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.

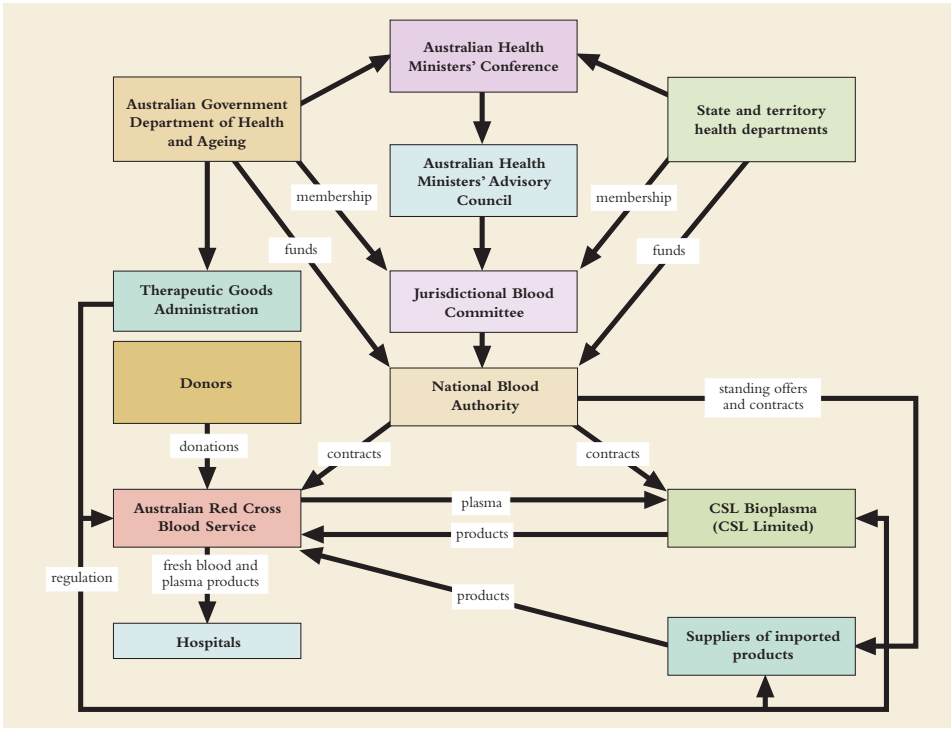
In line with the National Blood Agreement, and its aim of promoting national self-sufficiency in blood and blood products (the objectives and aims specified in the Agreement are outlined in the Introduction to this report), imported plasma products are supplied in Australia only when domestically fractionated 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>.

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.

- 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>.

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.

9 See National Blood Authority, *Annual Report 2005–06*.

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

10 Section 19Q in Division 4 of the CSL Act, as amended by the *CSL Sale Act 1993* (Cwlth), also makes provision for performance under the PPA.

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

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.

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

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.

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.