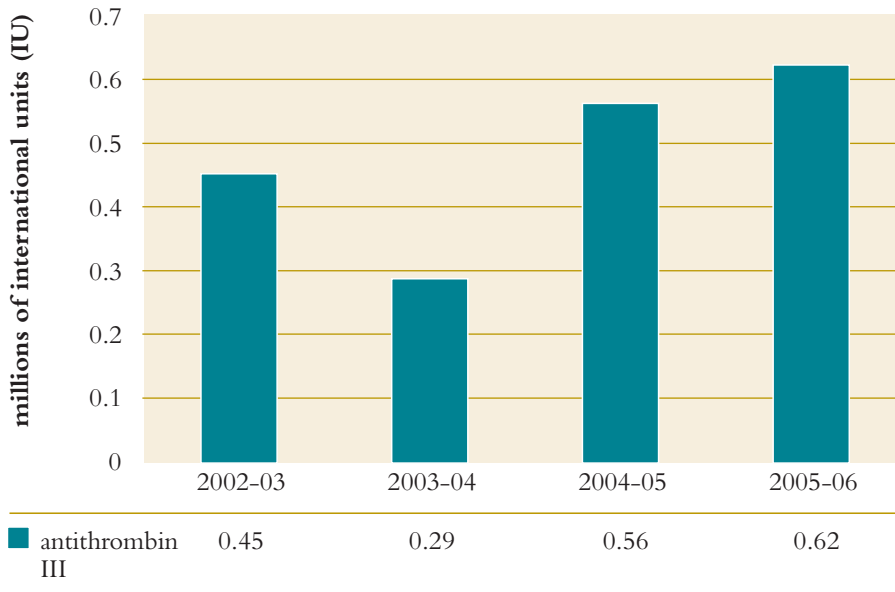
Source: Derived from data held by the Department of Health and Ageing.

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.

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.

Review of Australia's Plasma Fractionation Arrangements

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.

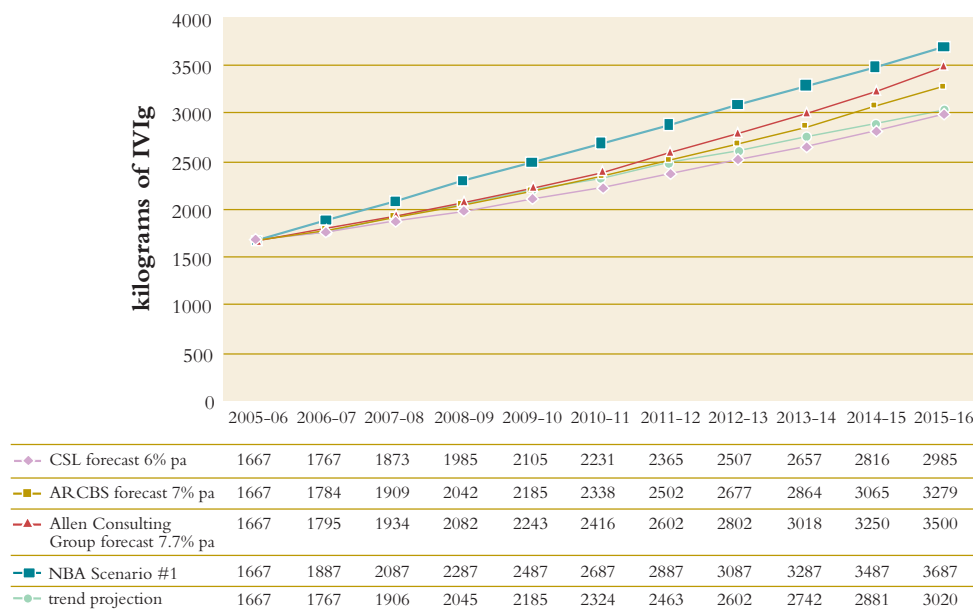
Intravenous immunoglobulin (IVIg)

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)



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.

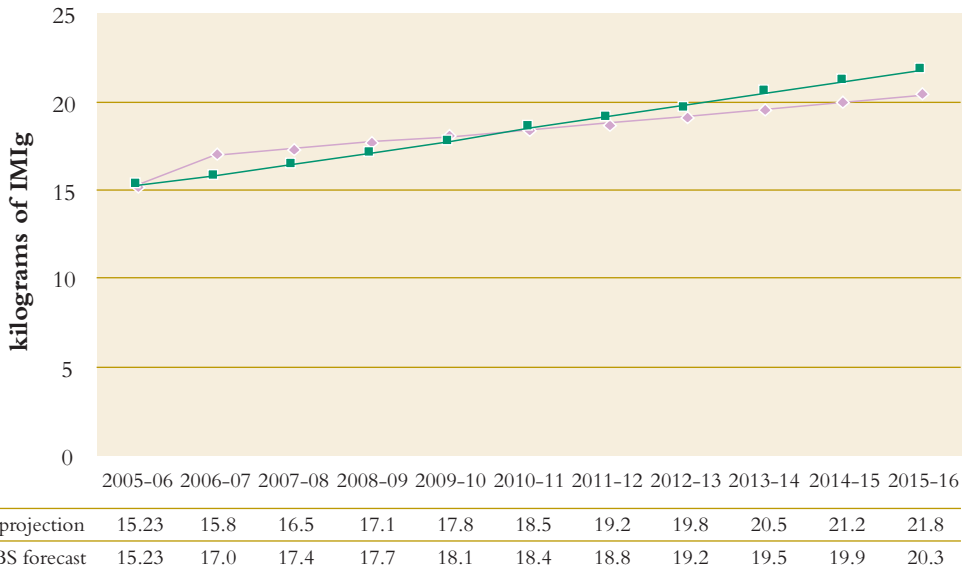
Despite the adoption of these strategies to minimise the rate of growth in demand for IVIg, and given the advice to the Review that within this time frame no synthetic substitutes are likely to emerge, Australia will need to significantly increase the quantity of plasma available for domestic fractionation, 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)



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



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.

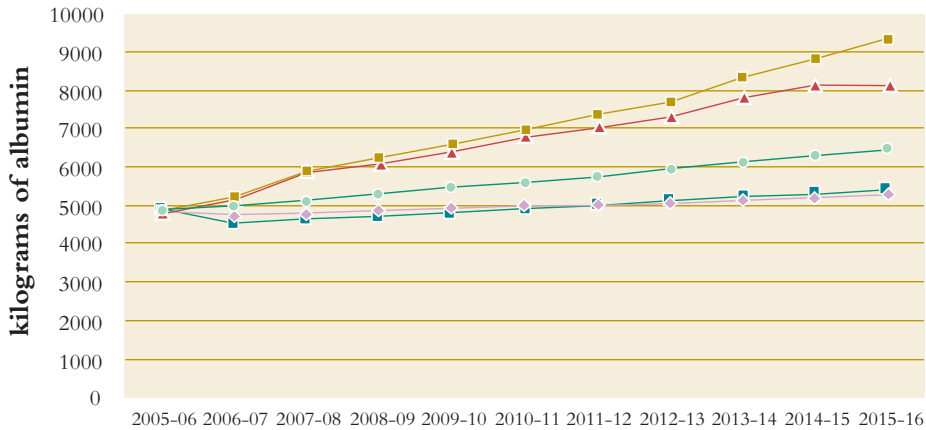
The ARCBS forecast is considered to be more reliable than the trend projection, because the strong growth in demand experienced in recent years is likely to extend to year 2006–07 but then to ease, to keep pace with anticipated changes in the birthrate. Importantly, it is deemed that the demand as forecast 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



—■— 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.

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Factor VIII

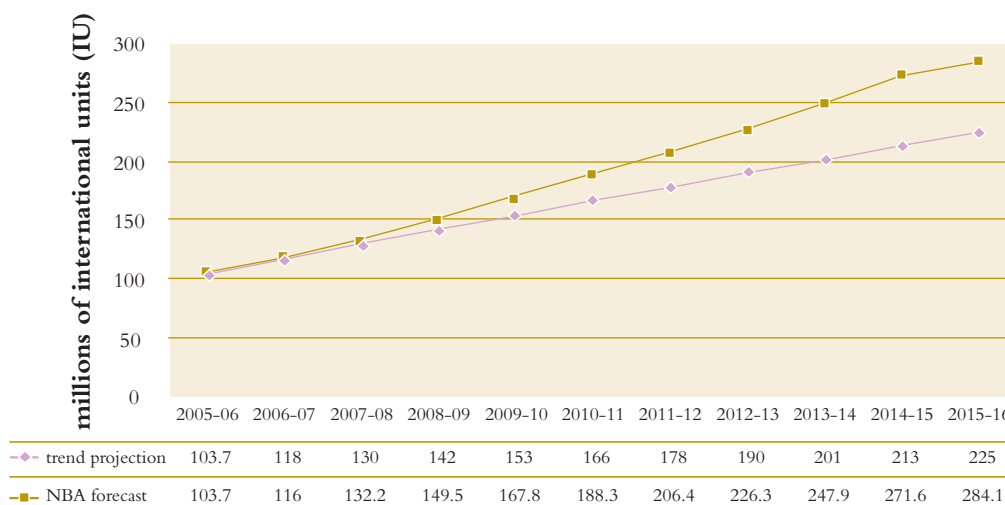
As noted earlier, there will continue to be demand for plasma derived Factor VIII for those people with haemophilia A who prefer to continue with a plasma derived product, and for use in the treatment of von Willebrand's disease. Currently, demand for therapy for this condition is not strong, as the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



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



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.

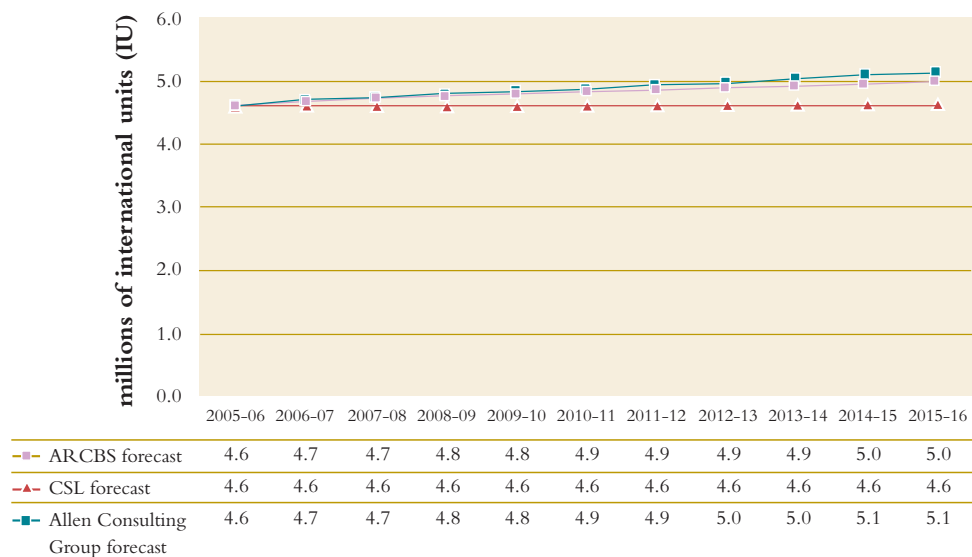
This quantity of special starting plasma was just sufficient to meet a demand of 15.58 million IU of plasma derived Factor VIII in 2005–06. If the more ambitious of the forecasts discussed here come to fruition, it follows that unless the TGA restriction is lifted (and there is currently no intention 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.

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



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)



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

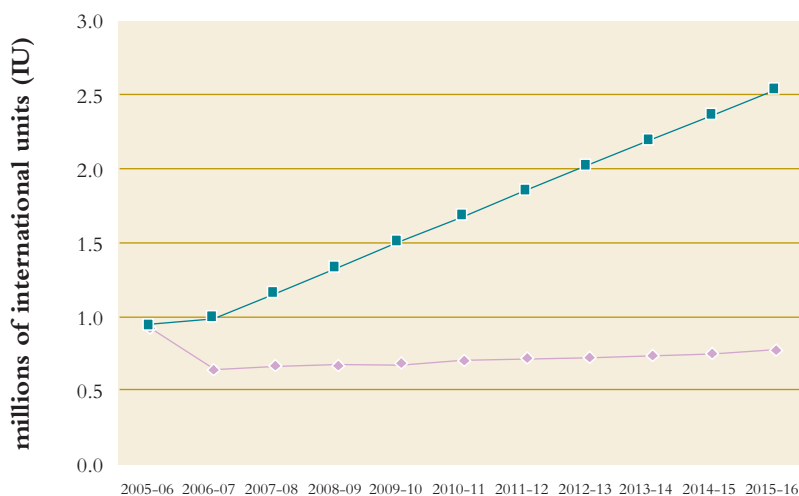
PCC is a complex of a number of blood factors and is supplied in Australia under the trade name Prothrombinex™-HT, by CSL Bioplasma. Estimates of future demand are shown in figure 6.17; the trend projection illustrated is based on historical demand.

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.

Fig. 6.18 Forecast demand for antithrombin III



■ 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.

Chapter 7

Future supply of plasma in Australia

The primary focus of this Review is the arrangements for the fractionation of plasma collected in Australia. These arrangements are predicated upon the Australian Red Cross Blood Service (ARCBS) collecting plasma from Australian voluntary, non-remunerated donors.

This chapter outlines the progress made to date by the ARCBS in increasing the overall amount of plasma collected. Also considered are the future challenges to be addressed by the ARCBS and by all Australian governments in order to respond to the continued growth in demand for plasma derived products.

This analysis of plasma supply in Australia must necessarily highlight the altruistic motivation of donors in contributing life-giving blood in order to provide an essential component of the treatment of thousands of Australians under medical care. The Australian blood system rests on this spirit as expressed by thousands of voluntary donors.

Domestic plasma collection

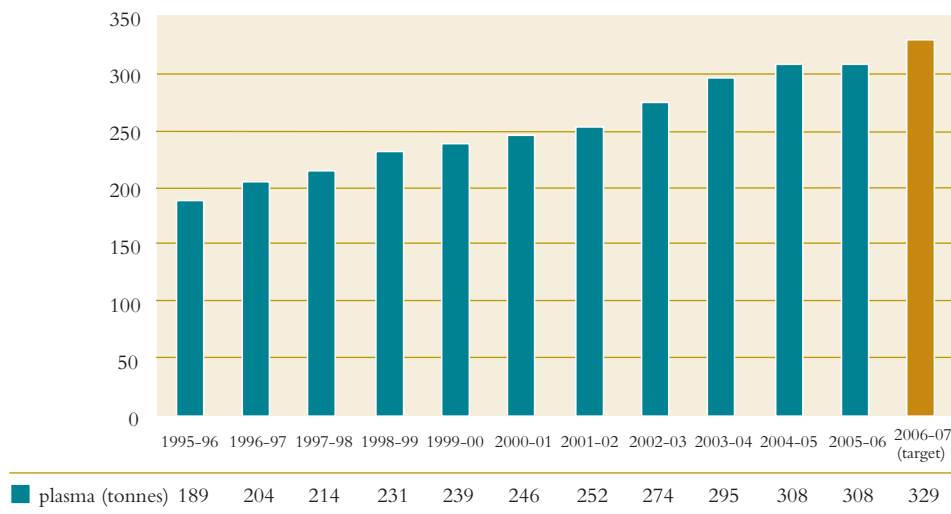
Plasma can be described either as source plasma (plasma obtained through plasmapheresis) or recovered plasma (plasma procured via whole blood donations). Most of the plasma collected in Australia is used for the manufacture of plasma derived blood products, while a small percentage, as noted in previous chapters, is retained by the Australian Red Cross Blood Service for clinical purposes.

The ARCBS is responsible for ensuring that collections overall are sufficient to provide an adequate supply of fresh blood products for hospitals and adequate starting plasma for the manufacture of plasma products, as stipulated in the annual National Supply Plan and Budget (or as revised and agreed during the year). Each year, all Australian governments, the ARCBS and the National Blood Authority (NBA) work together to negotiate plasma collection targets to meet demand for plasma products during the following 12 months. The targets generated by this supply planning process are then approved by the Australian Health Ministers' Conference (AHMC).

Growth in the total amounts of plasma collected by the ARCBS each year is illustrated in figure 7.1. Between 2000–01 and 2005–06, collections have increased at an average rate of 4.6% per annum.

The ARCBS has noted that it has achieved all annual targets for the collection of plasma for fractionation, with the exception of those for 2005–06. The ARCBS attributes the shortfall in 2005–06 to budget approval and funds flow, resulting in a sub-optimal performance during the first half of the 12-month period. The ARCBS contrasts this with performance in the second half of the year, when collections were running at an annualised rate of 329 tonnes, the target for 2006–07.

Fig. 7.1 Total plasma collected by ARCBS



Source: Derived from data in: Australian Red Cross Blood Service, *Annual Report 2004/05*, Australian Red Cross Blood Service, Sydney, 2005, p. 23, also available online at <http://www.arcbs.redcross.org.au/donor/aboutus/documents/annual%20report%2004_05.pdf>; and from data held by the Department of Health and Ageing.

Donor numbers

The total number of actual donors in Australia for 2005–06 (512 989) equates to approximately 2.5% of the population. This figure underestimates the true situation, however, since people under 16 may not donate blood, and people over 70 rarely donate. The proportion of donors in the population aged 16 to 70 is 3.5%.

Donor numbers, and numbers of total blood collections, for 2004–05 and 2005–06 are provided in table 7.1. The number of donations decreased slightly over this period but the total number of donors increased slightly. The total number of apheresis donors increased significantly without a corresponding decline in whole blood donor numbers, suggesting minimal transfer from the whole blood donor cohort to the apheresis donor pool.

Table 7.1 Donors and blood collections, 2004–05 and 2005–06

	2004–05	2005–06
Whole blood donors	481 118	479 251
Apheresis donors	25 218	33 738
Total number of donors	506 336	512 989
Total blood collections	1 116 636	1 111 154

Source: Derived from data in: ARCBS, *Annual Report 2004/05*, and from data supplied by ARCBS, 2006.

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The total number of donors in 2005–06 (512 989) is 17% higher than the total number of donors in 1996–97 (439 000). Over this period Australia's population has increased by approximately 11%.

Of the total 1 111 154 blood and blood component donations for 2005–06, about 95% are homologous donations (donations made for the benefit of an unknown recipient). The remainder of the donations are autologous donations (whereby blood is taken for the donor's own use during a medical procedure), directed donations (whereby blood is donated for use by a particular patient), or therapeutic donations (whereby individuals with specific haematological conditions reduce their blood volume through donation).

Collection facilities

The distribution of collection facilities varies widely across Australia. In all states and territories, blood and plasma donations are made via both collection centres (83 centres) and mobile donation services (36 mobile units). In 2004–05 the Australian Red Cross Blood Service reported that approximately 74% of its donors were drawn from metropolitan areas, with the remaining 26% drawn from regional areas. The ARCBS classification of metropolitan and regional areas is not particularly detailed. It is important to note that, while the number of regional collection centres has declined over the last decade, the volume of blood and plasma collected in regional collection centres is significant, with 24 of Australia's top 25 collection centres (by area of residence of the donor population) being located in regional areas.



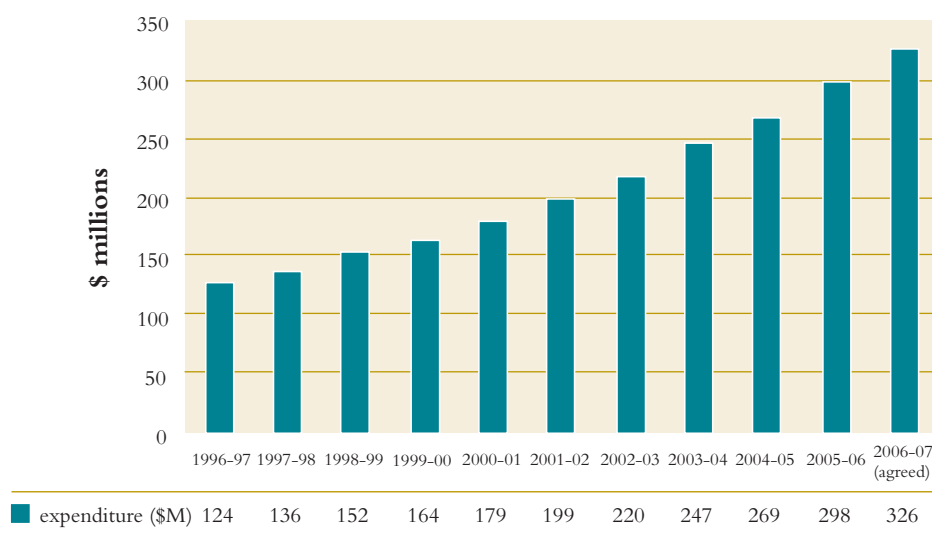
Visiting the ARCBS collection centre in Clarence Street, Sydney, in May 2006, Review Committee members Associate Professor Kevin A. Rickard AM, Mr Philip Flood AO and Sir Peter Lawler OBE.

Expenditure

The collection of starting pool plasma has been regulated in part by the funding provided through the supply planning process under Australia's national blood arrangements.

Total expenditure by Commonwealth, state and territory governments on Australian Red Cross Blood Service collections and supply of blood and blood products is set out in figure 7.2. Expenditure between 2000–01 and 2005–06 increased by 66%, from \$179 million in 2000–01 to \$297.7 million in 2005–06. In this period, plasma collections increased by 25%. This expenditure growth, however, reflected several factors in addition to plasma collection requirements; these factors include increased supply of other fresh blood components, and quality improvements in the collection process. Estimates indicate that expenditure will increase by a further 10%, to \$326 million, in 2006–07.

Fig. 7.2 Expenditure by government on ARCBS collections and supply of blood and blood products



Source: Derived from data in: National Blood Authority, *Annual Report 2004–05*, National Blood Authority, Canberra, 2005, also available online at <<http://www.nba.gov.au/PDF/NBA%20AR%2004-05.pdf>>; and from data held by the Department of Health and Ageing.

In 2005–06 the cost to Australian governments of providing patients with fresh blood products, plasma products and recombinant alternatives was \$565.4 million. This figure incorporates \$297.7 million to the ARCBS to provide fresh blood products, to collect plasma for fractionation, and to manage distribution and support services; \$136.8 million to CSL Limited for plasma product production and for imported products; and \$130 million to other suppliers (Baxter Healthcare \$68.5 million; Novo Nordisk \$23.6 million; Octapharma \$22 million; and Wyeth Australia \$15.9 million).

Expenditure on the ARCBS thus represents the largest component of the total budget for the supply of blood and blood products in Australia. Payments to CSL Limited for plasma product production, and payments for imported products, are the other major components.

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The National Supply Plan and Budget for 2006–07, approved by the Australian Health Ministers' Conference, was for \$650.7 million, including contributions of \$10.6 million for the operations of the National Blood Authority. The proposed expenditure for the supply of blood and blood products in 2006–07 is \$626.01 million, an increase of 10.6% on total expenditure in 2005–06.

Since its inception in 2003, one of the key objectives of the NBA has been to work in a collaborative manner with all governments and with other parties to ensure that Australia's blood supply is adequate, safe, secure and affordable. The NBA has worked closely with the ARCBS in improving management and accountability within the blood service.

Future funding requirements for the plasma collection sector are influenced by a number of competing factors. All Australian governments, the NBA and the ARCBS are continuing to explore mechanisms for gaining efficiencies, in order to achieve the best outcomes from the available resources.

The ARCBS has advised the present Review that it believes that, given additional funding from governments, and in view of other changes it is making, it could deliver Australia self-sufficiency in plasma by 2010–11. This advice is based on an ARCBS estimate that the total volume of plasma required in 2010–11 will be 507 tonnes; in order to reach 507 tonnes in 2010–11, collections would need to increase by 10% per annum from 2005–06.

The ARCBS estimates that the amount of additional funding it will require for the four years commencing in 2007–08, in order to reach collections of 507 tonnes by 2010–11, will be in the vicinity of \$5.9–\$9.9 million per annum. These figures represent approximately \$4.1–\$6.9 million in recurrent costs per annum and \$1.8–\$3.0 million in capital costs per annum.¹

In the light of demand estimates discussed in Chapter 6, if Australia is to achieve self-sufficiency by 2015–16, plasma collections would need to increase by 123%: from 308 tonnes in 2005–06 to 686 tonnes in 2015–16 (an annual increase of 8%).

International comparisons

International comparisons indicate that the Australian Red Cross Blood Service is performing well with respect to achieving high plasma collection levels. Currently the ARCBS collects 15.3 litres of plasma per 1000 head of population, a collection level that compares favourably with those in other, similarly industrialised countries. The per capita plasma collection rates shown in table 7.2 illustrate the difference between countries that adopt a policy of non-remunerated blood donation (including those, such as Germany, that provide reimbursement of direct costs associated with donation) and countries that permit payment for donation (such as the United States).

The ratio of whole blood donations to source plasma donations in various countries, including Australia, is set out in table 7.3. Areas of positive comparison include Australia's above-average number of collections per donor, and the fact that plasma collections by apheresis are also above the international average.

¹ Figures supplied by Australian Red Cross Blood Service, May 2006.

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Table 7.2 Plasma collection rates in selected developed countries, 2004–05

Country	Plasma collected (litres)	Population (millions)	Litres per 1000 population
United States	15 500 000	296.4	52.3
Belgium	230 000	10.4	22.2
Germany	1 719 000	82.4	20.9
Netherlands	300 000	16.4	18.3
Sweden	140 000	9.0	15.5
Australia	308 000	20.2	15.3
Denmark	80 000	5.4	14.7
Finland	66 000	5.2	12.6
Norway	50 000	4.6	10.8
France	576 000	60.8	9.5
New Zealand	38 000	4.1	9.3
Austria	50 000	8.2	6.1
Canada	200 000	32.9	6.1

Source: National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 10; also available online at <http://www.nba.gov.au/pubs.htm>. Source of data for United States: Figure 4.1 in Chapter 4 of this report, and <http://www.census.gov>. Data for Germany: B. Haschberger, A. Waterkamp, J. Hesse, M. Heiden & R. Seitz, *Meldungen an das PEI gemäß § 21 Transfusionsgesetz*, Paul-Ehrlich-Institut, Langen, 2006, http://www.pei.de/cln_042/nn_431538/SharedDocs/Downloads/21tfg/2006-poster-dgti,templateId=raw,property=publicationFile.pdf/2006-poster-dgti.pdf and <http://www.destatis.de>.

Table 7.3 International comparison: Whole blood and apheresis donations, 2004–05

Country/province	2004–05	
	Whole blood %	Apheresis %
Netherlands	68	32
United States	71	29
Australia	86	14
Canada	94	6
New Zealand	94	6
Quebec	95	5
Switzerland	95	5
Ireland	96	4
England	98	2
Finland	99	1
Average	90	10

Source: National Blood Authority, *The Supply and Use of Plasma Products in Australia*, p. 11, and data held by NBA.

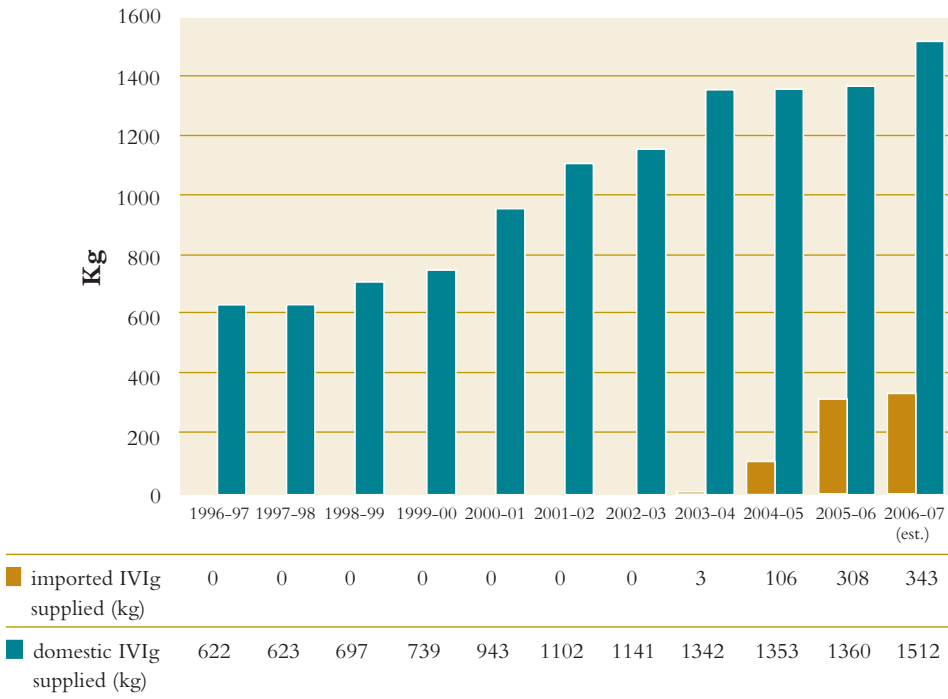
It is important to note that, despite Australia’s high collection rates, a significant percentage of collections are sourced from new donors, as opposed to existing donors. Currently 28% of Australia’s active donors are new donors, while the average across other selected countries is 15%. Reasons for this difference are not clear but the figures suggest a need for greater emphasis on retention of existing donors.

The ARCBS submission to the present Review notes that: ‘Increases in plasma productivity over the last ten years have been supported through initiatives such as expansion of plasmapheresis programs, re-suspending whole blood derived pooled platelets in platelet additive solution rather than plasma ... and a greater move towards production of platelets via apheresis’.² Use of the techniques referred to here allows for a greater volume of plasma to be available for clinical usage.

Imported intravenous immunoglobulin (IVIg)

Despite the good record of the Australian Red Cross Blood Service in collecting high volumes of plasma relative to collections in other countries, and the impressive increases in yields achieved by CSL Bioplasma, domestic production of IVIg has been unable to keep up with demand. Accordingly, in the last three years domestic IVIg has been supplemented with imported IVIg products. The volumes of IVIg supplied under the national blood arrangements for clinical use in Australia are set out in figure 7.3.

Fig. 7.3 Domestic and imported IVIg supplied



Source: Data for domestic IVIg derived from data in: ARCBS, responses to questions from Plasma Fractionation Review Committee, June 2006, p. 28; and from data held by the Department of Health and Ageing. Data for imported IVIg: NBA distribution reports.

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

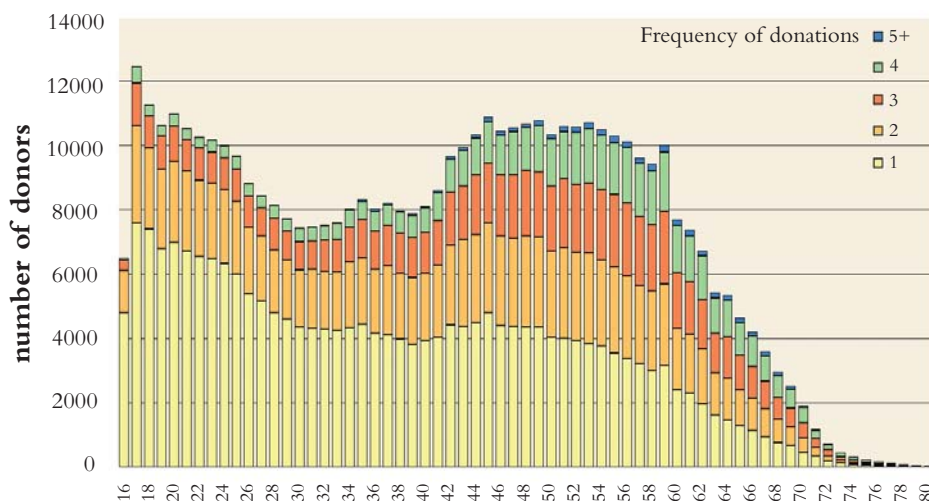
For 2006–07, Commonwealth and state and territory health ministers have planned on a possible need by the National Blood Authority to import 343 kilograms of IVIg, or up to 18% of the estimated requirements. In the event that CSL yields are higher than projected by the NBA, or if the ARCBS collects more than its target 329 tonnes of plasma, then the NBA would purchase proportionately less overseas IVIg, provided that clinical demand is in line with estimated volumes included in the 2006–07 National Supply Plan and Budget.

Donor profiles

General demographic characteristics of donors

Blood donors in Australia are currently drawn from a volunteer population aged between 16 and 70 years. The greatest amount of whole blood is collected from donors aged 40 to 60, as indicated in figure 7.4.

Fig. 7.4 Frequency of whole blood donations, by age, 2005–06

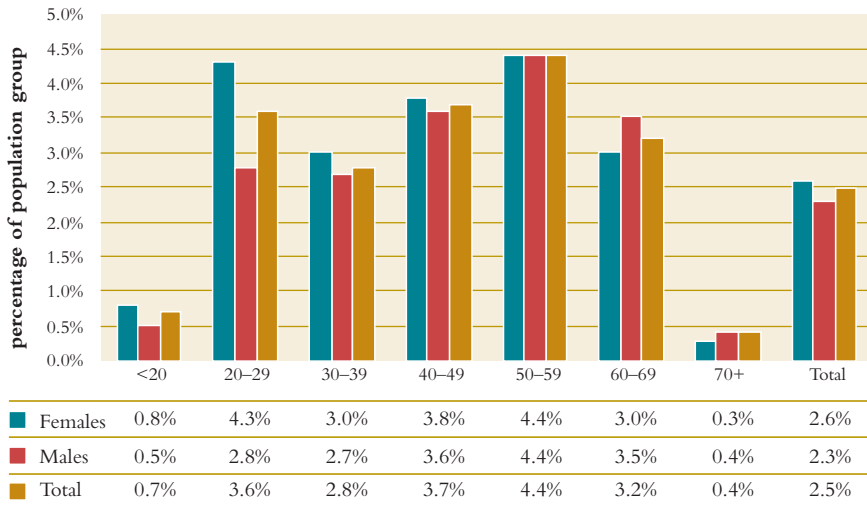


Source: Data supplied by ARCBS, 2006.

Figure 7.5 shows the percentages of male and female donors for each age cohort within the population. As noted previously, currently some 2.5% of the total Australian population donate blood. Within the donor population there are slightly more women (2.6%) than men (2.3%), and people aged 50 to 59 represent the highest proportion of donors. Overall, the 30–39 age group provides the lowest share relative to its share of the Australian population (this calculation excludes those younger than 20 years and over 70 years).

The Australian Red Cross Blood Service emphasises the importance of recruiting new donors for their lifetime. Donor participation tends to peak prior to, and after, the child-bearing and child-raising phase of life (i.e. roughly 30–45 years). The ARCBS states: ‘Even if we lose a youth/student donor for, say, the ages of 25–45, a previous youth donor tends to return once they have fewer demands on their leisure time’.³ A donor who is now 16 may not donate as frequently as his or her middle-

Fig. 7.5 Percentage of donors by age cohort

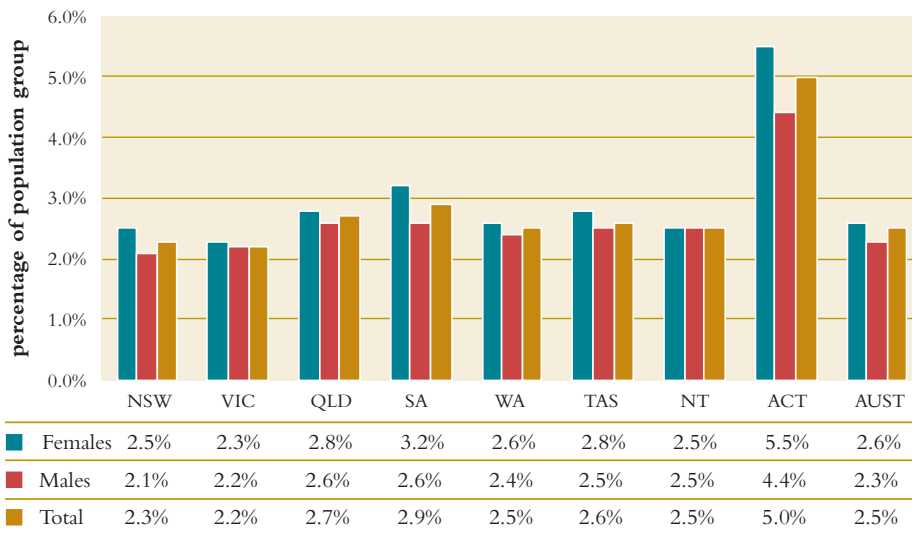


Source: Derived from data held by the Department of Health and Ageing.

aged counterparts. The number of his or her potential donations over a lifetime, however, exceeds that for a 40-year-old new donor. In the past 10 years in Australia, there has been a reduction in the participation rates of donors in the early twenties to mid thirties age group.

There are significant differences in the donor participation rates of Australia’s states and territories, as reflected in figure 7.6. New South Wales and Victoria are

Fig. 7.6 Percentage of donors by state/territory population



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

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represented by proportionately fewer donors than are South Australia, Queensland, Tasmania and Western Australia. The impressively high proportion of donors in the Australian Capital Territory seems to reflect the relatively small geographical size and concentrated population of Canberra, and the relatively high numbers of people employed in the public sector and thus having access to paid donation leave.

There are also differences between the states and territories in terms of the frequency of apheresis donations. ARCBS guidelines provide that whole blood donors may donate every 12 weeks, while apheresis donors may donate plasma every three weeks. Overall plasma yield from each jurisdiction can be seen in table 7.4.

Table 7.4 Plasma yields, and apheresis donations by individual donors, by state and territory, 2004–05

	NSW	Vic.	Qld	WA	SA	Tas.	ACT	NT	Total
Pop. ('000)	6 768	5 023	3 967	2 014	1 539	488	325	203	20 327
CSL plasma (kg)	82 238	71 132	63 553	37 940	32 516	7 833	9 393	3 157	307 762
Kg per '000 population	12	14	16	19	21	16	29	16	15
Average no. apheresis visits per year	6.99	7.06	7.52	5.15	5.56	6.62	5.39	N/A	

Source: Data supplied by ARCBS, 2006.

The minimum age at which an individual may give blood also differs among jurisdictions, an issue raised by the ARCBS with the Review Committee. There is currently no national consistency in this area (table 7.5).

South Australia, the ACT, and recently the Northern Territory, are the only jurisdictions where 16-year-olds can donate blood without parental consent. Overly prescriptive age-based requirements can present a disincentive to donation and can create barriers to donor commitment and retention in the key youth market.

The Review Committee's position on this issue is that all states should be encouraged to follow current practice in South Australia. A decision to drive a car, which requires no formal legal consent, carries far greater risk for a 16-year-old than the decision to donate blood.

Donor eligibility

Plasma collection is strongly impacted by regulations concerning eligibility of donors. The Australian Red Cross Blood Service, along with blood collection agencies in other developed countries, sets high standards for donor eligibility. Two of the fundamental tenets of national blood collection policies in developed countries are that donations must be sourced from individuals with a low risk of exposure to blood-borne pathogens, and that donors must not suffer adverse physical affects as a result of their choice to donate blood.

Table 7.5 Minimum donor age, by jurisdiction

	Minimum donating age	Consent required	Relevant legislation
NSW	16	Until age 18 (by legal guardian, at time of first donation)	<i>Human Tissue Act 1983 (NSW)</i>
Vic.	16	Until age 18 (medical and parental consent required at time of each donation)	<i>Human Tissue Act 1982 (Vic.)</i>
Qld	16	Until age 18 (medical and parental consent required each time)	<i>Transplantation and Anatomy Act 1979 (Qld)</i>
WA	16	Until age 18 (medical and parental consent required each time)	<i>Human Tissue and Transplant Act 1982 (WA)</i>
SA	16	None	<i>Transplantation and Anatomy Act 1983 (SA)</i>
Tas.	16	Until age 18 (medical and parental consent required each time)	<i>Human Tissue Act 1985 (Tas.)</i>
ACT	16	None	<i>Human Tissue and Transplant Act 1974 (ACT)</i>
NT	16	None	<i>Human Tissue Transplant Act 1979 (NT)</i>

Source: ARCBS, responses to questions from Plasma Fractionation Review Committee, June 2006.

In Australia, donor deferral policies have been developed in conjunction with the Therapeutic Goods Administration. As a public health policy option, donor deferral must balance the risk of disease transmission, and the potential health impacts of donation, against a potential and actual loss of donors. Donor deferral thus has the potential to significantly impact on the pool of available donors.

The ARCBS adheres to strict criteria in relation to donor selection. A person wishing to donate must:

- be aged between 16 and 70
- have good general health
- have a body weight of between 45 and 120 kilograms
- have a haemoglobin level of 130 g/L for men and 120 g/L for women (in order to donate blood).

A donor will be deferred from donating if on the day of donation he or she:

- is pregnant or breastfeeding, or
- has a cold, flu, sore throat or diarrhoea, or
- has been taking antibiotics in the previous five days, or

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- has had dental work (fillings or cleanings in the previous 24 hours, or root canal in the previous week).

A donor will be deferred for a period of 12 months if he or she:

- has recently received a blood transfusion, or
- has recently had a tattoo, or
- has recently undergone any piercing with clean, single-use disposable equipment, or
- has recently been in prison or a lockup, or
- has recently had male-to-male sex, or
- has recently had sex with a prostitute, or
- has a partner with hepatitis B or C.

Individuals will be unable to donate if they have:

- tested positive for HIV, or hepatitis B or C, or
- a history of non-prescribed intravenous drug use, or
- had open-heart surgery, or
- lived in the United Kingdom between 1980 and 1996 for a cumulative period of six months or more.

In addition, the standards set down by the TGA, which are based on the guidelines established by the Council of Europe, specify that the maximum number of whole blood donations for any individual in any one year should be four, while plasmapheresis donations should not be made more often than once every three weeks.

The most recent addition to the national donor deferral policy, and a change that has had a significant impact with respect to the available donor pool, is deferral related to potential exposure to variant Creutzfeldt-Jakob disease (vCJD). Donors are permanently deferred if they have resided in the United Kingdom at any time between 1980 and 1996, for a cumulative period of six months or more.

A study undertaken to determine the impact on blood donor numbers of travel restrictions recommended by the US Food and Drug Administration (FDA) has estimated that approximately 3.5% of donors would be deferred as a result of this policy.⁴ In Australia, a similar study undertaken in 2000, using data from 1998, estimated the exclusion of 5.3% of potential donors.⁵ It is unclear, however, how accurate these estimates have been.

In some instances a potential donor will choose to defer donating, because he or she is aware of donor deferral policies. Educating individuals to self-defer during periods of temporary illness or after exposure to high-risk behaviour has been found to result in positive donation behaviour in the future. On the other hand, for existing donors, advice from a blood service that a temporary deferral is required has been found to

4 See E. L. Murphy, J. D. Connor, P. McEvoy, N. Hirschler, M. P. Busch, P. Roberts, K.-A. Nguyen & P. Reich, 'Estimating Blood Donor Loss Due to the Variant CJD Travel Deferral', *Transfusion*, vol. 44, no. 5 (May 2004), pp. 645–50.

5 P. K. Correll, M. G. Law, C. R. Seed, A. Gust, M. Buring, E. M. Dax, A. J. Keller & J. M. Kaldor, 'Variant Creutzfeldt-Jakob Disease in Australian Blood Donors: Estimation of Risk and the Impact of Deferral Strategies', *Vox Sanguinis*, vol. 81, no. 1 (July 2001), pp. 6–11.

have a negative impact with respect to donor return.⁶ Measures to encourage donor return after a temporary deferral include immediate communication about the reasons for the deferral and, if appropriate, reassurance that the deferral may be temporary.⁷

The ARCBS has in place a number of strategies both for educating donors and potential donors about the need for self-deferral under certain circumstances, and for counselling donors when they are deferred at the point of donation. These strategies include brochures, information on the ARCBS website, and the recent media campaign 'It Takes Someone Special to Give Blood'. School programs on the fundamentals of blood donation are also an important means of raising general community awareness of blood donation requirements for younger donors.

Overall, while deferral policies have the potential to impact upon the number of eligible donors, minimising the risk of transmission of pathogens in the blood supply is of paramount importance. Ensuring the health and safety of donors by deferring donation during times of temporary illness is also important.

How important is it to increase plasma supply?

Increasing the supply of plasma goes to the essence of Australia's policy of self-sufficiency in blood and blood products, and is of vital importance. The Australian Health Ministers' Conference issued the following policy statement on 7 April 2006:

The Australian Health Ministers' Conference (AHMC) has determined that a clear statement is needed on the governments' current position on self-sufficiency in the blood sector. Self-sufficiency means Australia striving to source blood components and plasma from within Australia to meet appropriate clinical demand.

This statement has been developed in response to a number of questions about whether recent government decisions to import certain blood products are consistent with the national policy aim relating to promoting national self-sufficiency in the blood supply.

All Australian, State and Territory Governments are signatories to the National Blood Agreement 2003, which sets out, among other things, the policy objectives and aims for Australia's national blood sector.

The primary policy objectives in the National Blood Agreement are to:

- provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services; and
- promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.

Underpinning these primary policy objectives are a number of secondary policy aims, including promoting national self-sufficiency. This policy aim has not changed. However, importation of blood products does occur in a narrow range

6 See D. Halperin, J. Baetens & B. Newman, 'The Effect of Short-Term, Temporary Deferral on Future Blood Donation', *Transfusion*, vol. 38, no. 2 (February 1998), pp. 181–3.

7 See R. Beal, 'Deferred Blood Donors and Their Care', *Transfusion Medicine Reviews*, vol. 13, no. 2 (April 1999), pp. 89–94.

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of circumstances where there is an inability to meet clinical needs through the domestic supply, and where supply chain risks must be addressed. This happens within a framework that:

- ensures adequacy of supply to Australian patients in need;
- minimises the supply security and product safety risks to patients;
- ensures affordability of products to the Australian health sector; and
- recognises the practicalities of production and distribution.

Australia is self-sufficient in fresh blood components/products except for a few rare blood types, and is largely self-sufficient in plasma products. However, it is necessary to import products such as Intravenous Immunoglobulin (IVIg) where demand exceeds what is produced domestically and recombinant products, which are not produced in Australia.

The Australian Red Cross Blood Service is funded by all Governments to collect fresh blood and blood plasma for use in Australia. All blood and blood products are provided free of charge to patients.

Imported products are subject to the same safety and regulatory standards as domestic products prior to approval by the Therapeutic Goods Administration for release in Australia.

In highlighting self-sufficiency *in fresh blood components*, this statement reflects a policy similar to those of most developed countries. Transfusion components degrade rapidly. Whole blood cannot generally be stored longer than a few weeks and many components are unusable within hours or days (fractionated plasma products, by comparison, have shelf lives from one to two years). For this reason, virtually all developed countries are self-sufficient in transfusion components. In general, it is accepted that the safest transfusion is no transfusion, since there is always a level of risk.

The AHMC statement acknowledges that Australia is not totally self-sufficient in *plasma products*; indeed, Australia has never been totally self-sufficient in respect of these products. Nevertheless, the Review Committee believes that Australia should be as self-sufficient as possible and that self-sufficiency should remain an important goal. In the light of the projections presented in Chapter 6, meeting this objective will require a major, sustained increase in plasma collection by the ARCBS.

Recruitment and retention of donors

One of the key objectives of the Australian Red Cross Blood Service is to increase the numbers of blood and plasma donors in Australia and to encourage repeat donations to meet increasing demand.

Growth in plasma collections must occur either through the recruiting of new whole blood or source plasma (apheresis) donors, or the recruiting of existing whole blood donors to become plasma donors. It is generally considered preferable to recruit new donors rather than to reduce the numbers of available whole blood donors.

Review of Australia's Plasma Fractionation Arrangements

The report of the Review of the Australian Blood Banking and Plasma Product Sector (the Stephen Review) of 2001 noted that 'Australia's donors give their blood out of altruism, that is, for the general good of the community'.⁸ This altruism may be influenced by:

- personal experience, in cases where the donor or a family member has received blood products
- encouragement to donate, by friends, workmates, family members, or community groups
- a supportive workplace (making it possible, for example, for a donor to make donations during working hours).

The Stephen Review also discussed donor recruitment strategies, noting that different approaches are used to appeal to the motivations of different groups within the population. These strategies tend to fall into three broad categories:

- volunteer recruitment strategies, which rely heavily on the internally generated motives of potential donors – their sense of altruism or community responsibility – and offer no material incentives or rewards for donating
- incentive-based strategies, which may also emphasise the positive feelings derived from donating blood but which introduce a variety of small rewards to serve as further incentives
- social persuasion-based strategies, which introduce the encouragement or pressure of peers and colleagues as a mechanism for persuading individuals to donate blood (mobile blood drives, for instance, at workplaces or schools, fit within this category).⁹

Current ARCBS public-awareness and recruitment campaigns include all of these strategies:

- volunteer recruitment: 'It Takes Someone Special to Give Blood' – media campaign motivates individuals by reinforcing the image of blood donors as a select group of worthy, community-minded people
- incentive-based: programs such as the 'Frequent Donors Club' (donors commit to donating on three occasions within a set period of time and if successful receive a small gift) or the 'Donate for Your State' donor recruitment drives in Queensland and NSW (which target Rugby League supporters and offer them the chance to win State of Origin tickets)
- social persuasion-based: 'Club Red' corporate blood donor program – provides team building for companies, or competition between companies.

Research into the motivation of donors has found that

the importance of social networks as a recruitment channel for blood donation is significant. The decision to begin and continue blood donation is likely to be influenced more by community links (co-workers, neighbours) than close relationships (spouse, or close friends). Therefore, active blood donors are probably the ones best suited to recruit and to motivate other people to become committed donors.¹⁰

⁸ *Review of the Australian Blood Banking and Plasma Product Sector*, Commonwealth of Australia, Canberra, 2001, p. 61; also available online at <<http://www.nba.gov.au/PDF/report.pdf>>, p. 63.

⁹ *ibid.*

¹⁰ A. H. Misje, V. Bosnes, O. Gásdal & H. E. Heier, 'Motivation, Recruitment and Retention of Voluntary Non-remunerated Blood Donors: A Survey-Based Questionnaire Study', *Vox Sanguinis*, vol. 89, no. 4 (November 2005), p. 243.

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In this context, recruitment campaigns are also an important means of reinforcing the influence of friends and family.

Retention of existing donors is another essential aspect of blood collection. Having a pool of committed blood donors provides the foundation for certainty of supply, and saves a collection agency the time, effort and money associated with the recruitment of new donors.¹¹

The willingness of donors to make repeat donations is influenced by a number of factors. Intrinsic factors include a feeling of satisfaction for providing a worthwhile service or for having contributed to improving the health of another person, and increased self-esteem. Extrinsic factors include a positive donation experience, with limited discomfort, minimal side effects, and minimal delays.¹²

The ARCBS reports that as at 2004–05, on the basis of existing strategies, approximately 60% of new whole blood donors return after two years to make another donation, and approximately 40% of new plasma donors return after 180 days to make another donation.¹³ The Review Committee considers that, given the current relatively low rate of return for new blood donors and the current relatively high volume of blood donated by existing donors, it will be a challenge to increase the total volume of blood donated. Donor retention remains a key issue. Independent research, undertaken to examine the reasons first-time donors do not return, would be very useful in identifying areas where the ARCBS could focus its marketing and customer service efforts.

Current issues

Current strategies have not led to a decisive increase in donor numbers in recent years. The Australian community has been changing – in its age composition, in its access to free time, in its ethnic composition, and in its spiritual beliefs or lack of them – and these factors could be affecting the numbers coming forward to give blood.

It is important to note that Australians are generous in donating their leisure time to volunteering activities. A 2001 report by the Australian Bureau of Statistics indicates that an increasing proportion of the community is engaging in some form of voluntary work.¹⁴ In 2000, 32% of the population, or a total of 4 395 600 people, were engaged in some form of voluntary work, compared with 3 189 400, or 24%, in 1995. There has been no comparable increase in the number of blood donors.

Increased demands on leisure time

It has been suggested that some of the reasons for the difficulty in increasing the number of blood and plasma donors in Australia are: an increased participation in the workforce, a reduction in leisure time, and the increasing demands made on available leisure time by other volunteer and community activities.

11 See J. H. Chamla, L. S. Leland & K. Walsh, 'Eliciting Repeat Blood Donations: Tell Early Career Donors Why Their Blood Type Is Special and More Will Give Again', *Vox Sanguinis*, vol. 90, no. 4 (May 2006), pp. 302–7.

12 See Misje et al., pp. 236–44.

13 Information supplied by ARCBS, June 2006.

14 Australian Bureau of Statistics, *4441.0: Voluntary Work, Australia, 2000*, Australian Bureau of Statistics, Canberra, 2001, <<http://www.abs.gov.au/ausstats/abs@.nsf/0/124E5675AD3AED8CCA256A71000019C5?Open&Highlight=0,volunteers>>.

Figures from the Australian Bureau of Statistics reflect the increasing demands of work: between 1985 and 2005, full-time working hours for men increased by 1.9 hours per week, to 43.2 hours, and for women by 1.7 hours, to 39.3 hours. Over the same period, part-time hours worked by men increased 0.7 hours, to 16.4 hours, and for women by 1.4 hours, to 16.9 hours per week.¹⁵ In addition, changing social attitudes and smaller families have contributed to the increased participation of women in the workforce. The proportion of women in the workforce has increased, with 53% of women participating in the workplace in 2004 (4 314 000) compared to 40% in 1979 (2 178 300). However, women continue to carry the greater responsibility for caring and for other unpaid work, and are therefore placed under greater time pressures.¹⁶ Commuting times for workers have also increased, adding to the reduction in leisure time.

The Australian Red Cross Blood Service has noted in its submission to this Review that employees might be more inclined to donate if they had access to paid blood donation leave. The ARCBS proposed to the Review that Australian governments should legislate to ensure the rights of employees to donate blood during the working day, without loss of earnings. The Review Committee does not believe that it would be feasible to legislate for paid blood donation leave.

Volunteering and making charitable donations are an important part of the Australian culture. Voluntary work provides an important contribution to the general community and to the public good, and helps to develop and reinforce social networks and cohesion.

Generally people are motivated to volunteer their time and skills so as to be of benefit to the community and to achieve personal satisfaction.¹⁷ In addition, people generally choose a voluntary activity that relates to their paid work.¹⁸ Donating blood, however, can be characterised as different from volunteering one's time and skills to charitable or community organisations, and also as different from making donations such as goods or money.

Blood donation, in contrast to other voluntary activities, involves an individual making a gift of his or her blood to (generally) unidentified recipients. The donor is required to undergo a minor but invasive procedure in order to donate, and the effects of the donation are in most cases not directly seen by the donor.

In summary, a number of different factors currently impact upon existing leisure time and, if blood donation is to actively compete for a share of this time, it must be available to potential donors as a time-effective and family-friendly option.

15 Australian Bureau of Statistics, *4102.0: Australian Social Trends, 2006*, media release, 20 July 2006, Australian Bureau of Statistics, Canberra, <<http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/4102.0Media%20Release12006?opendocument&tabname=Summary&prodno=4102.0&issue=2006&num=&view=>>>.

16 See Australian Bureau of Statistics, *4102.0: Australian Social Trends, 2006* <<http://www.abs.gov.au/ausstats/abs@.nsf/7d12b0f6763c78caca257061001cc588/858BADAD39AFB98DCA2571B000153D73?opendocument>>.

17 See Volunteering Australia, *Volunteering Fast Facts*, Volunteering Australia, Melbourne, 2006, <http://www.volunteeringaustralia.org/html/s02_article/article_view.asp?id=502&nav_cat_id=222&nav_top_id=50&dsa=2931>.

18 See Australian Bureau of Statistics, *4441.0 Voluntary Work, Australia, 2000*, <<http://www.abs.gov.au/ausstats/abs@.nsf/0/124E5675AD3AED8CCA256A71000019C5?Open&Highlight=0,volunteering>>.

Donor recruitment within specific cultural communities

One option for enhancing blood donor recruitment and retention levels in Australia is to target recruitment to specific parts of the population, including people from non-English-speaking backgrounds.

In response to questions from the Review Committee, the Australian Red Cross Blood Service noted that:

Unfortunately, we have not had the funding available to undertake marketing and communications to Australia's diverse culture and linguistic communities appropriately. For example, we have only provided our literature, other promotional material and signage in English (including the donor questionnaire form) and our staff have not had cross-cultural awareness and communication training. If provided with sufficient funding, we would be delighted to do this.¹⁹

The ARCBS does not currently collect place of birth data from blood or plasma donors (other than those donors who are deferred due to the United Kingdom-related restriction), or data on first language or ethnicity. (Information on ethnicity and/or country of origin is collected by the ARCBS only in the case of specific tissue donors, such as bone marrow donors, where the data is necessary for the matching of donor and recipient.) Anecdotal evidence suggests that blood donors are predominantly Australians of Anglo-Celtic origin.

It is possible that recruiting donors from specific ethnic groups could result in an increased donor pool. Certainly the recruitment of a number of donors from one ethnic group could offset the costs involved in delivering services to that group (e.g. translation of forms, provision of interpreters, and provision of culturally specific collections services). Offering a positive donation experience to donors from a specific ethnic group could also reinforce the donation intention of individuals and/or increase the level of repeat donations from members of that cultural group.

In response to questions from the Review Committee concerning recruitment of donors, the ARCBS has noted that it is aware of anecdotal reports of differences in attitude towards blood donation among Australians from a range of culturally and linguistically diverse backgrounds, and particularly in those communities where thalassemia major/minor is endemic (including the Greek, Italian and Serbian communities).²⁰

Some community groups have indicated a willingness to give blood but require the provision of specific culturally sensitive donation conditions. For example, some women in the Muslim community will donate only if there are no other donors in the room and only if the staff present are female.²¹

There are indications, however, that community groups are willing to work towards overcoming cultural barriers to donation. The NSW Muslim community recently organised a campaign to encourage people of the Muslim faith to donate blood.²² While this campaign has operated within the standard donation environment, there

¹⁹ ARCBS, responses to questions from Plasma Fractionation Review Committee, May 2006.

²⁰ Thalassemias are hereditary disorders characterised by defective production of globin, the protein component of haemoglobin; this deficiency leads to low production, and excessive destruction, of red blood cells, and to anaemia. There are two forms of thalassemia: thalassemia major (alpha), which is severe and is treated with regular blood transfusions, and thalassemia minor (beta), which does not usually require active treatment.

²¹ ARCBS, responses to questions from Plasma Fractionation Review Committee, May 2006.

²² See NSW Muslim Blood Drive Campaign, Sydney, 2006, <<http://www.muslimblooddrive.org.au/>>.

is, given demand, potential to tailor donation opportunities to meet the needs of specific communities.

More research could be undertaken to determine whether targeting specific ethnic groups in Australia is likely to result in an increase in the overall donor population.

As a first step, the ARCBS could undertake research and liaison with community organisations in order to gain an understanding of perceptions among cultural groups with regard to blood donations, and of any obstacles that may be holding back donation rates. Some cost–benefit analysis, of the costs of improving collection centre facilities and information provision so as to better target, and address existing concerns of, specific cultural groups in the Australian community – against likely returns in the form of increased numbers of donors – could also be undertaken.

Reimbursement of expenses

The question of some form of taxation concession or reimbursement for expenses (essentially, transport costs) incurred by donors has been raised by many stakeholders in the course of the Review. While observing the National Blood Agreement policy aim of maintaining reliance on voluntary, non-remunerated donations of whole blood and plasma, the Review Committee has given consideration to this issue.

The Committee would not recommend that Australia introduce a system such as that in the United States, where donors are paid directly, but the issue here is that of reimbursement or compensation for direct expenses related to blood donation.

The Council of Europe has determined that small tokens, refreshments and the reimbursement of direct travel costs are compatible with the principle of voluntary, non-remunerated donation.²³ The Council of the European Union has included a similar provision in its definition of voluntary, non-remunerated donations.²⁴

While health care policy, including blood donation, is an area of EU competence, European countries differ in their individual arrangements. Most rely on small tokens or small gifts. In Germany, people donating through the German Red Cross may receive up to Euro 25 (A\$42) for lost time and for travel expenses; university and community blood services usually provide their donors with an expense allowance ranging from Euro 25 to Euro 45–55 (A\$75–\$92) for cytopheresis donors, and Euro 12–15 (A\$20–\$25) for plasmapheresis donors. In Australia, the Australian Red Cross Blood Service has non-financial incentive schemes in place, and small tokens are sometimes given to donors. The Review Committee appreciates that a scheme to reimburse expenses may pose a considerable administrative burden on the ARCBS.

One suggestion proposed to the Committee as a possible means of increasing blood and plasma donations in Australia involves the provision of a tax benefit to donors. Depending on the nature of such a benefit, it could be compared to an income tax deduction offered to those making charitable donations, or to tax relief granted as an offset to those taking out private health insurance.

23 See Council of Europe, *Guide to the Preparation, Use and Quality Assurance of Blood Components*, 11th edn, Council of Europe Publishing, Strasbourg, 2005, p. 33. The Council of Europe is an international organisation that aims to reflect an overriding human rights position when developing guidelines on social and legal practices in member countries. The Council of Europe is separate from the European Union and does not have a legislative function.

24 See Council of the European Union, *98/463/EC: Council Recommendation of 29 June 1998 on the Suitability of Blood and Plasma Donors and the Screening of Donated Blood in the European Community*, Council of the European Union, 1998, <<http://eur-lex.europa.eu/Notice.do?val=229757:cs&lang=en&list=229757:cs,&pos=1&page=1&nbl=1&pgs=10&hwords=blood%20and%20plasma-&checktexte=checkbox&visu=#texte>>.

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Providing an incentive through the tax system, by making donation-related expenses an allowable tax deduction from income, may be inequitable, however, because of the way that the tax system is structured. In addition, an allowable deduction from income is attractive only to those people who are required to submit a tax return. Individuals not required to do so, such as those people with an income under the tax-free threshold, would gain little benefit from this approach. (The ARCBS has advised that 19.6% of the donor base are not in paid employment and identify themselves as students, retired or undertaking home duties.) Blood donors are not currently entitled to an income tax deduction for expenses incurred as a direct consequence of donating blood, because donors do not earn income from this activity.

Another possible mechanism would be to provide a tax offset to donors. A tax offset is defined by the Australian Taxation Office as a mechanism for directly reducing the amount of tax that must be paid. Tax offsets are not the same as deductions, which are subtracted from income before tax is calculated. With a tax offset, taxation payable is reduced by the total amount of the offset. Tax offsets can be framed so as to provide a tax benefit for a particular purpose or to a particular age group. Current examples include the tax offset for mature age workers and the private health insurance rebate.

If the tax offset framework were to be implemented for blood and plasma donors, it would be necessary to calculate a standard amount for the inconvenience and expense associated with donation. Estimating the level of reimbursement required is hard to quantify – a token offset of A\$100 per annum may be more appropriate than estimating a 'true value'. Research would be needed in order to establish the merit or otherwise of such a tax offset and, especially, to ascertain the attitudes of current members of the donor community. A tax offset for blood donation would be a major statement by government of the importance attached to donating.

Improved business planning

One issue identified by the Australian Red Cross Blood Service as an impediment to enhancing donor recruitment levels is the lack of multi-year funding. This issue is directly related to the supply planning process under the national blood arrangements, as funding is set annually so as to allow response to changes in demand and to facilitate management of blood sector expenditure through government budget processes.

The importance for the ARCBS of planning multi-year recruitment and retention strategies should not be underestimated, and long-term planning is a key factor of successful business planning for any organisation. The Review Committee believes that current funding arrangements for all governments, through the Jurisdictional Blood Committee, should be re-examined in order to give the ARCBS greater capacity to plan ahead.

The Review Committee notes the recent decision by the Australian Health Ministers' Conference to arrange an independent business study of the ARCBS, with this study to be managed by the National Blood Authority. This study will, inter alia, identify cost options for improving the national efficiency and effectiveness of the ARCBS and will assess current governance arrangements, and financial and accounting principles and practices.

Conclusion

The Australian Red Cross Blood Service faces the major challenge of having to collect substantially increased quantities of plasma for use in fractionation. In recent years, demand for plasma products, specifically IVIg, has reached the point where Australia is reliant on a small but potentially increasing proportion of imported product to supplement domestically sourced IVIg. If the ARCBS is to continue to meet increasing target volumes for starting plasma, it is important that options for improving strategies for the recruitment and retention of donors be considered. Current ARCBS strategies to attract donors address the key motivational factors associated with potential donors, and ARCBS collection volumes compare well with those of other developed countries. However, there is room for much further work to be done, especially around donor retention strategies.

The effects of social, economic and demographic changes in the last 20 years in Australia must be recognised, and the ways in which the ARCBS recruits and retains donors must reflect these changes. While to an extent this is happening already, the Review Committee believes that the ARCBS, on the condition that adequate funding is secured from governments, could do much more to make the activity of donating blood accessible to a higher proportion of the Australian community – whether by operating collection centres at weekends or evenings, increasing collections in outer metropolitan and regional areas, or providing facilities and information tailored to people from a range of culturally and linguistically diverse backgrounds.

Maximising workplace and organisational donations is an important part of increasing the blood donor population. Given the strong motivational factors associated with sporting club, place of worship, and workplace-based donation, and the cost benefits of targeting large organisations, new strategies to increase organisational donation programs should be encouraged.

In acknowledging the debt the nation owes to blood donors, the Review Committee believes that there is much work that could be done in surveying donor attitudes, and attitudes of the broader community, in order to determine how donations might best be increased. Surveys would need to be independent of the ARCBS (and would possibly be commissioned by the National Blood Authority), with input from stakeholders across the blood sector.

The Review Committee notes that funding implications for any new initiatives would need to be considered by governments as an issue separate from future arrangements for fractionation services.

Chapter 8

Regulation of plasma products

The global plasma products industry is one of the most heavily regulated sectors within pharmaceutical manufacture. The World Health Organization (WHO) has observed that this is because all medicines regulators have faced ‘serious and complex challenges at a scientific, technological and regulatory level to ensure that these biological products are of good quality, safety and efficacy’.¹

The manufacturing paradigm for plasma products, like all biological products derived from human or animal tissue, differs significantly from that applicable to synthetically derived medicines. The manufacture of conventional medicines using chemically consistent raw materials and standard manufacturing techniques can produce generic bio-equivalent products. The manufacture of plasma products, in comparison, entails inherent variability in the following areas:

- **Source material:** Each batch of starting plasma may contain thousands of plasma units from donors that have been pooled for processing. Each plasma starting pool will contain a different protein profile, which is manufactured, through intermediate product stages, to produce a suite of final products that must conform with approved specifications unique to each product.
- **Risk factors:** The manufacture of plasma products, like all blood products, carries the risk of transmission of blood-borne pathogens (including bacteria, viruses and prions). This has been a tangible, not theoretical, risk, evident in the past transmission of hepatitis C and the Human Immunodeficiency Virus (HIV) through the blood supply, including through plasma products, prior to the introduction of specific screening tests and other safety measures in the 1980s and 1990s. Although the risk of viral transmission has decreased considerably over the past 20 years, the recognition that Transmissible Spongiform Encephalopathies (TSEs), including variant Creutzfeldt-Jakob disease (vCJD), could be transmitted by transfusion has sharpened the focus on regulatory requirements for addressing emerging pathogens. There is significant focus by manufacturers and regulators on the requisite measures to apply throughout the manufacturing chain so as to provide assurance of the safety and quality of the final products.
- **Manufacturing process:** Although common manufacturing steps are employed by fractionators, there are no standard universal manufacturing procedures for specific final products. Each fractionator adopts unique manufacturing procedures in order to maximise the yield, safety, quality and clinical efficacy of final products. Each manufacturing process requires individual assessment by regulators.
- **Final products:** The diversity of fractionation processes may mean differential clinical efficacy for different brands of the same product. Because different brands of the same product may have slightly different clinical properties and side effects, regulators require each product brand to be trialled in the clinical setting prior to marketing approval.

The issues identified here are fundamental to the safety, quality and efficacy of plasma products. Because of the global consolidation of plasma product manufacturers and an increasingly global market for these goods (see Chapter 3), the regulatory response has also shifted towards international harmonisation of standards. The WHO, while stating that individual countries should develop national regulations for plasma products, asserts that these should be based on current international standards and that national regulators should 'actively participate in initiatives towards international harmonisation of regulation'.² Australia has played a key role in this process of regulatory harmonisation.

This chapter provides an overview of the Australian regulatory framework implemented by the Therapeutic Goods Administration (TGA). The key issue of the regulatory oversight of overseas-manufactured plasma products, and whether this oversight should be strengthened if a toll fractionation model were adopted for Australia, is specifically addressed. This chapter also describes the international model for regulation of the safety and quality of plasma products, and looks at why some regulatory approaches are specific to Australia.

The Australian regulatory framework

The Therapeutic Goods Administration is part of the Australian Government Department of Health and Ageing, with responsibility for administering the *Therapeutic Goods Act 1989* (Cwlth) (hereafter 'the Act'). The TGA's key objectives in the regulation of therapeutic goods in Australia are to ensure that these goods:

- meet appropriate standards of safety, quality and efficacy
- are made available to the community in a timely manner.

The TGA currently regulates over 50 000 therapeutic goods, including prescription and non-prescription medicines, medical devices, blood, and blood and tissue products. The number of goods regulated by the TGA is continually increasing, as new therapies evolve, as new applications for existing therapeutic goods are found, and as international markets continue to expand. Manufacturing techniques are also changing and improving with the advent of new technologies. In 2004–05, the TGA assessed over 11 000 applications for product registration, listing or inclusion on the Australian Register of Therapeutic Goods (ARTG), and for variations to existing registrations or listings, and tested a total of 2861 samples of 1254 products, as part of post-market surveillance.

Plasma for fractionation and plasma products have been regulated by the TGA since its inception in 1991. This includes:

- plasma products derived from plasma collected and fractionated in Australia for use in Australia
- plasma products derived from plasma collected and fractionated overseas for use in Australia
- plasma products derived from overseas-sourced plasma fractionated in Australia for use overseas.

² World Health Organization, *Ensuring the Quality and Safety of Plasma Derived Medicinal Products*, <http://www.who.int/bloodproducts/publications/en/Infosheet_plasma_derived.pdf>.

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The Australian and New Zealand governments have commenced a consultation process to establish a joint regulatory agency. This would see a new authority that would replace both the TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Legislation to establish the Australia New Zealand Therapeutic Products Authority (ANZ/TPA) is expected to be introduced into Parliament in 2007. While no practical changes to the content of current regulations for plasma products are planned as part of the proposed establishment of a trans-Tasman therapeutic products agency, it is likely that under the new authority plasma products would be regulated within a discrete biologicals framework.

Plasma products in Australia are currently regulated as registered medicines. This results in their being subject to an intensive level of pre- and post-market scrutiny. The existing TGA regulatory model for plasma products includes:

- establishing standards and guidelines for the safety and quality of products
- pre-market product assessment before registration of a product on the ARTG and marketing approval in Australia
- licensing of domestic manufacturers, and certification of overseas manufacturers of the plasma products supplied in the Australian market
- controls on advertising and promotion
- post-market surveillance mechanisms, including Good Manufacturing Practice (GMP) audits, monitoring of adverse events, sampling and analysis of products, and recalls of defective products
- administrative and criminal penalties and sanctions for breaches of the Act
- special arrangements for the supply of products not approved for general marketing, including through the Special Access Scheme and for clinical trials.

The key elements of this framework are pre-market product assessment against relevant standards and guidelines for registration on the ARTG; manufacturer licensing (for Australian manufacturers) and certification of overseas manufacturers (either by the TGA or by an accepted overseas regulator); post-market product and manufacturer surveillance; and enforcement of compliance following breaches. Some plasma products, however (like other therapeutic products), can be supplied in Australia as unregistered products, with their supply being considered on a case-by-case basis under the Special Access Scheme.

Registration of plasma products

The Therapeutic Goods Administration undertakes a comprehensive assessment of the safety, quality and efficacy of all domestic and imported plasma products before they can be registered on the Australian Register of Therapeutic Goods and approved for supply in the Australian market.

The TGA has access to independent expert advisory committees. These include the Therapeutic Goods Committee (which provides advice on standards), the Australian Drug Evaluation Committee (ADEC) (which provides advice on product safety,

quality and efficacy) and the Adverse Drug Reactions Advisory Committee (which reviews adverse drug reactions).

The ADEC is composed mainly of practising specialist clinicians drawn from outside the TGA. The ADEC provides the TGA with expert advice on any issues that have arisen during the evaluation process of a product, and recommends to the TGA whether the product should be included in the ARTG.

The broad framework for the registration of all high-risk medicines, which includes plasma products, is outlined in the Australian Regulatory Guidelines for Prescription Medicines (June 2004). These guidelines describe:

- the Australian data requirements for applications for product registration
- the evaluation and decision-making process undertaken by the TGA on each application.

The Australian data requirements for product registration cover:

- **administrative information**, including product labelling and packaging, and evidence of manufacturer licensing or certification against GMP standards
- **product quality data**, including chemical, pharmaceutical and biological studies
- **product safety data**, including preclinical, pharmacological and toxicological studies
- **clinical data**, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies.

Applications for product registration are submitted to the TGA by an Australian product sponsor. The sponsor is responsible for the accuracy of all data submitted and for complying with all post-approval conditions specified by the TGA. These areas of obligation include responsibility for notifying the TGA of any change in product registration details or manufacturing process that may affect the safety, quality or clinical data previously submitted; and post-market responsibilities in relation to registered products. In essence the Australian sponsor is legally responsible for any unauthorised change in product registration details and for meeting many of the requirements imposed by the Act. A sponsor must be an Australian resident or an Australian incorporated body responsible for the manufacture, import or export of the product, or who has the product manufactured or imported on its behalf.

One critical issue raised with the Review has been the importance of confidence in the TGA in terms of the evaluation of the safety, quality and efficacy of domestic and imported plasma products. All products supplied in Australia, regardless of origin, are assessed against the same standards and guidelines for product registration.

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The Australian Regulatory Guidelines for Prescription Medicines make it clear that:

- Applications for product registration must comply with statutory standards established by Therapeutic Goods Orders made under the Act and monographs in the British Pharmacopoeia.³ Australia applies the standards of the European Pharmacopoeia by adoption of the British Pharmacopoeia.⁴ The Pharmacopoeia sets minimum mandatory standards for the manufacture and quality of pharmaceuticals for human and veterinary use. Specific monographs for final products include standards for: the definition of active substances; specification of the origin and quality of source materials (this includes standards for blood donor selection and screening; in respect of donors, Australia also has specific requirements in its own Therapeutic Goods Orders⁵); specifications for in-process testing and final product release testing, specific reference tests and assays for the purity and potency of products, and measuring residual impurities and permitted limits of impurities. The Pharmacopoeia includes specific monographs on human plasma for fractionation, and for individual plasma derived products.⁶
- Applications for product registration should comply with the European Union (EU) guidelines adopted in Australia by the TGA.⁷ Following consultation with the Australian pharmaceutical industry, the TGA adopts specific guidelines published by the European Medicines Agency (EMA), to ensure that Australia's technical data requirements for product registration are closely aligned with those in the EU. While the EU guidelines are not legally binding, sponsors must provide justification for any data that does not conform with requirements in a guideline.

The key EMA blood and plasma guidelines adopted in Australia are: the Note for Guidance on Plasma-Derived Medicinal Products,⁸ the Guideline on Assessing the Risk for Virus Transmission,⁹ the Guideline on the Scientific Data Requirements for a Plasma Master File,¹⁰ and the Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to vCJD Risk.¹¹

3 Sections 3(1) and 10 of the Therapeutic Goods Act provide that where the Minister has not determined a specific standard to apply to a therapeutic product under a Therapeutic Goods Order, then standards established in relevant monographs of the British Pharmacopoeia will apply. Current standards for plasma products are set by the British Pharmacopoeia 2005, which is harmonised with the European Pharmacopoeia 2005.

4 The TGA is an observer on several expert groups that advise the European Pharmacopoeia Commission on the maintenance and development of the product monographs that make up the European Pharmacopoeia. Since 1997 the TGA has been an observer on a specialist group concerned with plasma and related products.

5 *Therapeutic Goods Order No. 74: Standards for Blood Components*, Therapeutic Goods Administration, Canberra, 2006, <<http://www.tga.gov.au/docs/html/tgo/tgo74.htm>>.

6 For a list of the European Pharmacopoeia monographs for plasma derived products, see Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], European Medicines Agency, London, 2001, pp. 19–20 (Annexes I and II), <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

7 See Therapeutic Goods Administration, *European Union Guidelines Adopted in Australia*, Therapeutic Goods Administration, Canberra, 2006, <http://www.tga.gov.au/docs/html/euguide/euad_app.htm>.

8 Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

9 Committee for Medicinal Products for Human Use, *Guideline on Assessing the Risk for Virus Transmission* [CPMP/BWP/5180/03], European Medicines Agency, London, 2004, <<http://www.emea.eu.int/pdfs/human/bwp/518003en.pdf>> (also adopted as new Chapter 6 in the Note for Guidance on Plasma-Derived Medicinal Products (see note 6 above)).

10 Committee for Medicinal Products for Human Use, *Guideline on the Scientific Data Requirements for a Plasma Master File (PMF)*, revision 1 [EMA/CPMP/BWP/3794/03R.ev. 1], European Medicines Agency, London, 2006, <<http://www.emea.europa.eu/pdfs/human/bwp/379403en.pdf>>.

11 Committee for Medicinal Products for Human Use, *Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to vCJD Risk* [CPMP/BWP/5136/03], European Medicines Agency, London, 2004, <<http://www.emea.eu.int/pdfs/human/bwp/513603en.pdf>>.

Review of Australia's Plasma Fractionation Arrangements

Adoption of these guidelines has ensured provision to the TGA of extensive data relevant to the safety and quality of plasma products, including:

- quality assurance of the starting plasma – through annual updates of the sponsor's Plasma Master File covering donor selection, screening of donations, audits of collection centres, systems for tracing donors to finished products, storage and transport of donations
- quality assurance of the manufacturing process – through testing and control of intermediate products, specification, quality control and validation of the purification and viral-inactivation and removal processes.

Assessment of product registration data essentially occurs at a fixed point in time. Although the data provided in the application process address the quality assurance and control systems built into the manufacturing process, the post-market surveillance system provides for risk-based review of these systems through the monitoring of adverse events; periodic product safety updates; product testing; annual reviews of plasma master files; and GMP surveillance audits.

One issue for attention relates to the certification of product batch release by an appropriately qualified person. At present, sponsors are not required to certify that each batch of products for supply in Australia meets product registration specifications. This is already a requirement in the EU and the United States.

The TGA has experienced some difficulties in resolving issues related to product quality with representatives of sponsors in Australia when these representatives do not have a technical understanding of the product involved. The TGA will shortly enter into formal consultation with industry on the proposal that all batches of imported medicines should be released for supply only after an appropriately qualified person has certified that the batch meets required specifications for quality and safety. It is agreed that it is important to ensure that an appropriately qualified person is responsible for certification of batch release.

A second issue relates to the TGA's capacity to independently test products. The TGA employs a risk-based program of targeted testing of products in the marketplace to ensure compliance with specifications and registration data. The TGA has occasionally found problems with batches of products that have passed testing by the manufacturers. The Review supports independent testing by the TGA. The extent of this testing would vary depending on the risk posed by the product and TGA experience of the particular manufacturer. In the EU, there is a system of Official Medicines Control Laboratories that test all batches of plasma products prior to release in Europe. The regulatory agencies of North America, which include the Food and Drug Administration (FDA) and Health Canada, test products on a risk management basis that is more targeted. It is anticipated that the presence of a qualified person representing the sponsor will assist the TGA in the establishment of a similar program for plasma derivatives in the Australian market.

Licensing and certification of manufacturers

The regulation of manufacturers in Australia is an essential part of the TGA's regulatory framework. The aim is to ensure that medicines are manufactured in accordance with standards of GMP, in order to 'build in' safety, quality and efficacy.

Review of Australia's Plasma Fractionation Arrangements

The current Australian Code of Good Manufacturing Practice for Medicinal Products (the Code of GMP) was introduced in August 2002.¹² It is based on the 2002 Guide to Good Manufacturing Practice for Medicinal Products published by the Pharmaceutical Inspection Cooperation Scheme (the PIC Scheme) and is a key element in the movement towards international harmonisation of therapeutic goods regulation. The PIC Scheme Guide provides an international benchmark for certification of medicine manufacturers.

The Australian Code of GMP is extracted from the PIC Scheme Guide and is the mandatory standard for the regulation of medicine manufacturers in Australia. The Code provides a standard framework for assessing compliance with quality management requirements in: the manufacture of medicines; standards for premises and equipment; personnel; documentation; production and quality control; contract manufacture; complaints handling; product recall; and self-inspection.

Australian manufacturers are assessed by the TGA against the Code of GMP before being issued a manufacturing licence. The TGA subsequently undertakes (scheduled) announced and (risk-based) unannounced audits to assess whether a domestic manufacturer remains compliant with the Code. Generally, scheduled audits are conducted every two years. A licence is perpetual, subject to satisfactory audit outcomes, regular re-audits being conducted, and payment of an annual licence charge. Licences can be suspended or revoked if audit outcomes are very unsatisfactory.

Some of the key issues assessed in GMP audits of plasma fractionators are:

- **critical process steps:** control of plasma starting pools, virus inactivation and removal, and aseptic processing
- **prevention of contamination and cross-contamination in manufacture:** handling and segregation of materials, qualification of critical equipment, cleaning and sanitation of facility and equipment
- **process consistency:** process validation and quality control.

Overseas manufacturers of medicines supplied in the Australian market are outside the licensing jurisdiction of the Therapeutic Goods Act. However, under the Act, the TGA must be satisfied that 'if a step in the manufacture of the goods has been carried out outside Australia ... the manufacturing and quality control procedures used in the manufacture of the goods are acceptable'.¹³

Overseas manufacturers are certified by the TGA as part of the pre-market product assessment and post-market approval conditions placed on Australian sponsors in the product registration process. Certification is provided by:

- TGA acceptance of a certificate of GMP compliance issued by an overseas regulator with which Australia has a Mutual Recognition Agreement (MRA) or other accepted agreement; or by
- TGA certification of GMP compliance on the basis of an on-site audit of the overseas manufacturer, when there is no other acceptable information available.

¹² Therapeutic Goods Administration, *Australian Code of Good Manufacturing Practice for Medicinal Products*, Therapeutic Goods Administration, Canberra, 2002, <<http://www.tga.gov.au/docs/pdf/gmpcodau.pdf>>.

¹³ *Therapeutic Goods Act 1989* (Cwlth), s. 25(1)(g); see also ss. 25(2), 26(1)(g), 26(2).

The TGA accepts certificates of GMP compliance through Mutual Recognition Agreements. MRAs are legal instruments between Australia and one or more countries. Prior to entering an MRA, each signatory is expected to assess the GMP standards and audit procedures adopted in the other countries, in order to establish regulatory equivalence. Other agreements, such as Memoranda of Understanding (MOUs) or 'cooperative agreements', provide for exchange of information between signatories but do not impose an obligation to accept certificates of GMP compliance, generally because GMP regulatory equivalence has not been formally established for signatory countries. The TGA has recently introduced a process of conducting thorough 'desk audits' to assess the GMP reports for non-MRA countries.

Australia is currently signatory to four MRAs for GMP assessments of medicines: (1) the European Union MRA (known as the EC MRA), coupled with the European Free Trade Association MRA (EFTA MRA), and bilateral MRAs with (2) New Zealand, (3) Canada (specifically excludes from its scope medicines derived from human blood or plasma) and (4) Singapore. Since 1993 Australia has had an MOU on GMP for medicines with Japan, and has also had a cooperative information-sharing agreement with the United States, which expired in October 2005. This agreement, on GMP for pharmaceutical products, is currently in the process of being renewed.

The EC MRA was entered with the European Community and covers the 15 countries that were members of the EC when the MRA came into effect.¹⁴ The status of the 10 new members of the EU with regard to the MRA is under review while the TGA is negotiating to establish GMP regulatory equivalence.¹⁵ A key provision of the EC MRA is that, although parties should generally accept the certificates of GMP compliance provided by other member countries, individual members have a limited capacity, in exceptional circumstances, to conduct GMP audits of manufacturers in the other jurisdictions. The TGA has used this provision on one occasion. For this to occur, however, the TGA must notify the European Commission, outlining very strong reasons. In such a case, the Australian product sponsor must agree to pay for the audit.

The relevant European regulators for the overseas fractionators with facilities in Europe at this time are shown in table 8.1.

The EFTA MRA was negotiated on terms almost identical to the EC MRA. It extends the regime of the EC MRA to include Norway, Liechtenstein and Iceland. The Pharmaceutical Inspection Convention (PIC) agreement, which applies to Australia and Switzerland, differs from the EC MRA in that members do not have the right to undertake their own GMP audits in exceptional circumstances. Under Swiss law, Swissmedic (the national regulator) must lead any audit involving another national regulatory authority.

The Pharmaceutical Inspection Cooperation Scheme (the PIC Scheme) was established to promote harmonised GMP standards and guidance documents; to promote consistent training and auditing practices across regulatory authorities; and

¹⁴ These were: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom.

¹⁵ Ten new members joined the EU as of 1 May 2004: Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Slovak Republic and Slovenia.

Table 8.1 European medicines regulators

Fractionator	Regulators
Baxter	<ul style="list-style-type: none"> • Austria – Ministry for Health and Women • Belgium – Directoraat Generaal Geneesmiddelen (DGG) / Direction Générale Médicaments (DGM)
BPL	<ul style="list-style-type: none"> • United Kingdom – Medicines and Healthcare Products Regulatory Agency (MHRA)
CSL Behring	<ul style="list-style-type: none"> • Germany – Paul-Ehrlich-Institut • Switzerland – Swiss Agency for Therapeutic Products (Swissmedic)
LFB	<ul style="list-style-type: none"> • France – Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) (French Health Products Safety Agency)
Octapharma	<ul style="list-style-type: none"> • Austria – Ministry for Health and Women • France – Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) (French Health Products Safety Agency) • Germany – Paul-Ehrlich-Institut • Sweden – Medical Products Agency / National Board of Health and Welfare
Sanquin	<ul style="list-style-type: none"> • Netherlands – Netherlands Medicines Inspectorate (Ministry) • Belgium – Directoraat Generaal Geneesmiddelen (DGG) / Direction Générale Médicaments (DGM)

to undertake peer assessment of audit practices.¹⁶ The PIC Scheme is not a GMP regulatory equivalence scheme.

The frequency of GMP audits is comparable for Australian and overseas manufacturers covered by GMP agreements. The TGA has noted that the frequency of scheduled audits in Australia, generally conducted every two years, is consistent with the PIC Scheme standard.

With regard to the conduct of unannounced audits, the Review has considered the implications of current differences between the situation for domestic manufacturers and the situation for overseas manufacturers. Unannounced audits in Australia are one component of GMP regulatory practice. Several factors can trigger an unannounced audit (including tip-offs, issues associated with sample testing, a manufacturer's GMP

¹⁶ For the PIC Scheme, see *Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme*, <<http://www.picscheme.org>>. The PIC Scheme is a cooperative arrangement between 28 participating countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Malaysia, the Netherlands, Norway, Poland, Portugal, Romania, Singapore, the Slovak Republic, Spain, Sweden, Switzerland and the United Kingdom.

audit track record, and product recalls). Over the last five years, fewer than 5% of GMP audits in Australia were unannounced.

The situation is different for overseas manufacturers. Under the MRAs to which it is a signatory, Australia has very limited capacity to conduct its own GMP audits, but can request that the relevant local regulator undertake an unscheduled audit. Where the TGA is able to conduct overseas audits under the MRAs, in practice all such audits are announced in advance, because product sponsors must agree to pay for the audits.

As of 31 October 2005, legislation has been in place within the EU countries so that unannounced inspections can be undertaken when necessary. In some EU countries (e.g. Portugal and the United Kingdom) some audits are unannounced, but attitudes to such inspections vary widely within the EU. If the TGA were to rely upon the MRAs in their current form, then unannounced audits may well be achievable overseas. The more pertinent issue is whether Australia should clarify with MRA partners its role in these audits, particularly if a toll fractionation model were implemented for Australia, giving rise to a strong national interest in the conduct of GMP audits. This issue is discussed later in the chapter.

The Act provides strong civil and criminal penalties and sanctions for Australian sponsors and manufacturers who fail to comply with product and manufacturing standards.

Ensuring safety and quality of plasma products

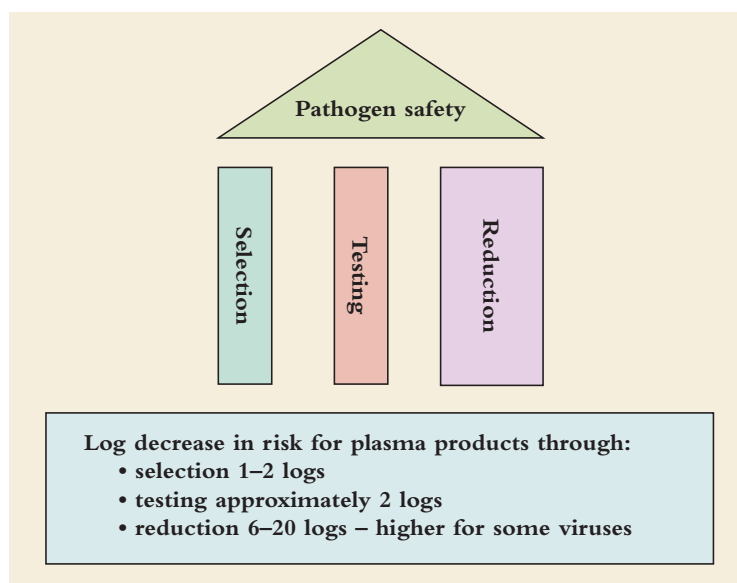
The safety of blood and blood products has been a recurring theme internationally over the last 25 years. The transmission of hepatitis C and HIV through fresh blood products and plasma derived products in the mid 1980s was a major catalyst for the push towards international harmonisation of medicines regulation.

While strong regulatory consistency has been achieved between Australia and the EU, there are still some areas where countries have adopted unique regulatory requirements. This section describes the pathogen 'safety tripod' adopted internationally and some of the measures that are specific to Australia.

Figure 8.1 shows the pathogen safety tripod and the relative contribution of each leg towards the reduction of risk of transmission of blood-borne viruses. The figure sets out reduction factors that are normally expressed on a logarithmic scale. The reason is to imply that, although residual virus infectivity will never be reduced to absolute zero, it may be greatly reduced to a negligible level.¹⁷ While selection of donors and testing of donations each reduce the theoretical risk of transmission approximately 10–100 fold, the third leg of virus inactivation and removal reduces the risk of transmitting a virus approximately another one hundred million fold. This illustrates that the manufacturing process itself plays a central role in ensuring the safety of final products. In combination these three steps significantly reduce the risk of transmission of most current known viruses via plasma products.

¹⁷ See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*, [CPMP/ICH/295/95], European Medicines Agency, London, 1997, p. 10, <<http://www.emea.europa.eu/pdfs/human/ich/029595en.pdf>>.

Fig. 8.1 Pathogen safety tripod



Source: Adapted from information in: Thomas R. Kreil, 'Differences between Blood and Plasma: Emerging Pathogens and the Safety of Blood Products – What to Do, or Not, and Why?', *eSource* (June 2006), p. 2, <<http://www.esourcemagazine.org/content/view/39/32/>>.

The more recent challenge to the plasma products sector has been the recognition that Transmissible Spongiform Encephalopathies, including variant Creutzfeldt-Jakob disease, could be transmitted by transfusion. While there is currently no evidence that vCJD or other prion diseases could be transmitted through plasma products, national regulators have uniformly adopted a precautionary approach to reviewing the safety tripod measures.

Prion proteins are normally present in many organs and tissues (including the brain, spinal cord and eyes) of healthy humans and animals. The prion diseases are caused by an abnormal folding and accumulation of prion proteins, which progressively damages the brain. The TSE diseases – fatal degenerative diseases that affect both humans and animals – include Creutzfeldt-Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE), or 'mad cow disease', in cattle, and scrapie in sheep. Classical CJD occurs in approximately one person per million of the population per year and it mainly affects older people.

In 1996, variant Creutzfeldt-Jakob disease was first identified in a younger cohort of patients in the United Kingdom, exhibiting a number of distinctive features when compared with classical CJD. Over 150 cases of vCJD have since been identified worldwide, mostly in the United Kingdom but with significant numbers appearing in France. There is strong evidence that vCJD is causally linked to BSE,¹⁸ the likelihood being that infection occurs as a result of eating BSE-contaminated beef

¹⁸ See R. G. Will, M. Zeidler, G. E. Stewart, M. A. Macleod, J. W. Ironside, S. N. Cousens, J. Mackenzie, K. Estibeiro, A. J. E. Green & R. S. G. Knight, 'Diagnosis of New Variant Creutzfeldt-Jakob Disease', *Annals of Neurology*, vol. 47, no. 5 (May 2000), pp. 575–82.

products. Recent reports strongly suggest that the transmission of vCJD has occurred by blood transfusion from apparently healthy donors, prior to their development of vCJD. As of 2006, there have been three overseas reports of possible transmission of vCJD through the use of fresh blood products.¹⁹

Donor selection

Before potential blood or plasma donors can donate they are initially screened. The purpose of this screening is to determine whether a person is in good health, in order to safeguard both his or her health and the health of recipients. Collection centres implement protocols in line with requirements in the European Pharmacopoeia, assessing a donor’s medical history, general health and relevant lifestyle.

The assessment of each donor is carried out by a suitably qualified person working under the supervision of a physician. The assessment involves an interview, a questionnaire and further direct questions if necessary. The screening process also involves the provision of educational materials to all donors. This material explains the donation process, the transmission of blood-borne infections, and the donor’s responsibility in the prevention of such transmission.

The potential transmission of TSEs through the blood supply has led to many countries introducing donor deferral measures as part of the donor selection process,

Table 8.2 Period of UK residency requiring donor deferral, by country

	UK residency: cumulative period during 1980–96
Austria	6 months
Canada	6 months
Czech Republic	6 months
Finland	6 months
France	6 months
Germany	6 months
Greece	6 months
Ireland	5 years
Italy	6 months
New Zealand	6 months
Spain	12 months
Switzerland	6 months
United States	3 months

¹⁹ See C. A. Llewelyn, P. E. Hewitt, R. S. G. Knight, K. Amar, S. N. Cousins, J. Mackenzie & R. G. Will, ‘Possible Transmission of Variant Creutzfeldt-Jakob Disease by Blood Transfusion’, *Lancet*, vol. 363, no. 9407 (7 February 2004), pp. 417–21; A. H. Peden, M. W. Head, D. L. Ritchie, J. E. Bell & J. W. Ironside, ‘Preclinical vCJD after Blood Transfusion in a PRNP Codon 129 Heterozygous Patient’, *Lancet*, vol. 364, no. 9433 (7 August 2004), pp. 527–9; and ‘New Case of Transfusion-Associated vCJD in the United Kingdom’, *Eurosurveillance*, vol. 11, no. 2 (2006), <<http://www.eurosurveillance.org/ew/2006/060209.asp#references>>.

Review of Australia's Plasma Fractionation Arrangements

in particular with regard to the donation of blood and plasma that could be affected by a donor's having lived in the United Kingdom for an extended period.²⁰ In Australia, persons who have spent six months or more in the United Kingdom between 1980 and 1996 are not permitted to donate blood. Table 8.2 sets out the practice in other countries in regard to deferring donors who lived in the United Kingdom during the period considered to represent the greatest risk.

Testing

Following collection, all donations are tested for relevant infectious disease markers. In-vitro diagnostic (IVD) tests are regulated in Australia, the EU and North America. The tests must meet sensitivity and specificity requirements prior to obtaining regulatory approval. In Australia, IVD test performance is monitored through laboratories' participation in external quality assurance schemes.

Current tests used for infectious disease screening of blood and plasma donations are based on the detection of a relevant antigen and/or antibody, and gene sequences. As required by the British Pharmacopoeia, plasma donations are tested for infectious disease markers at two stages: the individual donation and the first manufacturing plasma pool. Each donation is tested for antibodies against human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2), for hepatitis B surface antigen (HBsAg) and for antibodies against hepatitis C (HCV). The first manufacturing plasma pool is tested for HIV antibodies and HBsAg, and is also tested for HCV, using nucleic acid amplification technology. In addition to the requirements of the British Pharmacopoeia, the Therapeutic Goods Administration requires that donations are tested for HIV-1 and HCV using nucleic acid amplification technology. If a repeat positive result is found for any of these tests, the donation or pool must not be used.

Pathogen inactivation and removal

Inactivation and removal of infectious agents is the third and final stage of the pathogen safety tripod. Inactivation and removal processes target viral and prion-based agents.

The EMEA Note for Guidance on Plasma-Derived Medicinal Products states that the fractionation and purification process adopted by manufacturers of plasma products can contribute to the removal of viruses, quite separately from dedicated viral-inactivation and removal steps. This capability is quite specific to the type of manufacturing process employed. The two principal fractionation techniques are:

- **Cold-ethanol fractionation** (often referred to as Cohn fractionation). This involves the addition of varying concentrations of ethanol to cooled plasma; this process, together with variations in salt and pH, precipitates protein fractions. The fractions are further purified into individual plasma products. Cold-ethanol

20 In addition to restrictions on former UK residents, in August 2006 the US Food and Drug Administration (FDA) adopted a draft guidance policy in which a donor deferral recommendation is made to collection establishments in respect of individuals who have received a transfusion of blood or blood components in France since 1980 (Center for Biologics Evaluation and Research, *Guidance for Industry: Amendment (Donor Deferral for Transfusion in France since 1980) to 'Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products'— Draft Guidance*, US Food and Drug Administration, Rockville, MD, 2006, <<http://www.fda.gov/cber/gilns/cjdfrance.htm>>). In Canada, potential donors who have spent a cumulative total of six months or more in France between 1980 and 1996 are deferred from donating blood or plasma (see Health Canada, *Health Canada Issues Precautionary Directive for Deferral of Blood and Plasma Donors Who Have Spent Extended Periods of Time in France*, media release, 31 August 2000, Health Canada, Ottawa, <http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2000/2000_85_e.html>).

fractionation has been employed since the beginning of the plasma products industry in the 1940s and continues to be the predominant methodology used by fractionators around the world. Several variants of cold-ethanol fractionation are employed by manufacturers, chiefly the Cohn-Oncley process in the United States and the Kistler-Nitschmann process in Europe. Cold-ethanol fractionation is well established, and products manufactured using this method have a long history of safety and efficacy.

- **Chromatography** is a process by which the components of a mixture – in this case, plasma – are separated according to size, charge, or other chemical properties, via interaction with a solid medium such as a gel. The chemical properties of the gel provide the basis for the separation. Chromatographic techniques are increasingly being used in plasma fractionation, because higher yields and greater purity can be achieved, less damage is caused to the plasma proteins, and potentially a larger range of proteins can be extracted from the starting plasma. Many products manufactured by CSL Bioplasma at its Broadmeadows plant are purified predominantly by chromatographic techniques. Other manufacturers of plasma derivatives do not have the same reliance on chromatography as CSL Bioplasma. In general, other fractionators have introduced one or more chromatography stages at the end of cold-ethanol manufacturing processes following viral-inactivation procedures.

The European Medicines Agency (EMA) recommends use of two distinct inactivation/removal steps, which are designed to complement each other in their mode of action. At least one of these steps should be effective against non-enveloped viruses. The EMA recognises that ‘designing steps which will complement each other and also be effective against a wide range of viruses including enveloped and non-enveloped viruses of diverse physico-chemical characteristics, is not a straightforward task’.²¹

The TGA requires a minimum of two effective viral-inactivation steps in the manufacturing process. These dual inactivation steps must target both:

- enveloped viruses (such as hepatitis B and C, HIV-1 and HIV-2, and West Nile Virus) and
- non-enveloped viruses (such as hepatitis A and parvovirus B19).

The viral-inactivation procedures used by plasma fractionators vary between products but may include solvent detergent, dry heat, pasteurisation, viral filtration and low pH incubation. Table 8.3 provides an overview of the various viral-inactivation and elimination methods.

Enveloped viruses are generally easier to inactivate than non-enveloped viruses, because enveloped viruses can be inactivated through solvent detergent processes and a number of heat treatment processes.

It is arguable that the most effective of the viral-elimination processes for non-enveloped viruses is nanofiltration. Nanofiltration is a filtration process that can remove small particles such as a virus. However, nanofiltration is not appropriate for all plasma products. For example, nanofiltration for the removal of non-enveloped

²¹ Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], p. 15, <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

Table 8.3 Viral-inactivation and elimination methods

Treatment	Advantages	Points to consider
Solvent detergent	<ul style="list-style-type: none"> Extremely efficient against enveloped viruses Relatively simple equipment Non-denaturing effect on proteins High recovery of protein functional activity 	<ul style="list-style-type: none"> Requires a subsequent manufacturing step to eliminate the solvent detergent agents Not effective against non-lipid-enveloped viruses (e.g. parvovirus or hepatitis A virus)
Pasteurisation	<ul style="list-style-type: none"> Potential to inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus Relatively simple equipment 	<ul style="list-style-type: none"> Protein stabilisers may protect viruses Does not inactivate parvovirus Low recovery of fragile coagulation factors Potential generation of neoantigens
Vapour-heat	<ul style="list-style-type: none"> May inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus 	<ul style="list-style-type: none"> Possible risk of transmission of hepatitis C virus and hepatitis G virus Does not inactivate parvovirus
Terminal dry-heat	<ul style="list-style-type: none"> May inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus Treatment applied on the final container 	<ul style="list-style-type: none"> Does not inactivate parvovirus 10–20% loss of coagulation factor activity Requires strict control of residual moisture content
Acid pH	<ul style="list-style-type: none"> Effective against enveloped viruses Relatively simple equipment 	<ul style="list-style-type: none"> Restricted to IgG Limited efficacy against non-lipid-enveloped viruses
Nanofiltration on 15 nm membranes	<ul style="list-style-type: none"> Elimination of viruses based on size-exclusion effect Eliminates all major viruses, including hepatitis A virus and parvovirus May possibly eliminate prions Filter's integrity and removal capacity is validated after use High recovery of protein activity Non-denaturing for proteins Risks of downstream contamination are limited when filtration is performed prior to aseptic filling Filters are commercially available; no royalties 	<ul style="list-style-type: none"> Non-applicable to high molecular weight protein concentrate (without significant protein loss)
Nanofiltration on 35 nm membranes	<ul style="list-style-type: none"> Similar to 15 nm membranes Applicable to some Factor VIII and von Willebrand factor concentrates 	<ul style="list-style-type: none"> Elimination of small viruses not total

Source: Derived from information in: A. Farrugia, *Guide for the Assessment of Clotting Factor Concentrates for the Treatment of Hemophilia*, World Federation of Hemophilia, Montreal, 2003, p. 8, also available online at <http://www.wfh.org/2/docs/Publications/Safety_and_Supply/GuideClottingFactor_Eng.pdf>.²²

²² Farrugia table adapted from: F. Ala, T. Burnouf & M. M. El-Nageh, *Plasma Fractionation Programmes for Developing Countries: Technical Aspects and Infrastructural Requirements*, WHO Regional Publications, Eastern Mediterranean Series, no. 22, World Health Organization, Alexandria, 1999; and T. Burnouf & M. Radosevich, 'Reducing the Risk of Infection from Plasma Products: Specific Preventative Strategies', *Blood Reviews*, vol. 14, no. 2 (June 2000), pp. 94–110.

viruses cannot be used in the case of Factor VIII plasma products, because Factor VIII is such a large protein that it may also be removed by the nanofiltration process.

In the cleaning undertaken between batches of plasma, harsh chemical and physical treatments are used to eliminate prions from the equipment used in fractionation. These treatments cannot be used on the gels employed in chromatographic fractionation. This is because the gels are made up of polymerised sugars, and similar substances, that cannot withstand these processes. Other processes are used to clean gels; these treatments are effective for the inactivation of viruses but less effective for the inactivation of prions.

The TGA introduced segregation of Australian plasma as a regulatory requirement because of the risk of prion contamination from multiple plasma sources. Given that CSL Bioplasma fractionates plasma from a number of countries, including countries with a BSE status inferior to that of Australia, the TGA considered that the application of segregation as a precautionary measure based on scientific uncertainty around prion infectivity was justified. Due to the particular manufacturing procedures used predominantly by CSL Bioplasma at its Broadmeadows plant (i.e. chromatography and not cold-ethanol fractionation), segregation in this instance has meant using separate chromatography columns for fractionating Australian plasma. This use of separate equipment provides an effective barrier between plasma starting pools from different sources, to negate the potential risk of prions being transferred from one pool to another during processing. The segregation measures adopted at different fractionation plants (all of which typically fractionate plasma from multiple countries) are not necessarily identical, and measures to minimise risk are determined with reference to the production technology in use at a particular facility.

It is generally thought that the risk of transmission of vCJD by plasma products is low because the manufacturing processes (particularly those involving cold-ethanol fractionation) remove prions to a significant extent from the fractions that are separated to obtain therapeutic products.²³ However, there is a level of uncertainty, because science has yet to develop a testing procedure that is sensitive enough to detect prions in donor blood and therefore able to accurately test the effectiveness of prion inactivation. In addition, although none of the patients exposed to plasma products sourced from potentially contaminated plasma have developed prion disease, the incubation periods are such that low-titre inocula, as would occur with plasma products, may have transmitted as yet undetected disease. It is partly because of these uncertainties that current regulatory practice around the world is to recall any plasma product made from a plasma pool containing a donation from a person who subsequently develops vCJD, regardless of the theoretical extent to which the production process may have rendered the final product non-infectious. It should be acknowledged that under these circumstances most of the product would have been used by the time the donor became ill.

The TGA uses international best-practice guidelines, and the advice of the Australian National Health and Medical Research Council (NHMRC) Transmissible

²³ For a comparison of fractionation techniques in this respect, see P. R. Foster, A. G. Welch, C. McLean, B. D. Griffin, J. C. Hardy, A. Bartley, S. MacDonald & A. C. Bailey, 'Studies on the Removal of Abnormal Prion Protein by Processes Used in the Manufacture of Human Plasma Products', *Vox Sanguinis*, vol. 78, no. 2 (March 2000), pp. 86–95.

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Spongiform Encephalopathies Advisory Committee (TSEAC),²⁴ in minimising any risk of prion transmission through plasma products. Each plasma product on the Australian market is assessed for this risk regardless of its origin. As mentioned in Chapter 6, the TGA recently introduced a policy that has created a restricted donor pool for the production of the plasma derived Factor VIII product Biostate. Biostate is principally used to treat people with haemophilia A who have developed inhibitors to recombinant clotting factors, and people with von Willebrand's disease. There have been no reported cases of vCJD in recipients of plasma products. The consensus of expert opinion, however, is that people with haemophilia and von Willebrand's disease who require treatment with plasma products are under a higher theoretical risk than recipients of other products because of their lifelong reliance on these products to maintain their health.

TSEAC's risk assessment found that although the theoretical risks of vCJD transmission were very small and that Biostate has an excellent safety record with no cases of transmission of pathogens, further precautions should be taken to reduce that already small risk. While many Factor VIII purification methods clear prions to a large extent,²⁵ the manufacturing process used by CSL to manufacture Biostate was judged by TSEAC to result in a small residual risk.²⁶ TSEAC's requirements for prion clearance guide the TGA in its approval of plasma products, whereby an overseas product²⁷ has been approved which has a prion clearance reflective of TSEAC's advice.²⁸

Following the increased access to government-funded recombinant Factor VIII and the consequent reduction in demand for Biostate, it was possible to introduce a new precautionary measure to further reduce the theoretical risk. A plasma collection policy was introduced in June 2005 and came into full effect after 1 April 2006 to ensure that plasma used in the production of Biostate was sourced from donors who had not lived or travelled outside Australia and New Zealand since 1980.²⁹ Such donors have an extremely low risk of being exposed to vCJD because there have been no confirmed cases of BSE or vCJD in either country. Through this measure an additional level of protection against the theoretical risk of prion transmission is available to protect people who receive Biostate.

24 As opposed to the FDA's TSEAC, which is charged with providing similar advice to the FDA; see <<http://www.fda.gov/cber/advisory/tse/tsechart.htm>>.

25 T. Kriel, 'Industry TSE Clearance Studies for Plasma-Derived Factor VIII', presentation, September 2006, <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1_7_files/frame.htm>

26 S. Caris, 'New Donor Requirements for Plasma Derived Factor VIII in Australia', *National Haemophilia*, no. 153, March 2006, p. 6, <<http://www.haemophilia.org.au/sitebuilder/knowledge/files/254/nhno153march2006pg1-10.pdf>>.

27 Australian Register of Therapeutic Goods entry for Octanate, <<http://www.tgasime.health.gov.au/SIME/ARTG/ARTGPublicWeb.nsf/MEDpublic?SearchView&Query=octanate&start=1&searchOrder=4&searchMax=1000&searchWV=0&searchFuzzy=0>>.

28 A. Neisser-Svae, et al., 'Prion Protein Removal during Manufacturing of High-Purity VWF/FVIII Concentrates', *Haemophilia*, vol. 12 (suppl. 2), 2006, p. 20, 05 PO 122.

29 Caris, 'New Donor Requirements for Plasma Derived Factor VIII in Australia'.

Regulatory issues arising with toll fractionation

In the event that Australian governments agree to an option for future fractionation arrangements that results in the overseas processing of Australian plasma, either (a) new products would need to be registered on the Australian Register of Therapeutic Goods, or (b) variations in registration details of products already on the ARTG would be required, given the change in the use of Australian plasma in their manufacture for supply to this country.

Under a toll fractionation model, the Therapeutic Goods Administration would continue to monitor safety, quality and efficacy through the product registration process, and then on an ongoing basis through post-market surveillance via the monitoring of adverse reactions; periodic product safety updates; product testing; annual reviews of plasma master files; and GMP surveillance audits. There are six issues that may need resolution:

1. product registration
2. compliance with European provisions regarding eligibility criteria for donors
3. GMP auditing in MRA countries
4. GMP auditing in non-MRA countries
5. costs of overseas audits
6. contractual provisions.

Two important considerations in regard to the overseas fractionation of Australian plasma are: whether there is equivalence of manufacturing requirements between Australia and the countries where manufacturing takes place; and whether the regulatory authorities in those countries will monitor compliance with manufacturing standards to a level that satisfies the TGA for the purposes of meeting the provisions of the Therapeutic Goods Act. These issues arise for toll fractionation particularly because the plasma products made under toll fractionation arrangements would be supplied to the Australian market only, rather than for use in the country of manufacture. Also, the regulator in the country of manufacture may exercise a different level of oversight for products for export only, as distinct from products for the home market.

Product registration

The TGA currently places specific requirements on the domestic fractionator in relation to the manufacturing process, through the Manufacturing Principles. Currently, the Manufacturing Principles include the provision that any fractionation plant that is used to process Australian plasma into products for use in Australia shall not be used to process any plasma collected outside of Australia unless the TGA is satisfied that the overseas-sourced plasma will not contaminate Australian product with blood-borne pathogens. The Manufacturing Principles specify that the TGA is to do this by evaluation of the Plasma Master File of the overseas-sourced plasma and consideration of the fractionation plant's processes.

While the Manufacturing Principles do not apply outside Australia's jurisdiction, under Section 25 of the Act the TGA is required, when evaluating applications of overseas-manufactured products, to take into account whether 'the manufacturing and quality control procedures used in the manufacture of the goods are acceptable'.

Compliance with European provisions regarding eligibility criteria for donors

Directive 2004/33/EC issued by the European Commission currently requires that blood and blood components imported from third countries, including starting plasma for fractionation, must be sourced from a donor pool that meets EU eligibility criteria for donors of whole blood and blood components. Australian recovered plasma would technically be rendered noncompliant with the Directive because its minimum haemoglobin levels for whole blood donors are lower than those of the EU. The TGA has been in contact with the EMEA on this matter. The intent of the provisions for haemoglobin levels is to protect donor health and have no bearing on the safety and quality of starting plasma and finished products. The European Commission and the EMEA are aware of this issue. It is the TGA's understanding that, in the event that Australian plasma were fractionated in Europe, shipments would not be impeded on the basis of this potential breach that currently exists under the Directive.

In the event that Australia moves to a tender process for future fractionation contracts, negotiations between Australian and European regulatory agencies would need to be held to identify and resolve any regulatory requirements that do not apply to the safety and quality of plasma and finished products but could nonetheless have the effect of impeding the shipment or processing of Australian plasma at a manufacturing facility in Europe. It could be a requirement for tenderers to demonstrate that there were no such impediments in their country.

GMP auditing in MRA countries

The MRAs covering plasma derived products with the European Union, and the PIC agreement with Switzerland, are most pertinent, as these include countries with fractionation plants. Some of the key elements of the EC/EFTA MRAs and PIC agreement for the purposes of this discussion are:

- GMP inspections of overseas fractionation plants are carried out by an overseas regulator in accordance with their GMP requirements, which are agreed to be equivalent to those of Australia.
- The TGA can request the overseas regulator to carry out an inspection to certify that the manufacturer is appropriately authorised to manufacture the products, is regularly inspected and complies with the national GMP requirements of the overseas regulator. Certificates are generally issued within 30 days; however, this may be extended to 60 days in exceptional circumstances. Each regulator is obliged to recognise the conclusions of the audits.
- The TGA can request an inspection report of the last inspection of the manufacturing site. Where the last inspection is more than two years old or where there is a particular need to inspect the site, an up-to-date and detailed report may be requested. A report may comprise a Site Master File and a narrative report describing the most recent audit and any GMP deficiencies, or it may respond to specific queries by the TGA. However, the details in the inspection reports can be quite variable. The same timing for delivery of inspection reports applies as described above. Each regulator is obliged to recognise the conclusions of the audits.

- Under the EC/EFTA MRAs the TGA may conduct an audit of an overseas manufacturer but only in exceptional circumstances. It must identify its reasons for doing so to the overseas regulator and the overseas regulator may join the inspection. Costs may be recovered by the TGA from the Australian sponsor in such circumstances.
- The overseas regulator must communicate to the TGA with appropriate urgency a suspension or withdrawal of product based on noncompliance with the GMP and which could affect the protection of public health.³⁰

The current provisions in the EC/EFTA MRAs permit the TGA to conduct an audit in exceptional circumstances. In Switzerland the local regulator must lead the audit. If Australia were to move to overseas toll fractionation this might be considered to be a previously unanticipated circumstance requiring an increased ability for the TGA to conduct joint audits with regulators in MRA countries. This is because plasma products are considered high-risk, the products would be for the Australian market only, and because Australia would be completely reliant for its supply of plasma products on manufacturing sites outside Australian jurisdiction, in contrast to the current arrangements. The Australia–EC/EFTA MRAs could be renegotiated to enable joint inspections by the TGA and designated EC/EFTA GMP Inspectorates of manufacturers of high-risk products, such as fractionated products, in appropriate circumstances. This would maintain Australia's commitment to regulatory harmonisation while enabling the TGA to have input into the scope and depth of the audit. It is noted that a joint audit program would require ongoing negotiations with the relevant European regulatory authorities. Amendments tend to take a long time to negotiate and implement, and would need to involve a detailed examination of how these amendments would operate in practice.

GMP auditing in non-MRA countries

The only non-MRA country with any major commercial fractionators that could undertake toll fractionation of Australian plasma is the United States. The Review undertook liaison with the Food and Drug Administration (FDA) to ascertain the regulatory issues that would arise from toll fractionation in the United States.

The United States Federal *Food, Drug, and Cosmetic Act* (the FDC Act) specifies provisions for the importation of components, including plasma, that are used in the manufacture of therapeutic goods (e.g. drugs) when the finished drug products are to be exported rather than distributed in the United States. This is referred to as 'Import for Export' (IFE). Blood, blood components, and plasma have special requirements under the IFE provisions. If a company were fractionating plasma imported from Australia at a plant in the United States, the company would need FDA permission under the plasma-specific IFE provisions of the FDC Act to import shipments of plasma and would also need to comply with the export provisions of the FDC Act to export finished products to Australia. While neither the imported plasma nor the exported finished products would require FDA-approved biologics licences, a number of the IFE provisions are directed at promoting the safety and quality of products so as not to present a health risk to the country of export under such arrangements.³¹

³⁰ See *Guide to the MRAs in Operation* [EMEA/MRA/22/03 Final], European Medicines Agency, London, 2003, <<http://www.emea.europa.eu/inspections/docs/0002203en.pdf>>. This guide published by the EMEA relates to the MRAs between the EU and the respective parties to agreements and is dated 8 May 2003.

³¹ See, for example, the requirements in Section 802 of the Federal *Food, Drug and Cosmetic Act*.

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The scope of regulatory oversight by the FDA for a toll fractionation arrangement would depend on the facts and circumstances of each particular arrangement.³² For example, if the IFE arrangement involved a US licensed manufacturer, the FDA would inspect, according to its standard policies and procedures, the facilities, including areas and systems involving IFE manufacturing. (This could be either a comprehensive or a streamlined evaluation, depending on the level of inspectional coverage that is deemed appropriate according to perceived risk.) The Review was also interested in whether, if regulatory breaches relating to production for the United States market resulted in the FDA revoking or suspending a fractionator's licence, this would automatically result in suspension of toll fractionation activities at the plant. While a US licence is not necessary for IFE arrangements to exist, action taken by the FDA would be based on the FDA's assessment of the particular circumstances and factors leading to the revocation or suspension of a licence. In practice, the FDA would notify relevant foreign regulators of action against a plant and a formal cooperation agreement between the FDA and the TGA could potentially specify how this could take place.

With regard to whether the TGA could conduct unannounced inspections of facilities in the United States, there are no FDA policies or procedures that require or recommend the TGA to pre-announce an inspection to the company. Conversely, FDA regulations do not require manufacturers to allow such inspections. Provisions in the contract with the fractionator could be employed to facilitate auditing of a US plant by the TGA (contractual provisions are discussed in greater detail below).

Such an understanding could be memorialised in an Agency-to-Agency arrangement. As noted above, the information-sharing agreement between the TGA and the FDA has expired and the agencies are in the process of reviewing it.

Costs of overseas audits

Undertaking an overseas audit of a toll fractionation facility is costly. It is estimated by the TGA that an audit could cost approximately A\$100 000. The TGA will establish a schedule of fees specifically for plasma products. Given the high cost of overseas audits, the TGA should consider the need to amend the Therapeutic Goods Regulations so that fees may be imposed on a sponsor to recover the costs of GMP auditing by the TGA. This would arguably be best undertaken through amendments to the regulations imposing a fee on the sponsor, but it should be noted that the MRAs also address the issue of costs of inspections and any amendments to the regulations would need to take this into account.

It is noted that an overemphasis on frequent and/or unannounced site audits may bring risks of disruption to production and that any special, or unscheduled, audits should be justified by an assessment of product risk.

Contractual provisions

When used in conjunction with other mechanisms, such as regulatory provisions and risk management strategies, contractual provisions in supply contracts between Australian product sponsors and the National Blood Authority (NBA) could be a

³² The FDA has issued a draft Guidance for Industry document on Exports and Imports under the FDA Export Reform and Enhancement Act of 1996 which, when finalised, will explain the basic requirements and procedures for exporting and importing biologicals and other therapeutic goods, including those that may not be sold or distributed in the United States: <<http://www.fda.gov/oc/guidance/frexport.html>>.

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useful mechanism for reinforcing the roles and responsibilities of the parties, and of third parties such as the TGA, in relation to ensuring the safety, quality and efficacy of plasma products. By way of example, the Plasma Products Agreement with CSL Limited includes a number of provisions that reinforce CSL's obligations under the Therapeutic Goods Act and provide for remedial action if a unit of product does not meet the standards for safety, quality and efficacy, or any other requirements, associated with the product's registration or listing. It must be noted, however, that, as will be discussed in Chapter 9, legal and practical impediments may be encountered in enforcing a contract involving a manufacturer in another country. It must also be noted that major risks arising from an overseas toll fractionation process, such as threats to the security of supply of plasma and finished products during transportation phases, need to be addressed by mechanisms other than the regulatory framework for the safety, quality and efficacy of products. This issue is also discussed further in Chapter 9.

The Review considers that should Australia adopt an overseas toll fractionation arrangement there are a number of provisions that should be included in a supply contract with an Australian sponsor in relation to the provision of fractionation services by an overseas fractionator. These would include:

- requiring that the company comply with all Therapeutic Goods Act requirements and other relevant Australian laws; and/or
- performance standards designed to ascertain and measure certain aspects of quality control; and/or
- requiring the company to have, maintain and implement an approved risk management plan, which properly deals with the risks associated with ensuring safe, high-quality products (i.e. identifies those risks, the likelihood of occurrence, the impact of occurrence, and strategies to minimise the likelihood or impact of occurrence).

The contract provisions on compliance with the Act will rely on the TGA's regulatory monitoring regime (including activities by overseas regulators, as part of international agreements). The TGA would need to report noncompliance to the NBA so that the NBA could implement or ensure the implementation of appropriate contractual protections (these could include change in payments, withdrawal of a product, supply planning changes).

The contract could also require the company to ensure that it does not enter into any subcontract (in connection with the contract to fractionate Australian plasma) without first complying with certain conditions and NBA approval and Therapeutic Goods Act compliance.

In addition to imposing quality requirements, the contract would also need to include:

- reporting mechanisms (to be adhered to by the sponsor and/or the manufacturer) with regard to TGA requirements/performance measures
- provision for audits of the manufacturing process to be conducted and for access to relevant premises
- undertakings about:
 - who is to conduct the overseas audits (TGA or an equivalent overseas regulator),
 - how often and how they are to be conducted, and who is to bear the cost

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- contractual remedies for failure to permit the conduct of audits, such as:
 - (a) the ability for the Commonwealth to terminate the contract; and/or
 - (b) reduction in/suspension of payments if the manufacturer does not permit and facilitate auditing; and/or
 - (c) provision for the conduct of tests of the products received in Australia, pursuant to TGA requirements. The contract would need to specify who would conduct such tests, who pays for the conduct of the tests, and the consequences of a product failing any such test.

Conclusion

Plasma products are biologicals that carry an inherent risk of pathogen transmission. They are regulated as high-risk medicines by the Therapeutic Goods Administration. The TGA regulates the safety, quality and efficacy of domestic and imported plasma products in the Australian market.

The infectious disease safety of plasma products is ensured through donor selection and testing of starting plasma, followed by inactivation and removal of pathogens during the fractionation process. This third step has the greatest effect upon the safety of finished plasma products. In well-regulated environments, plasma products have a long record of safety and for over ten years there have been no international reports that plasma derivatives have transmitted a blood-borne pathogen.

Through the product registration process, the TGA requires acceptable evidence of manufacturing processes and quality control to be demonstrated and maintained. If a toll fractionation model were adopted in Australia, the TGA would apply the same standards as are applied to locally manufactured products.

To ensure the continued supply of high-quality products, the Review considers independent testing of plasma products by the TGA is appropriate.

A key policy issue in considering the feasibility of overseas toll fractionation of Australian plasma is the ability to ensure satisfactory oversight of manufacturing. In terms of post-market surveillance in the case of MRA countries, it would be desirable for the TGA to have a greater scope to conduct and instigate audits of fractionators supplying Australia from plants in these countries. Australia would need to give strong consideration to whether the TGA's current ability to undertake audits of manufacturing sites within an MRA partner's territory would remain adequate. A reappraisal of these provisions could be warranted in order to permit joint inspections by the TGA and counterpart organisations of manufacturers of high-risk therapeutic goods such as fractionated plasma products. The possibility of renegotiating relevant sections of MRAs must take into account, however, the scale of such a task and the need for any such initiatives to be sensitive to the element of reciprocity in MRAs.

For countries where there is no MRA in place, there may be fewer impediments to Australian authorities conducting audits within the terms of existing formal arrangements. However, a greater amount of work by the TGA rather than its counterparts in inspecting overseas facilities would be likely. The costs and resources

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associated with regulating the fractionation of Australian plasma overseas would need to be addressed for both MRA and non-MRA countries.

In the event that Australian plasma is fractionated overseas, there must be a strong emphasis on contractual provisions between the NBA and the product supplier to reinforce appropriate regulatory oversight by the TGA, together with recognised overseas regulatory agencies as may be required under any applicable international agreements. The role of the TGA in relation to oversight of GMP compliance, including the cost and conduct of GMP audits of relevant manufacturing sites, would need to be confirmed.



*Rove McManus, from the TV show Rove Live, seen here donating blood.
The Herald & Weekly Times Photographic Collection.*

Chapter 9

Options for increasing competition for plasma fractionation

The Review has considered three potential options that could deliver fractionation services for Australia in future years. These are:

1. Maintenance of the current arrangements involving fractionation of Australian plasma in a domestic fractionation facility.
2. Open tender for the fractionation of all Australian plasma.
3. Open tender for the fractionation of part of the plasma collected in Australia, with a defined quota being fractionated in Australia.

Option One

Australia's current fractionation arrangements, agreed by the Australian Health Ministers' Conference (AHMC), provide for the fractionation of all Australian plasma onshore in Australia, by CSL Bioplasma. The arrangements also provide for the importation of plasma derived products that either are not manufactured domestically or, as in the case of intravenous immunoglobulin (IVIg), are required to augment domestic supply where plasma collected in Australia is insufficient to meet clinical demand for a particular product.

It is necessary to distinguish between CSL Bioplasma, which is a stand-alone fractionation operation located at Broadmeadows, Victoria, and CSL Limited. CSL Bioplasma has been Australia's national fractionator since 1953 and is a business operating unit of CSL Limited. Other business operating units of the CSL Group include CSL Behring. The CSL Bioplasma plant at Broadmeadows is dedicated, as a first priority, to the fractionation of Australian plasma and is separate from the much larger CSL Behring 'centres of excellence' model, which is described elsewhere in this Report and which serves international markets.

Option Two

This option involves an open tender process to secure the fractionation of all plasma collected in Australia. It would involve the National Blood Authority (NBA) entering into a contract with a domestic sponsor representing an overseas fractionator, although it may be possible to have this contract executed as a tripartite arrangement that could enhance the legally enforceable relationship between the NBA, representing Australia's Commonwealth, state and territory governments, and an overseas fractionator. Alternatively, an agreement could be a bilateral arrangement between the NBA and the domestic sponsor, with an offshore principal providing a financial guarantee of performance, to underpin the agreement. It is possible, of course, that CSL Bioplasma could secure such a tender; in this case, most of the circumstances of Option One would apply, although against the background of a competitive tender process.

A prerequisite for participation in an Option Two tender would be the completion of registration procedures with the TGA for all of the products involved, prior to contract implementation.

Unlike the standing offer arrangements where the supplier undertakes to provide supply of a product configured to the needs of the international market (e.g. strength and pack size), a tender for the fractionation of Australian plasma would include product specifications set by the NBA and similar to those contained in the schedules to the existing Plasma Products Agreement (PPA).

Thus, a tender participant may need to develop and register entirely new product forms in order to meet Australian specifications. This process could take up to two years to complete, particularly if clinical trials are required to support the registration dossier. On the other hand, if a tender participant already has products registered in Australia that meet Australian requirements in terms of strength, pack size and presentation, then only a variation to the existing registration, involving a revised Plasma Master File, would be required; the resulting registration process could be as short as three to six months.

Option Three

The third option involves a split of Australian-sourced plasma resources between an overseas fractionator or fractionators, and a domestic fractionator. This option would cater in part for a government policy position that may seek to maintain, for national interest reasons, a domestic fractionation capacity while opening the market to a competitive process.

There would be a number of subsidiary scenarios available for consideration under this option, including:

1. The tendering for a minimum viable amount of plasma (say 48 000 litres annually) for overseas fractionation into IVIg and plasma derived Factor VIII, with the remainder of the supply being allocated to CSL Bioplasma for the manufacture of all fractionated products in the current domestically produced range.
2. The splitting of the total plasma collection into two allocations – one for overseas fractionation into all products and the other for fractionation by CSL Bioplasma into all products. This alternative would see the production of hyperimmunes continuing in Australia.
3. The splitting of the total plasma collection across a number of fractionators, including CSL Bioplasma, with contracts being awarded according to best value for money for each individual product.

A possible benefit to Australia from any one of these arrangements would be that it would allow the National Blood Authority to benchmark prices on the basis of bids received from all fractionators.

Criteria

Each of the three options has particular advantages and disadvantages, and these will be explored further in this chapter. The plasma fractionation industry is a complex sector that calls for careful evaluation and weighting of multiple criteria when considering options. Arrangements for the fractionation of Australian plasma require consideration of matters well beyond those associated with value for money, although this remains one of the foremost issues to be taken into account.

In regard to the concept of Australia having a domestic fractionator, the Review observes that there is only one fractionation plant in Australia. The Review has attempted to draw the international industry on the potential for a second plant to be constructed. This attempt has not resulted in any definitive responses but it is prudent to assume for the purposes of this report that Australia will continue to host only one fractionation plant.

The criteria identified by the Review as being appropriate for testing each of the options are as follows:

- security of supply, and logistics
- product safety, quality and efficacy
- yield
- expenditure and value for money
- plant capacity
- product range
- product registration
- market share and competition
- legislative issues
- domestic industry and research
- regional relationships
- contract duration
- contract enforcement
- product liability.

The most important issues bearing on public confidence in the Australian blood supply are security of supply as well as product safety, quality and efficacy. Yield has the potential to impact heavily in terms of reducing the supply of IVIg derived from Australian plasma and increasing reliance on imported products manufactured from overseas-sourced plasma. Another important issue is the national strategic value of a domestic fractionation facility.

Security of supply, and logistics

The Review has concluded that the greatest degree of security available lies in the maintenance of a domestic source of supply, because of the relative remoteness of Australia from major global centres of population and because of the existence of long lines of supply between Australia and alternative fractionation sites, which in turn pose additional levels of risk to supply. The Review appreciates that Australia's

pharmaceutical product needs are met in large part by imports, but recognises that blood and blood products represent a special case for consideration. The Commonwealth Procurement Guidelines acknowledge this special case by exempting from the Mandatory Procurement Procedures the procurement of blood plasma products or plasma fractionation services.¹

In considering the supply of plasma and plasma derived products in Australia, there are multiple factors to be addressed, including the need for maintenance of cold chain conditions throughout the supply and manufacturing arrangements; the scarcity and irreplaceable nature of the Australian plasma collected for fractionation, and the need for certainty in the continuity of supply of finished products. Domestic fractionation within Australia clearly offers the best guarantee of security of supply when all factors are taken into account. In terms of logistics, the key points that have been considered are:

- length of lines of supply
- number of transshipment points
- duration of shipments
- exposure of shipments to acts of neglect, terrorism or sabotage
- ability of the Therapeutic Goods Administration (TGA) to apply direct controls over supply arrangements

The amount of plasma that needs to be transported for fractionation is measured in tonnes. Total volume is currently in excess of 300 tonnes per annum. Projected estimates for 2015–16 indicate a total tonnage of between 600 and 700 tonnes. Transporting this volume of plasma, or even a proportion of this volume, by airfreight to either North America or Europe is considered to be impractical. Sea shipment appears to be the logical option, and this view is shared by all but one overseas fractionator. Depending on the overseas fractionator involved, shipping times could vary from between 30 to 40 days after sailing. Frequency of sailings to given overseas ports is an additional consideration. Land handling would be required at both ends of the shipment process and would increase the number of transshipment points.

In considering the feasibility of overseas fractionation, the Review has taken into account increased risks associated with long lines of supply, special shipping conditions and multiple transshipment points.

This point needs to be qualified, however, with the observation that no supplier – whether domestic or offshore – is immune to disruptions to processing and transportation. It is more a question of degrees of risk relative to each situation.

A change to a system whereby all of Australia's plasma was fractionated overseas would require a considerable change in logistical arrangements, involving both internal lines of supply within Australia and external arrangements.

The transportation of Australian plasma to CSL Bioplasma is currently handled by the Australian Red Cross Blood Service (ARCBS). This arrangement could continue, with a different central collection point being nominated by a successful tenderer. Alternatively, a successful tenderer may undertake internal logistics within Australia,

¹ *Commonwealth Procurement Guidelines – January 2005*, Financial Management Guidance, no. 1, Department of Finance and Administration, Canberra, 2004, p. 46 (Appendix B, item 13); also available online at http://www.finance.gov.au/procurement/docs/CPGs_-_January_20051.pdf.

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including the pick-up of plasma stocks from ARCBS collection points; the plasma would then be consolidated for international shipment. The choice of arrangements would depend on demonstrated efficiency and cost benefits. Onwards shipment to the overseas fractionation site would be arranged by the successful tenderer, and the associated costs and assumption of risks would be factored into the overall fractionation fee-for-service.

All overseas fractionators contacted by the Review have indicated that a minimum 60-day withholding period (measured from the date of collection) is applied for safety reasons to all plasma received. The withholding is for the purposes of 'look-back' – a process that enables suspect plasma to be identified and removed from the starting pool batch prior to fractionation, if a donor is discovered to have an infection risk subsequent to the time of donation.

In Australia, the domestic fractionator is not required by the TGA to apply a withholding period. It would be a matter for negotiation as to whether there would need to be a withholding period applied to Australian plasma fractionated overseas.

It is of note that any withholding period applied in this case would more than cover the amount of time required for the sea shipment of plasma from Australia to the overseas fractionation site. It is estimated that the minimum turnaround time between plasma collection in Australia and the availability of finished products to Australian patients would be between six and nine months. At present the turnaround between plasma collection and delivery of finished product is on average ten weeks.

The length of turnaround time associated with the overseas fractionation of Australian plasma would hold implications for continuity of supply. An additional stockholding in the National Reserve, equivalent to at least six months' demand for all plasma products required for use in Australia, is considered to be an essential requirement in the event that all of Australia's plasma is sent overseas for fractionation.

While this would be a once-only requirement, it would nevertheless pose an additional potential burden on the National Reserve and would be difficult if not impossible to meet from domestic sources, given the scarcity of Australian plasma. It seems likely that the only way in which this requirement could be met is through the acquisition of finished products made from overseas plasma. This scenario has implications in terms of Australia's policy of self-sufficiency and could result in undesirable impacts on patients and clinicians, as a consequence of brand switching.

The cost of acquiring on the open international market an additional six months' inventory of the key plasma products (IVIg, albumin, Factor VIII and Factor IX) could be as high as A\$75 million, based on prices in the current National Supply Plan and Budget. The procurement of the necessary quantity of product (equivalent to the output from up to 150 000 litres of plasma) would potentially be undertaken by the National Blood Authority through the mechanism of a single Request for Tender (RFT) process.

The prospect of such a large acquisition also raises the prospect of two rounds of brand switching in a relatively short period of time – a process strongly disfavoured by clinicians and product recipients alike, for sound clinical reasons.

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The return of finished goods from an overseas fractionator to Australia, under Option Two or Option Three, would need to be undertaken by airfreight. This would limit the turnaround time between collection of plasma and availability of finished products in Australia. The alternative, sea shipment (which is favoured by one fractionator), could effectively add a further two to three months to the turnaround time. Under existing arrangements, an order for IVIg placed under Australia's contingency standing offer agreement with a European fractionator takes a minimum of two to three months to be filled. Again, the cost of returning finished products to Australia would be factored into the fractionator's fee-for-service.

Distribution of finished products to hospital blood banks could be undertaken either via the ARCBS network, as is now the case, or directly by the overseas fractionator's Australian sponsor, depending on the relative costs and efficiencies of the arrangement (but taking due account of gatekeeping functions presently performed by the ARCBS in conjunction with jurisdictional authorities).

Under existing arrangements, CSL Bioplasma is required to provide an alternative source of product supply in the event of a disruption to domestic production for any reason. The contingency requirement is addressed by means of a guarantee of product supply from CSL Bioplasma's sister organisation CSL Behring. This important security of supply guarantee effectively reduces to an acceptable level the supply risk associated with single-site fractionation. A similar undertaking from an alternative fractionator would be necessary in the event of overseas fractionation.

A contract for the fractionation of all or part of Australia's plasma at an overseas location would amplify the level of inherent risk associated with the supply of finished plasma products. Of particular concern is the possibility of loss – through damage, neglect or criminal act – of an entire container (eight tonnes) of Australian plasma, and the effect that such a loss would have on continuity of supply.

Due to the long lead times involved in collecting plasma domestically, it would not be possible to replace such a loss promptly, and resort to a contingency arrangement would be required. A similar risk attaches to the return of finished product to Australia (which would presumably be by airfreight). Here the risks of loss or damage relate particularly to loss of cold chain integrity at transshipment points or in airport handling – not unknown occurrences.

Under current arrangements, as noted above, the ARCBS is responsible for the delivery of starting plasma from collection sites to the domestic fractionator. This is achieved using a variety of transportation methods, including road transport and airfreight. Many of these arrangements are a legacy from the time when each state or territory branch of the ARCBS was a discrete entity.

CSL Bioplasma carries the responsibility for the return of finished products to ARCBS for onwards supply to hospital blood banks. In practice, CSL provides some of the warehousing function to support these arrangements, noting that distribution in Australia involves large distances to serve relatively small populations.

CSL has provided the Review with a submission that explores the possibilities of rationalisation of current distribution arrangements. The Review has not made a detailed assessment of distribution efficiency but believes that this issue should be further investigated.

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In any case, under Option Three the ARCBS would be faced with the prospect of operating duplicate systems for the bagging, bar coding, storage, handling and transport of the plasma collection. Under this option, the ARCBS would also be required to provide for the handling and distribution of two brands of some or all of the finished product range. This duplication, while entirely feasible, represents yet another new element of risk arising from the possibility of human error.

The introduction of a second or third fractionator would involve the need to set up in Australia one or more consolidation points where international shipments of plasma could be assembled and despatched. Freezer storage (circa -20° to -25°C) would be required at each location. International forwarding would require the use of specialised containers capable of reliably maintaining cold chain conditions. Continuous temperature monitoring would be required throughout the forwarding process, and the plasma shipments would need to be checked on arrival at their destination.

The additional costs of these arrangements would be factored into the tendered price for overseas fractionation. In the context of overall fractionation costs, additional transportation costs are a marginal consideration but it is the additional risk involved that represents the greater concern.

The loss of plasma or finished plasma products in transit between Australia and an overseas fractionator is likely to be insurable, although it is not likely that full coverage could be obtained. The cost of insurance would be factored into the fractionator's fee-for-service. But the physical loss of plasma or finished plasma products cannot be compensated for in economic terms alone. The point is that Australian plasma is regarded by many stakeholders as a unique, scarce and irreplaceable resource, as are the products manufactured from it.

It is nevertheless true that reliance upon a single fractionation site carries a remote but severe risk of loss through plant breakdown, fire or sabotage. As noted earlier, under present contractual arrangements, whereby Australia relies on CSL Bioplasma for the provision of most of this country's plasma product needs, there is a contingency arrangement in place such that, in the event of a major disruption to supply, plasma products would be provided by CSL Behring.

In reaching a conclusion on the issue of security of supply, the Review has taken account of a wide range of factors, including those that inspire confidence in the global nature of the fractionation industry as well as those particular to Australia's geographic location, remote as it is from Northern Hemisphere concentrations of the fractionation industry. In respect of security of supply, the Review favours Option One because, given the contingency arrangements that are in place, it provides the best guarantee of supply security.

Product safety, quality and efficacy

As described in Chapter 8, the Therapeutic Goods Administration regulates the safety, quality and efficacy of both plasma collection in Australia and the fractionation of Australian plasma into finished therapeutic products. The possibility of enhancing the regulatory process in regard to plasma derived products under the various options is canvassed elsewhere in this report.

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There are regulatory advantages to the continuation of the fractionation of Australian plasma within Australia. These are:

- continuing close oversight by the TGA of the entire supply chain, from blood and plasma collection, through the transportation and the fractionation of plasma, to delivery of finished products to hospital blood banks
- ability of the TGA to enforce, as necessary, regulatory requirements and inspections and to apply sanctions directly and within an Australian jurisdictional context, as opposed to relying on a third party regulator in an overseas country or on attempts to enforce contractual or regulatory compliance on a product sponsor or an overseas manufacturer, with all of the attendant jurisdictional difficulties.

Conversely, it has been argued that reliance on a single, domestic fractionator may deny Australia access to the most recent advances in plasma product technology. The Review notes that avenues do exist for new, imported products displaying advanced clinical benefits to be made available to Australian patients, under the national blood arrangements, should clinical demand so justify. The fully subsidised supply of recombinant clotting factors, a measure adopted in 2004, is evidence of this capability under existing arrangements.

If a European-based fractionator were to be awarded a contract to fractionate all of Australia's plasma, there would be few, if any, concerns regarding safety, quality and efficacy of products, because all European manufacturers operate under the regulatory guidance of both the European Medicines Agency (EMA) and a country-specific regulator. The standards that the TGA applies are derived from the same source as those applied in the European Union: Australia has adopted the standards contained in the British Pharmacopoeia, which in turn is harmonised with the European Pharmacopoeia.

In broad practical terms, there is no apparent reason why a European-based fractionator could not satisfy the TGA registration and certification requirements in respect of product safety, quality and efficacy, although changes to product presentation and plasma master files would be required.

Post-market surveillance of Good Manufacturing Practice (GMP) is potentially another matter. Under existing arrangements, the TGA has been able to certify fractionation plants that are undertaking or could undertake production of plasma derived products for Australian consumption. However, in circumstances where all Australian plasma, or a substantial proportion of it, were sent to Europe for fractionation, the need for closer inspection and audit by the TGA may arise. Certainly if Australia were willing to accept inspection and audit by European inspectorates in lieu of direct TGA surveillance, as occurs under existing Mutual Recognition Agreement (MRA) provisions, there should be no insurmountable problem. If for any reason, however, the TGA found it necessary to conduct its own inspections or audits, difficulties might arise.

The Review has been advised by the EMA that joint inspections or accompanied inspections should be possible, given notice. Either arrangement would involve prior notice both to the EMA and to the fractionator whose plant is to be inspected. Options for regulatory reform under a toll fractionation model are discussed in Chapter 8.

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The situation in the United States is different again. In regard to plasma imported into the United States for fractionation and subsequent export as finished product, the US Food and Drug Administration (FDA) applies a regulatory regime different from that exercised for products marketed domestically. The main involvement of the FDA in respect of the fractionation of Australian plasma by a US fractionator would arise in the context of FDA inspections of US fractionation plants generally. It would be up to the TGA to conduct any product-specific inspections or audits in US plants, and provision to cover this eventuality could be included in any contract with a US-based fractionator.

All three of the options discussed in this chapter have the potential to provide assurance of the safety, quality and efficacy of plasma products manufactured for the Australian market. On balance, the Review Committee believes that Option One offers the TGA the most efficient alternative in terms of hands-on monitoring and surveillance of the fractionation of Australia's plasma. While the TGA has in place well-established arrangements, under MRAs, for ensuring regulatory equivalence in the certification, and auditing of GMP compliance, of overseas manufacturers, these arrangements could need review if Options Two or Three were implemented. As discussed in Chapter 8, in these circumstances there may be need for renegotiation of those provisions in the EC/EFTA MRAs that relate to the conduct of joint inspections and audits of manufacturers of high-risk products such as plasma products.

Yield

Yield, particularly for IVIg, is an important parameter and has been given close consideration by the Review. Improving IVIg yield narrows the gap between plasma collected and IVIg demanded. The higher the yield of IVIg, the more efficient is the use of plasma, a scarce and valuable resource.

Australia's high level of self-sufficiency in plasma products has been bolstered by the steadily increasing yields of IVIg delivered by the domestic fractionator. The most recent public indication of yield confirms a level of greater than 5.0 grams of IVIg per litre of starting plasma.² The current contract with CSL Limited specifies a minimum yield for IVIg, and CSL Bioplasma is currently performing well above that minimum specification.

At present levels, domestic yield is well in excess of the global industry average yield, which, according to unpublished and anecdotal data, is between 4.0 grams and 4.75 grams per litre. The only publicly available yield data comparable to that provided by CSL Limited is the yield rate reported for Norwegian plasma fractionated in Europe, which stands at approximately 4.2 grams of IVIg per litre.³

As IVIg yield rates increase, there is a corresponding lessening of pressure on plasma collection rates, because all plasma collected (except for that used for hyperimmune production and clinical purposes as fresh frozen plasma) is used for IVIg production. However, the rate of growth in IVIg demand in Australia has not been matched by a corresponding increase in the amount of plasma available for fractionation, even though the Australian Red Cross Blood Service has missed collection targets in only one year (2005–06).

2 See <<http://www.csl.com.au/Investors.asp>>: CSL Full-year Result Announcement for 2006, 23 August 2006.

3 B. G. Solheim, reported in a paper presentation and panel discussion at the 2006 Australia New Zealand Society for Blood Transfusion, Hobart, 15–18 October 2006.

Yield would be a determining factor in the award of any contract to an overseas fractionator. The benchmark against which yield would be adjudicated would be the yield for IVIg that was being achieved domestically at the time a new contract was under consideration.

On the basis of information provided to the Review, it appears unlikely that any other fractionator could match the IVIg yield currently being achieved by CSL Bioplasma. The CSL Bioplasma yield is known, whereas the yield rates of most other fractionators are either unknown or not supported by verifiable data. Those overseas fractionators that have lodged submissions to the Review have argued that yield data is highly commercially sensitive; however, although unwilling to provide this data for consideration during the Review process, they have advised that they would furnish yield rates as part of any tender for fractionation services for Australia.

Because of insufficient domestic plasma collections, Australia is already importing some IVIg manufactured from overseas-sourced plasma. Should an overseas toll fractionator realise a lower overall yield for IVIg than is being achieved under the current arrangements, there would be a net increase in the requirement for plasma.

Another aspect of yield that is of concern relates to the production of plasma derived Factor VIII. While many Factor VIII purification methods clear prions to a large extent,⁴ the manufacturing process used by CSL to manufacture Biostate was judged by the Transmissible Spongiform Expert Advisory Committee (TSEAC) to result in a small residual risk.⁵ The Therapeutic Goods Administration now requires, as an additional precautionary measure, that plasma used in the manufacture of this product be collected from donors who have not travelled outside Australia or New Zealand since 1 January 1980.

This measure has raised the concern that in future years there may be insufficient special plasma available for the domestic production of plasma derived Factor VIII. This is despite the fact that 85% of current demand for Factor VIII is being met by recombinant product.

A move to overseas fractionation would relieve this concern, because all overseas fractionators that have expressed an interest in fractionating Australian plasma use different technologies; should a contract be awarded to a manufacturer relying on other processes, the entire collection of Australian plasma would be available for the production of plasma derived Factor VIII.

In summary, on the criterion of yield, there is an apparent level of risk associated with resorting to overseas fractionation of Australian plasma, whether in whole or in part. Overseas fractionation may result in a reduction in the total amount of IVIg produced from Australian plasma, leading in turn to a greater reliance on IVIg manufactured from overseas-sourced plasma. On the other hand, overseas fractionation may remove the risk to supply sufficiency currently associated with plasma derived Factor VIII.

On balance, the supply of IVIg is considered to be of much greater consequence for Australia. Should supplies of domestically manufactured plasma derived Factor VIII prove to be insufficient in the future, it would be a relatively simple process to put in place as a contingency measure a standing offer arrangement for the supply of imported plasma derived Factor VIII.

4 T. Kriel, 'Industry TSE clearance studies for plasma-derived Factor VIII', presentation, September 2006.
<http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1_7_files/frame.htm>

5 S. Caris, 'New donor requirements for plasma derived Factor VIII in Australia', *National Haemophilia*, 153, March 2006, p 6.
<<http://www.haemophilia.org.au/sitebuilder/knowledge/files/254/nhno153march2006pg1-10.pdf>>

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It is not possible for the Review to forecast the competitive yields that may emerge during any future tender process, but the Review is mindful of the need to maintain the highest possible yields for all products fractionated from Australian plasma, and for IVIg in particular, if Australia's present level of self-sufficiency is to be maintained. On the evidence available to the Review, the IVIg yield being achieved by CSL Bioplasma would appear to be high when compared with that achieved in the fractionation sector generally.

Expenditure and value for money

The Review's terms of reference call for an assessment of options having regard to value for money and expenditure considerations. The ability of the Review to make such an assessment is constrained by the restricted nature of available information on the global plasma fractionation industry and the global market for plasma derived products. Similar shortcomings in the available data were noted by the Stephen Committee, which reported to government in 2001.

Unlike the related pharmaceutical industry, the fractionation sector is characterised by a heavy dependence on tenders and bipartite (and therefore confidential) procurement agreements. There are no published price lists or reliable sources of pricing intelligence to assist in the development of alternative value-for-money models.

Only one small organisation (Marketing Research Bureau Inc.) routinely surveys, and publishes global market reports on, the fractionation industry; even then, the authors of these reports qualify them as being based on information provided by companies and individuals rather than being drawn from material in the public domain. In the case of Australia, prices applicable under the Plasma Products Agreement with CSL are agreed only after protracted and intense negotiations conducted by the National Blood Authority on behalf of all Australian governments. This process is directed at achieving the best possible value for money given that international price comparisons are not readily available.

The absence of global pricing information means that opportunities for benchmarking are limited, and presently occur only when the NBA is able to obtain commercial-in-confidence information during its fact-finding missions or when a standing offer is negotiated for the contingency supply of a plasma product. These constraints notwithstanding, much of the NBA's activity to date has been directed towards achieving lower prices for plasma and recombinant products, and indeed this effort appears to have been conspicuously successful.

The Review notes that the Commonwealth Procurement Guidelines seek to encourage competition as an important component of achieving value for money. In respect of plasma products, Australia's existing contingency arrangements, which involve the negotiation of standing offers, do allow for some limited competitive elements to be introduced into the Australian market. These arrangements provide the opportunity for participation in the Australian market by those international fractionators that wish to compete for Australia's contingency supply business. To date, only one international fractionator has availed itself of the opportunity to compete for a market segment valued at A\$24 million in 2006–07; this manufacturer has registered its products in Australia and has bid for standing offer status for its

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products. There are opportunities for other international fractionators to follow this lead, given the indications that, for IVIg at least, the gap between domestic demand and supply will widen over time, thus making the contingent supply segment of the market more attractive.

It needs to be recognised that there would be substantial costs associated with a move to a toll fractionation arrangement in respect of Australian plasma, following a competitive procurement process. These additional costs would not be limited to those arising as a result of longer lines of supply or the greater level of risk to supply security. There would be an inescapable impost on an international fractionator (in terms of registration costs), just as there would be additional costs for the Australian government sector, arising from the need to build a larger National Reserve of products to compensate for a longer turnaround time between plasma collection and finished product delivery.

Ultimately all additional costs would be borne by the Australian taxpayer either in the form of product prices to compensate an overseas fractionator or by direct additional costs incurred by government agencies. It is estimated that an additional six months of inventory of finished products would be required overall, thereby detracting to that extent any potential benefit that may be achieved in terms of lower prices.

The cost to Australian governments of fractionation services provided by CSL Bioplasma is currently in the vicinity of A\$400 per litre (excluding the cost of plasma). This figure includes the cost of manufacturing low-volume, high-value hyperimmune immunoglobulins. It is quite possible that a contested procurement process could lead *prima facie* to lower fractionation charges, notwithstanding the additional but marginal logistical costs involved in a toll fractionation arrangement.

However, as indicated previously, Australia could not escape substantial one-off costs if it moved to an arrangement whereby all Australian plasma was fractionated overseas. Any projected savings in terms of direct fractionation charges would need to be offset against these additional costs, as well as against national interest factors. There may also be recurrent additional costs for the acquisition of additional imported IVIg, should the yield achieved by an overseas manufacturer be lower than that currently being achieved by CSL Bioplasma.

Finally it should be noted that consideration of value for money cannot be restricted to consideration of price alone, but has to include assessment of intangibles related to the national interest. These include the need to maintain a domestic biotechnology capacity, the value of Australian infrastructure and investment, the engagement of Australian intellectual talent in an essential domestic industry, and the broader strategic value to the nation of a world-class domestic fractionation capacity.

Plant capacity

The current annual capacity of CSL Bioplasma is 500 000 litres of plasma. Australia's present requirement for fractionation capacity, which takes contractual and legislative precedence over any toll fractionation arrangements, stands at approximately 329 000 litres (2006–07), inclusive of hyperimmunes. This requirement is expected to double by year 2015–16.

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CSL has indicated to the Review that the throughput capacity at the Broadmeadows plant can be increased to 750 000 litres annually through the introduction of additional equipment, within the existing infrastructure. A further expansion to 1 000 000 litres capacity is feasible at the existing Broadmeadows plant site but would require additional buildings and services.

Expanded capacities of this order would be sufficient to accommodate Australia's projected plasma collections out to year 2015–16, as well as a continuation of toll fractionation capacity for regional countries.

Of the seven overseas fractionators that have expressed interest in processing Australian plasma, three are considered to have the capacity to fractionate the entire Australian plasma collection. These are Baxter Healthcare, CSL Behring and Talecris. A further three, Bio Products Laboratory (BPL), Sanquin and Laboratoire Français du Fractionnement et des Biotechnologies (LFB), have limited spare capacity and would most likely not be candidates for the fractionation of the entire Australian plasma collection. Octapharma currently has a capacity of 1.8 million litres, spread across three plants, but has stated intentions of building capacity to 3.0 million litres and in these circumstances could probably accommodate all of Australia's fractionation requirements. All seven organisations would be capable of fractionating a share of the total Australian plasma pool.

Existing plant capacities are detailed in table 9.1.

Table 9.1 World's largest plasma fractionators

Fractionator	Commercial (C) or Not-for-profit (NFP)	Capacity - '000 litres	2005 Throughput - '000 litres	Utilisation (%)
CSL Limited (incl. CSL Bioplasma)	C	5950	5050	84.9
Talecris	C	4100	2710	66.1
Baxter	C	4000	3400	85.0
Grifols	C	3400	1768	52.0
Octapharma	C	1800	1600	88.9
Kedrion	C	1200	1050	87.5
Chengdu Inst.	C	800	350	43.8
Japan Red Cross	NFP	800	525	65.6
LFB	NFP	800	650	81.3
Shanghai Blood Inst.	NFP	800	600	75.0
BPL	NFP	750	400	53.3
Sanquin*	NFP	800	425	53.1

Source: Derived from Marketing Research Bureau data, 2006.

* If the proposed joint initiative between Sanquin and Biotest proceeds, the resultant entity would have a capacity of around 1 million litres, ranking it seventh on the list, by capacity (after Kedrion).

The Review's assessment of the plant capacity of those organisations that have expressed interest in the possibility of fractionating Australian plasma may be summarised as follows.

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Table 9.2 Assessment of plant capacity of major fractionators

Fractionator	Capable of fractionating all Australian plasma	Capable of fractionating a share of Australian plasma	Comments
CSL Behring	yes	yes	Some question as to whether CSL Behring would compete against CSL Bioplasma. CSL Behring plants operate under a centres-of-excellence model.
Baxter Healthcare	yes	yes	Has indicated that capacity exists in Vienna plant complex.
Talecris	yes	yes	Currently no information on spare capacity but company has expressed interest. Production spread across two plants.
Octapharma	perhaps	yes	Plans to increase capacity to 3 million litres. Has three plants in Europe, each capable of producing entire Octapharma product range.
LFB	no	yes	LFB interested in fractionating a maximum of 100 000 litres of Australian plasma. Production spread across two plants.
BPL	no	yes	Participation in a tender would depend on outcome of current government review of operations.
Sanquin	perhaps	yes	May be capable of fractionating all Australian requirements, depending on outcome of Biotest joint venture negotiations. Production spread across two plants.
CSL Bioplasma	yes	yes	Current and future capacity sufficient to meet Australian needs. CSL Bioplasma operates under a tailored self-sufficiency model.

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

Thus all of the above fractionators may be considered in terms of Option Three, but Option Two would probably result in a reduced field of four to five fractionators.

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Product range

CSL Bioplasma currently produces a range of 13 individual plasma derived products in 21 different pack sizes and presentations, tailored to the requirements of Australian clinicians and end users. Even though this range does not represent the entire range of therapeutic agents that can theoretically be produced from human plasma, it does represent one of the more extensive ranges to be found among the various fractionators. The products that are not manufactured domestically (such as Factor XI and Factor XIII) are those that are not economically viable or those that are yet to reach domestic demand levels that would justify domestic production (e.g. protein C or alpha-1 antitrypsin).

Included in the current domestic product range are six low-volume, high-value products made from special plasma and described as hyperimmunes. With the possible exception of Rh(D) immunoglobulin, it may be difficult to secure overseas fractionation of hyperimmune products using Australian plasma, because of the very low volumes involved. The domestic fractionator currently manufactures these low-volume products using a small-scale dedicated Cohn fractionation plant at Broadmeadows.

The research and development activities of the CSL Group are centred in Melbourne, at the Parkville and Broadmeadows sites but principally the former. Australia is therefore well placed to benefit from new or improved products that are researched and developed in Australia for the global markets.

One of the issues confronting the Review has been the fact that none of the overseas fractionators that have expressed an interest in the possibility of fractionating Australian plasma currently have a product range that directly matches that currently required by Australian clinicians and end users.

Table 9.3 compares the current Australian domestic product range with the current suites of products made by international fractionators.

In each case where there is a gap, one of two events would need to occur if Australia's requirements were to be fully met by a single overseas fractionator. Either the successful fractionator would need, as a prerequisite to contract implementation, to develop and register the missing products in the range – a process that could take up to two years, with no guarantee of the fractionator being awarded the contract. Alternatively, the Australian Health Ministers' Conference could deem the missing product(s) as being of marginal importance and agree to acquire them on the open global market (as is currently the case with a number of very low-volume products). The latter alternative would necessarily involve a dilution of Australia's preference to use domestic plasma wherever possible.

It is essential to note that even though an overseas fractionator may presently manufacture a given product type, this does not mean that the product is available in the strength, concentration or pack size used in the Australian clinical setting. It is not just a matter of adjusting the strength of a product to suit Australian requirements. A new formulation will require substantial additional development and clinical trial work in order to demonstrate safety, quality and efficacy prior to registration of the reformulated product on the Australian Register of Therapeutic Goods (ARTG). A current example is imported IVIg. Under contingency

Table 9.3 Manufacturers and products

	CSL Bioplasma	CSL Behring	Baxter	Octapharma	Sanquin	LFB	Talecris	BPL
Albumin	registered	produces	produces	produces	produces	produces	produces	produces
IVIg (liquid)	registered	produces	produces	registered	produces		produces	produces
IMIg	registered	produces			produces			
CMV immunoglobulin	registered							
Hepatitis B immunoglobulin	registered				produces	produces	produces	produces
Rh(D) immunoglobulin	registered		produces	produces	produces	produces		produces
Tetanus immunoglobulin	registered		produces		produces	produces	produces	produces
Zoster immunoglobulin	registered				produces			produces
Plasma derived Factor VIII	registered	produces	produces	registered		produces		produces
Plasma derived Factor IX	registered	produces	produces	produces	produces	produces		produces
Antithrombin	registered		produces	produces		produces	produces	produces
Prothrombin complex	registered		produces	produces	produces	produces		produces

Source: Adapted from information held by the Department of Health and Ageing.

arrangements, there are a variety of strengths, pack sizes and presentations for clinicians and other health professionals to deal with.

The Review has received representations that seek to limit, as far as possible, the variety of strengths, pack sizes and delivery methods appearing in the clinical environment. It is highly likely that the National Blood Authority would, when issuing a Request for Tender, specify strength, pack size, form of presentation and number of different pack sizes, according to established domestic market needs and preferences in order to restrict the impact on clinicians and recipients as a result of any prospective change of manufacturer. It is also likely that the Therapeutic Goods Administration would require labelling, package inserts and prescribing monographs to be in a form adapted specifically to Australian requirements. A successful tenderer would need to have demonstrated, as a prerequisite to contract implementation, compliance in regard to all of these requirements.

Even though a number of fractionators currently manufacture some of the low-volume products (particularly hyperimmunes), there is no guarantee that a successful tenderer would necessarily consider the production of such products from Australian plasma to be an economic proposition. In the case of at least one product, Rh(D) immunoglobulin, the continued use of Australian plasma would be considered as being essential and this would raise questions for at least one fractionator that does not include this product in its existing product range.

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Fractionators use different operating models that are designed to maximise particular efficiency goals in production. CSL Behring, for example, uses a 'centres of excellence' model, whereby each of three plants specialises in the production of one group of products. CSL Bioplasma is not part of the 'centres of excellence' model but remains a 'stand-alone' fractionator using predominantly chromatography technology (except for hyperimmune production) to produce a product range specifically tailored to Australian clinical requirements.

On the criterion of product range, it follows that what Option One offers is superior in terms of supplying Australia's specific needs in the foreseeable future. Option Two, and to a lesser extent Option Three, would require prospective tenderers to have developed and registered a range of products that meet Australian specifications prior to the implementation of any contract. These options could involve substantial expense for interested tenderers, thereby prospectively limiting the number of tenderers to those that are prepared to accept the financial risks involved.

Product registration

Under Option One, the plasma derived products required by the Australian community are already registered under the Australian Register of Therapeutic Goods. However, registration, while being an essential prerequisite in most cases, does not translate into automatic listing under the national blood arrangements. These arrangements anticipate that only one domestically produced or imported brand of each product type will be supplied free of charge to end users. The exception is where domestic supplies of a product type are insufficient to meet total demand, in which case a second imported brand may be added to the list as a contingency.

These arrangements limit the number of registrations that the Therapeutic Goods Administration is required to process in order to provide for Australia's plasma product demands. Should the provision of fractionation services in respect of Australian plasma be opened to competition, the TGA would need to cope with multiple applications for registration of each product type as a prerequisite to contract implementation by a chosen manufacturer.

While the direct costs of registration are fully recoverable from manufacturers, there would still be timing and capacity questions for the TGA in respect of the provision of sufficient trained scientific staff and adequate resources to carry out the registration and subsequent regulatory processes. Cost recovery alone might not offset the additional structural and resource demands to be borne by the TGA in this case, and the additional financial burden would ultimately fall on the Australian taxpayer.

Prior to the commencement of a contract arising from a Request for Tender process for the fractionation of all of Australia's plasma, intending overseas participants in the process would need to ensure that the candidate products have been included on the ARTG. All candidate products, regardless of whether registered in Australia or not, would require some level of registration or re-registration depending on how closely the products conform to Australian requirements in terms of strength, pack size, presentation and route of administration and plasma source.

Essentially this could mean that all candidate products will be subjected to a full registration process because the only imported products already registered in Australia that would prospectively be manufactured from Australian plasma are of differing strengths and volumes and employ differing methods of administration compared with the equivalent domestically produced products. Presumably, the intent of the competitive process would be to simply replace the domestically produced products with direct equivalents manufactured by an alternative fractionator.

At the very least, a candidate product will need to have a revised Plasma Master File submitted (based on Australian plasma) and that will take between three and six months to achieve upgraded registration status following lodgement. All other candidate products would need to be the subject of a full dossier submission, which will take at least 18 months to process for inclusion in the ARTG following receipt of dossiers.

In the case of an open tender for the fractionation of all of Australia's plasma collection, this could mean a registration workload for the TGA amounting to as many as 60 or more additional candidate products, although it is doubtful that some manufacturers would commit to this degree of expense as a prerequisite to the award of a contract.

One measure of the reluctance of some overseas fractionators to commit to registrations prior to the announcement of a contract can be seen in the small number of the same fractionators who sought to register product and participate in the IVIg contingency supply standing offer, a market segment valued at A\$24 million in 2006–07.

There is no doubt that a move to Option Two or Option Three would involve the TGA in a substantial additional workload in terms of new product registrations. Such a move would also involve the TGA in more extensive GMP surveillance and audit operations at overseas sites post product registration. On this basis, Option One must be preferred.

Market share and competitiveness

The overall market for plasma derived and related products in Australia is now split among CSL Bioplasma, which fractionates all Australian plasma, and the overseas suppliers that provide all other products, including both fractionated and recombinant forms. In value terms, the split is approximately 50:50.

CSL Bioplasma enjoys an overwhelming majority share of the IVIg market segment and the totality of the albumin market segment but has lost most of the clotting factor business to imported recombinants, predominantly supplied by Baxter and to a lesser extent by Wyeth and Novo Nordisk.

In the case of IVIg, there has been some erosion of the domestic fractionator's market share, due to the importation of a competing brand product arising from the shortfall in domestic plasma collections. These imports provide some element of competition in respect of the largest segment of the plasma products market.

Legislative issues

Provisions in the CSL Act constrain CSL in respect of the operations of the CSL Bioplasma plant at Broadmeadows. These national interest provisions were included in the legislation when CSL was privatised, in order to secure the domestic supply of plasma derived products for the Australian community. Should Option One continue, these provisions will remain in place and will serve to ensure that Australia continues to enjoy the security of an onshore fractionation facility.

Alternatively, if either Option Two or Option Three were to be implemented, there would need to be a review of legislative provisions so as to ensure that CSL Bioplasma could compete with other fractionators on an equal footing. This process could involve significant amendment to the CSL Act and other legislation.

The Review is of the opinion that for security of supply reasons, maintenance of the provisions of the CSL Act should continue. This would be consistent with a preference for Option One and is also consistent with the Commonwealth Procurement Guidelines currently in force.

Domestic industry and research

The Review has received strong representations from the Government of the State of Victoria, supported by the Government of the State of South Australia, in favour of maintaining the existing domestic facility as the dedicated national fractionator of Australian plasma.

The continued presence in Australia of the CSL headquarters, and of the research and development operations of CSL Limited, cannot be separated from the continued existence in Australia of CSL Bioplasma. The loss of CSL Bioplasma would have major implications for the biotechnology sector in Australia, including for research and collaboration opportunities between industry and the tertiary education and research sector in Australia.

CSL's research and development effort in Victoria has provided and continues to provide substantial benefits in the form of major new products, such as Gardasil®, the first vaccine against cervical cancer, and products essential to Australia, such as other vaccines and anti venoms specific to Australia's needs. CSL in Australia provides one of four World Health Organization centres collaborating in influenza control and is the only such centre in the Southern Hemisphere.

CSL Limited is the Australian Government's partner of choice to provide influenza vaccine to protect Australians, both during the annual flu season and in the event of an influenza pandemic; CSL is currently working closely with the government to accelerate its prototype pandemic influenza vaccine clinical trial program based on the H5N1 avian virus. CSL has helped ensure that Australia has one of the largest antiviral stockpiles per capita in the world. By early 2007, Australia will have enough antivirals to provide coverage for nearly 44% of the Australian population.⁶

Regional relationships

Under Option One there would be no disruption to fractionation operations at the domestic fractionation plant. New Zealand, Malaysia, Singapore and Hong Kong would be free to continue existing toll fractionation arrangements should they be required.

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Two of these governments have lodged submissions supportive of a continuation of operations at Broadmeadows and have indicated that each would experience difficulty in economically replacing toll fractionation services currently provided by the Broadmeadows plant. Another government has indicated its reliance on CSL over many years and confirms that this is likely to continue.

In each case, the annual volume of regional toll fractionation arrangements is low (maximum 38 000 litres annually), which implies difficulty in attracting interest from large-scale fractionators.

New Zealand in particular has indicated to the Review that it is content with the current toll fractionation arrangements and has indicated that there would be substantial disadvantage for New Zealand should that arrangement cease.

The ability of the domestic fractionator to continue to offer toll fractionation facilities to regional countries depends on the ability to meet domestic Australian requirements as a first priority. If the Australian business diminished significantly, then it follows that the plant may no longer be in a position to offer fractionation services to regional countries.

Option One has the advantage of preserving the current constructive regional relationships.

Contract duration

The duration of a contract to fractionate Australian plasma overseas would need to be determined having regard to a range of factors that do not necessarily apply in the case of existing arrangements. These include:

- exchange risks
- plant capacities
- competing priorities
- product ranges
- international transport costs.

A short-term contract may be preferred for exchange risk reasons, even if the contract provides for Australian currency to be specified. The Department of Finance and Administration advises that the provisions of Financial Management Guidance #2 indicate that the Australian Government has a policy that its entities should not engage in direct or indirect hedging of foreign exchange risks. One form of indirect hedging is through specifying fixed prices in Australian dollars. Instead, as a general principle, unless exceptional circumstances apply, price provisions should allow for variation according to movements in exchange rates between Australia and other countries.

An overseas fractionator may not wish to commit to priority fractionation of Australian plasma if existing plant capacity is tight and market demands and opportunities are volatile. A fractionator may wish to maintain flexibility through a short-term contract in order to be better placed to accept new and more attractive assignments.

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The product mix of a fractionator may be in the process of change (for example, to focus on recombinants), in which case the fractionator may not wish to be locked into a longer-term contract involving fractionation products. Given the uncertainty of global oil prices and the knock-on effects on freight rates, a fractionator may not wish to extend exposure to additional freight costs over the longer term.

Conversely, it would be in the interests of Australia not to indulge in a short-term contract when this implies a potential future change in product brand and even product characteristics. The cost of contracting is high for both the client and the supplier alike. One or both parties may prefer a longer contract period in order to lessen the costs of contract renewal.

In considering duration of contract, the nature of toll fractionation needs to be borne in mind. While Australia may be seeking to ensure supply continuity through priority provisions in a contract, the fractionator will in all likelihood be quoting on the basis of marginal rather than full pricing in order to fill short-term unused capacity. Being locked into a marginally priced contract over a significant period of time may be seen to deny the fractionator the opportunity to secure alternative business at a higher rate of return.

On the whole, however, issues of duration arise in respect of all three options and are not the most critical factors in a judgement about the merits of each option.

Contract enforcement

The existing Plasma Products Agreement between the National Blood Authority (on behalf of all Australian governments) and CSL Limited (on behalf of CSL Bioplasma) is a contract drawn for the benefit of Australian parties operating in an Australian environment. Contractual obligations on both parties are therefore adapted to particular domestic needs of the parties and include remedies that may be readily applied in circumstances of default.

A contract to secure the overseas fractionation of Australian plasma would be a much more complex instrument. As a first principle, it would be desirable to be able to ensure that the contract would be capable of enforcement for specific performance not only in Australia but also in the country where the fractionation takes place. Clearly this presents major problems of legal jurisdiction. In turn, it limits the extent of sanctions that can effectively be applied in an overseas context; that is, both legally and practically.

For example, under the PPA, the NBA enjoys 'step-in' rights in the event that CSL fails to meet specific contractual obligations. In the case of an overseas fractionator, contractual 'step-in' rights would seem superfluous. This is because an overseas fractionator would be highly unlikely to agree to such a stipulation in the first place and, even if it did, the practical difficulties of 'stepping-in' under an overseas jurisdiction would render such a provision of doubtful value.

The best guarantees of performance that could be expected would arise from a tripartite agreement between the NBA, the Australian sponsor of the registered products (preferably a corporate subsidiary of the overseas fractionator) and the overseas fractionator.

While the practical difficulties of enforcement in the case of the fractionator in an overseas jurisdiction would exist, some level of comfort could be afforded by an irrevocable bank guarantee against specific performance. This may provide some level of monetary compensation, but it does nothing to secure or restore the critical flow of finished products derived from Australian plasma. The domestic sponsor would of course be exposed to the full force of the applicable state or territory law.

The degree to which contractual limitations exist when an overseas-based fractionator is involved is a matter for consideration in deciding whether a contract to fractionate all or part of Australia's plasma overseas is a viable and acceptable option. A failure to perform for whatever reason could place at risk Australia's supply of life-preserving plasma derived therapeutics.

The relevant contract or performance guarantee should therefore specify that the governing law is that of the state or territory in which the Commonwealth agency is located and that the parties submit to the jurisdiction of the relevant state or territory courts. Nevertheless, even if the Commonwealth were successful in obtaining a judgement from an Australian court against an overseas fractionator, it would be difficult to enforce that order overseas, particularly in the United States. Enforcement of judgements overseas (where this can be done) is usually a costly and protracted process.

Product liability

Product liability is already a complex area of law; the possibility of exporting Australian plasma for processing at an overseas location adds another dimension to product liability that has not previously been encountered in the Australian blood sector. In its report on actuarial, demographic and insurance issues to the Review, the Allen Consulting Group observed:

There has been only one HIV infected transfusion of blood since screening commenced in 1985 and no Hepatitis C infected transfusions in Australia in the last five years. There have been three cases of variant CJD transmission, associated with non-leuco-depleted red cell transfusions in the UK, but no transmissions reported for plasma products.

ARCBS estimates of probabilities of transmission of viral infections in transfusions subject to HIV antibody testing and Nucleic Acid Testing (NAT) are one in 7,299,000 and the probabilities of transmission of viral infections in transfusions subject to HCV antibody testing and NAT are one in 3,636,000 based on data from July 2000 to June 2003. The risks for plasma products are lower again.

The liability costs associated with a single case of infectious product may be extremely high, but the probability is extremely low, producing a moderate risk cost. For example, a new virus may infect several hundred people before being discovered, at a cost of hundreds of millions of dollars. However, given the viral testing and inactivation processes in place, the probability is extremely low. Overall we have assumed an annual risk cost of 0.5% of production based on a one in a hundred year event and a cost of \$200 million.

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The Australian community is no stranger to international product liability processes. A number of class actions involving claims against international suppliers are a matter of record. It is noteworthy that a very high proportion of Australia's pharmaceutical product needs are manufactured overseas. The fractionation of Australian plasma overseas represents just another opportunity among many for issues of product liability to arise. In the circumstances, overseas fractionation would not present problems in terms of product liability that are different from those affecting pharmaceutical products generally. Nevertheless, there are still potential difficulties in bringing actions in the event of a claim for negligence arising.

Summary of options

Option One

Under this option, CSL Bioplasma would continue to receive plasma for fractionation from the Australian Red Cross Blood Service and would maintain the present product range, with new additions where appropriate (e.g. subcutaneous immunoglobulin and an improved product range). A perceived disadvantage of Option One is that it is not an internationally competitive procurement option but instead represents a continuation of sourcing from a single preferred supplier.

On the other hand, there would be some very substantial advantages. The Therapeutic Goods Administration would retain its ability to directly regulate the domestic fractionator and to apply sanctions as circumstances may dictate. There would be no need to modify existing negotiations and MRAs that serve to provide the Australian community with a high level of guarantee in respect of the safety and continued supply of essential fractionation products. The need to register multiple brands of product in order to facilitate an open tender process would be obviated.

CSL as the domestic fractionator would continue to maintain its global research activities in Melbourne, thus enabling ongoing collaborative research with Australia's tertiary institutions. CSL's research and production effort would also serve to maintain a critical mass of biotechnology expertise in Australia as opposed to the export of this capacity to the Northern Hemisphere, together with the accompanying loss of intellectual capital.

In view of the prospective supply and demand situation, the National Blood Authority would be able to effectively benchmark prices for at least one major product (IVIg) through the operations of standing offer arrangements already in place. At the same time, overseas fractionators would be able to participate in the Australian market for plasma derived and related products through the various procurement arrangements, including standing offers, undertaken by the NBA.

The domestic fractionator would continue to be in a position to offer toll fractionation services to regional countries.

Option Two

While overseas fractionation is potentially achievable in a technical sense, Australia could not move to a situation involving the overseas fractionation of all of Australia's plasma collection without making a number of compromises on important issues of principle and policy.

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The domestic fractionation plant at Broadmeadows in Victoria is a national strategic asset. This plant employs 500 staff, including many with tertiary training in biotechnology. It is currently the largest fractionation plant in the Southern Hemisphere and provides fractionation services not only for Australia but also for other countries in the region.

The loss of the contract for the fractionation of Australian plasma would almost certainly signal the closure of this plant and this would have wide ramifications, including a loss of domestic production, the loss of export markets and an increase in imports, and, potentially, an increase in Australia's trade deficit. Broadmeadows is a facility that was designed and built to service the Australian market. It does not compete internationally, apart from providing toll fractionation services for small markets in the region. Moreover, the plant is an integral part of CSL's total operations in Victoria and from a research perspective is integrally linked to CSL's operations at Parkville.

No substantial alternative fractionator currently manufactures the entire range of products presently sourced from the domestic fractionator. It also needs to be recognised that the economic basis for the maintenance of the blood and blood products supply in Australia (the national blood arrangements) is provided not only by the Commonwealth Government but also by the various state and territory governments. It is doubtful whether any state or territory government would accept Option Two. It is also certain that several would strongly oppose this option as well as Option Three.

A move to open competition would be inviting concerted opposition from the Australian public as is evidenced by the numerous submissions received and considered by the Review. It is an inescapable fact that the blood supply in Australia depends on a high degree of public confidence in the system, and any erosion of that confidence, for whatever reason, would be to the detriment of Australia and the Australian community.

Option Three

Of the three scenarios presented, Option Three would be the most complex to manage in terms of administration and logistics. It has the potential to provide an additional limited element of competition.

In terms of overall value for Australia, Option Three appears to offer only limited advantages but still suffers from most of the disadvantages of Option Two, with the additional disadvantage of significant administrative and management complexity.

The Victorian Government, supported by the Government of South Australia, has made strong representations to the Review that maintenance of the current arrangements is in the national interest of Australia. The submissions cite the need to maintain an onshore fractionation capacity in Australia and the need to retain Australia's leading biotechnology industry in Australia for the benefit of Australians.

The Victorian Government has indicated that the loss of CSL Bioplasma as the national fractionator could have serious implications for the biotechnology sector in Australia and for research and collaboration opportunities between industry and the

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tertiary education and research sector in this country. The Victorian Government, supported by the South Australian Government, identifies the need to sustain employment opportunities for a growing cadre of tertiary-qualified workers in biotechnology. Both governments note also the level of security afforded the Australian community against adverse international events through the maintenance of CSL Bioplasma's onshore operations.

The views expressed by the governments of these two states are supported by the preponderance of submissions received by the Review from a wide range of Australian stakeholders representing consumer, clinical, academic and industry viewpoints.

A major concern arising out of Option Three is the likelihood that a split of plasma resources between a number of fractionators, while providing a means of benchmarking prices, may ultimately result in the discontinuation of fractionation activities at Broadmeadows. Once ceased, it would be highly unlikely that operations at the domestic fractionation site could be recommenced at some future date.

The Review has received strong representations to indicate that, if fractionation of Australian plasma were to take place overseas, then this could result in a substantial fall-off in the numbers of Australian volunteers willing to donate blood and plasma. Such a development would be contrary to Australia's policy of seeking self-sufficiency in blood and blood products. The Australian Red Cross Blood Service cites an unpublished survey of donors that indicates a strong preference for the retention of the current onshore fractionation arrangements. The survey suggests that significant numbers of donors would view adversely the possibility of their 'gift' being sent for processing overseas. While such research is not conclusive, the implied threat for Australia's blood and plasma supplies has to be taken seriously.

Submissions received by the Review leave little doubt that the Australian community at all levels does not support the concept of moving to open competition for the fractionation of Australian plasma. In some cases, the opinions expressed are based on a perceived increased level of risk of contamination if Australian plasma is sent overseas. Even though some of these opinions may not be well founded from a technical point of view, they are genuine and strongly felt concerns.

Of all the domestic concerns identified during the Review process, public confidence in the Australian blood supply is of paramount importance. Without in any way seeking to impugn the safety of the blood supply in other countries, the Review perceives that all sectors of the Australian community strongly prefer a closed system whereby blood and plasma are collected in Australia, plasma products are processed in Australia, and these products are provided for the benefit of Australians.

The overwhelming majority of submissions received by the Review consider that reliance on overseas fractionation, given Australia's remoteness from Northern Hemisphere fractionation sites, is a risk not worth taking. Open and unrestricted global markets for plasma derived products is not a view that would be supported by the weight of public opinion in Australia as evidenced by submissions to the Review.

Chapter 10

Conclusions, recommendations and implementation strategy

The global plasma fractionation industry, together with individual countries' national arrangements for supplying blood and blood products, plays a major role in contributing to enhanced health care for many millions of people throughout the world. Over 400 000 people in Australia receive a blood product each year, and it is estimated that more than 50% of Australians will require blood or blood products in their lifetime.

Just as there are many people in this country who are recipients of blood and blood products, so there are large numbers of Australians who voluntarily donate blood or plasma on a regular basis. In so doing, these donors make a unique and vital contribution to the health and wellbeing of others – it is difficult to conceive of a more personal or altruistic contribution to one's community than a gift that is, in the most fundamental sense, a gift of the self. Within the wider landscape of voluntary community service, the blood or plasma donor is exceptional. Not only do donors rarely know those who will benefit from their goodwill, but their gift can be a donation of life itself.

The remarkable generosity of the Australian donor community is at the very heart of Australia's national blood arrangements. Also playing a vital role is the Australian Red Cross Blood Service (ARCBS), an operating division of the Australian Red Cross Society. From modest beginnings, the ARCBS has evolved to become a world-class blood service. Currently charged with all collections of Australian blood and plasma, the Australian Red Cross in its capacity as a humanitarian organisation has enjoyed community regard and respect for nearly a century. The association between the Australian Red Cross and Australia's blood supply system is therefore likely to instil confidence in donors, and potential donors, for years to come.

The third major participant in the supply of plasma products to the Australian community is CSL Limited, which, through its CSL Bioplasma business unit, is the national fractionator. Since its foundation in 1916 as the Commonwealth Serum Laboratories, CSL Limited has made a key contribution to health care in this country, not only through the company's fractionation activities but also through its cutting edge research and through the production of vaccines and other pharmaceutical products in quantities sufficient to enable Australia's health system to respond quickly and effectively to emerging public health crises.

The global industry

The global market for plasma derived products, and recombinant alternatives, has a combined value of close to US\$10.5 billion per annum. The market is dynamic, complex and highly competitive, and in respect of some products there is virtually unrestricted global trade.

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There has been dramatic change over the past 20 years in the global plasma products industry, due mainly to mergers and acquisitions, the emergence of recombinant alternative products, and increasing safety requirements. The industry is particularly geared to supplying the needs of markets in Europe, Asia and North America, which between them account for 90% of total world demand for fractionated products.

Annual global plasma fractionation capacity is around 34 million litres. Commercial enterprises account for 81% of this capacity, while the state-owned and not-for-profit share is 19%. The global industry is dominated by six commercial fractionators, of which CSL Limited is the largest. The other five major players are Baxter Healthcare (United States), Talecris Biotherapeutics (United States), Grifols (corporate headquarters in Spain), Octapharma (headquarters in Switzerland), and Kedrion (headquarters in Italy). Talecris, Kedrion and Octapharma are solely concerned with plasma products, while the other companies have more diverse businesses and product ranges. Baxter Healthcare is the largest enterprise overall, with a global turnover of US\$9.8 billion, of which plasma fractionation accounts for 14%. Plasma collection and fractionation account currently for 90% of CSL Limited's global sales revenue.

Consolidation and rationalisation within the industry in recent years have resulted in an increase in the average capacity of fractionation plants (although fewer plants remain). In the United States, average plant capacity is now just over 1.1 million litres, whereas 20 years ago it was around 570 000 litres.

The United States is the only country in the world that is totally self-sufficient in whole blood and in the full range of plasma products. Some 70% of the plasma collected globally is collected in the United States. Domestic consumption absorbs under 40% of this plasma, and over 60% is exported, either as finished product or as starting plasma.

In other countries, national arrangements for the collection of plasma reflect domestic demand together with a diversity of economic, demographic and historical considerations. Canada, for example, in 2005 collected from domestic donors only 24% of the plasma required for the production of domestic IVIg requirements, relying on the United States for the balance. The United Kingdom is wholly dependent on US donors for its supply of plasma, due to the advent of the bovine spongiform encephalopathy (BSE) epidemic in the 1980s: plasma is collected in the United States for UK use and is subsequently transported to Britain for fractionation. Europe is increasingly opening up to greater movement of plasma, and finished plasma products, across national borders. Australia's arrangements for the collection of plasma are discussed in detail below.

The supply of plasma products in the 25 European Union member states and in the United States is frequently via the open market, reflecting, in many instances, health systems in which public sector agencies and funding do not play a key role in the plasma sector.

While many developed countries have plasma fractionation facilities, toll fractionation – whereby plasma collected in one country is processed in another on a fee-for-service basis – is becoming increasingly common. Canada's plasma is fractionated in the United States by Talecris. Plasma from Belgium and Finland is

processed by the Dutch not-for-profit foundation Sanquin, in both Belgium and the Netherlands. Plasma collected in Norway is fractionated by Octapharma, in Austria and in Sweden. CSL Behring toll fractionates for Denmark. Plasma from Poland is fractionated in Austria by Baxter Healthcare. The Laboratoire Français du Fractionnement et des Biotechnologies (LFB), a majority state-owned company in France, fractionates plasma collected in Belgium, Luxembourg, Brazil and Morocco. Brazil's plasma is also processed by other fractionators in Europe. Plasma from New Zealand, Malaysia, Singapore and Hong Kong is fractionated by CSL Bioplasma in Australia.

The reasons a country enters into toll fractionation arrangements with an offshore fractionator usually relate either to a level of demand for plasma products that is insufficient to support a domestic fractionator, or to the considerable financial and technological resources, and technical expertise, required for the operation of a domestic fractionation industry. Those European countries that have elected to toll fractionate generally collect less than 100 000 litres of plasma per annum.

Individual fractionators seek to maximise both yield and product range, although within the parameters imposed by market demand. No single fractionator, therefore, produces the complete range of plasma derivatives, which encompasses albumin, immunoglobulins (including hyperimmune immunoglobulins), and coagulation factors. Hyperimmune production is particularly specialised. It is low-volume, high-value and of limited commercial interest to most fractionators.

Global market for plasma products

The global market for plasma products grew by 5% between 2003 and 2005 and is forecast to expand by a further 11.5% between 2005 and 2008. Products expected to experience significant growth in the immediate future are intravenous immunoglobulin (IVIg), alpha-1 antitrypsin, fibrin sealants, and minor coagulant products. Albumin sales and sales of plasma derived Factor VIII and Factor IX are forecast to grow only modestly.

Global demand for IVIg, commercially by far the most important of the plasma derivatives and currently accounting for some 40% of total demand, is projected to grow from around 78 tonnes in 2006 to 129 tonnes in 2016. The use of IVIg for new indications, changes in clinical practice, or entry by the product into additional markets, could generate demand beyond these levels.

Demand for IVIg worldwide reflects strong and expanding markets in the United States and Europe and steady demand in other developed countries and regions. There is less demand for IVIg and other high-cost plasma products in developing countries, and it is likely to be a considerable time before China (where the major driver of demand is albumin), India, the Middle East and Africa exert significant influence upon the world market. Rising income levels and improved health standards worldwide will ultimately, however, have an impact upon global demand.

Until the mid 1990s, plasma derived Factor VIII was the driving product for plasma fractionators. By 2002, however, demand for recombinant alternatives, which had first become available in 1994, had overtaken demand for the plasma derived product. For

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various reasons – among them, clinical preferences and the emergence of immune tolerance and inhibitor issues for some people treated with the recombinant form – demand for plasma derived Factor VIII has nevertheless continued to grow, albeit at a much slower rate than that exhibited by the recombinant form. Annual global demand for plasma derived Factor VIII is forecast to increase from 2240 million international units (IU) in 2006 to 2612 million IU in 2016. Demand for recombinant Factor VIII is projected to grow from 2767 million IU to 4735 million IU over the same period.

Worldwide demand for albumin is forecast to grow from 474 tonnes in 2006 to some 544 tonnes in 2016.

In any discussion of current and future demand for plasma derived products, it is important to record that at present an estimated 15% of the world's population consume over 90% of the world's plasma product output. It is of considerable concern to the world community, and in particular to the World Federation of Hemophilia and its member organisations, that in developing countries very few people with haemophilia have access to the products they need in order to increase life expectancy.

Australia's arrangements

Australia's arrangements with respect to the supply of fresh blood and fractionated plasma products are unique and are not replicated in any other country. The close engagement of key government agencies with the role of the not-for-profit Australian Red Cross Blood Service as collector of blood and plasma, and with the role of CSL Bioplasma as the national fractionator – and the generosity of Australia's many voluntary, non-remunerated blood and plasma donors – are factors that combine to create a world-class blood system.

Governance

The National Blood Agreement (2003) between the Commonwealth and the states and territories provides the framework within which blood and blood products are funded and are supplied to the Australian community. Under the Agreement, the Australian Health Ministers' Conference (AHMC), a committee comprising the health ministers of Australia's nine jurisdictions, has responsibility for the oversight and management of the Australian blood sector. The National Blood Authority (NBA), a federal agency, manages the national blood supply system on behalf of Australia's governments, monitoring demand for blood and blood products, managing procurement arrangements with product suppliers, and undertaking annual supply planning and budgeting.

The NBA is overseen by the Jurisdictional Blood Committee (JBC), which operates on behalf of Australia's health ministers and is a subcommittee of the Australian Health Ministers' Advisory Council (AHMAC). Representing the perspectives of the individual jurisdictions, the JBC considers national policy, ongoing demand for blood and blood products, supply planning, product distribution, funding, and emerging products, services and technologies, and provides advice and support to AHMC on these matters.

The Review notes that in its short period of existence the NBA has been conspicuously successful in ensuring greater value for governments, particularly in relation to pricing negotiations for albumin and recombinant Factor VIII.

Policy

Under the National Blood Agreement, policy setting is a joint function of the Commonwealth, state and territory governments, and includes responsibility for compiling the annual National Supply Plan, for developing best-practice systems and for considering policy issues associated with the supply and administration of blood and blood products in clinical settings.

The Jurisdictional Blood Committee has a key support role in seeking evidence-based advice on the safety, quality, efficacy and cost-effectiveness of existing or proposed blood-related products, services or other activities; and in arranging for the preparation of evidence-based guidelines promoting the safe, efficient and effective collection, distribution, storage and use of blood and blood products in Australia.

Regulatory framework

The Therapeutic Goods Administration (TGA), an arm of the Australian Government Department of Health and Ageing, carries out a range of assessment and monitoring activities to ensure that therapeutic goods available in Australia are of an acceptable standard, and that the Australian community has access, within a reasonable time, to therapeutic advances. In order to obtain TGA approval for release in Australia, both imported and domestic therapeutic products must meet the same safety standards and regulatory requirements.

Plasma products are subject to the highest standard of regulation applicable to therapeutic goods. Because they are sourced from humans, these products, classified as biologicals, carry an inherent risk of transmitting acquired pathogens. Product safety is therefore of paramount importance and is guarded by stringent TGA regulations throughout the supply and manufacturing chain. At the point of donation, the Australian Red Cross Blood Service operates strict donor screening and deferral policies, and tests individual donations for key viral markers. Prior to its pooling for fractionation, the plasma is subjected to further rigorous testing at the CSL Bioplasma plant, while purification and viral-inactivation measures are undertaken by CSL during the manufacturing process. These mandatory viral-inactivation procedures are critical to ensuring the safety of plasma products.

The TGA conducts regular audits, announced and unannounced, of the CSL Bioplasma plant.

Funding

Responsibility for funding Australia's national blood arrangements is shared by the Commonwealth, state and territory governments. The Commonwealth provides 63% of the funding, and the remaining 37% is sourced from the states and territories. A National Supply Plan and Budget for blood and blood-related products and services is approved by the Australian Health Ministers' Conference on an annual basis. The Supply Plan is based upon the recommendations of the Jurisdictional Blood

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Committee and requires each jurisdiction's authorisation before implementation of changes with financial implications.

In 2005–06 the cost to Australian governments of providing patients with fresh blood products, plasma products and recombinant alternatives was \$565.4 million. This figure incorporates \$297.7 million to the Australian Red Cross Blood Service to provide fresh blood products, to collect plasma for fractionation, and to manage distribution and support services; \$136.8 million to CSL Limited for plasma product production and for imported products; and \$130 million to other suppliers (Baxter Healthcare \$68.5 million; Novo Nordisk \$23.6 million; Octapharma \$22 million; and Wyeth \$15.9 million). Expenditure on management of the National Blood Authority in 2005–06 was \$8.2 million. For 2006–07 the total cost of funding Australia's national blood arrangements is estimated to be \$650.7 million. The figures do not include costs (other than the purchase of blood products) associated with treatment in a hospital or with same-day clinical care.

Supply

The great majority of plasma products supplied to the Australian community are manufactured in Australia from domestically sourced plasma. The importance of ensuring an adequate and secure supply of plasma derivatives for Australian patients necessitates the importation of some products, either where clinical demand exceeds what can be provided from domestic plasma collections, or where a required product is low-volume and is not manufactured by CSL Bioplasma. All suppliers of plasma products for use in Australia operate under agreements that ensure both security of supply and reserve stocks of product.

National capacity

Production of plasma derived products in Australia takes place at the CSL Bioplasma plant at Broadmeadows, Melbourne. The plant currently has the capacity to fractionate 500 000 litres of plasma per annum. CSL advises that additions to the existing plant could see capacity increased to 750 000 litres per annum (with existing infrastructure in place) or to 1 million litres per annum (given additional buildings and services on the Broadmeadows site).

Public attitudes

The current system governing the blood sector in Australia, characterised by strong levels of cooperation between federal, state and territory governments, the Australian Red Cross Blood Service, the National Blood Authority and CSL Limited, gives outstanding service to Australians.

CSL's Broadmeadows and Parkville plants are widely perceived as iconic establishments within the biotechnology sector, in terms both of technology and research and development capacity, and employment opportunities provided. CSL Bioplasma Broadmeadows is the only plant of its kind in Australia with the technology and expertise to fractionate efficiently the quantities of plasma collected by the ARCBS from Australian donors.

Across the broad range of local submissions received by the Review Committee, almost universal concern was expressed with regard to any perceived threat, or

likelihood of change, to Australia's current blood arrangements. Maintaining the existing integrity and reliability of these arrangements, and the level of safety at which they function, is seen by stakeholders to be of vital importance.

While the submissions in general did not favour changes to the status quo, particular concern was expressed about the possibility that Australian plasma might be processed overseas. Questions were raised as to whether products manufactured from Australian plasma by offshore fractionators could meet the levels of safety, quality and efficacy currently required of domestically fractionated products, and whether the circumstances of overseas fractionation arrangements would permit the Therapeutic Goods Administration to exercise its appropriate supervisory and regulatory powers.

One issue of stated concern in various submissions was that Australian plasma fractionated overseas might be mixed with plasma from other countries, including those at a greater risk with respect to agents like variant Creutzfeldt-Jakob disease (vCJD), or viral contamination.

Australia's future demand

IVIg

Demand for IVIg is a critical factor in any assessment of demand for plasma products more broadly, as the IVIg requirements of a given jurisdiction set the level of starting plasma it requires for the production of all plasma derived products, excluding hyperimmunes. Over the past decade, demand for IVIg in Australia has increased by 14% per annum. Australian consumption in 2005–06 was 83 grams per 1000 population, which represents a total consumption of 1667 kilograms.

Forecasts provided to the Review suggest that by 2015–16 Australian demand for IVIg will be between 2985 and 3687 kilograms per annum. The average of these two figures, 3336 kilograms, represents more than double the amount of IVIg currently being issued in Australia, and consequently would require more than double the amount of plasma (at current yields). If the Allen Consulting Group forecast of 7.7% annual growth in demand for IVIg proves accurate, Australia will need 686 tonnes of plasma in 2015–16, compared with 308 tonnes in 2005–06: an increase of 123% over the next ten years.

This scenario assumes, based on advice to the Review, that no synthetic substitutes for IVIg are likely to emerge over the next ten years – immunoglobulins are very complicated molecules, and their synthesis via genetic engineering or recombinant technology will prove extremely difficult. The demand for plasma derived immunoglobulins will almost certainly not be met in the near future by the advent of recombinant alternatives.

Albumin

Both the Australian Red Cross Blood Service and the National Blood Authority forecast significant increases in demand for albumin over the coming decade: from 4836 kilograms in 2005–06, to 9355 kilograms and 8150 kilograms respectively by 2015–16. In making these projections, the ARCBS and the NBA point to the increased usage of albumin in the surgical treatment of cardiovascular disease.

Clotting factors

The treatment of haemophilia A and B with Factor VIII and Factor IX respectively was traditionally one of the key reasons for the collection and fractionation of plasma. While these clotting factors brought considerable health benefits to people with haemophilia, for a short period in the 1980s the use of these products resulted in the transmission of viral diseases, such as hepatitis C and HIV, to recipients; although the industry 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 campaigned to replace plasma derived Factor VIII and IX with recombinant alternatives.

The decision made by Australia in August 2004 to provide funds to enable all people with haemophilia A and B to have access to recombinant Factor VIII and Factor IX has, to a large extent, ensured a balance between supply and demand for these products. By the end of 2006, around 85% of people with haemophilia A were receiving recombinant Factor VIII.

There will continue to be demand for plasma derived Factor VIII, however, for the treatment of von Willebrand's disease and in circumstances where people prefer or need to continue using plasma derived products.

The National Blood Authority predicts an 11.6% average annual growth rate in the issuing of Factor VIII (both plasma derived and recombinant) in Australia over the next decade, with 12.0 IU per head of population being issued by 2015–16; CSL Limited on the other hand predicts a stable level of demand over the same period. The average of the various forecasts received by the Review suggests that at year 2015–16 there will be an annual demand of 24.75 million IU for plasma derived Factor VIII (assuming that this product will continue to be used by a small number of patients who fare better on the plasma derived form than on its recombinant alternative).

The supply of CSL's plasma derived Factor VIII product Biostat® is complicated by the fact that the Therapeutic Goods Administration requires, as an additional precautionary measure, that the plasma used in the manufacture of this product 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 production of plasma derived Factor VIII to approximately 100 tonnes (out of the year's total collections of 308 tonnes), a quantity just sufficient to meet a demand of 15.6 million IU of plasma derived Factor VIII for the year.

If the more ambitious of the forecasts provided to the Review prove to be accurate, it follows that Australia may be obliged to import some plasma derived Factor VIII, sourced from overseas plasma, in future years.

Forecasts with respect to future demand for Factor IX share many of the characteristics of projections for Factor VIII. From a supply point of view, future demand for plasma derived Factor IX can be readily met by normal plasma collections in the foreseeable future.

Future supply of plasma in Australia

A key issue, perhaps *the* key issue, in respect of Australia's current plasma fractionation arrangements is the importance of increasing the volume of plasma collected in this country, in order to meet increasing demand for plasma derived products, especially IVIg.

Over the last ten years, demand for IVIg – which continues to be the driving factor in the plasma products sector – has increased at a rate much higher than the growth in the supply of starting plasma available for fractionation. Since 2003–04, in order to meet demand, the domestic IVIg supply has been supplemented with imported IVIg products.

This situation is not peculiar to Australia but is a global trend; worldwide, there is potential for an ever-increasing unmet demand for plasma products, particularly IVIg.

While CSL Bioplasma strives on an ongoing basis to improve IVIg yields (yields are already high, helping to minimise the supply–demand gap) the central issue is that of blood donations. The Australian Red Cross Blood Service continues to develop strategies for increasing both donor numbers and frequency of donations by existing donors. Australian blood and plasma collection rates are already high by international standards, at 15.3 litres per thousand population. Australian donation trends to date, however, do not offer any certainty that the donor pool can be increased to levels sufficient to provide the quantity of plasma needed to meet forecast demand.

The ARCBS is developing some proposals for strategies that it believes will bridge the supply–demand gap. These include aiming to increase plasma supply via an increase in plasmapheresis collections.

Nevertheless, there is a need both for donor numbers to be augmented very significantly, and for an increase in the proportion of donors prepared to be subjected to the time-consuming and relatively invasive procedure of plasmapheresis (which yields substantially more plasma than whole blood donation). It is also important, though, that the supply of red cell units is maintained through whole blood donations, as there have been shortages of this product in the last year. A related issue is that all strategies for increasing donor numbers and participation rates place considerable additional demand on the resources of the ARCBS.

Self-sufficiency

The promotion of national self-sufficiency in respect of blood and blood products is a policy aim of Australia's Commonwealth, state and territory governments. The Australian Health Ministers' Conference Policy Statement on National Self-Sufficiency in the Supply of Blood and Blood Products, issued in April 2006, defines self-sufficiency as:

Australia striving to source blood components and plasma from within Australia to meet appropriate clinical demand.

The AHMC policy statement continues:

This statement has been developed in response to a number of questions about

Review of Australia's Plasma Fractionation Arrangements

whether recent government decisions to import certain blood products are consistent with the national policy aim relating to promoting national self-sufficiency in the blood supply.

All Australian, State and Territory Governments are signatories to the National Blood Agreement 2003, which sets out, among other things, the policy objectives and aims for Australia's national blood sector.

The primary policy objectives in the National Blood Agreement are to:

- provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services; and
- promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.

Underpinning these primary policy objectives are a number of secondary policy aims, including promoting national self-sufficiency. This policy aim has not changed. However, importation of blood products does occur in a narrow range of circumstances where there is an inability to meet clinical needs through the domestic supply, and where supply chain risks must be addressed. This happens within a framework that:

- ensures adequacy of supply to Australian patients in need;
- minimises the supply security and product safety risks to patients;
- ensures affordability of products to the Australian health sector; and
- recognises the practicalities of production and distribution.

The AHMC statement acknowledges that Australia is not totally self-sufficient in plasma products. In fact, Australia has never been self-sufficient in all plasma derivatives. The Review agrees, however, that Australia should be as self-sufficient as possible, and that self-sufficiency should remain an important goal.

Voluntary donors

The principle of voluntary, non-remunerated blood donation was first discussed by the World Health Assembly (WHA) in 1975 and articulated in WHA resolution 28.72. As a member of the WHA, Australia supported this resolution, which urged WHA member states to promote the development of national blood services based on voluntary, non-remunerated blood donation.¹ The main motivation for the resolution was to reduce risk to the blood supply in developing countries and to inhibit exploitation of donors. The most recent reference by the WHA to voluntary, non-remunerated donation occurred in May 2005, in a resolution that exhorts member states to:

establish or strengthen systems for the recruitment and retention of voluntary, non-remunerated blood donors and the implementation of stringent criteria for donor selection.²

1 World Health Organization, *Twenty-Eighth World Health Assembly, Geneva, 13–30 May 1975: WHA28.72 Utilization and Supply of Human Blood and Blood Products*, World Health Organization, Geneva, 1975, <<http://www.who.int/bloodsafety/en/WHA28.72.pdf>>.

2 World Health Organization, *Fifty-Eighth World Health Assembly: WHA58.13 Blood Safety: Proposal to Establish World Blood Donor Day*, World Health Organization, Geneva, 2005, p. 1, <http://www.who.int/bloodsafety/WHA58_13-en.pdf>.

Australia and European countries adhere to the definition of voluntary non-remunerated donation prescribed by the Council of Europe in its publication *Guide to the Preparation, Use and Quality Assurance of Blood Components* (January 2005). The Council of Europe has determined that small tokens, refreshments and the reimbursement of direct travel expenses are compatible with the voluntary and unpaid donation of blood. The Council of the European Union has included a similar provision in its definition of voluntary, non-remunerated donations.³

The question of reimbursement of donors for expenses incurred as a direct consequence of donating blood or plasma has been raised by many stakeholders in the course of the Review. While acknowledging the National Blood Agreement policy aim of maintaining reliance on voluntary, non-remunerated donations of whole blood and plasma, the Review has given consideration to this issue.

Reimbursing donors for travel expenses, or providing a taxation offset to cover part of these expenses, would be a departure from current government policy with regard to volunteerism – which is underpinned by the principle that services performed by volunteers should not attract recompense for costs incurred. It is the opinion of the Review, however, that this approach may need to be reconsidered in the light of the exceptional need to increase the number of blood donors in Australia. The Review would not recommend that Australia consider any system of direct payment to donors. The case for retaining the current system, whereby donors donate freely and without expectation of remuneration, rests not only on issues of WHA advocacy or on precedents in other countries, but – much more importantly – on a sense in the Australian community of the value and merit of the existing arrangements.

Distribution of plasma and plasma products within Australia

The Australian Red Cross Blood Service distributes fresh blood products, and some plasma, directly to hospitals and clinicians. The bulk of the plasma collected by the ARCBS is delivered to CSL Bioplasma for fractionation. Finished plasma products are generally transported from CSL Bioplasma to the ARCBS, which then carries responsibility for their distribution; distribution is effected through ARCBS business units, in cooperation with hospital blood banks, pathology laboratories and clinicians. The ARCBS also undertakes the role of distributor for specific imported plasma products.

There are two exceptions with regard to the distribution of domestically fractionated product: normal immunoglobulin is distributed in some states directly from local CSL facilities, with or without the ARCBS playing a role in ordering; and the 4000 IU IV tetanus product is shipped direct from CSL to customers.

Requests for plasma products for patients can be received by the ARCBS at any time, day or night, making a robust distribution system essential.

Under current National Blood Authority agreements for the supply of certain imported plasma products and recombinant products, distribution of these products is in most cases carried out directly by suppliers.

³ Council of the European Union, 'Council Recommendation of 29 June 1998 on the Suitability of Blood and Plasma Donors and the Screening of Donated Blood in the European Community (98/463/EC)', Official Journal of the European Communities, L 203, vol. 41 (21 July 1998), p. 18; also available online at <http://eur-lex.europa.eu/LexUriServ/site/en/oj/1998/l_203/l_20319980721en00140026.pdf>.

Future fractionation arrangements

The Review has examined very carefully fractionation arrangements in the United States and Europe, and has given close consideration to possible alternative arrangements for Australia.

Any change to the current arrangements, whereby Australia's plasma would be fractionated overseas rather than at a locally based fractionation plant, would require significant initial expenditure, extensive transitional planning, contingency plans, risk mitigation plans, and investment associated with registration and other compliance and approval processes.

The lead times involved in overseas fractionation of Australian plasma would be almost double the current lead times 'vein to vein' (i.e. from donation, through processing and distribution, to the recipient of a finished plasma product).

There would be significant additional costs involved in the overseas manufacture of plasma products for Australia. Some of these costs (e.g. for the transportation of Australian plasma to an overseas fractionation facility, for the return of finished plasma products to Australia, for cold storage and warehouse facilities, etc.) would be borne by the fractionator and reflected in price structures for fractionation services.

Major costs arising from the offshore fractionation of all Australian plasma would include a one-off 'transition cost' of approximately A\$75 million. This amount would be needed for the collection (if feasible) of sufficient additional domestic plasma to cover the 60-day withholding period if required (and the period required for sea transport) and scheduled processing time, or for the one-off purchase of the same quantity of imported finished product. Either strategy would increase the National Reserve from its present target inventory of three months' supply of plasma products, by an additional six months' stockholding.

Any ongoing shortfall in IVIg supply related to the yield of overseas fractionators would need to be addressed via the importation of IVIg products, which would have implications for Australia's national self-sufficiency policy.

Further, there are potential significant risks involved in the overseas fractionation of Australian plasma. While some of these scenarios are of low probability, their consequences would be expensive and disruptive. For example, loss of a 20-foot reefer container of plasma would represent a major disruption to Australian supply and would necessitate the acquisition of overseas-sourced plasma, or of the equivalent in finished products manufactured from overseas-sourced plasma, to compensate.

Conclusions

1. The three key public policy challenges in respect of Australia's future plasma fractionation arrangements are to ensure that:
 - future arrangements maintain the safety, quality and efficacy of plasma products fractionated for Australian use
 - arrangements provide the basis for delivering security of supply of plasma products for Australia
 - future arrangements provide the best possible value for money for Australia.
2. The key drivers of plasma fractionation arrangements for Australia, given projected demand over the next ten years, are intravenous immunoglobulin (IVIg) and plasma derived Factor VIII and Factor IX, and the safe and secure supply of these products must be ensured.
3. If Australia is to be self-sufficient in the plasma required for the production of IVIg, then, given projected demand over the next ten years, a significant increase in domestic plasma collections by the Australian Red Cross Blood Service will be necessary. Achieving this increase will require of all Australian governments vigorous review and reform of current domestic plasma collection arrangements.
4. In any event, Australia will need to maintain imports of plasma derived product in order to meet domestic demand. If the increases in plasma collections projected by the ARCBS are not met, then the requirements for imported products will increase considerably.
5. A key factor in determining the most appropriate plasma fractionation arrangements for Australia are the relative yield rates of potential fractionators. Any change in current arrangements that delivered a lower yield rate would have flow-on implications for costs and logistics, in terms of higher plasma collection requirements or alternative replacement strategies, and additional transport and manufacturing costs. While it is not possible to predict with any accuracy future national or global yield rates, Australia's current fractionation arrangements appear to deliver a very high IVIg yield rate by world standards (more than 5.0 g/L in 2005–06).⁴ It appears unlikely that any other fractionator could presently match the IVIg yield being achieved by CSL Bioplasma.
6. Overseas fractionation of Australian plasma would involve significant transitional costs and, because of yield considerations, there would be the potential for an ongoing shortfall in the supply of IVIg and other plasma derived products. The consequent need to source these products via imports would have implications for the national self-sufficiency policy.
7. There are potential supply chain risks involved in overseas fractionation of Australian plasma. While some of the risk scenarios are of low probability, their consequences would be expensive and disruptive. Addressing these risks would require either an impost on the National Reserve of plasma products or an added call on existing standing offers for imported product.
8. The overseas fractionation of Australian plasma could mean that some products that are not manufactured under the current arrangements could be fractionated using Australian plasma. However, given that the products concerned are of

4 <<http://www.csl.com.au/Investors.asp>>.

Review of Australia's Plasma Fractionation Arrangements

relatively low volume, in comparison to IVIg, albumin and the major clotting factors, their manufacture under these conditions would be of limited benefit to Australia, and unlikely to be economically viable for a fractionator.

9. Any supply to Australia of plasma products from overseas fractionators would require significant lead times and investment in registration and other approval processes. If registration of products were to be a prerequisite to tendering for the supply of plasma products to Australia, not all overseas fractionators would be likely to want to incur the costs of registration in the absence of a supply contract. If, on the other hand, product registration were to be required only after a tender contract had been agreed, then a lead time of at least two years would be needed for registration and approval processes.
10. Increased transparency with respect to collaboration between stakeholders; longer-term planning; and streamlining ordering systems in line with emerging technologies would significantly increase the efficiency of the current distribution system.
11. Public opinion in Australia is strongly in favour of maintaining the current plasma fractionation arrangements, particularly with regard to the role of the ARCBS and the domestic handling of the donation of 'the gift of blood'.
12. When the transitional costs, the risks, and the indeterminate yield ratios of overseas fractionation are considered against the national self-sufficiency objective, and when account is taken of the national strategic importance of CSL's plant at Broadmeadows, then overseas fractionation of Australian plasma is not an advantageous option for Australia.

Recommendations

1. Ministers should note the Review's conclusion that overseas fractionation of Australian plasma is not an advantageous option for Australia. Ministers should also note the substantial regulatory and other changes, as set out in this report, that would be necessary in the event it were desired to alter present arrangements and invite overseas manufacturers to tender for the fractionation of Australian plasma.
2. In view of the prospect of substantial shortfalls between projected demand for plasma products in Australia, and domestic plasma collected by the Australian Red Cross Blood Service, urgent action must be taken to increase plasma collection rates. There needs to be a vigorous and creative campaign, led by Commonwealth, state and territory governments, to energise the community in favour of blood donation.
3. The Commonwealth, state and territory governments should safeguard the security of supply of plasma products for Australians by importing plasma products to address any shortfall and risks in supply of domestically manufactured products. Procurement of imported plasma products should be undertaken by an international competitive tender process, which could include provision for tiered pricing related to the volume of specific products required. This may also facilitate benchmarking by the National Blood Authority of domestically manufactured plasma products against prices for imported plasma products, in order to further

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the objective of value for money in future contract negotiations, consistent with other policies. Existing contracting, risk management and mitigation strategies for Australia's plasma fractionation arrangements should be reviewed by the Australian Health Ministers' Conference in consultation with relevant parties and, where appropriate, upgraded in line with world's best practice.

4. The ARCBS needs to enhance innovation in its marketing efforts and customer service strategies in order to recruit donors from a broader cross section of the Australian community and to retain existing donors. In particular, there is a need for new strategies for encouraging more young Australians and members of ethnic communities to donate blood. The ARCBS will need additional funding support from governments to develop and implement such strategies. In the future, consideration may need to be given as to whether travel costs incurred by blood donors and plasma donors should be reimbursed or permitted to be treated as an allowable taxation offset; taxation offset for costs incurred as a direct consequence of blood or plasma donation would be a powerful statement of the importance attached by Government to the voluntary donation of blood.
5. The present annual planning and budgeting framework for plasma supply should be reviewed, with a view to moving to a four- to five-year business planning cycle. The current annual planning cycle is not consistent with best practice in strategic planning and can limit capacity for ensuring operational efficiency.
6. Uniform provisions concerning the age at which a person is eligible to donate blood should be introduced by all state and territory governments. A uniform approach along the lines of the system operating in South Australia would be in the best interests of collections by the ARCBS.
7. There should be greater consistency between states and territories in the application of revised national guidelines for IVIg usage.
8. The Therapeutic Goods Administration regulatory base should be revised to provide explicitly for the conduct of unannounced audits of overseas manufacturers. The new arrangements should be supported and confirmed through either Mutual Recognition Agreements or provisions in contracts with manufacturers. Consideration should be given to negotiating amendment of the Australia–EC/EFTA MRAs, to enable joint inspections of manufacturers of high-risk medicines (including plasma products) by the TGA and designated EC/EFTA GMP inspectorates, where appropriate. Consideration should be given to amending the Therapeutic Goods Regulations to ensure that fees may be imposed on Australian product sponsors to cover the costs of GMP auditing of overseas manufacturing sites.
9. The Australian Health Ministers' Conference should continue to monitor and assess industry developments, with the aim of ensuring that the range of Australian plasma derived products remains appropriate to clinical requirements.
10. Australia should maintain its reservation regarding the procurement of blood fractionation services under the Australia–United States Free Trade Agreement. The reservation exempts the procurement of plasma fractionation services from the government procurement provisions in Chapter 15 of the Agreement. The CSL Act should also be maintained.

Implementation strategy

1. Contingency

Australia will need to maintain imports of plasma derived products in order to meet future domestic demand. The supply–demand gap will potentially always exist. The current fractionation arrangements agreed by the Australian Health Ministers' Conference provide for the fractionation onshore, by CSL Bioplasma, of all Australian plasma, and for the importation of plasma derived products that either are not manufactured by CSL Bioplasma or, in the case of IVIg, are required in order to augment domestic supply, as a contingency measure. There is therefore the opportunity for international fractionators that wish to compete for this contingency supply business to participate in the Australian market. It is in the national interest that:

- i) The Jurisdictional Blood Committee and AHMC continue to monitor and assess industry developments, both domestic and international, with a view to ensuring that the Australian community continues to benefit from the provision of an appropriate range of safe, efficacious and high-quality therapeutic products derived from human plasma, and that these products are derived from Australian plasma wherever possible, and complemented with imported product only as a contingency measure.
- ii) Risk management and mitigation strategies for Australia's plasma fractionation arrangements be continuously maintained, reviewed and upgraded by the National Blood Authority, as advised by the JBC, in accordance with world's best practice and so as to ensure Australia's ongoing access to safe, high-quality plasma derived products.
- iii) The existing contingency supply arrangements, which involve the negotiation of standing offers, do allow for some limited competitive elements to be introduced into the Australian market, and this arrangement should be used to maximise the opportunity for competition. The procurement of imported plasma products should be undertaken by international competitive tender and could include provision for tiered pricing related to the volume of specific products or type of specific services required.
- iv) The NBA should undertake price benchmarking of domestically manufactured plasma products against prices for imported plasma products to inform future contract negotiations.

2. Collection

All Australian governments should consider the reform of current and future domestic plasma collection arrangements. Following the 2006–07 business study of the efficiency and effectiveness of the Australian Red Cross Blood Service, a comprehensive change agenda may need to be developed.

3. Distribution

The National Blood Authority and the Jurisdictional Blood Committee should initiate a review of current distribution arrangements between the Australian Red

Cross Blood Service and CSL Bioplasma, and should, in particular:

- i) review and reduce the number of stocking points and the number of products stocked at each, having regard for the need to maintain sufficient stocks in strategic locations so as to be able to meet urgent requirements
- ii) set inventory target levels, according to product and demand profiles, and review these target levels on a regular basis and in a systematic manner
- iii) share patient de-identified clinical requirements data (orders data) with all supply chain partners
- iv) facilitate collaboration between supply chain partners, through information transparency
- v) foster collaboration with hospital administrators so as to improve operating efficiencies (e.g. by pre-labelling deliveries with patient identifiers, when and if appropriate)
- vi) develop a range of whole-of-supply-chain performance indicators.

In the longer term:

- i) prepare a formal analysis of the supply chain requirements of different groups of approved health providers
- ii) adopt multiple distribution channels, to the extent that this proves to be the most cost-effective and efficient means of meeting the needs of different end users
- iii) consider combining the strengths of the ARCBS and CSL by developing an improved distribution channel in which the ARCBS services the medical information needs of approved health providers and ensures appropriate clinical use of plasma products, while CSL provides efficient and robust cold chain distribution services. Consideration should also be given to the use of a dedicated specialist cold chain provider to deliver plasma derived and recombinant products provided under the National Blood Agreement.
- iv) encourage approved health providers to develop long-term plans for investment in supply chain enhancements, including greater reliance on e-commerce solutions that work best within the health providers' own environments and that integrate effectively with the systems of other supply chain partners.

4. NBA plasma collection and fractionation agreements

Because of the critical national reliance on National Blood Authority agreements for plasma collection and fractionation, the NBA, in conjunction with all governments and other stakeholders in the health sector, should seek at all times to ensure that such agreements deliver best-practice outcomes on:

- product range, quality and price
- supplier services and performance
- risk mitigation.

Summary assessment

In the light of a comprehensive analysis of the existing system, and following a considered, objective and thorough examination of alternatives, it is concluded that the current structural arrangements whereby domestically collected plasma is fractionated by CSL Bioplasma are, subject to careful monitoring of prices, in Australia's best interests. The present system is well entrenched in the 'hearts and minds' of the Australian population and of the Australian medical community and, particularly, in the strategy, thinking and reliance of all end user groups.

Annex A

Exchange of letters forming part of the AUSFTA



18 May 2004

The Honourable Robert B. Zoellick
United States Trade Representative
600 17th Street, NW
Washington, DC 20508

Dear Ambassador Zoellick

In connection with the signing on this date of the Australia–United States Free Trade Agreement (the “Agreement”), I have the honour to confirm the following understanding reached by the Governments of Australia and the United States during the course of the negotiation regarding treatment to be accorded products derived from blood plasma (“blood plasma products”) and blood fractionation services for the production of such products:

1. Any contract with a central government entity of Australia for blood fractionation services in effect on the date of entry into force of the Agreement shall conclude no later than 31 December 2009, or earlier if Australia deems it appropriate.
2. Australia shall undertake a review of its arrangements for the supply of blood fractionation services that shall conclude no later than 1 January 2007. The Commonwealth Government will recommend to Australia’s States and Territories that future arrangements for the supply of such services be done through tender processes consistent with Chapter 15 (Government Procurement) of the Agreement.
3. Should the Commonwealth and State and Territory governments reach agreement to make future arrangements for the supply of blood fractionation services through tender processes consistent with Chapter 15, Australia shall withdraw its Annex 15-A, Section 5 reservation regarding the procurement of such services.
4. A Party may require any producer of blood plasma products or supplier of blood fractionation services to fulfil requirements necessary for ensuring the

Review of Australia's Plasma Fractionation Arrangements

The Honourable Robert B. Zoellick

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safety, quality, and efficacy of such products. Such requirements shall not be prepared, adopted, or applied with a view to, or with the effect of, creating unnecessary obstacles to trade.

5. A Party may require that blood plasma products for use in its territory be derived from blood plasma collected in the territory of that Party.
6. Australia confirms that it will not apply any requirement for an applicant for approval of the marketing and distribution of a U.S. blood plasma product to demonstrate significant clinical advantage over Australian-produced products.
7. Article 21.2(c) (Scope of Application) of the Agreement shall apply to paragraphs 1 through 6.

I have the honour to propose that this letter and your letter in reply confirming that your Government shares this understanding shall constitute an integral part of the Agreement.

Yours sincerely



Mark Vaile
Minister for Trade

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**EXECUTIVE OFFICE OF THE PRESIDENT
THE UNITED STATES TRADE REPRESENTATIVE
WASHINGTON, D.C. 20508**

May 18, 2004

The Honorable Mark Vaile MP
Minister for Trade
Parliament House
Canberra ACT 2600

Dear Minister Vaile:

I have the honor to acknowledge receipt of your letter of this date regarding the treatment to be accorded to blood plasma products and blood fractionation services, which reads as follows:

“In connection with the signing on this date of the Australia-United States Free Trade Agreement (“the Agreement”), I have the honour to confirm the following understanding reached by the Governments of Australia and the United States during the course of negotiations regarding treatment to be accorded products derived from blood plasma (“blood plasma products”) and blood fractionation services for the production of such products:

1. Any contract with a central government entity of Australia for blood fractionation services in effect on the date of entry into force of this Agreement shall conclude no later than 31 December 2009, or earlier if Australia deems it appropriate.
2. Australia shall undertake a review of its arrangements for the supply of blood fractionation services that shall conclude no later than 1 January 2007. The Commonwealth Government will recommend to Australia's States and Territories that future arrangements for the supply of such services are done through tender processes consistent with Chapter 15 (Government Procurement) of the Agreement.
3. Should the Commonwealth and State and Territory governments reach agreement to make future arrangements for the supply of blood fractionation services under tender processes consistent with Chapter 15 (Government Procurement), Australia shall withdraw its Annex 15-A, Section 5 reservation to that chapter regarding the procurement of such services;
4. A Party may require any producer of blood plasma products or supplier of blood fractionation services to fulfil requirements necessary for ensuring the safety, quality and efficacy of such products. Such requirements shall

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The Honorable Mark Vaile MP

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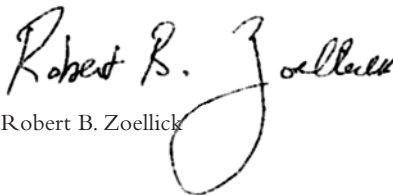
not be prepared, adopted, or applied with a view to or with the effect of creating unnecessary obstacles to trade.

5. A Party may require that blood plasma products for use in its territory be derived from blood plasma collected in the territory of that Party.
6. Australia confirms that it will not apply any requirement for an applicant for approval of the marketing and distribution of a U.S. blood plasma product to demonstrate significant clinical advantage over Australian produced products.
7. Article 21.2(c) (Scope of Application) of the Agreement shall apply to paragraphs 1 through 6.

I have the honour to propose that this letter and your letter in reply confirming that your Government shares this understanding shall constitute an integral part of the Agreement.”

I have the further honor to confirm that my Government shares this understanding and your letter and this reply shall constitute an integral part of the United States–Australia Free Trade Agreement (the “Agreement”). The United States expects that Australia will undertake any future arrangements for blood fractionation services through tender processes consistent with Chapter 15 (Government Procurement) of the Agreement.

Sincerely,



Robert B. Zoellick

Robert B. Zoellick

Annex B

Organisations and individuals from whom submissions were received

Australian & New Zealand Society of Blood Transfusion Ltd

Australian Fair Trade & Investment Network

Australian Federation of AIDS Organisations Inc.

Australian Haemophilia Centre Directors' Organisation

Australian Haemophilia Nurses' Group

Australian Hepatitis Council

Australian Medical Association Limited

Australian Red Cross Blood Service

Baxter Healthcare Pty Limited

Bio Products Laboratory (BPL), United Kingdom

Blood User Group, Victoria

Burke, John

Campbell, Heather

Country Women's Association of NSW

CSL Limited

Department of Defence

Department of Foreign Affairs and Trade

Department of Health and Human Services, Tasmania

Department of Health, Hong Kong

Department of Health, South Australia

Department of Premier and Cabinet, Tasmania

Haematology Society of Australia and New Zealand

Haemophilia Foundation Australia

Haemophilia Foundation ACT

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Immune Deficiencies Foundation Australia

Independent Blood Council

Inflammatory Neuropathy Support Group of Victoria Inc. (the IN Group)

Laboratoire Français du Fractionnement et des Biotechnologies (LFB), France

MDA Pharma/Medical Dynamics Australia

Miller, Kylie

Ministry of Health, Labour and Welfare, Japan

Ministry of Health, New Zealand

Ministry of Health, Singapore

Ministry of Health, Welfare and Sport, Netherlands

National Blood Authority

National Centre for Epidemiology and Population Health, Australian
National University

National Serology Reference Laboratory

NSW Health

NSW Immunoglobulin User Group (IVIg User Group) and Australasian
Society of Clinical Immunology and Allergy

Octapharma Group

Plasma Protein Therapeutics Association

Queensland Health

Royal Australasian College of Surgeons

Royal College of Pathologists of Australasia

Schier, Mark

South Australian Immunoglobulin User Group (IVIg User Group)

Talecris Biotherapeutics Inc.

Victorian Government

Annex C

Persons interviewed by the Review Committee

The Hon Tony Abbott MP, Minister for Health and Ageing

Mr Joel Abelson, Vice President, Talecris Biotherapeutics

Mr Jason Appleby, Policy Analyst, Australian Federation of AIDS Organisations

Mr Jim Bacon, Director, Talecris Biotherapeutics

Professor Chris Baggoley, Chief Medical Officer, Department of Health, South Australia

Mr Larry Bagwell, Director, Talecris Biotherapeutics

Dr Hilary Bambrick, Research Fellow, National Centre for Epidemiology and Population Health, Australian National University

Mr Mark Bebbington, Manager, Australian Federation of AIDS Organisations

Ms Joan Bedford, Senior Portfolio Officer, Statewide Contracting, Health System Support, Department of Health, Western Australia, and member of Plasma Fractionation Review Advisory Group

Professor Rinaldo Bellomo, Clinician, Australian and New Zealand Intensive Care Society

Dr Amar Bhat, Director, United States Department of Health & Human Services

Ms Linley Bielby, Bloodsafe IVIg Nurse, Australian Red Cross Blood Service (South Australia)

Mr Neil Boal, Consumer Representative, Plasma Fractionation Review Advisory Group

Mr Thomas Bollyky, Director, Office of the US Trade Representative

Mr Paul Bordonaro, Senior Adviser, CSL Limited

Mr Anthony Bourke, Operations Manager, Australian Red Cross Blood Service (Queensland)

Dr Anne Brand, Deputy Secretary, Department of Health and Human Services, Tasmania

Mr David Brochu, Senior Director, Talecris Biotherapeutics

Dr Chris Brook, Director, Rural and Regional Health and Aged Care Services, Department of Human Services, Victoria

Ms Isobel Brown, Senior Adviser, Office of the Minister for Health and Ageing

Dr Stewart Bryant, Transfusion Medicine Specialist, Australian Red Cross Blood Service (Queensland)

Review of Australia's Plasma Fractionation Arrangements

Mr Jan Bult, President, Plasma Protein Therapeutics Association

Ms Amanda Caples, Director, Biotechnology, Department of Innovation, Industry and Regional Development, Victoria

Ms Sharon Caris, Executive Director, Haemophilia Foundation Australia

The Hon Jim Carlton AO, Director, Carlton International Consulting Pty Ltd

Mr Peter Cheong, Production Services Manager, Australian Red Cross Blood Service (Queensland)

Mr Doug Chester, Deputy Secretary, Department of Foreign Affairs and Trade

Ms Judy Ciaraldi, Consumer Safety Officer, US Food and Drug Administration

Ms Gina Clare, Manager, Co-ordination, Planning & Research Unit, Queensland Health

Dr Shlomo Cohny, Physician and Transplant Nephrologist, Royal Melbourne Hospital

Ms Gillian Conley, Director, Division of Inspection & Surveillance, US Food and Drug Administration

Dr Matthew Cook, Director, Immunology Department, The Canberra Hospital

Dr Elliot Cowan, Chief, Product Review Branch, US Food and Drug Administration

Ms Maree Coy, Chief Executive Officer, Baxter Healthcare, Australia

Ms Sally Cross, Policy Officer, Australian Medical Association

Mr Darryll Cullen, Owner and Chief Executive Officer, MDA Pharma/Medical Dynamics Australia

Mr John Dalton, Director, Industry and Trade Policy, Department of Innovation, Industry and Regional Development, Victoria

Mr Michael Daniel, Consumer Representative, Immune Deficiencies Foundation Australia

Dr Rachel David, Director, Public Affairs, CSL Limited

Dr Jeff Davies, General Manager, CSL Limited

Mr Philip Davies, Deputy Secretary, Department of Health and Ageing

Mr Ken Davis, President, Australian & New Zealand Society of Blood Transfusion

Mr Stephen Deady, First Assistant Secretary, Department of Foreign Affairs and Trade

Mr Scott DeAthos, Plant Manager, Baxter BioScience, Baxter Healthcare

Mr Peter De Graaff, Deputy General Manager, National Blood Authority

Review of Australia's Plasma Fractionation Arrangements

Dr Peta Dennington, Transfusion Medicine Specialist, Australian Red Cross Blood Service

Mr Scott Dobbie, Regional Business Manager, Octapharma Australia

Dr Paul Dugdale, Chief Health Officer, ACT Health

Dr Nicole Farina, Regulatory Affairs Manager, Octapharma Australia

Professor Albert Farrugia, Principal Scientific Adviser, Office of Blood, Devices and Tissues, Therapeutic Goods Administration

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Mr Steve Faulkner, Donor Service Manager, Australian Red Cross Blood Service (South Australia)

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Ms Meribeth Fletcher, Director, Department of Health and Community Services, Northern Territory

Dr Peter Fogarty, President, Haemophilia Foundation Queensland

Dr Martyn Forrest, Secretary, Department of Health and Human Services, Tasmania

Mr Toby Forwood, Government Affairs Counsel, Baxter Healthcare, Australia

Mr Michael Furey, Manager, Pharmaceutical Programs, Metropolitan Health and Aged Care Services, Department of Human Services, Victoria

Mr James Gerrand, Director, Inflammatory Neuropathy Support Group of Victoria (the IN Group)

Mr Tom Giarla, President, Asia Pacific, CSL Bioplasma

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Dr David Graham, National Manager, Therapeutic Goods Administration, and member of Plasma Fractionation Review Advisory Group

Review of Australia's Plasma Fractionation Arrangements

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Dr Robert Hetzel, Chief Executive Officer, Australian Red Cross Blood Service

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Review of Australia's Plasma Fractionation Arrangements

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Dr Mary Ann Lamb, Vice President, Talecris Biotherapeutics

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Mr Sam Lovick, Chief Economic Strategist, CSL Limited

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Ms Robyn McCormack, Executive Assistant to CEO, MDA Pharma/Medical Dynamics Australia

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Mr Wolfgang Marguerre, Chairman and Founder, Octapharma Group

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Review of Australia's Plasma Fractionation Arrangements

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Dr Ann Roberts, Board Member, Haemophilia Foundation Australia

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Mr Michael Sands, Project Officer, Marketing and Communications, Australian Red Cross Blood Service (South Australia)

Ms Edwina Sargeant, Policy Officer, Industry and Trade Policy, Department of Innovation, Industry and Regional Development, Victoria

Dr Megan Sarson-Lawrence, Project Officer, Australian Haemophilia Centre Directors' Organisation

Mr Simon Sestich, Assistant Director, Octapharma Australia

Mr Tony Shelton, Bio Pharmaceutical Manager, Baxter Healthcare, Australia

Dr Andrew Singer, Director, Emergency Department, The Canberra Hospital

Ms Ros Sipponen, Haematology Department, The Canberra Hospital

Dr Glenn Smith, Clinician, Office of Blood, Devices and Tissues, Therapeutic Goods Administration

Review of Australia's Plasma Fractionation Arrangements

Ms Perry Sperling, Adviser, Office of the Prime Minister
The Right Hon Sir Ninian Stephen KG AK GCMG GCVO KBE KStJ
Mr Michael Stone, General Counsel, National Blood Authority
Associate Professor Alison Street, Clinician, Australian Haemophilia Centre Directors' Organisation
Mr Tor-Einar Svae, Head, Product Development, Octapharma
Dr Amanda Thompson, Clinician, Australian & New Zealand Society of Blood Transfusion
Ms Susan Thomson, Executive Assistant, Australian Red Cross Blood Service
Ms Fran Thorn, Secretary, Department of Innovation, Industry and Regional Development, Victoria
The Hon Robert Tickner, Secretary General and Chief Executive Officer, Australian Red Cross Society
Dr Alison Turner, General Manager, National Blood Authority
Mr Johan Vandersande, Vice President, Global Engineering & Technology, Baxter BioScience, Baxter Healthcare
Mr Greg Vickery AM, Chairman, Australian Red Cross Society
Mr Jean-Marie Vlassembrouck, Vice President, Global Industry Affairs, Baxter Healthcare, Belgium
Mr Peter Walsh, Adviser, CSL Limited
Mr Colin Webster, Manager, Australian Red Cross Blood Service (ACT)
Dr Mark Weinstein, Associate Deputy Director, Office of Blood Research & Review, US Food and Drug Administration
Ms Barbara Weisel, Assistant US Trade Representative, Southeast Asia, Pacific & Pharmaceuticals, Office of the US Trade Representative
Ms Trudy Witbreuk, Director, Department of Foreign Affairs and Trade
Mr Ken Whitson, Operations Manager, Australian Red Cross Blood Service (South Australia)
Ms Cathryn Willis, Regional Manager, Australian Red Cross Blood Service (Tasmania)
Ms Joan Wilmarth Blair, International Affairs Advisor, US Food and Drug Administration
Mr Garry Wolfe, Operations Unit Manager, Sydney Donor Collection Facility, Australian Red Cross Blood Service (New South Wales)
Dr Erica Wood, Transfusion Medicine Specialist, Australian Red Cross Blood Service

Review of Australia's Plasma Fractionation Arrangements

Dr Rosalie Woodruff, Research Fellow, National Centre for Epidemiology and Population Health, Australian National University

Dr Andrej Wozniak, Manager, Manufacturer Assessment Branch, Therapeutic Goods Administration

Associate Professor John Ziegler, Chair, NSW Immunoglobulin User Group (IVIg User Group) and Member, Australasian Society of Clinical Immunology and Allergy

Overseas consultations

Plasma Fractionation Review Committee members Mr Philip Flood AO, Mr Peter Wills AC and Associate Professor Kevin A. Rickard AM, together with Ms Yael Cass, held consultations with the following in the United States:

- Baxter International Inc
- Office of the US Trade Representative
- Talecris Biotherapeutics
- US Food and Drug Administration

In addition, members of the Secretariat held consultations with the following organisations and government ministries in Europe and Canada:

- Baxter Healthcare, Austria
- Bio Products Laboratory (BPL), United Kingdom
- Canadian Blood Services (CBS)
- Department of Health and Children, Ireland
- European Medicines Agency (EMA), United Kingdom
- Grifols, Spain
- Health Canada
- International Plasma Fractionation Association (IPFA), Netherlands
- Laboratoire Français du Fractionnement et des Biotechnologies (LFB), France
- Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom
- Ministry for Health and Women, Austria
- Ministry of Health and Care Services, Directorate of Health and Social Affairs, Norway
- Ministry of Health, Czech Republic
- Ministry of Health, Welfare and Sport, Netherlands
- Octapharma Group, Austria
- Paul-Ehrlich-Institut, Germany
- Public Health Agency of Canada
- Sanquin, Netherlands
- State Institute for Drug Control, Czech Republic
- Ullevaal University Hospital, Norway

Annex D

Major fractionators

CSL Limited

CSL Limited is a global biopharmaceutical company that develops, manufactures and markets products to prevent and treat serious human medical conditions. Innovation, and the development of new products to address unmet medical needs, are the main drivers of CSL Limited's continued growth. Headquartered in Melbourne, Australia, the CSL Group includes CSL Bioplasma, CSL Biotherapies (previously CSL Pharmaceuticals) and CSL Behring, incorporating ZLB Plasma Services. With facilities in Australia, Germany, Switzerland and the United States, CSL Limited has approximately 7500 employees, working in 26 countries.

In the past six years, CSL Limited has negotiated several key business acquisitions. In 2000, ZLB (now part of CSL Behring) was purchased. The following year, CSL Limited acquired 47 US-based plasma collection centres. The acquisition of Aventis Behring followed two years later, extending CSL Limited's assets and ensuring it a place as a major player in the global fractionation industry. CSL Limited's Research and Development Division is based in Parkville, Victoria.

In 2005–06 CSL Behring (which has manufacturing operations in the United States and Europe) consolidated the momentum from the integration of Aventis Behring, with sales reaching A\$2.4 billion, an increase of 11% over sales for the previous year. Several industry policy changes have contributed to an 8% reduction in sales revenue, to A\$191 million, for CSL Bioplasma in 2006. Sales revenue for CSL Biotherapies reached A\$212 million, up 3% for 2005–06.¹ In its submission to the Review, CSL Limited reported that in 2004–05 its operations in Australia contributed 18% of total earnings before tax and interest.²

CSL Bioplasma

CSL Bioplasma has been Australia's national fractionator of plasma derived therapeutics since 1953, and currently has a five-year contract to fractionate Australian plasma until 31 December 2009. Under the terms of this contract with Australia's National Blood Authority (the Plasma Products Agreement), CSL Bioplasma fractionates plasma donated by Australian donors. This plasma is manufactured into plasma derived therapeutic products at CSL Bioplasma's chromatographic fractionation facility, located at Broadmeadows in Victoria.

The CSL Bioplasma Broadmeadows plant, which has cost over A\$350 million to develop, is one of the most sophisticated plasma fractionation facilities in the world, and the only commercial-scale facility of its type. The Commonwealth invested 50% in the current plant, recouping this outlay when CSL was floated as a public company in 1994. The current capacity of the Broadmeadows plant is 500 000 litres, with current annual production at approximately 400 000 litres.

1 See CSL Limited, *Annual Report 2005–2006*, CSL, Parkville, Vic., 2006; also available online at <http://www.csl.com.au/files/1/CSL_AR_2006.pdf>.

2 CSL Limited, submission to Plasma Fractionation Review, 2006, pp. 42, 43.

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The plant is principally chromatographic in its technology, with the exception of that used for hyperimmune production. CSL Limited maintains that the total capacity of the CSL Bioplasma plant could be extended to as much as 750 000 litres per annum within the existing infrastructure; capacity could be further increased, to 1 million litres, given additional infrastructure and services.

CSL Bioplasma is the toll fractionator for New Zealand, Hong Kong, Malaysia and Singapore and also manufactures a range of diagnostic products used to determine compatibility in blood transfusion settings.

CSL Behring

CSL Behring is one of the world's leading biopharmaceutical companies specialising in the manufacture of plasma products, with plants located in Bern, Switzerland; Marburg, Germany; and Kankakee, Illinois. Three major companies constitute what is now known as CSL Behring: ZLB, Behringwerke, and Armour. ZLB was established in 1949, as a department of the Swiss Red Cross. In 1904, Emil von Behring created Behringwerke in Marburg, Germany, to produce sera and vaccines to cure infectious diseases.

CSL Behring has a worldwide plasma fractionation capacity in the order of 5.2 million litres. CSL Behring is the designated contingency supplier in the case of an interruption to supply at CSL Bioplasma. CSL Behring toll fractionates for Denmark.

Profile

- CSL Behring manufactures plasma products and sells them to markets in the United States, the rest of the Americas, Europe, Japan, South-East Asia, China and the Middle East.
- CSL Behring is one of the largest suppliers of plasma products globally, with approximately 23.5% of the global market (a market share that rises to 25% if the rest of CSL Limited's production output is considered).
- The plasma fractionated by CSL Behring is collected or purchased under contract by its plasma collection business, ZLB Plasma Services, based in Florida in the United States.
- CSL Behring operates 70 plasma collection centres in the United States and Germany. Plasma is collected at these centres via apheresis.

CSL Behring has implemented a 'centres of excellence' model:

- The Bern plant is the centre of excellence for immunoglobulin manufacture.
- The Marburg facility is the centre of excellence for the manufacture of coagulation and specialty products.
- Kankakee is the centre for alpha-1 antitrypsin and monoclonal product manufacture.
- All plants produce albumin.

- ZLB Plasma Services is the centre of excellence for the collection, acquisition, testing, distribution and management of plasma.
- The 'centres of excellence' structure allows CSL Behring to operate its three facilities at the optimal scale of between 2 million and 4 million litres per annum on a plasma equivalent measure (PEQ), which corresponds to the total amount of plasma received.

Baxter International, Inc.

Baxter is a large multi-divisional, multinational corporation engaged in the manufacture and supply of products to the global health care industry. In 2005 Baxter recorded sales of US\$9.8 billion, and had approximately 47 000 employees. Unlike other global-scale fractionators, Baxter's plasma fractionation business represents only a relatively small part of its overall operations.

In 2004 approximately 50% of Baxter's sales were outside the United States, and more than half of the company's workforce was located in other countries. Baxter has 64 manufacturing facilities, located throughout the world, and four fractionation facilities (Los Angeles, Vienna, Rieti, and Lessines).

Baxter has a total capacity of 4 million litres and primarily fractionates plasma collected at self-owned collection sites in the United States and at other sites operated by the American Red Cross and other collectors. Three-quarters of Baxter's plasma throughput in 2005 was source plasma.

Baxter has a significant presence in Europe, with manufacturing and research facilities in more than a dozen countries: Austria, Belgium, the Czech Republic, France, Germany, Ireland, Italy, Malta, Poland, Spain, Switzerland, and the United Kingdom. Baxter also operates facilities in Tunisia and Turkey, Argentina, Brazil, Chile, Colombia, Costa Rica, the Dominican Republic and Mexico.

In Japan, Baxter has a manufacturing plant and product development centre and also maintains several distribution centres and sales offices. The company has a growing presence in Asia, including manufacturing facilities in China, India, the Philippines and Singapore.

Baxter currently has three business divisions: BioScience; Medication Delivery; and Renal.

BioScience

2005 sales: US\$3.8 billion

Baxter is a leading manufacturer of plasma-based and recombinant proteins used to treat haemophilia. Other biopharmaceutical products include plasma-based therapies to treat immune disorders, and vaccines.

Review of Australia's Plasma Fractionation Arrangements

Medication delivery

2005 sales: US\$4 billion

Baxter is a leading manufacturer of intravenous solutions and administration sets, and other products used to deliver fluids and drugs to patients.

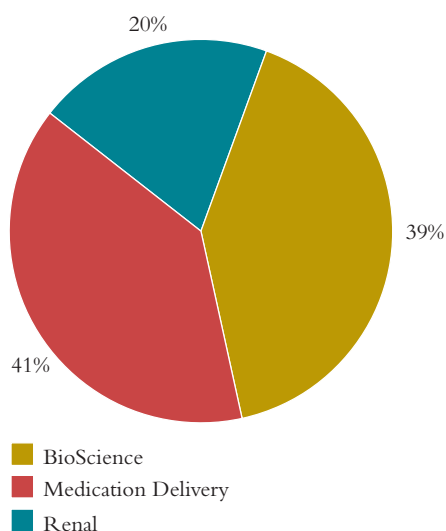
Renal

2005 sales: US\$2 billion

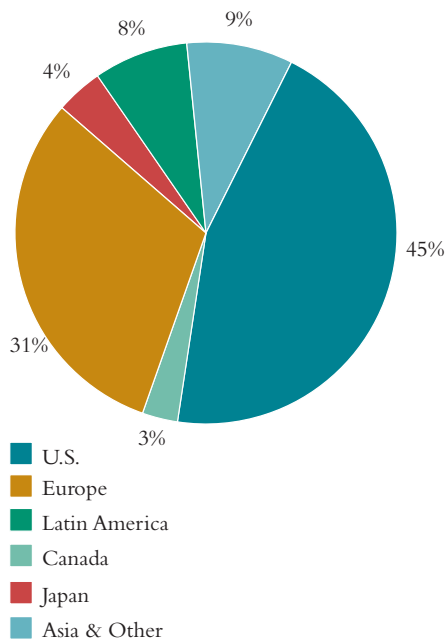
Baxter is a leading manufacturer of products for peritoneal dialysis, a home therapy for people with end-stage renal disease, or irreversible kidney failure.

The following charts are from the Baxter website <www.baxter.com> and from Baxter annual reports.

Baxter sales by business group



Baxter sales by region

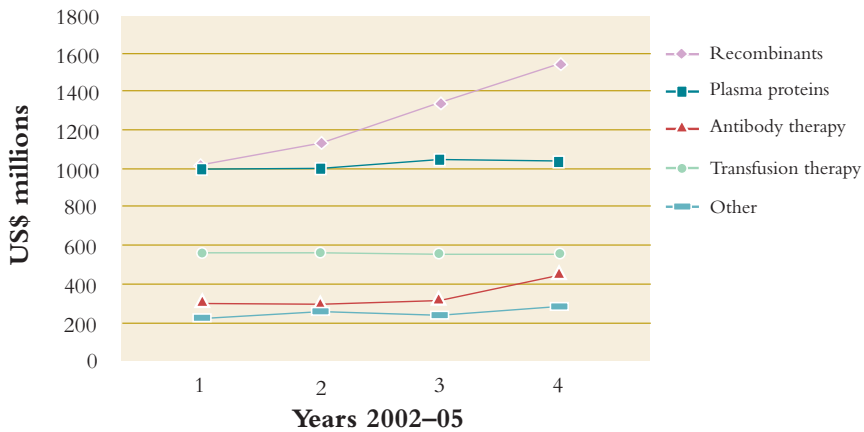


Source: <<http://www.baxter.com>>.

Review of Australia's Plasma Fractionation Arrangements

Plasma derived products are becoming less important to Baxter, as 'the primary driver of sales growth for Baxter BioScience in both 2004 and 2003 was increased sales volume of recombinant Factor VIII products'.³ This trend continued in 2005. The changing mix in product group sales over the years may be illustrated as follows:

Baxter International, Inc. – sales BioScience



From this chart it can be seen that growth in Baxter's BioScience division is being driven by recombinant products, whereas sales for plasma protein/antibody therapy products have grown only slightly over the four-year period, with virtually all growth being recorded between 2004 and 2005. It should also be noted that Baxter secured a license from Cangene, commencing 2005, for the marketing of WinRho™ (SDF) in the United States, a factor that contributed to Baxter's growth in antibody therapy sales.

Talecris Biotherapeutics

Talecris Biotherapeutics is a newly formed company, established in 2005. Two US-based private investment firms, Cerberus Capital Management and Ampersand Ventures, provided the financial backing for the purchase of Bayer's plasma products business, to create Talecris as a business entity. With global headquarters in Research Triangle Park, North Carolina, and primary manufacturing facilities for Talecris products in Clayton, North Carolina, Talecris employs approximately 1600 people.

Talecris marked its first anniversary with significant growth, including the addition of more than 200 employees, and posted 2005 revenues of approximately US\$1 billion. Talecris is the fractionator for the Canadian blood service. In April 2006 Talecris established an office in Toronto, Canada, with headquarters and an additional office in Ottawa. Canadian Blood Services and Héma-Québec chose Talecris to continue delivering on a 60-year-legacy contract arrangement originally established with Bayer HealthCare.

³ Baxter International, Inc., 2004 Annual Report, Baxter, Deerfield, IL, 2004, p. 19.

Review of Australia's Plasma Fractionation Arrangements

Talecris plasma products include: Gamunex, Prolastin, hyperimmune line (Fraction II), Plasbumin (Bayer Albumin), Koate DVI and Thrombate III. The recombinant Factor VIII business comprising the Kogenate product line, for the treatment of haemophilia A, was not part of the transaction with Bayer and remained in the Bayer HealthCare portfolio.

Talecris fractionation capacity has been significantly increased by the addition of the recognised plasma fractionation expertise of Precision Pharma Services and its employees. Precision Pharma had a longstanding relationship with Bayer, providing fractionation services to produce intermediate materials for key products, Gamunex®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified and Prolastin® Alpha1-Proteinase Inhibitor (Human).

In May 2005 Talecris announced that it had become the first plasma fractionator to use an FDA-licensed test to perform in-house nucleic acid testing (NAT) of source plasma for hepatitis B. Talecris is also the first fractionator to conduct in-house testing for Human Immunodeficiency Virus (HIV) and for hepatitis C, using FDA-approved tests.

Grifols

Grifols is a privately owned plasma fractionation company headquartered in Barcelona, Spain. With a production capacity of 3.4 million litres annually, Grifols is one of the six largest global fractionators. The company maintains fractionation plants in Spain and in the United States.

Octapharma

Octapharma, which is based in Lachen, Switzerland, is one of the largest privately owned plasma products companies in the world and is an independent plasma fractionation specialist. Octapharma's core business is the development, production and sale of plasma derivatives.

Since its founding in 1983, Octapharma has become one of the key players in the global plasma products market, with sales in over 70 countries. Octapharma maintains manufacturing facilities in five countries. Today, the company has more than 1482 employees and has experienced year-on-year growth.

Vienna, Austria, is home to one of Octapharma's production plants, and to the company's Plasma Quality Control and Assurance and International Clinical and Regulatory Affairs functions. Octapharma has other production facilities in Lingolsheim, France, and Stockholm, Sweden. Octapharma owns a fractionation plant in Mexico that produces products exclusively for the local market.

In addition, Octapharma operates the plasma fractionation plant of DRK PVG in Springe, Germany, the blood fractionation company owned by NSTOB, and other German Red Cross blood transfusion services.

Review of Australia's Plasma Fractionation Arrangements

Plant	Capacity	Staff	Starting batch size
Vienna	850 tonnes	500	2750 litres
Stockholm	500 tonnes	400	1200 litres
Lingolsheim	400 tonnes	275	1400 litres
Springe	450 tonnes	70	1200 litres

While Europe is still its principal market, Octapharma has trading partners throughout the world, and new business opportunities have been developed in Asia, South America, North America, the Middle East and Russia. Octapharma continues its expansion, most recently establishing Octapharma sales offices in the United States, Australia, New Zealand, Poland, Finland and China.

Octapharma obtains plasma as raw material for its products from approved blood banks and plasma collection centres in Austria, Germany, Sweden and the United States. The combined annual plasma fractionation capacity of the company's plants exceeds 2.2 million litres. Included in this figure is the capacity to produce 110 000 litres of SD-treated plasma. Octapharma has indicated that it plans to expand capacity to 3 million litres.

Octapharma research and development centres are located at Vienna (Corporate Product Development, Pre-Clinical and Clinical Research and Development), Stockholm (Pre-Clinical and Clinical Research and Development), Berlin (Molecular Biochemistry), Frankfurt (Virus and Prion Validation) and Munich (Recombinant Products and Gene Therapy).

Octapharma reports that its research and development groups are currently working on more than 100 projects. The three lead products to which research and development focus is being given are:

- alpha – 1 antitrypsin (A1AT)
- Uniplas® – a unique universally applicable virus-inactivated plasma for transfusion
- a high – yielding liquid intravenous immunoglobulin

With the founding of a new research company, Octagene, Octapharma also seeks to enter the field of gene therapy.

After two years of consolidation, 2005 saw a 22% increase in Octapharma's sales, which have reached Euro 410 million (A\$724 million). The launch of two new products in Europe: Wilate® (von Willebrand factor/Factor VIII concentrate) and Octaplex® (prothrombin complex concentrate) contributed to a successful year for the company in 2005. Furthermore, its US subsidiary achieved sales of approximately US\$100 million – a significant increase over levels for 2004, chiefly through sales of the product Octagam®.

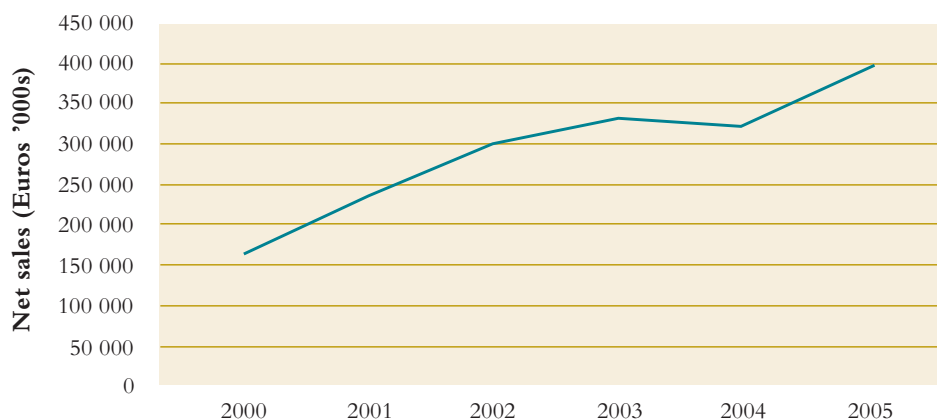
Review of Australia's Plasma Fractionation Arrangements

Octapharma established a representative office in Beijing in March 2006. Entry into the Chinese market began with albumin, which to date is the only plasma product that China permits to be imported.

In 1995, 95% of Octapharma's sales were within Europe. Today the European market accounts for only 63% of sales. Octapharma expects that European sales will represent less than 50% of total sales within the next three years.

An examination of Octapharma's financial results over the period 2001–05 reveals a company experiencing a strong overall growth phase when measured by a range of indicators. However, on a year-to-year basis, Octapharma experienced sluggish financial growth in 2003 and 2004, as evidenced by substantial contraction in operating income and return on equity. The results were consistent with a general industry downturn, caused by the collapse of global prices for IVIg in particular during this period. In 2005 Octapharma recorded a significant profit increase as represented by the following chart.

Octapharma net sales (in Euros '000s)



Source: <<http://www.octapharma.com>>.

Key milestones

- 1999** Acquisition of plasma fractionation plant at Lingolsheim
- 2002** Acquisition of Biovitrum's plasma business in Sweden
- 2003** Acquisition of Pro bifasa SA, a Mexican plasma fractionation company
Opening of Octapharma subsidiaries in United States and Spain
- 2004** Octagam® approved in United States
First virus-inactivated universally applicable transfusion plasma – Octaplas®
Opening of Octapharma Australia and New Zealand
- 2005** First double virus-inactivated Factor VIII/von Willebrand factor concentrate product

Kedrion

Kedrion is a global fractionator with plants located in Italy. Kedrion markets its range of plasma derived products throughout Europe and in export markets, principally in the Middle East and South America. Kedrion has a reported annual throughput capacity of 1.2 million litres.

Laboratoire Français du Fractionnement et des Biotechnologies (LFB)

The Laboratoire Français du Fractionnement et des Biotechnologies (LFB) is a not-for-profit organisation managed and owned by the French Government. LFB was created under law on 4 January 1993 and is one of Europe's leading pharmaceutical laboratories for the manufacture of plasma derived medicinal products. France is self-sufficient in most plasma derived products. LFB is legislated to be the sole fractionator for all plasma from blood collected in France.

LFB has two processing plants, at Lille and at Les Ulis (Paris). LFB's total capacity is 800 000 litres. LFB processed 650 tonnes of plasma in 2005. LFB's toll fractionation clients include Red Cross of Luxembourg, National Blood Transfusion Centre of Morocco, Red Cross of Belgium, National Blood Transfusion Centre of Tunisia and the Ministry of Health of Brazil.

A French ruling of 28 July 2005 converted LFB from a Groupement d'Intérêt Public (GIP – public interest group) into a Société Anonyme (SA – limited company) with majority state-owned capital. LFB keeps its public health mission, which includes the obligation to give priority to meeting French needs.

LFB is the only laboratory in France that manufactures a wide range of products that includes albumin and immunoglobulins as well as products for the treatment of rare pathologies, such as those defined in the European Program on Rare Diseases. LFB produces a suite of 19 plasma derived therapeutic products, including hyperimmunes.

LFB has 1250 employees, 200 of whom are employed in research and development, and in 2005 recorded a Euro 253 million sales turnover. As a state-owned organisation, LFB does not publish its financial results. However, based on material provided to the Review and on observations made by the Review's European fact-finding mission, it would seem that the French Government has a firm commitment to the continued operation of LFB and to its international expansion. There have been substantial investments in new infrastructure during recent years, which have produced a state-of-the-art fractionation facility at Lille.

Bio Products Laboratory (BPL)

Bio Products Laboratory (BPL) is a not-for-profit organisation, wholly owned by the British Government. BPL's research, development, manufacturing and UK and overseas marketing departments are all based at Elstree on the outskirts of London. BPL is in a unique position in that since 1998 – despite having been established as a national fractionator – it has been prohibited from fractionating domestically sourced plasma, due to the incidence of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom.

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The Department of Health's purchase of Life Resources, the largest remaining independent US plasma collector, ensured the long-term supply of non-UK-derived plasma for all BPL customers. Life Resources maintains 24 plasma collection centres in the United States and has its head office in New York.

The capacity of the BPL plant is 750 000 litres; current utilisation is relatively low, with a throughput of 400 000 litres per annum (53% of capacity). BPL currently supplies 45% of all plasma derived products required by the UK National Health Service and has been using US plasma since 1998 as part of the vCJD risk reduction strategy. The United States, which collects 70% of the world's plasma, is the only country capable of supplying the quantity of plasma that BPL requires. BPL relies on exports principally to South America, the Far East and the Middle East for 50% of annual sales revenue.

The National Health Service Blood and Transplantation (NHSBT) has overall responsibility for National Blood Authority (NBA), BPL, the Blood Centres in England and Wales and the International Blood Group Reference Laboratory (IBGRL). The NBA is directly responsible to the NHS and Department of Health.

BPL has expressed interest in the possibility of fractionating Australian plasma. Financial information relative to the operations of this state-owned company is not published. The Review's European fact-finding mission visited the Elstree site. It is known that the production facility was commissioned in 1988 and is therefore well advanced in its economic life cycle.

The future of BPL is somewhat clouded by the current government review of the fractionator's operations. A facility operated by PFC (a division of Scottish National Blood Transfusion Service) in Edinburgh is to close in 2006, following a review. Recent cost-cutting exercises and an aggressive three-year development plan are in place to ensure the continuing viability of BPL.

Sanquin

The Sanquin Blood Supply Foundation is a Dutch not-for-profit organisation that provides blood and blood product supplies and promotes transfusion medicine. Sanquin provides products and services, carries out fundamental and developmental research, and employs about 3000 people.

Under the mandate provided by the Netherlands Government, Sanquin operates a network of blood collection and blood bank sites across the country. The blood banks manufacture fresh blood products, which are provided directly to hospitals. The blood banks also recover plasma, both for fresh frozen plasma usage in hospitals and for fractionation by Sanquin. All plasma gathered in the Netherlands, apart from that required for fresh frozen plasma purposes, is retained by Sanquin for fractionation into finished therapeutic products.

Sanquin has a partnership arrangement with the Belgian Red Cross for the fractionation of Belgian plasma into some of that country's finished product requirements. Sanquin has also recently undertaken toll fractionation on behalf of Finland, following the country's decision to close its domestic fractionation facility.

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If the outcome of negotiations is positive, Sanquin will integrate the manufacturing activities of its Plasma Products Division into Biotest Pharma GmbH, currently a subsidiary of Biotest AG, with Sanquin receiving a share in this company in return. If this transaction were to proceed, the Biotest Group would own a majority shareholding in Biotest Pharma GmbH and the company would be included in the Group's scope of consolidation. Biotest and Sanquin would continue to operate independently in the sales of pharmaceutical plasma products. The other business segments of Biotest would not be part of the deal. Similarly, the activities of Sanquin, securing self-sufficiency in the Netherlands for (cellular) blood components and plasma products, would not be affected.

Annex E

Secretariat, clinical advisers and Review consultants

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Annex F

Acronyms and abbreviations

ABDR	Australian Bleeding Disorders Registry
ACG	Allen Consulting Group
ADEC	Australian Drug Evaluation Committee
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
AHCDO	Australian Haemophilia Centre Directors' Organisation
AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
AIDS	Acquired Immune Deficiency Syndrome
ANZTPA	Australia New Zealand Therapeutic Products Authority
ARC	American Red Cross
ARCBS	Australian Red Cross Blood Service
ARTG	Australian Register of Therapeutic Goods
AUSFTA	Australia–United States Free Trade Agreement
BPL	Bio Products Laboratory
BSE	bovine spongiform encephalopathy
C1-INH	C1 inhibitor
CBS	Canadian Blood Services
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CJD	Creutzfeldt–Jakob disease
CMV	cytomegalovirus
CVID	common variable immunodeficiency
DGG/DGM	Directoraat Generaal Geneesmiddelen/Direction Générale Médicaments (Belgium)
EC	European Council
EC MRA	Australia–European Union Mutual Recognition Agreement
EFS	Établissement Français du Sang

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EFTA MRA	Australia–European Free Trade Association Mutual Recognition Agreement
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypass Agent
FFP	fresh frozen plasma
GMP	Good Manufacturing Practice
HANE	hereditary angioneurotic oedema
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDN	Haemolytic Disease of the Newborn
HFA	Haemophilia Foundation Australia
HIV	Human Immunodeficiency Virus
HMOs	Health Maintenance Organizations
HSANZ	Haematology Society of Australia and New Zealand
IFE	Import for Export
IMiG	intramuscular immunoglobulin
ITP	idiopathic thrombocytopenic purpura
IU	international units
IVD	In-vitro diagnostic
IVIg	intravenous immunoglobulin
JBC	Jurisdictional Blood Committee
LFB	Laboratoire Français du Fractionnement et des Biotechnologies
LPDs	lymphoproliferative disorders
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
NBA	National Blood Authority
NBS	National Blood Service (United Kingdom)

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NHMRC	National Health and Medical Research Council
NHS	National Health Service (United Kingdom)
NRL	National Serology Reference Laboratory
NZBS	New Zealand Blood Service
PCC	prothrombin complex concentrate
PIC	Pharmaceutical Inspection Convention
PID	primary immune deficiency
PPA	Plasma Products Agreement
RFT	Request for Tender
SCIg	subcutaneous immunoglobulin
SECTSE	Special Expert Committee on Transmissible Spongiform Encephalopathies
TGA	Therapeutic Goods Administration
TSEs	Transmissible Spongiform Encephalopathies
TSEAC	Transmissible Spongiform Encephalopathies Advisory Committee
vCJD	variant Creutzfeldt-Jakob disease
vWD	von Willebrand's disease
WFH	World Federation of Hemophilia
WHA	World Health Assembly
WHO	World Health Organization

Annex G

Glossary

Albumin The major protein in plasma, which is important in maintaining blood volume via osmotic pressure.

Antibody A protein, an immunoglobulin, produced by the immune system and found in the blood in response to the presence of antigens.

Antigen A substance, often a foreign protein, that stimulates the immune system to form an antibody.

Anti-(Rh)D antibody Antibody against the Rhesus blood group D-antigen.

Apheresis A procedure in which whole blood is temporarily withdrawn from a donor, one or more of its components are selectively removed, and the remainder of the blood is then reinfused into the donor.

Autologous donation Blood donation for the donor's own use.

Biologicals Medicines or medical devices derived from human or animal tissues.

Blood components Therapeutic components that have been manufactured from blood; these include red cells, white cells, platelets and plasma for transfusion.

Blood group Complex chemical substances, found on or in the surface of red cells, distinguish each blood group. The two more important blood group systems in transfusion work are the ABO (blood types A, B, O and AB) and the Rh(D) systems.

Bovine spongiform encephalopathy (BSE) An infection of the nervous system in cows. Also known as 'mad cow disease'.

Chromatography Process by which plasma is separated into its components, based on size, charge or other chemical properties, via interaction with a 'gel', which provides the basis for the separation.

Coagulation factors Proteins that when activated function as enzymes, leading to the production of thrombin and then fibrin, which together with platelets form a thrombus or clot that prevents loss of blood after vessel injury.

Code of Good Manufacturing Practice (GMP) A set of standards that provide assurance that a manufacturer has a quality system in place that meets the requirements for the product being made.

Cold-ethanol fractionation Often referred to as Cohn fractionation, this process involves the addition of varying concentrations of ethanol to cooled plasma in order to precipitate fractions, which are further purified into individual plasma products.

Creutzfeldt-Jakob disease (CJD) A central nervous system disease that causes presenile dementia, neurological degeneration and distinctive electroencephalographic changes, caused by an abnormal prion.

Cross-match A term used when testing the patient's serum against the donor's red cells to ensure compatibility prior to blood transfusion.

Cryoprecipitate A clotting factor preparation derived from plasma. It includes Factor VIII and fibrinogen and may be used in the treatment of massive bleeding and, occasionally, for the treatment of haemophilia A and von Willebrand's disease.

Directed donation Donations of blood from relatives or friends of a recipient that are specifically requested to be given to that recipient.

Factor VIII A clotting factor that, as a concentrate, is used to treat haemophilia A (classic haemophilia).

Factor IX A clotting factor that, as a concentrate, is used to treat haemophilia B (also known as Christmas disease).

Fibrinogen A soluble protein in blood plasma that is involved in the clotting mechanism and that when activated by thrombin becomes fibrin.

Fractionation The separation of a substance into its basic constituents.

Haemolysis The breakdown of red cells with the release of haemoglobin. Normally occurs at the end of the life span of a red cell. Haemolysis may occur in red cell antigen/antibody reactions.

Haemolytic Disease of the Newborn (HDN) A disease that can arise when there is incompatibility between the red cells of a foetus and those of the mother.

Haemophilia A hereditary deficiency of clotting factors in blood (usually referred to as haemophilia A or haemophilia B).

Haemovigilance Monitoring of untoward transfusion events and outcomes in hospitals.

Hepatitis B Viral inflammatory disease of the liver caused by the hepatitis B virus.

Hepatitis C Viral inflammatory disease of the liver caused by the hepatitis C virus. Now the most commonly reported notifiable disease in Australia.

Homologous blood Blood donation given for transfusion to an unknown recipient.

Hyperimmune immunoglobulins Immunoglobulin products prepared from the plasma of donors with high concentrations of specific antibodies.

Immunoglobulins Plasma proteins that combat infection.

Inhibitors Acquired antibodies that recognise as foreign clotting factors that have been administered as replacement therapy. Inhibitors attack and neutralise the Factor VIII or Factor IX that has been introduced into the body or even the patient's own Factor VIII or Factor IX.

Intramuscular immunoglobulin (IMiG) An immunoglobulin preparation designed for intramuscular rather than intravenous use.

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Intravenous immunoglobulin (IVIg) An immunoglobulin designed for intravenous use.

Leucodepletion Removal of white cells from blood.

Licensing (or certification) audit Initial audit conducted by the Therapeutic Goods Administration to confirm that a manufacturer has complied with mandated requirements.

Memorandum of Understanding (MOU) A legal document that establishes a bilateral agreement between parties but is not a binding agreement and is not enforceable at law.

Mutual Recognition Agreement (MRA) An international agreement by which two (or more) countries agree to recognise and accept the findings of each other's conformity assessment bodies (e.g. regulatory agencies for medicinal products).

Nanofiltration A filtration process, used in the manufacture of plasma products, that can remove small particles such as a virus.

Pathogen Disease-causing agent.

Pharmaceutical Inspection Convention (PIC) PIC is a formal treaty between countries. PIC members are legally bound to recognise the manufacturer inspections of PIC members. Australia joined the convention in 1993.

PIC Scheme An informal cooperative arrangement between national health authorities, having no legal status. Its purpose is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of auditors.

Plasma Liquid portion of blood that contains proteins and electrolytes.

Plasmapheresis Automated procedure for removing whole blood from the donor, separating and collecting the plasma, and returning the remaining components to the donor.

Plasma starting pool Pool of numerous units of donated plasma used to manufacture a batch of plasma derived products.

Platelet One of the cellular components of blood that contribute to haemostasis and blood clotting.

Prion Protein that occurs normally in many organs and tissues, including the brain, spinal cord and eye of healthy humans and animals.

Recombinant product Recombinant products are produced by inserting a human gene into a cell line, which then synthesises the required human protein (e.g. Factor VIII or Factor IX). This product is then harvested from the supernatant for clinical use.

Recovered plasma Plasma obtained, after centrifugation, from whole blood donations.

Source plasma Plasma obtained through plasmapheresis.

Special Access Scheme Arrangements that provide for the import and/or supply of an unapproved therapeutic good for a single patient on a case-by-case basis.

Sponsor (product sponsor) Australian importer, exporter and/or supplier of a therapeutic good. The sponsor is required to be a resident of Australia, or registered as a business in Australia.

Therapeutic donation Where individuals with specific haematological conditions reduce their blood volume through controlled venesection.

Tolerisation The procedure of administering high doses of clotting factors to swamp inhibitors or other antibodies. Tolerisation may be used in a general immunological sense for failure of a person to respond to a foreign antigen.

Toll fractionation Exporting of plasma for fractionation, whereby plasma collected in one country is processed in another on a fee-for-service basis.

Transmissible spongiform encephalopathies (TSEs) A group of transmissible infections of the nervous system caused by an abnormal prion; TSEs including Creutzfeldt-Jakob disease and bovine spongiform encephalopathy.

Variante CJD A form of Creutzfeldt-Jakob disease, thought to be caused by eating beef infected with bovine spongiform encephalopathy ('mad cow disease').

