Submission to the Review of Australia's Plasma Fractionation Arrangements

April 2006

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Executive Summary

This review of Australia's plasma fractionation arrangements is being undertaken by the Australian Government as part of their commitments under the Australia-United States Free Trade Agreement (AUSFTA), to consider whether this fractionation process should be opened up to competition as part of the FTA.

Currently all plasma collected by the Australian Red Cross Blood Service (ARCBS) is sent to an Australian company, CSL Limited, for fractionation in Australia.

Due to regulations applied by the Therapeutic Goods Administration (TGA), plasma from Australian donors is fractionated in exclusive and specific use containers (columns) to ensure the best possible safety profile for Australians who require plasma products.

The ARCBS would be concerned if competition means that Australian plasma generously and freely provided by Australian donors was shipped off shore for fractionation, then to be returned to Australia.

This possibility raises questions concerning safety and quality of the plasma products, costs, Australian capability, national security and – of fundamental importance to the ARCBS – the impact on our Australian donors and ultimately, their willingness to continue to donate.

The ARCBS questions why 'competition' needs to be introduced into a system which has served Australia well by providing one of the safest blood systems in the world.

The ARCBS believes fractionation of Australian plasma to meet Australia's need for plasma products must be undertaken on Australian soil. This does not contravene World Trade Organisation (WTO) guidelines, which enable countries to have country specific national requirements for the protection of public health and safety.

Australia has learned from its experiences of world war, the threat of exotic diseases to humans, flora and fauna, and more recently, terrorism, that its geographic isolation requires that it must have its own national capacity to meet essential services' needs. Certainty in the supply of the safest blood and plasma products is fundamental to the national interest.

Australia is fortunate already to have in place fractionation capacity and a voluntary donor base to enable it to be self-sufficient in meeting demands for fresh blood and plasma products. This capacity not only enables Australia to meet its commitments as a signatory to the World Health Assembly resolution that countries aim for self-sufficiency in blood and blood product requirements, but that they do so using voluntary donations from unremunerated donors in their own countries.

Australia has, because of the generosity of Australians, perhaps the safest blood collection in the world. We have been self-sufficient in meeting our needs for blood and most plasma products in the past, and have the capacity to meet these needs now and in the future.

The Australian Government Department of Health and Ageing has as its guiding principle that Australia have the safest blood system possible.

The ARCBS believes that there are safe, safer and safest models for national blood supplies.

Australia has the safest model because of the integrated nature of our blood system. It is the safest because:

- we have our own Australian voluntary, non-remunerated donors;
- we have our own Australian based fractionator;
- we have a strong, active, vigilant, national regulator of fractionation operations, armed with powerful domestic sanctions, including criminal penalties; and
- we have the requirement for Australian plasma to be segregated from other potentially more pathogenic collections through the use of exclusive fractionation columns.

Australia has, as a result of this domestic integration, an openness and transparency amongst clinicians, Australian health institutions, researchers, the ARCBS, the domestic fractionator and the TGA, generating an unprecedented level of cooperation and commitment to free exchange of information. It engenders a high degree of confidence amongst critical players in the blood system, providing a fundamental strength to the Australian blood system that ultimately benefits Australian users and potential users of blood products.

The ARCBS believes that Australian governments should only ever allow importation of plasma products where shortages occur, or for niche products which are not available domestically. The deliberate strategy of importing an increasing proportion of blood products by purchasing off-the-shelf finished product, utilising plasma sourced from paid donor collections, provides a less safe blood system.

The ARCBS further believes that the Australian Government should immediately reverse this strategy and resume its commitment to 100% reliance on Australian-sourced voluntary, non-remunerated blood donations for its plasma product needs. Any risk of supply interruptions because of a domestic manufacturing failure is best mitigated by having an adequate National Reserve capacity of domestic product to meet both potential product shortages as well as contingency needs.

1 Introduction

The Australian Red Cross Blood Service (ARCBS) is a key player in ensuring Australians have access to blood and blood products that meet the needs of Australians.

While the risk of infection from blood or blood products in Australia is, and has generally been, very low by world standards, the ARCBS recognises that there are residual risks which cannot be eliminated. Each step in the process from donor recruitment through to transfusion to the patient for both blood and blood products brings with it some risk, however small.

In Australia, blood is collected and manufactured from Australian donors under the most stringent safety and quality requirements, based on world's best practice regulation by Australia's Therapeutic Goods Administration (TGA).

The guiding principle set down by the Australian Government Department of Health and Ageing (DoHA) has always been to maintain the safest possible blood supply.[1]

This principle is shared by the ARCBS, and is further underpinned by Australia's long-standing commitment to self-sufficiency[2] in blood and blood products sourced from Australian voluntary, non-remunerated donors.

The ARCBS and the Australian Red Cross (ARC), of which the ARCBS forms its part, hold these factors to be non-negotiable guiding principles.

In essence, to have the safest blood supply possible, the ARCBS is of the view that:

- the commitment to Australia being self-sufficient in blood and blood products must be maintained;
- the commitment to sourcing blood and blood products from voluntary unpaid donors must be maintained;
- there must be no diminution in the pursuit of the safest possible blood supply in Australia; and
- the public's confidence in the blood supply is critical to the quality and safety of the Australian health system.

It is, therefore, important the Review Committee has as the overriding objective in the framing of its conclusions, to ensure not just a safe blood supply for Australia, but the safest blood system possible.

[1] Australian Government Department of Health and Ageing, 'Submission to the Senate Community Affairs References Committee Inquiry into Hepatitis C and Blood Supply in Australia', 2004.

[2] *ibid.*

2 Background to the review and terms of reference

The Review of Australia's Plasma Fractionation Arrangements was established by the Minister for Health and Ageing, the Hon Tony Abbott, MP, as a requirement of the Australia-United States Free Trade Agreement (AUSFTA) that came into effect on 1 January 2005.

In a side letter to the AUSFTA, Australia committed to undertake a review of its current contractual arrangements for supply of plasma fractionation services by 1 January 2007. Procurement of plasma fractionation services is currently excluded from coverage of the Government Procurement Chapter applying to the purchase of goods and services by listed government agencies.

Under the terms of the side letter, the Australian Government is obliged to recommend to the States and Territories that, in future, suppliers of such services be selected through tender processes consistent with the Government Procurement Chapter of the AUSFTA. If agreed by States and Territories, Australia has undertaken to remove this exclusion from the Government Procurement Chapter.[3]

Importantly, the side letter acknowledges:

- the right of governments to have self-sufficiency policies consistent with Australia's present policy for use of plasma collected from Australians in Australia; and
- the role of Australia's regulator of blood and blood products, the TGA.

The terms of reference for the Review are at Attachment 1 and Attachment 2 lists additional issues for comment, required by the Review secretariat, by the ARCBS. In summary, 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 key elements the Review has been asked to address follow.

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.

[3] Australian Government Department of Foreign Affairs and Trade (2005), 'United States – Australia Free Trade Agreement – Guide to the Agreement'

3 Current Australian blood system arrangements

3.1 Overview

The Australian blood supply system is based on goodwill.

Donation of blood is voluntary and no payments are made to donors, nor are recipients charged for supplies of blood or blood products. The ARCBS is the sole collector of blood from Australia's voluntary donors for both fresh blood use in blood transfusions and for input to plasma fractionation manufacturing processes in Australia.

The ARCBS not only distributes fresh blood for use in hospitals, it is also the major distributor of plasma products.

CSL Limited is the sole domestic fractionator of plasma collected in Australia.

The TGA regulates the safety, quality and efficacy of plasma products.

In Australia, the manufacture of most plasma derived products is currently funded through a single supplier arrangement between the National Blood Authority (NBA), acting on behalf of all nine Australian jurisdictions, and CSL Limited. These products are sourced from the domestic blood supply and are manufactured in Australia. It is current Australian Health Ministers' policy that plasma products are imported only when domestic supply cannot meet clinical need, or where supply chain risks must be addressed.[4]

The role of the NBA is to manage the national supply and the funding agreements with the ARCBS and CSL Limited, and to report regularly to Australian Health Ministers on progress with administration of the agreements and outcomes.

The National Blood Agreement between the Australian Government and all State and Territory governments provides the framework for funding and policy for Australia's supply of blood and recombinants, including plasma products.

The primary policy objectives of the National Blood Agreement 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.

3.2 Plasma Fractionation in Australia

The Commonwealth Serum Laboratories, as CSL Limited was originally named, was established in 1916 to ensure Australia had a continuing supply of biological agents, including vaccines to prevent diseases such as diphtheria, tetanus, typhoid, plague and whooping cough. In 1949, the Commonwealth Government decided that fractionation of blood should be undertaken in Australia.

[4] Australian Health Ministers Council, Meeting of 7 April 2006

The Commonwealth Serum Laboratories, when fully funded by the Australian Government, and later CSL Limited, has provided plasma fractionation services to the Australian community since1953. CSL Limited is the sole fractionator of all Australia's plasma collections. It provides plasma fractionation services under the Plasma Products Agreement managed by the NBA. The need for a national fractionator to safeguard the national interest was recognised by the Stephen Review[5] which, in 2001, concluded that Australia's future plasma fractionation needs are best met domestically.

[5] Commonwealth of Australia (2001), Review of the Australian Blood Banking and Plasma Product Sector, Canberra

4 The Role of the Australian Red Cross Blood Service

The ARCBS is an integral part of the Australian Red Cross and collects blood from voluntary, non-remunerated donors …

The ARCBS is an operating division of the Australian Red Cross Society (ARCS) and, as such, is part of the worldwide humanitarian movement of the International Federation of Red Cross and Red Crescent Societies.

It is the national organisation responsible for providing the Australian community with safe, high quality blood products and related services, sourced solely from Australia's volunteer blood donors. The ARCBS distributes blood and blood products to hospitals 24 hours a day, 365 days a year.

… the ARCBS is the owner of the blood collected and any blood products manufactured from it …

Australia's voluntary donors vest ownership of their gift of blood in the ARCBS.

As the owner of these blood collections, the ARCBS is the legal entity responsible for meeting Australia's regulatory requirements and for the distribution of the blood and blood products subsequently manufactured from them.

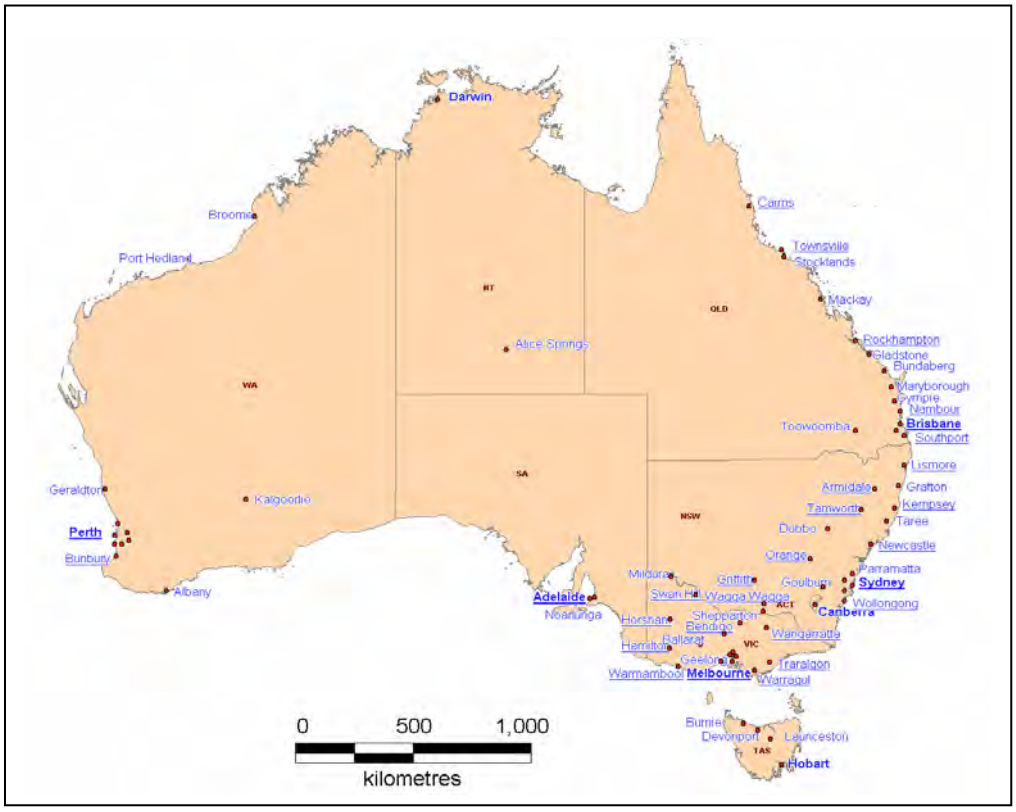
The ARCBS has an obligation to donors to ensure the optimal and ethical use of their precious gift to ARCBS. This stewardship role extends both to ensuring blood is used appropriately and that wastage of blood is minimised. ARCBS medical specialists play a key role in ensuring appropriate clinical use of blood components and plasma products, as well as providing expertise on management of adverse reactions, hospital inventory management and clinical supply planning.

… The ARCBS operates nationally and is supported by Australians from all walks of life …

More than half a million voluntary blood donors, around 2,500 dedicated volunteers and full time equivalent staff of 2,355 deliver a national blood service which is essential to Australia's health system. The ARCBS has the prime advocacy role for donors and in particular, donor safety in Australia.

There are 119 ARCBS dedicated collection centres, including mobile facilities, throughout Australia as shown in Figure 1. There are approximately 1000 individual donor panels established and accessible to the ARCBS throughout Australia.

Figure 1: ARCBS collection centres



The ARCBS also provides vital services related to organ and tissue donation and tissue typing for transplantations. In these areas it works closely with a number of peak not for profit organisations and others in the health sector to ensure availability of these services to patients in need.

… The ARCBS plays a key role in relevant research …

ARCBS services are also supported by a research program covering issues such as clinical transfusion practice, new and emerging diseases, introduction of new tests and enhanced blood component manufacturing processes.

Donor research is a key area of interest and involves the investigation of long term cultural and behavioural trends in social capital and donor motivation to assist with preparing effective ways to maintain a safe and sufficient donor panel. This research uses psycho-social indicators to develop future recruitment and retention campaigns and helps to inform ARCBS responses to issues such as more stringent donor eligibility criteria, emergent diseases and changes in community attitudes to blood donation. It also assists with the development, sustenance and support for new and existing donor panels and future market segmentation.

… The ARCBS uses Australia's domestic fractionator, CSL Limited, to provide its fractionation services …

The involvement of both the ARCS and CSL Limited in the blood sector grew out of Australia's war efforts. CSL was originally the Commonwealth Serum Laboratories, established in 1916 as a public sector entity to ensure Australia had a supply of biological products and reagents (such as vaccines and blood typing diagnostics). Since 1994, CSL has been a public company, CSL Limited.

Modern medical practice rarely involves transfusion of whole blood. Accordingly, the ARCBS separates whole blood into its major cellular components and the liquid portion called plasma. Only those specific components of blood that are needed in a particular clinical situation are transfused, for example, red cells or platelets or plasma.

The ARCBS sends the vast bulk of the plasma it collects to CSL Limited for fractionation. The fractionation process extracts the specialised proteins contained in plasma, such as albumin, specific clotting factors, or immunoglobulins. Some fresh frozen plasma is retained by the ARCBS for distribution direct to hospitals.

Plasma products have a much longer shelf life than fresh blood components. Their manufacture involves a much longer lead time – taking many weeks – and each finished product is manufactured from pools of many thousands of plasma donations. Pooling, together with the fact that many patients require very frequent use of some plasma products, increases the level of any residual risk remaining in the donor pool following testing and manufacturing processes.

… the ARCBS believes confidence in the safety of the blood system is its primary objective.

Hence, the primary objective of the ARCBS is to ensure Australia's blood supply is managed in a way that maintains people's trust, commitment and confidence by providing the safest blood supply possible. To this end, the ARCBS has been at the forefront around the world in introducing improved testing regimes and other measures to reduce residual risks at the earliest opportunity.

Security, affordability and accessibility of supply of quality blood and blood products are also critical elements of this objective.

The ARCBS transfusion medicine team provides the key link between external health professionals and the ARCBS, acting as the donor's advocate by ensuring appropriate clinical use is made of the donor's gift and as the patient advocate by always maintaining the highest possible standard of safety in manufacturing balanced against sufficiency of supply. The aim is to promote appropriate use of blood and blood products by reviewing blood usage patterns, promoting best transfusion practice and encouraging strategies to reduce wastage of blood components. This is achieved by working in partnership with a wide range of healthcare professionals, including clinicians, hospital blood bank managers and nurses who administer transfusion to patients.

Prior to the establishment of the NBA in July 2003 the ARCBS received its funding through individual State and Territory Health departments, despite having been established as a national organisation in 1996. This presented the ARCBS with many operational challenges related to historical funding bases, different jurisdictional attitudes to manufacturing strategies and product priorities, and strategic direction.

Despite ARCBS being a national organisation, the clinical supply plan for both fresh blood components and plasma products is based on a composite of both State and Federal systems, whereby the relevant State Health Minister approves the local plan. As a result, differences in equity of access in both blood product quality (such as access to pre-storage leucodepleted platelets) and quantity exist.

The establishment of the NBA has enabled the ARCBS to introduce more cohesive and nationally efficient responses to the provision of blood services.

5 Relevant findings of the Review of the Australian Blood Banking and Plasma Product Sector to the terms of reference

The Rt Hon Sir Ninian Stephen, KG AK GCMG GCVO KBE chaired a review of the Australian blood system to examine and report on the safety and quality of the production and supply of blood and blood products for use in the Australian health care system.

The ARCBS strongly believes the findings of the Stephen Review remain highly relevant and applicable to this Review of Australia's Plasma Fractionation Arrangements.

The Stephen Review involved a comprehensive examination of that part of the health system responsible for meeting Australia's blood and blood product needs. It assessed current and future needs, and advised on areas for improvement, related to:

- the giving of blood by volunteer donors;
- collection, testing and banking of blood;
- processing and production of blood and plasma products; and
- distribution and clinical use.

The Review findings were released in March 2001 and included an examination of the principle of self-sufficiency in relation to the supply of plasma products and Australia's plasma fractionation industry.

In 2001 the Stephen Review endorsed the role of the ARCBS …

The Review endorsed the provision of the national blood service by the ARCBS based on the giving of blood by voluntary non-remunerated donors..

… and the importance of self-sufficiency …

Stephen noted that self-sufficiency should remain an important national goal for Australia, recognising that it is a national and international obligation and responsibility.

… including only importing as a strategy for plasma product shortfalls …

Stephen concluded the importation of foreign-sourced plasma was not recommended as a strategy for meeting Australia's plasma product shortfalls. Stephen observed that Australia's achievement of near self-sufficiency in its supply of blood and plasma products gives Australia a high level of control over the quality of future supplies and that given these circumstances, continuing high levels of safety and quality should be achievable "as long as careful national policy measures and strong regulatory oversight are maintained".[6]

[6] Commonwealth of Australia (2001), Review of the Australian Blood Banking and Plasma Product Sector, Canberra, p.xi.

… and that Australia should continue to use CSL Limited in Australia for its plasma product needs …

Most cogently, Stephen found "Australia's future plasma fractionation needs are best met through the national facility operated by CSL".[7]

Stephen recommended the Australian Government should enter a second Plasma Fractionation Agreement with CSL Limited to ensure Australia's future needs for plasma products are met.

… these findings are highly relevant to the Plasma Fractionation Review.

The ARCBS believes the findings of the Stephen Review are still as relevant and applicable today as they were in 2001.

[7] Commonwealth of Australia (2001), Review of the Australian Blood Banking and Plasma Product Sector, Canberra, p.xii

6 The fundamental commitment to the principle of self-sufficiency in the blood system

Self-sufficiency in blood and blood products is an internationally agreed objective …

The term "sufficiency" means having enough blood and blood products to meet demand. For many developing countries, this primarily means sufficiency in fresh blood components such as red cells, platelets, and fresh plasma separated from a whole blood donation. Most developed countries are also able to ensure sufficiency of the supply of both fresh blood components and the more specialised fractionated products derived from plasma (for example, albumin and immunoglobulins).

"Self-sufficiency" means being able to achieve sufficiency through a national blood program without having to source products from other countries. A population donation rate of 50 per 1,000 population is the generally accepted minimum donation rate required for a developed country to meet this objective but this will be influenced by local demand. The ARCBS achieved 57.58 per 1,000 population in February this year.

The policy of self-sufficiency arose out of an international concern that some commercial fractionators were buying plasma from persons in developing countries, irrespective of their state of health. This posed a risk both to the paid donors and the recipients of products made from the plasma.

… Australia is a signatory to the World Health Assembly resolution on self-sufficiency …

In 1975 the World Health Assembly (WHA) passed a resolution recommending that:

- whole blood donation and supplementary plasmapheresis should be voluntary and unpaid;
- nations try to become self-sufficient in blood and blood products;
- donors not be compensated for giving whole blood or plasma; and
- nations enact legislation to regulate the collection, processing, distribution, export and import of blood and blood products.

Australia was a signatory to that resolution.[8]

Self-sufficiency in supply covers collection of blood and the manufacture of plasma products, including a national plasma fractionation capacity. Self-sufficiency is seen by the World Health Organisation (WHO) as being in the national interest as well as an international responsibility. Australia's response to the WHA resolution (WHA 1975) was to impose constraints on imported products by declining to register any foreign plasma product unless it has a demonstrably significant clinical advantage over the local product. This was enunciated in Appendix 19 of the *Australian Guidelines for the Registration of Drugs*[9] but has now been removed as a result of the commitments given by Australia in the side letter to the AUSFTA.

[8] Department of Health and Ageing (2004), Submission to Senate Community Affairs References Committee, 'Inquiry into Hepatitis C and Blood Supply in Australia'

[9] *ibid.*

… the EU has reiterated its commitment to the self-sufficiency principle …

In 1989, the European Economic Community (EEC 1989) reinforced the principle of national self-sufficiency through Directive 89/831 of the European Union which states:

> "*Member states shall take all necessary measures to promote self-sufficiency in human blood and human plasma. For this purpose they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations.*"

Continuing support for the "objective of Community self-sufficiency" and encouragement of "voluntary unpaid donations" was reiterated by Directive 2002/98/EC of the European Parliament on 27 January 2003 and the Council of Europe *Guide to the preparation, use and quality assurance of blood components* 12th edition, January 2006.

The ARCBS is aware from its international liaison that countries such as Canada are reviewing their current plasma derivative importation policies and have recently commenced planning for self sufficiency in plasma products, recognising that an ongoing program of donor recruitment and loyalty will be required to address the current shortfall of 60%.

… and its relevance to Australia today has been reconfirmed …

In Australia, the most recent independent review of the blood banking and plasma product sector (commissioned by the Australian Government) recommended that "*self-sufficiency should remain an important national goal for Australia recognising that it is a national and international obligation and responsibility."* [10]

Australia's commitment to self-sufficiency is also set out in the 2005 National Blood Agreement between the Australian and State/Territory Governments where one of the policy aims is to "promote national self-sufficiency".

… and Australia is generally self-sufficient in blood and blood products …

Self-sufficiency has served Australia well in securing an adequate and safe blood supply, enabling Australia to be largely protected from the volatility of world markets.

Australia is self-sufficient in all fresh blood products except for:

- patients with very rare blood types where international registries are searched for compatible donors; and
- occasional requirements for haematopoietic progenitor cells where rare tissue types in patients mandate access to overseas donors through the International Bone Marrow Donor Registry (administered by ARCBS) to which Australia also actively contributes.

Plasma derived products are mainly supplied from the domestic blood supply through products manufactured by CSL Limited. In some cases, clinical need cannot be met through the domestic supply and then products are imported, (for example, rare coagulation deficiencies such as Factors XI and XIII).

Overall, Australia is one of the few countries in the world that has been completely self-sufficient in fresh blood components and almost completely self-sufficient in plasma products. Further, this is achieved through the commitment of voluntary, non-remunerated donors. Each week, 20 000 donations are needed to ensure sufficiency of the supply.

[10] Commonwealth of Australia (2001), Review of the Australian Blood Banking and Plasma Product Sector, Canberra

… and importantly has its own domestic plasma fractionation capacity.

Importantly, Australia is also now one of only a small number of countries with a domestic fractionation capacity. CSL Limited fractionates plasma collected by the ARCBS from Australian donors to make a number of specialised plasma products, with fractionation taking place in separate columns as required by the TGA. This fractionation is done under contract to the NBA, acting on behalf of all Australian governments.

CSL Limited also undertakes toll fractionation services for other nations in the Asia Pacific region which do not have this facility, including New Zealand, Malaysia, Singapore, Hong Kong and Indonesia.

Recommendations

1. ***The ARCBS recommends that the Review Committee endorses self-sufficiency as an ongoing goal for Australia for both fresh blood and blood products, and reaffirms its importance in ensuring the safest blood supply in Australia.***
2. ***The ARCBS also recommends the Review Committee should use self-sufficiency as an overall guiding principle in determining its position on future arrangements for plasma fractionation services in Australia.***
3. ***The ARCBS believes that the Review Committee should address the need to maintain adequate domestic fractionation capacity to meet Australia's future needs for plasma products.***

7 The fundamental commitment to the principle of non-remunerated voluntary donation

Australia is a signatory to the World Health Assembly Resolution on voluntary non-remunerated donation …

As a signatory to the 1975 World Health Assembly resolution (WHA 1975), Australia remains committed to maintaining a voluntary, non-remunerated donor base. This principle is expressed in State and Territory Human Tissue Acts that prohibits the sale of organs and tissue, including blood. It has been inherent in the development of blood transfusion services by the ARCS.

In early 2005, member states unanimously adopted the WHA resolution 58.13 to "support the introduction of legislation, where needed, to eliminate paid blood donation except in circumstances of medical necessity and in such cases, to require informed assent of the transfusion recipient." This was reinforced in October 2005 by the WHO Expert Committee on Biological Standardization which amended relevant guidelines to state: "The provision of blood, blood components and plasma derivatives from voluntary, non-remunerated donors should be the aim of all countries."

In keeping with this principle, Australia's volunteer, non-remunerated donors meet almost all of the nation's blood product needs. ARCBS homologous donations (blood donations given for transfusion to an unknown recipient) represent over 95 per cent of all recorded blood and blood component collections. Other less common types of donations are autologous collections (involving blood taken from patients for their own use before a medical procedure) and directed donations (involving blood donated by another for use by a particular patient).

… voluntary, non-remunerated donations are safer than private directed blood collections …

While the Review terms of reference have indicated Australia is committed to voluntary donation, it does not explicitly rule out either remuneration or compensation for donors. Hence, it is important to underscore that voluntary, non-remunerated donations also produce the safest blood collection system. In general, the safest blood donor collections are from repeat voluntary, unremunerated donors. Private autologous or directed donations in Australia have been shown to have a higher prevalence of infectious disease markers and cannot be generally advocated as a safer alternative.[11]

… paid donation collections are the riskiest …

Furthermore, analyses of relative risk estimates for infectious disease markers among paid and unpaid donors from 28 different published data sets indicates paid donors are still more likely than unpaid donors to donate blood in the window period (the period during which infectious donations escape detection by blood screening tests.) Therefore, paid donations have a higher risk of infectivity than unpaid donations.

[11] Pink J, Thomson A, and Wylie B, 'Infectious disease markers in autologous and directed donations', Transfusion Medicine, 5, pp135-138m p135.

These analyses also indicate evidence was not found that the difference in infectious disease markers between paid and unpaid donors had diminished over time.[12]

In a survey reported in Vox Sanguinis of 27 countries, only the USA and Germany indicated that some donors are still paid.[13]

In addition, utilising paid donations debases the status of the voluntary donor and undermines confidence in the Australian blood system.

… therefore governments should act to enable Australian employees to donate.

While arguments have been put forward to provide compensation for donors for the time involved in donation, particularly for apheresis, the ARCBS strongly opposes this because it is antithetical to the principles of the International Federation of Red Cross and Red Crescent Societies, as well as the principle of the WHA resolution, and may compromise the primary safety of blood collections as indicated above.

One of the arguments made in favour of compensation relates to employers not agreeing to provide employees with paid leave of absence to make a voluntary blood donation.

As giving blood is in the national interest, the ARCBS believes that Australian governments should ensure industrial relations provisions mandate that this 'gift of life' activity is compensable by employers.

Recommendations

4. ***The ARCBS believes the Review Committee's conclusions and recommendations should reiterate the importance of a fundamental cornerstone of the Australian blood service being based on non-remunerated voluntary donors.***
5. ***The ARCBS also believes the Review Committee should recommend that Australian governments legislate to enshrine the right of employees to donate blood during their working day without loss of earnings.***

[12] Van der Poel CL, Seifried E, and Schaasberg WP, 'Paying for blood donations: still a risk?', Vox Sanguinis (2002) 83, pp285-293, p 285.

[13] Vox Sanguinis (2006) 90, 'Paid vs. unpaid donors', pp63-70, p63.

8 The importance of confidence in the blood system

The public expects government to do everything possible to make blood safe …

Risk can be simplistically defined as the probability of an adverse outcome following a decision to take a course of action. However, this does not adequately deal with the importance of public perception of what are acceptable risks when it involves the blood supply, and community expectations that governments will do all they can to eliminate these risks. In Australia, health advisors and blood service professionals must temper their judgements to take account of "contemporary political and social realities and the public's real and disproportionate horror of catastrophe" when considering risk related actions.[14]

The usual concepts of risk management cannot be applied with any consistency in the area of blood transfusion. The public's fear of acquiring a deadly disease as a result of receiving a life saving blood transfusion translates to holding governments accountable for not taking all steps possible to eliminate these risks. Therefore, confidence in the blood system is problematic. This is not unique to Australia.

The prosecution of Ministers and officials in France and Canada following the transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) through blood transfusions is a lesson policy makers and regulators appear to have absorbed with the application of the precautionary principle to the use of blood and blood products.[15,16]

… perceptions that there is risk in the blood system drive the public to private collections …

The blood supply system is very vulnerable to crises of confidence which can have a dramatic impact on the public's willingness to accept transfusions from public blood donor collections.[17]

This is cogently illustrated by the results of a telephone survey in the USA of the perceived risks of the blood supply which elicited responses that showed a substantial proportion of people do not consider the US blood supply to be safe and that they would not accept blood if hospitalised. Health policy makers are concerned about these perceptions, but more particularly at the proportion of people who say they are unwilling to receive a blood transfusion from the public system.[18]

[14] Whyte G, 'Risk management in blood transfusion services', Vox Sanguinis 74, Supplement 2, 1998, pp105-109, p105.

[15] Wilson K, Ricketts M, 'The success of precaution? Managing the risk of transfusion transmission of variant Creutzfeldt-Jakob disease', Transfusion, Vol. 40(8) 2004, pp1475-1478, p1475.

[16] Farrugia A, Ironside J, Giangrande P, 'Variant Creutzfeldt-Jakob disease transmission by plasma products – assessing and communicating risks in an era of scientific uncertainty', submitted to Vox Sanguinis for Publication, May 2005, pp1-22, p8.

[17] Smit S, 'Risk Management: an important tool for improving quality', Transfusion Clinique et Biologique, Vol. 7(3), June 2001, pp214-217, p214.

[18] Finucane M, Slovic P, Mertz C, 'Public perception of the risk of blood transfusion', Transfusion Vol. 40(8), August 2000, pp1017-1022, p1017.

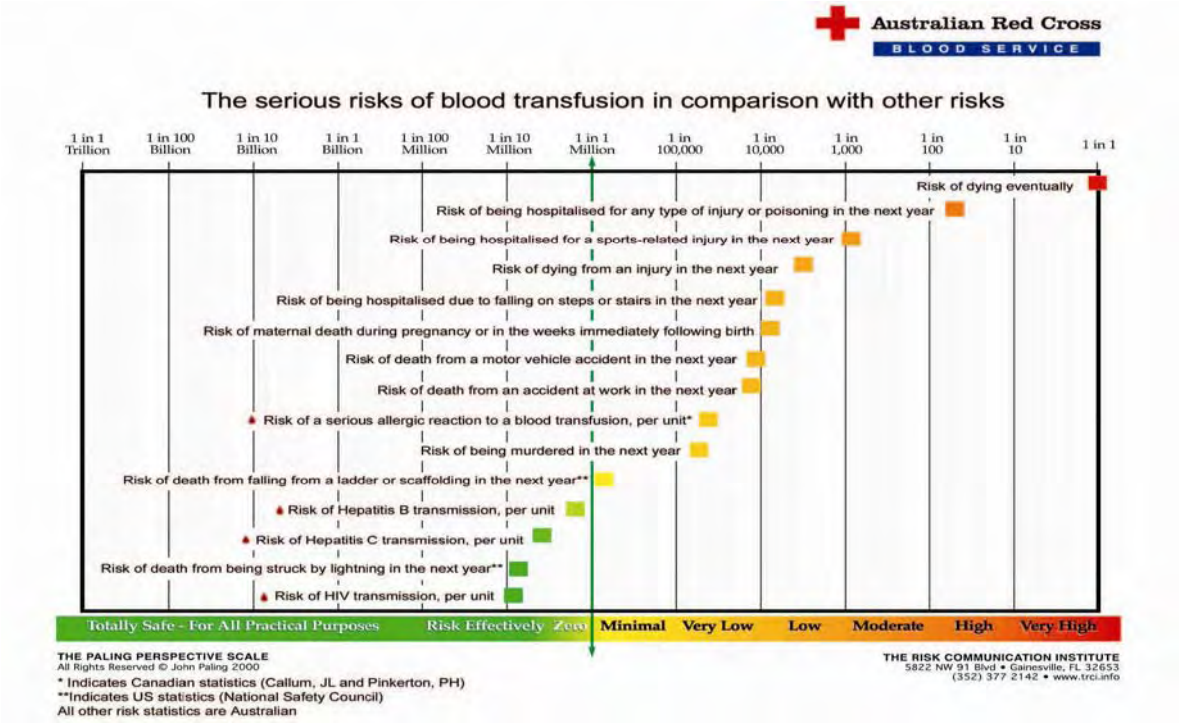
This finding has also been confirmed in a survey of public perceptions of the safety of the blood supply in the USA, where 85% of respondents indicated if they needed a blood transfusion they would prefer to receive their own blood, or that of a relative or friend, rather than from the public supply. More than half the respondents believed the likelihood of contracting a disease through blood transfusion from the public supply is 1 in a 1,000 or greater, compared with the true likelihood per unit of 1 in 1,000,000 for HIV and HCV in the USA.

These fears appear to be fuelled by perceptions of infectious disease transmission rather than a lack of knowledge of existing blood safety measures. It indicates a lack of confidence in the safety of blood that may not be tempered by initiatives providing further incremental advances in blood safety. While public education about the actual risks arising from blood transfusion are clearly needed, the survey findings underscore the perceived needs of the American public for technologies and interventions to be pursued to make the blood supply safer.[19]

… Australia has one of the safest blood supplies in the world …

It is important to note that the risks are even lower with the Australian blood supply than that of the USA, with a residual risk per unit of 1 in 7,299,000 for HIV and 1 in 3,636,000 for HCV. In comparison with other risks, as set out in Figure 2, the risk of acquiring HIV via transfusion within Australia is similar to the risk of death from being struck by lightning in the next year. The risk of being murdered in the next year and the risk of death from a motor vehicle accident in the next year are both significantly higher than the risk of acquiring either HIV or HCV via a blood transfusion in Australia.[20]

Figure 2: Risks of blood transfusion compared with other risks



[19] Press C, Ivansco L, Hillyer C, 'Public attitudes and perceptions about the safety of the United States blood supply' Blood, November 16, 2003, Vol. 102, No. 11, pp818a-819a, p818a.

[20] Paling, J, 'Helping patients understand risk', The Risk Communication Institute, 2006

… private collections are riskier …

As referenced in section 7 above, Pink et al have benchmarked the relative risk of public repeat donor collections against private autologous and directed donations and found them to be generally a safer alternative.

… current Australian plasma fractionation arrangements promote openness and transparency …

The worldwide focus on safety and risk identification and mitigation, together with the strength of the powers of Australia's regulator, TGA, drives an openness and transparency amongst clinicians, Australian health institutions, researchers, the ARCBS, the domestic fractionator, and the TGA to exchange information on possible adverse events, incidents or non-conformities in any aspect of collection, testing, manufacturing, storage, distribution and patient/clinical usage.

The National Health and Medical Research Council (NHMRC) Special Expert Committee on Transmissible Spongiform Encephalopathies (SECTSE) has also acted to protect the blood supply in Australia by monitoring international information and developments relating to BSE and vCJD and recommending to governments actions to limit transmission of prions by both fresh and fractionated blood products in Australia.

This cooperation and commitment to free exchange of information generates a high degree of confidence amongst critical players in the blood system, providing a fundamental strength to the Australian blood system that ultimately benefits Australian users and potential users of blood and blood products.

… alternative arrangements are unlikely to be as open …

It is highly unlikely Australia would enjoy the benefits of the same levels of openness and transparency with overseas fractionation services or multiple fractionation services competing within the Australian market.

In Australia adverse drug reactions are reported to the Adverse Drug Reactions Advisory Committee (ADRAC), which is a subcommittee of the Australian Drug Evaluation Committee (ADEC) and was formed in 1970 to advise the TGA on the safety of medicines. It is composed of independent medical experts who have expertise in areas of importance to the evaluation of medicine safety.

ADRAC particularly requests reports of:

- all suspected reactions to new medicines;
- all suspected reactions to Drugs of Current Interest listed in the Adverse Drug Reactions Bulletin;
- all suspected drug interactions;
- serious reactions which are suspected of significantly affecting a patient's management; and
- unexpected reactions, ie not consistent with product information or labelling.

For this pharmaco vigilance system to be effective, it is paramount that health professionals report suspected adverse drug reactions to the manufacturer in a timely fashion. It is also relevant to note that the manufacturer does not have an obligation to report reactions which are consistent with product information or labelling. However, the frequency of such reactions is of interest and relevance to the treating clinician. For this reason, open dialogue with regard to reporting and evaluation of specific adverse events and their trends is paramount and underpins clinician confidence in the use of the product.

CSL Limited is supportive of the ARCBS facilitating clinician reporting of adverse reactions to plasma products manufactured by CSL Limited. The ARCBS is able to forward a copy of the CSL Limited Adverse Drug Reaction Form to clinicians who contact the ARCBS following such an event. On a regular basis, the ARCBS and CSL Limited review all reports of adverse drug events and take further action as required. This may include the preparation and distribution of educational support materials on rare but recognised adverse events to improve general clinician awareness and subsequent management of such events, for example, an article on aseptic meningitis was included in the ARCBS Medilink newsletter for health professionals in April 2006.

In contrast some other suppliers within Australia are not willing to allow ARCBS to facilitate reporting of adverse drug events for their products, nor are they willing to share or discuss reports of adverse reactions to their products.

Open dialogue with the ARCBS about the management of batches, particularly where there has been non-compliance with, or the potential for non-compliance with, product specifications is also imperative for clinician confidence in the use of the product.

An examination of two contrasting approaches to openness, transparency and cooperation between players is quite instructive.

Stability data on a product batch of a small volume presentation manufactured by CSL Bioplasma was identified as having an aluminium level at the upper limit of the product specifications at 18 months storage at extreme room temperature storage. The aluminium level of the product which had been refrigerated was well within specifications.

It is important to note that the aluminium in the final product is not derived from the plasma product but rather it leaches out from the glass container over time. The degree of leaching of aluminium relates to the surface area to volume ratio (higher for small volume containers), the temperature of storage and time.

CSL Limited contacted both the TGA and ARCBS and as the implicated batch may have exceeded the specification towards the end of its shelf life, it was recalled. CSL Limited worked closely with ARCBS to prepare relevant information for health professionals.

In contrast, earlier this year an alternate overseas-sourced product supplier was reluctant to discuss the concerns raised by clinicians about their product with ARCBS even though the ARCBS was responsible for distribution of the product.

On this occasion a clinician advised the ARCBS that two patients, who had undergone routine infectious disease screening as part of their routine treatment regime, were found to have antibodies to a particular virus. Both patients had received blood components as well as a plasma product manufactured by the alternate overseas product supplier. It is important to highlight that intravenous immunoglobulin (IVIg) preparations are designed to transfer antibodies to a whole range of antigen stimuli, including antibodies to viruses not screened out of donations prior to pooling for fractionation.

Testing plasma for fractionation for this particular virus is not a regulatory requirement and for this reason plasma sourced by the alternate supplier for the manufacture of this product was not tested for the presence of antibodies to this particular virus. In this case, there is evidence to support the passive transfer of the specific viral antibodies from the product to the two patients. While this did not result in patient harm, it did initially cause concern for the treating medical practitioner, including the potential for misdiagnosis. The TGA confirmed that the product conformed to the required Australian safety standards and that no recall or quarantine of the implicated batches was required. This issue could have been resolved more swiftly with a closer and more transparent relationship with the overseas supplier.

Similarly, imported plasma derivatives recently supplied to the ARCBS for distribution to Australian hospitals recently failed ARCBS acceptance testing due to smearing of the batch number on external packaging, rendering it unreadable. The batch number is the critical link to tracing the product to patients in the event of subsequent product recall. It was evident that a packaging inspection step by the manufacturer prior to product release failed to identify the problem which occurred in up to 16% of vials. The ARCBS sought guidance from the TGA and the supplier subsequently initiated a recall for product correction. Of greater concern was that it appears the manufacturer did not disclose their full regulatory obligations to the NBA.

An integrated system facilitates immediate investigation of potential problems. In contrast, the involvement of an intermediary, such as an importer or external fractionator, potentially adds delays in critical information sharing.

… it is crucial public confidence is maintained.

The blood supply has aspects that make it vulnerable to crises of confidence as the subject of blood can easily become stigmatised. "It is therefore not sufficient to simply state that the blood is safe; it must also be made safe" and risk information communicated in a way that both informs people and builds up public and political confidence.[21]

Recommendations

6. ***The ARCBS strongly urges the Review Committee to ensure future plasma fractionation services for Australian plasma do not impact on levels of public confidence in the Australian blood system.***

7. ***The ARCBS believes the Review Committee should stress the importance of the maintenance of openness and transparency already achieved by Australia's integrated blood system.***

[21] Smit S, 'Risk Management: an important tool for improving quality', Transfusion Clinique et Biologique, Vol. 7(3), June 2001, pp214-217, p214.

9 The attitudes and expectations of Australia's blood donors

The Review secretariat located in DoHA specifically requested the ARCBS to obtain the views and attitudes of Australia's blood donors on the issues associated with the review and to incorporate those views and attitudes in this submission.

More than half a million Australians give blood each year.

The unifying reason why they do so is because they recognise and understand the need for blood and wish to give something to the community. Not only is their gift doing something for other Australians, but it is also doing something for them. In this respect the ARCBS, through its voluntary unpaid donors, makes a substantial contribution to Australia's social capital.

The ARCBS consulted with its Donor Advisory Committees, donors and non-donors on attitudes to issues inherent in the Review …

The ARCBS consulted with its Donor Advisory Committees in each State, and also separately conducted quantitative and qualitative market research with donors and non-donors through an independent market research company, Worthington Di Marzio.

… the views of the Donor Advisory Committees were not supportive …

The Committee members were asked a series of specific questions, the first of which was what issues they identified arising out of fractionation services being provided overseas. Typical comments included:

> *"Australian donors may be unhappy to see their donation contributing to the profit of a company located overseas. As well as damaging public perception this may affect sufficiency."*
>
> *"There is also a safety issue; the further and more often product has to travel, the more risk there is of compromising safety."*
>
> *"If products are sourced from overseas donations, it is essential that they are collected according to the same standard as Australian donations. Can this be guaranteed?"*

In relation to the level of imports, typical comments included:

> *"We were not aware Australia imported such a high proportion of its plasma fractionated product. If this was common public knowledge it would undermine the motivation of Australian donors."*
>
> *"If there are shortfalls, we should strive harder for self-sufficiency and ensure there is adequate funding."*

The Committees were also asked about the extent to which they are concerned about the cost of delivering a high quality blood supply system and typically responded:

> *"Donors give blood freely. We don't sell it. We don't ask for anything. We help to keep down the basic cost of blood and blood products and the cost of the health system."*
>
> *"Cost should not be an issue for Government. All the Government should be concerned about is maintaining the highest quality standards, and ensuring we are self sufficient, even if that is at additional cost."*

In the view of the Committees, the AUSFTA would appear to give Australia the right to self-sufficiency in blood products, as set out in the side letter. Donors take their role as donors seriously and try to ensure their donations are safe by ensuring that they are healthy at the time of donation. Donors do not want plasma from other countries where the donors do not have the same safety profile or level of personal commitment to quality and safety.

The members of the Donor Advisory Committees are amongst our most committed donors and supporters, but there was significant and overwhelming concern amongst committee members that the issues before the Review Committee have the potential now, or in the future, to put at risk the high standards of quality for blood products used in Australia, particularly surrounding the issues of self-sufficiency and voluntary, unpaid donors.

The Committee members were also overwhelmingly of the view that Australia derives enormous benefits from a world class blood system which has been built up over many years, and there was significant resistance to the concept that this could be compromised due to overseas processing of plasma arising from an FTA with any country.

… neither were the views of donors and non-donors …

(i) Quantitative Research

Worthington Di Marzio conducted telephone interviews of over 500 non-donors and donors in the last week of March 2006.

The non-donor sample was selected randomly from people aged 18+ with the donors selected randomly from the ARCBS donor base. Respondents were selected from all States and Territories and the data was weighted to the population statistics by State and metro/rural.

While there was little initial awareness of what happens to blood donations (10% non-donors/33% donors), prompted awareness was higher at 71% and 98% respectively.

The initial reaction to the review of Australia's plasma fractionation arrangements was negative with 64%/69% having a negative opinion and 12%/10% having a positive opinion. The negative views reflected:

- a preference to keep the blood in Australia and use it for Australians;
- concerns about quality standards not being as high as Australia's; and
- the risk of shortages of product when it's needed, as well as a loss of jobs and control of the blood supply system.

When asked their reaction to the possibility of the fractionation process being taken offshore, and to plasma products including blood from overseas donors, 80% in each group expressed concern.

When asked specifically if they supported the two key policy cornerstones of the ARCBS:

- 91%/95% were of the view that blood should be collected from voluntary, unpaid donors; and
- 96% (both groups) were of the view that Australia should be self sufficient.

(ii) Qualitative Research

Five focus group discussions were conducted by Worthington Di Marzio, comprising:

- two donors groups (male and female, 25-55 years);
- two non-donor groups (male and female, 25-55 years); and
- one recipient group (male and female, 25-55 years), that is, people who are regular recipients of donated blood and blood products.

The group discussions sought to develop insight and direction rather than be quantitatively precise. The findings were exploratory in nature and should be viewed as directional. However, taken together with the consultation with the Donor Advisory Committees and the quantitative research, the focus groups provide a consistent and compelling view.

In relation to the AUSFTA the typical thoughts expressed included:

"… the scariness of all this is just sinking in."

and

"I feel very confident in the existing arrangement."

and

"I'd like to see no change."

and

"… you can't separate fractionation from collection."

People give blood for a variety of reasons but 'doing the right thing' as a community member is an overriding motivation.

The review of Australia's plasma fractionation arrangements has the potential to make not only donors, but recipients of blood products and others in the community, angry. Importantly, from the ARCBS perspective, it has significant potential to impact unfavourably upon donation as evidenced by the following responses:

"I'd think, why bother if it's going to America."

"I would stop being a blood donor."

"I would not push myself to keep making appointments."

"I will not accept that blood is sent offshore for any type of processing. I will not give blood anymore."

"There would be uproar – blood is a product that's given for free."

It would also undermine the confidence of recipients and, within the community, the health system overall:

"I absolutely do not trust the American health care system."

"… confidence would be eroded in the whole process."

"If it ain't broke, why fix it?"

The view amongst non-donors is similar. They also spoke about confidence in:

"… a product produced here from people I know and which isn't exposed to the outside world."

There were also questions about why this was occurring:

"I don't want blood collection to be driven by economic rationalists."

"The bottom-line is the Government wants to trade blood for dollars."

"Operating a call centre overseas is different to fractionating blood overseas."

Overwhelmingly, the view was that if it was an issue of funding or cost:

"I'd prefer the Australian Government helped them out and provide more money if it's a financial issue."

"Doesn't the Government value the system we have now? If so, they should fund it properly instead of stuffing around with the United States."

Summary

Amongst blood donors, there are a number of 'givens' which contribute to significant confidence in, and support for, the Australian system of blood supply, viz:

- that the Australian blood system is amongst the safest in the world;
- that giving blood is voluntary;
- that they are helping their fellow Australians; and
- that the blood which is donated is used appropriately.

Giving blood is perceived as being a valuable and worthwhile thing to do because it involves volunteerism, community spirit and generosity (of time and commitment). It is seen as something which embodies Australian values.

Consultation with the Donor Advisory Committees and quantitative and qualitative research of donors, non-donors and recipients shows overwhelming support for the continuation of Australia's system of voluntary, unpaid donors and support for ARCBS to, once again, be funded appropriately to achieve self sufficiency in the blood supply (as it last was in 2002-03).

In a nutshell, overseas fractionation services:

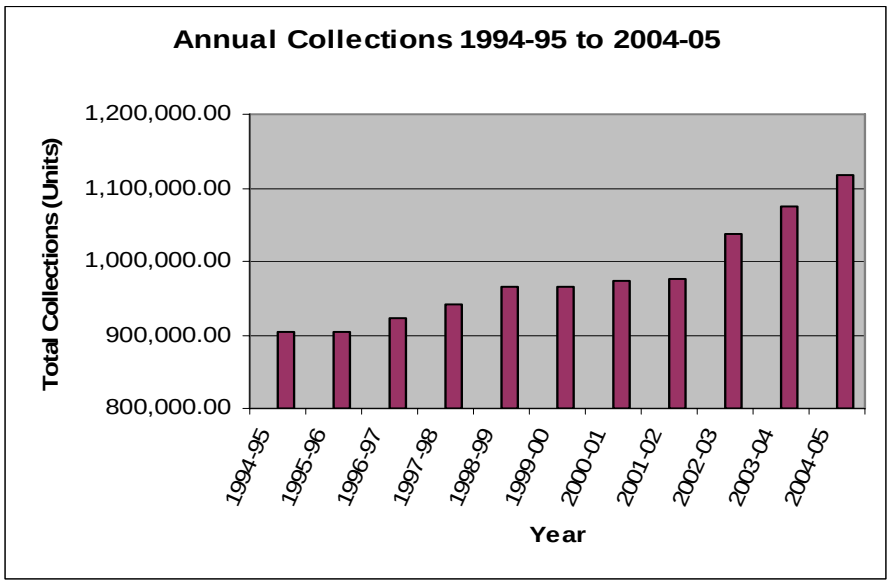
- do not provide Australians with the same level of certainty as the current system of fractionation on Australian soil;
- will undermine the confidence and trust that the Australian community has in the quality and safety of the current system;
- will have a significant impact on the donor base, which keeps the Australian health system going; and
- will represent a further erosion of one of the aspects of Australian life which Australians hold dearly and in high esteem.

10 Term of Reference 1 – Demand trends for plasma products

The ARCBS has increased its blood collections by more than 20% over the last decade …

The ARCBS has increased its annual blood collections by more than 20% over the last ten years as set out in the following table and corresponding graph.

Figure 3: Annual blood collections 1994-95 to 2004-05



Note: This 20% increase over 10 years, compares with the 11% increase in Australia's population during this period.

Table 1: Annual Collections Results

Year	Total Collections Units
1994-95	905,164
1995-96	904,770
1996-97	922,911
1997-98	940,125
1998-99	964,574
1999-00	965,821
2000-01	972,702
2001-02	976,527
2002-03	1,037,489
2003-04	1,074,711
2004-05	1,116,636

… and ARCBS has also increased its plasma collections by more than 50% in this period …

Over the ten year period from 1995-96 to 2004-05, the ARCBS has managed to meet Australia's requirements for plasma input to CSL Limited for plasma fractionation as set out in Table 2.

Table 2: Plasma provided to CSL Limited for plasma fractionation 1995-96 to 2005-06

	95-96	96-97	97-98	98-99	99-00	00-01	01-02	02-03	03-04	04-05	05-06
Domestic Plasma Starting Pool (tonnes)	189	205	217	232	238	246	253	275	295	308	317
Annual % Increase	n/a	8.5%	5.9%	6.9%	2.6%	3.4%	2.8%	8.7%	7.3%	4.4%	2.9%
% Domestic IVIg	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	92.7%	84.9%
Domestic IVIg (kg)	523	622	623	697	739	943	1102	1141	1342.1	1353.4	1432.9
% Imported IVIg	0%	0%	0%	0%	0%	0%	0%	0%	0.2%	7.3%	16.1%
Imported IVIg (kg)	0	0	0	0	0	0	0	0	3.2	106.3	275.3

Note 1: ARCBS implemented a standard national reporting process of supply which applies to the 2001-02 to 2004-05 data. The process uses CSL Limited receipt data reconciled to ARCBS consignments. Data prior to 2001 -02 has been provided by CSL Limited. All donations have been scanned and weighed by CSL Limited since 1994.

Note 2: Data for 2001-02 and 2002-03 includes plasma lost through a manufacturing failure funded by insurance cover held by CSL, totalling 1.3 tonnes in 2001/02 and 8.6 tonnes in 2002-03, Limited.

In addition to the products listed above, the ARCBS has supplied sufficient plasma for fractionation to meet 100% of domestic demand for the plasma derived products, as detailed in Table 3. (For further detail see Attachment 3).

Table 3: Products derived from ARCBS supplied plasma

• Albumex	4%
• Albumex	20%
• Biostate	250IU
• Tetanus Immunoglobulin	250IU
• Tetanus Immunoglobulin	4000IU
• Zoster Immunoglobulin	200IU
• CMV Immunoglobulin	1.5 x 10^6 IU
• Hepatitis B Immunoglobulin	400IU
• Hepatitis B Immunoglobulin	100IU
• Normal Immunoglobulin	160mg/mL x 5mL
• Normal Immunoglobulin	160mg/mL x 2mL
• Prothrombinex HT	500IU in 20mL
• MonoFIX	500IU
• Thrombotrol VF	1000IU

Tables 2 and 3 indicate that, until 2002-03, Australia was self-sufficient in its key plasma product requirements. ARCBS was not only able to meet domestic demand but also:

- increased its plasma donor collections by about 50% over the ten year period until 2004-05 to meet the increased demand for plasma products; and
- managed to meet the somewhat unforeseen massive growth in domestic demand for IVIg which increased by more than 150% in the same period.

The ability of ARCBS to deliver plasma in the last decade has been driven by funding and Federal, State and Territory jurisdictional policy. As a result, the current per capita plasma production by jurisdiction for plasma production is highly variable and reflects these historic trends. For example, the South Australian and Western Australian governments funded the collection of a higher plasma volume per capita to ensure the production of sufficient plasma to meet local clinical needs. Some States under-funded plasma collections, resulting in the need for interstate supplementation to meet their local clinical demand.

Table 4 illustrates kg plasma harvesting yields per thousand population for 2004-05. These vary on a State and Territory basis due to historic activity and priorities.

Table 4: Plasma yield (kg per 1000 population) by jurisdiction for 2004-05

	NSW	VIC	Qld	WA	SA	Tas	ACT	NT	Total
Pop ('000)	6768.2	5023.4	3966.6	2014.3	1539.4	487.6	324.9	203.2	20,327.60
CSL Plasma (kg)	82,238.20	71,132.50	63,553.00	37,939.80	32,515.60	7,832.70	9,393.30	3,157.30	307,762.40
kg per '000 Population	12.15	14.16	16.02	18.84	21.12	16.06	28.91	15.54	15.14

The introduction of restrictive eligibility for plasma derived FVIII (Biostate) in June 2005 has meant that ARCBS has had to change its collection strategy with an increased requirement for regional plasmapheresis to target eligible donors. This expansion is planned for early in the 2006-07 year. It is clear that there is significant capacity remaining in other States and if a national minimum plasmapheresis benchmark was set at 25kg per thousand population, an additional 400 tonnes of plasma capacity would be available.

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 solutions rather than plasma, specific funding for the Anti-D program and, in some jurisdictions, a greater move towards production of platelets via apheresis. Collection of platelets via apheresis technology has many advantages, including the generation of plasma as a by-product from each collection. Further gains in plasma productivity will be made through the remaining jurisdictions also moving towards increased platelet production via apheresis. The ARCBS is also currently evaluating the re-suspension of apheresis platelets in additive solution rather than plasma. Implementation is planned in 2006-07, and will allow 70% of the plasma to be harvested per therapeutic apheresis dose of platelets.

… the plasma target set by the NBA for 2005-2006 is 317 tonnes representing only 84% of Australia's requirements for IVIg…

Since 2002-03, the NBA has instituted a policy to move away from 100% self-sufficiency for IVIg (using CSL Limited's Intragam P) to progressively introduce imported products purchased off-the-shelf. Importations have risen progressively from 0% in 2002-03 to 0.2% in 2003-04 to 7.3% in 2004-05 to a target of 16.1% in 2005-06.

Table 5: 2005-06 plasma target, showing % increase over previous collections

	2005-06 Target	Increase in 2005-06 over 2004-05	Total % increase over 1995-96
Domestic Plasma Starting Pool (kg)	317,000	3%	67%
Domestic IVIg (kg)	1,432.9	5.9%	173.98%
Imported IVIg (kg)	275.3	159%	N/A
Total IVIg (kg)	1,708.2	17.05%	226.62%
% Domestic IVIg of total pool	84%		
% Imported IVIg of total pool	16%		

… ARCBS, adequately funded, can meet self-sufficiency demand …

The ARCBS has demonstrated that, with appropriate funding, it can increase plasma collection to meet specific product demand. The most recent example of ARCBS success in this area was the Rh (D) project.

Universal prophylaxis with Rh (D) Immunoglobulin for Rh (D) negative women at 28 and 34 weeks gestation is generally regarded as best practice and was recommended by NHMRC in the "*Guidelines on the prophylactic use of Rh (D) Immunoglobulin (Anti-D) in Obstetrics",* published in 1999. The aim of the Rh (D) project was national self-sufficiency in the supply of domestic Rh (D) immunoglobulin.

The project commenced in 2002 with the ARCBS introducing a number of strategies to increase the collection of the specialised Anti-D plasma required for Rh (D) immunoglobulin production. Currently there are about 260 Anti-D donors who have either undergone boosting of a pre-formed Anti-D or primary immunisation.

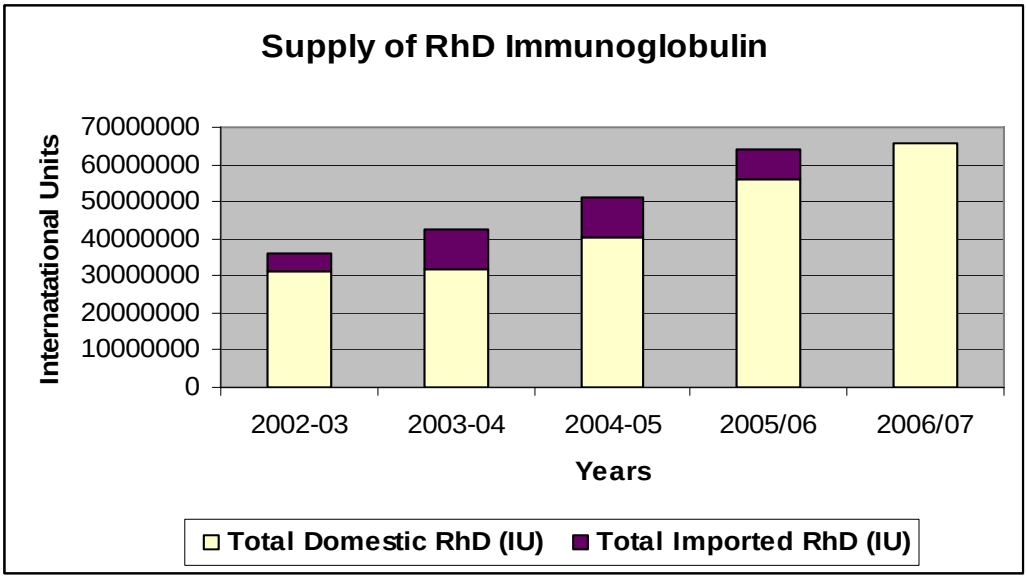
The project was divided into three stages to allow an increase in stocks of Rh (D) Immunoglobulin and a phased implementation of universal antenatal prophylaxis with the final stage being self-sufficiency in meeting demand from domestic supplies of Rh (D) Immunoglobulin. Each stage has a defined outcome and reportable targets which had to be achieved to enable progression to the next stage, as set out below.

Situation up to October 2002	Routine antenatal prophylaxis unable to be recommended.
Stage 1 Introduced November 2002 Implemented late 2002	Routine antenatal prophylaxis at 28 and 34 weeks for Rh (D) negative women during their first pregnancy. Supply was augmented with imported product (WinRho SDF^{TM}) for postnatal prophylaxis
Stage 2 Announced August 2004 Implemented 1 January 2005	Routine antenatal prophylaxis at 28 and 34 weeks for ALL Rh (D) negative women. Supply was augmented with imported product (WinRho SDF^{TM}) for postnatal prophylaxis
Stage 3 (final stage) Announced January 2006 Implemented 31 March 2006	Routine antenatal prophylaxis at 28 and 34 weeks for ALL Rh (D) negative women. Australia self-sufficient in domestic derived Rh (D) immunoglobulin. WinRho SDF^{TM} no longer required for postnatal prophylaxis.

During Stages 1 and 2, the Australian supply of domestic Rh (D) immunoglobulin was supplemented with imported Rh (D) products as ARCBS steadily increased the supply of Anti-D plasma for fractionation into Rh (D) Immunoglobulin.

Figure 4 demonstrates the growth in domestic product supply to the Australian community which was achieved by appropriate funding of the Rh (D) project. Implementation of Stage 3 was completed in March 2006 and Australia is now self sufficient in supply of domestic derived Rh (D) Immunoglobulin.

Figure 4: Growth in domestic product supply of RH (D) Immunoglobulin



Historically the ARCBS has been able to meet the demand for plasma collections to meet domestic fractionation service requirements for Australian self-sufficiency.

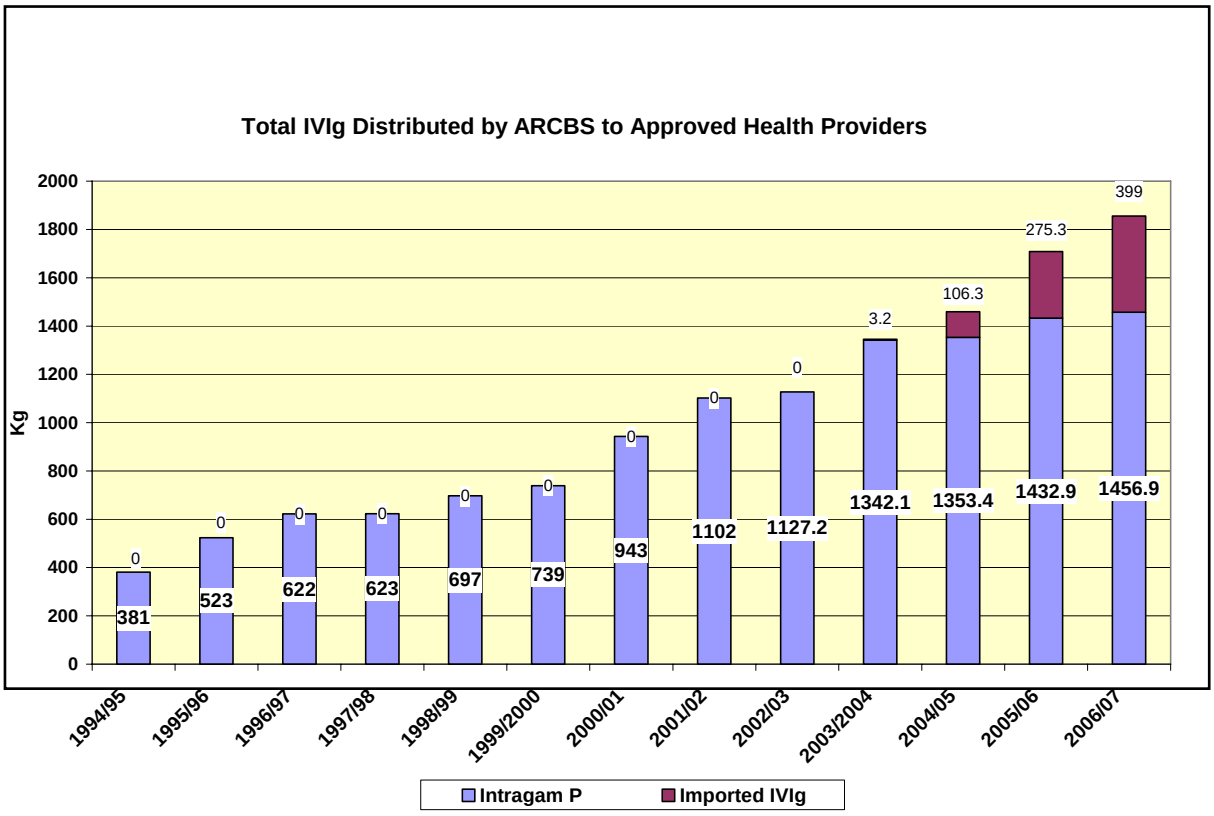
However, Australia has not been self-sufficient in IVIg, the biggest contributor to domestic demand, since 2002-03, as set out in Figure 5, because of specific strategic decisions made by the NBA to import off-the-shelf alternatives (on the basis of supply risk mitigation). This is at odds with Australia's policy of national self-sufficiency in blood and plasma products.

The routine introduction of overseas sourced products on the basis of supply risk mitigation also brings disadvantages, apart from eroding Australia's policy of national self-sufficiency in the areas of clinical management of patients and management of the blood system:

- there is the need to rotate this product through the blood supply to avoid product expiry which causes additional workload for all parties within the blood sector, such as the amendment of hospital blood management systems with the new product codes to enable traceability, amendment of hospital standard operating systems and the need for training of staff with regards to the characteristics and administration details for the product; and
- some patients may need to swap between the alternate and domestic product, which on some circumstances can increase the risk of adverse side effects and can cause anxiety for the patient or their parent with the introduction a different, and unknown to them.

While the ARCBS strongly supports contingency planning within the blood sector, it would also favour the establishment of a National Reserve of plasma products sourced solely from Australian donors and manufactured locally as it provides the safest blood supply possible.

Figure 5: Total IVIg distributed by ARCBS to approved health providers.



Note 1: Data represents volume of Product distributed by ARCBS to the State and Territory health systems i.e. provided to Hospitals, medical centres, etc for clinical use.
Note 2: 1994-95 to 2001-02 data has been sourced from the ARCBS Annual Reports.
Note 3: 2002-03 to 2005-06 data has been sourced from the ARCBS Supply Reports to NBA as at 30 June of relevant year.
Note 4: 2005-06 data is the approved Government supply plan for IVIG (both domestic and imported product)
Note 5: 2006-07 data is the draft Government supply plan received by ARCBS from the NBA as of March 2006.

Since the establishment of the NBA in 2003-04, the plasma target has been set by the Australian governments with the approval of the local Health Minister and the ARCBS is notified annually of the quantity of plasma to be delivered to CSL.

In an environment of increasing demand for IVIg, the NBA has moved from a position of Australian being self-sufficient in IVIg and other key plasma products to one where the supply target it advised the ARCBS on 30 March 2006 (for the 2006-07 financial year) will provide only 79% of Australia's needs.

This means that, within four financial years, the NBA will has taken Australia's reliance on imports from 0% to 21%.

With the appropriate planning and funding, Australia has a sufficient population base and a longstanding culture of volunteerism to ensure national self-sufficiency in IVIg. Given the anticipated annual increase in demand for IVIg, the ARCBS estimates that, with the appropriate funding, national self sufficiency in domestic derived IVIg could be achieved in a staged process. The ARCBS would need to increase its plasma apheresis collections markedly to achieve this goal.

… and do it more cheaply than comparable countries …

The ARCBS is fully funded by Australian governments to undertake its donor recruitment, blood collection, plasma products processing and distribution of blood and plasma products to hospitals and clinicians. A comparison of the ARCBS cost per collection of a unit of blood with comparable countries is set out in Table 6.

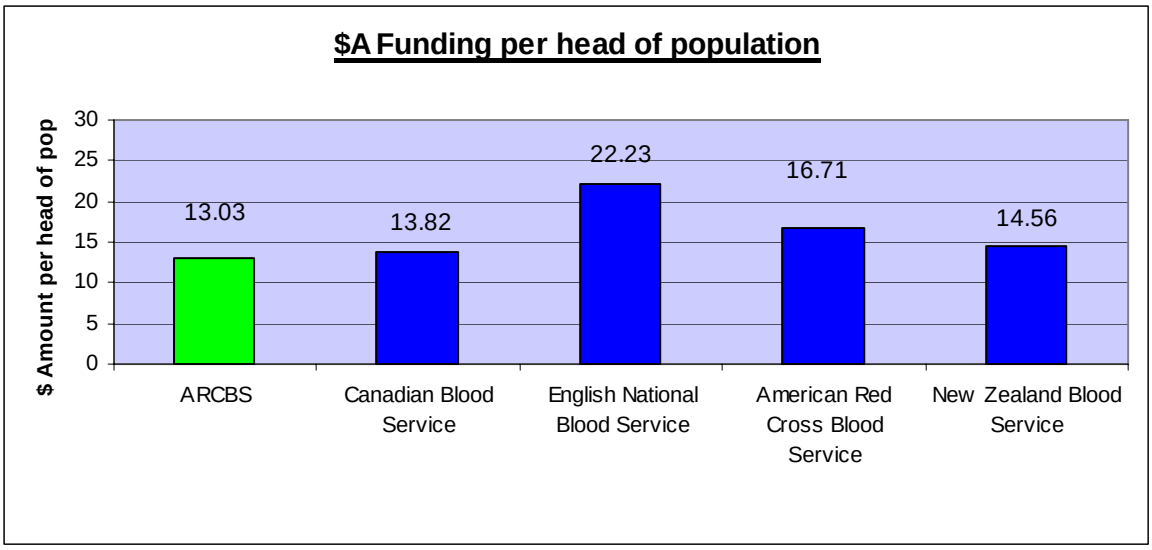
Table 6: Cost per collection of one unit of blood from annual reports

Service	$AUD cost per unit
ARCBS	236
English National Blood Service	460
Canadian Blood Service	483
American Red Cross	453
New Zealand Blood Service	344

Table 6 shows that the ARCBS provides the lowest cost per unit of blood collected amongst comparable countries. Furthermore, it provides the lowest cost blood service for the cost per unit of clinical fresh frozen plasma compared with comparable western nations.

Compared with similar blood services, ARCBS funding per head of population is markedly lower. Obviously, there are differences between the various blood services including the range of blood products supplied and the type and number of tests performed on each donation. However, at the aggregate level, taking the financial data from each services' annual report, ARCBS funding per head of population is lower that the equivalent national blood services in England, Canada and New Zealand as can be seen in Figure 6.

Figure 6: Funding per head of population per annum



Note1: Population sourced from www.infoplease.com; American Red Cross population is pro-rated based on current market share (43%); Canadian population excludes Quebec (as not served by CBS); NBS population is total UK and includes Scotland, Northern Ireland and Wales
Note 2: Funding is sourced from annual reports; American Red Cross funding is based on 'BioMedical' funding and may include some non-blood related activities
Note 3: Source - Annual Reports 2004 or 2005
Note 4: Exchange rate based on 28 April 2006

… with the following 5 and 10 year forecasts for plasma demand …

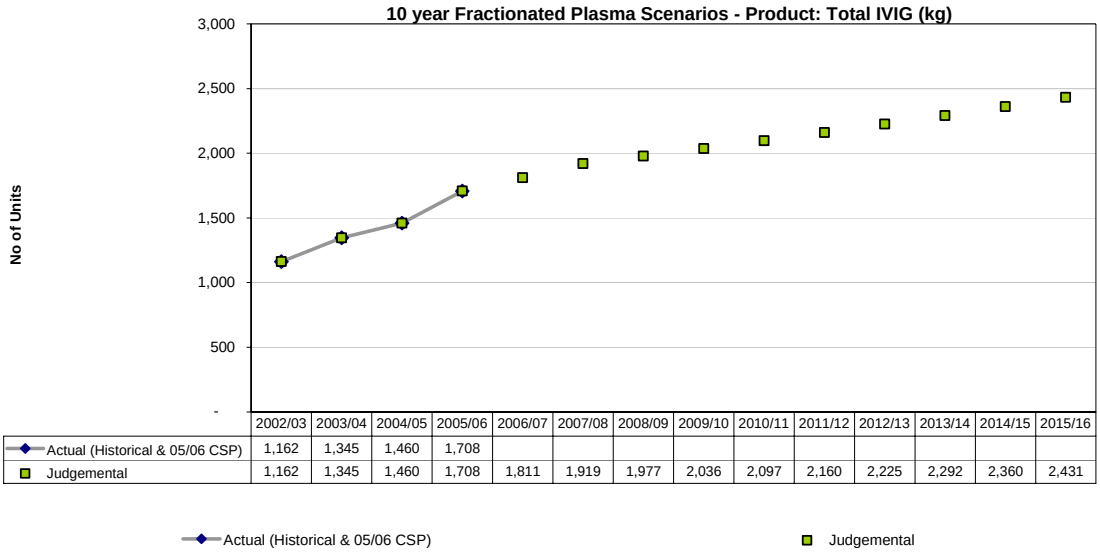
The ARCBS has developed a sophisticated model, providing a ten year forecast of demand for each plasma product. The largest single driver of demand over this period is seen to be IVIg requirements. The usage of IVIg in clinical settings has expanded significantly in recent years.

It is difficult to be certain of the impact of developments in medical technology and the state of knowledge in the current climate where medical research is changing the landscape of clinical options so rapidly and so dramatically. It is anticipated that whilst new indications for intravenous immunoglobulin will be supported (especially neurological conditions and other conditions where an autoimmune aetiology is proven or suspected), the growth in demand will only slow if and when support for effective alternate therapies increase. In particular, many of these conditions are chronic illnesses of middle and later life and will increase in a growing and ageing population.

The ARCBS also notes that the NBA is currently facilitating development of new clinical guidelines which may lead to a change in usage within the next two to three years. ARCBS also notes that the employment of an IVIg specialist nurse, an initiative funded by the South Australia Department of Health, has demonstrated that demand can be contained by sustained focus. Hence, the ARCBS has developed two forecasts of IVIg demand over the next ten years.

Figure 7 sets out the conservative view of how these factors will influence demand for IVIg. ARCBS estimates that growth will continue at 6% for the next two years while intensive clinician management of IVIg usage is implemented drawing on the success of the IVIg nurse in South Australia. Thereafter growth is expected to slow to 3% per year as similar programs are introduced in all states and territories.

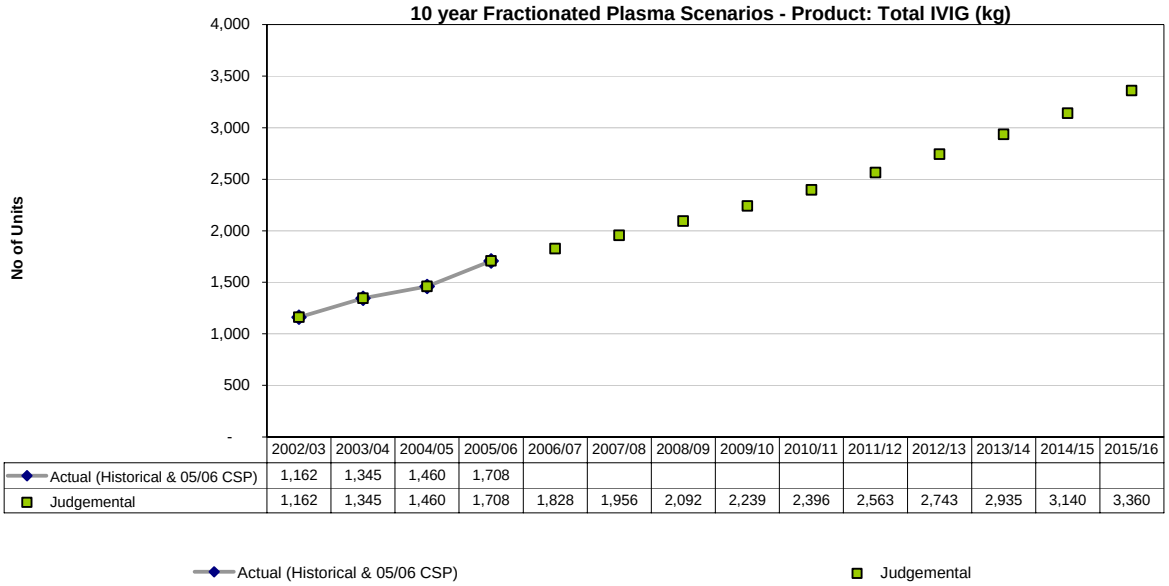
Figure 7: 10 year fractionated plasma scenarios – product: total IVIg (kg) (Conservative Scenario)



	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Actual (Historical & 05/06 CSP)	1,162	1,345	1,460	1,708										
Judgemental	1,162	1,345	1,460	1,708	1,811	1,919	1,977	2,036	2,097	2,160	2,225	2,292	2,360	2,431

Figure 8 demonstrates a more aggressive demand forecast, based on expanded treatment regimes for IVIg following the publication of new IVIg guidelines which could see demand for IVIg double over the next ten years, with an increase of about 7% per annum.

Figure 8: 10 year fractionated plasma scenarios – product: total IVIg (kg)- (Aggressive Scenario)



	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Actual (Historical & 05/06 CSP)	1,162	1,345	1,460	1,708										
Judgemental	1,162	1,345	1,460	1,708	1,828	1,956	2,092	2,239	2,396	2,563	2,743	2,935	3,140	3,360

Factoring these two options into ten year forecasts of demand for other plasma products generates the overall ten year projection of demand for plasma as set out in Table 7 below.

In summary, the ARCBS models forecast that by 2015-16 between 500 and 700 tonnes of domestic plasma will be required to meet self-sufficiency, depending on the different scenarios depicting the demand for IVIg. The detailed ARCBS modelling of demand forecasts for all plasma products for the period to 2015-16 are set out in Attachment 3.

… but long term planning needs to be improved to provide sustainability and certainty …

Since the establishment of the NBA and its annual approach to supply planning by moving away incrementally from Australian self-sufficiency for plasma products, the ARCBS has had no long term basis for sound resource planning for blood and plasma collection activities as it is only given annual targets just prior to the commencement of a financial year.

The ARCBS does not support the view that Australia should move to a significant import dependency when it has the capacity to meet 100% of its requirements through local plasma collections. The only exceptions to 'Australian blood for Australians' should be for low demand, niche products where it is uneconomic to be manufactured in Australia.

Annual supply plans provided by the NBA in the lead up to the commencement of a financial year limits the ARCBS's ability to look beyond an annual horizon for operational and financial planning. The absence of high level, medium to long term planning strategy advice to ARCBS from the NBA, setting out general directions and objectives, such as NBA's shift away from domestic fractionation for plasma to purchase of off-the-shelf product, impacts the ARCBS's ability make longer term planning decisions, particularly in the area of capital investment and the pursuit of financial efficiencies.

Recommendations

8. The ARCBS recommends the Review Committee should note that until 2002-03 Australia was self-sufficient in very large scale plasma requirements for IVIg and blood clotting factors, and that the ARCBS believes that given adequate funding, Australia can meet self-sufficiency targets in the future.

9. The ARCBS recommends the Review Committee should examine the approach adopted by the NBA to progressively increase Australia's dependence on imports to 15% in 2005-06 and to almost one quarter of Australia's requirements in 2006-07 in the light of Australia's long held commitment to national self-sufficiency.

10. The ARCBS believes that the Review Committee should recommend improved medium and long term planning processes be introduced to model the demand for plasma products.

Table 7: Forecasted Plasma Product Requirements 2006-07 through 2015-16

Product	Forecast	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	Average Growth Rate pa (AGR) 2006-07 t0 2015-16
Albumex (kg)	Likely	5,241	5,869	6,222	6,595	6,991	7,410	7,855	8,326	8,826	9,355	6.6%
Biostate (250IU)	Likely	65,710	68339	71072	73,915	76,872	79,947	83,145	86,470	89,929	93,526	4.0%
Tetanus IG (250IU)	Likely	4,066	4,147	4,230	4,315	4,401	4,489	4,579	4,670	4,764	4,859	2.0%
Tetanus IG (4000IU)	Likely	32	32	33	34	34	35	36	36	37	38	1.9%
Zoster IG (200IU)	Likely	2,815	2,872	2,929	2,988	3,047	3,108	3,170	3,234	3,298	3,364	2.0%
CMV IG (1.5x 106IU)	Likely	2,646	2,699	2,753	2,808	2,864	2,921	2,980	3,039	3,100	3,162	2.0%
Hepatitis B IG (400IU)	Likely	3,979	4,059	4,140	4,223	4,307	4,393	4,481	4,571	4,662	4,755	2.0%
Hepatitis B IG (100IU)	Likely	2,377	2,424	2,473	2,522	2,573	2,624	2,676	2,730	2,785	2,840	2.0%
Normal IG (160 x 5mL)	Likely	17,011	17,351	17,698	18,052	18,413	18,781	19,157	19,540	19,931	20,329	2.0%
Normal IG (160 x 2mL)	Likely	6,291	6,417	6,546	6,676	6,810	6,946	7,085	7,227	7,371	7,519	2.0%
RhD IG (625IU)	Likely	97,000	98,940	100,919	102,937	104,996	107,096	109,238	111,423	113,651	115,924	2.0%
RhD IG (250IU)	Likely	22,083	22,525	22,975	23,435	23,903	24,381	24,869	25,366	25,874	26,391	2.0%
Prothrombinex HT	Likely	14,138	15,552	16,330	17,146	18,004	18,904	19,849	20,841	21,883	22,978	5.5%
MonoFIX	Likely	9,382	9,467	9,547	9,622	9,692	9,757	9,817	9,873	9,923	9,969	0.7%
Thrombotrol VF	Likely	643	655	669	682	696	709	724	738	753	768	2.0%
Total IVIG (kg) - 1	Likely	1,828	1,956	2,092	2,239	2,396	2,563	2,743	2,935	3,140	3,360	7.0%
Total IVIG (kg) - 2	Conservative	1,811	1,919	1,977	2,036	2,097	2,160	2,225	2,292	2,360	2,431	3.3%

This leads to the following forecasts of domestic plasma requirements in tonnes:

	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	AGR pa
Likely	390	417	445	475	507	542	579	618	660	705	6.8%
Conservative	387	409	421	434	446	460	474	488	502	518	3.35

11 Term of Reference 2 – Regulatory requirements

Plasma and plasma products are biologicals …

Blood plasma fractionated products, like other biological medicinals, are not generic products. Each product has to be assessed in the clinical setting separately to evaluate its clinical impact, relevance and properties, including clinical efficacy and adverse reactions.

Moreover, it is common for even a single product to require individual batch release testing to verify its purity, concentration and/or sterility, as individual batches arising from the same manufacturing processes can have considerable variation in key biological parameters.

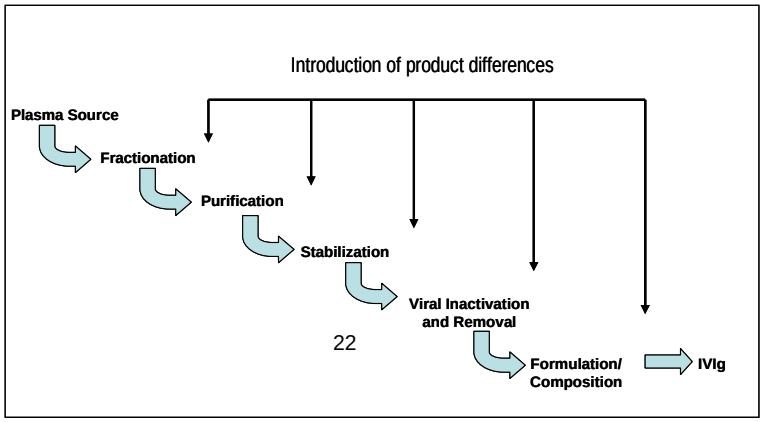
Hence, the nature of the product, and the application of each individual manufacturing step used in the fractionation processing scheme, requires thorough evaluation of the product and the strictest application of manufacturing standards and vigilance in the oversight of fractionation services.

… different fractionation schemes lead to differences in plasma product risks …

Differences in manufacturing processes for biologicals have a profound effect on product specifications safety, efficacy, side effects and quality. Each step in the plasma manufacturing process has the capacity to result in significant differences between products and even batches of the same product. The final quality and inherent safety of the fractionated plasma product will vary with, and be dependent on, each step in the processing chain.

IVIg is a perfect example. IVIg currently is, and is expected to continue to be, the major driver of demand for plasma and plasma products. The fragile nature and size of IgG, the antibody fraction, makes its isolation technically difficult with virtually every step of the purification process having the potential to alter protein structure modifying biologic activity, as shown in Figure 11 for Cohn fractionation techniques.

Figure 11: *Introduction of product differences* [22]



The processes differ considerably between manufacturers with the time for fractionation and purification, the exposure to harsh chemicals, the need for repeated precipitation-

[22] Gelfand EW, 'Critical Decisions in Selecting an Intravenous Immunoglobulin Product', Journal of Infusion Nursing, Vol. 28, No. 6, November-December 2005, pp366-374, p369.

solubilisation, and the final formulation, all contributing to product differences. Furthermore, differences in the approaches to eliminating infectious agents not only lead to safety profile differentials, they can also affect biological parameters. Many procedures may compromise the biologic activity of the final IVIg product and each step in the process can introduce product differences. [23]

These differences can potentially have an impact on safety, tolerability and efficacy.[24]

Not surprisingly, the side effects of different IVIg preparations vary considerably.

Some serious side effects are more likely to be associated with certain formulations of IVIg. More than 100 cases of acute kidney failure have been recognised following the administration of IVIg, usually associated with product containing high concentrations of sucrose. More than 50 cases of thrombotic events have been reported, usually associated with a hyper-osmolar product that increases blood viscosity. In rare cases of IgA deficient patients with anti-IgA antibodies, use of a product with traces of IgA can result in a life-threatening reaction called anaphylaxis. These complications can be reduced by careful product selection.[25]

There are three IVIg products currently registered for use in Australia – one of these is manufactured domestically by CSL Limited (Intragam P) and two are sourced from overseas suppliers (Octagam and Sandoglobulin). These products have been reviewed by an Australian forum of medical specialists (called the National IVIg Forum) who have expertise in the clinical use of IVIg. The National IVIg Forum recommended that Sandoglobulin, which is sucrose-based, not be used in patients with reduced kidney function where an alternate maltose-based IVIg product (such as Intragam P) is available. The Forum also expressed concern that the level of IgA in both Octagam and Sandoglobulin was significantly higher than the levels in our domestic IVIg and recommended that Intragam P be provided for patients with IgA deficiency.

The ARCBS notes that the following concerns have been raised by some Australian clinicians about the currently registered two imported alternatives to CSL Limited's Intragam P, and their relative suitability for patient use:

- The potential need for additional patient consent requirements as plasma used for the manufacture of Octagam can be collected from paid donors and plasma for both Octagam and Sandoglobulin can be collected in countries where BSE has been identified.
- There is concern regarding the need to avoid patients swapping between the available IVIg products as the introduction of a new IVIg product is associated with a higher risk of adverse reactions. This may occur for example where a volume of overseas IVIg is purchased for Australia's National Reserve of plasma products and needs to be rotated into the clinical supply on a regular basis to avoid product expiry.
- Sandoglobulin is lyophilised (freeze-dried) and needs to be reconstituted. For this reason concern was raised in regards to the additional time required to reconstitute the product.
- Sandoglobulin also needs to be administered over a longer period of time, requiring overnight hospitalisation for some patients compared with previous administration of Intragam P in a day ward.

[23] Gelfand, E. W., 'Critical Decisions in Selecting an Intravenous Immunoglobulin Product', Journal of Infusion Nursing, Vol. 28, No. 6, November-December 2005, pp366-374, p367.

[24] Ballow M 'Clinical and investigational considerations for the use of IGIV therapy', Am J Health-Syst Pharm, Vol 62, Aug 15, 2005, Suppl. 3

[25] Stiehm, ER, Editorial, Journal of Pediatrics, January 2006, pp6-7, p7.

- There are concerns about the potential efficacy of the two imported IVIg alternatives because their donor pool inputs are not drawn from Australian donors. Where IVIg is utilised as a treatment for immunodeficient patients, it is believed that IVIg therapy is optimal when the recipient belongs to the same population as the donors.[26] This is because the spectrum of protective antibodies in the IVIg is more likely to reflect the spectrum of infectious diseases that these patients will be potentially exposed to within the Australian community.

Therefore, the ARCBS recommends, to the extent practicable, IVIg products transfused to Australian patients should be manufactured from Australian plasma collections and not imported off-the-shelf purchased product.

… plasma fractionation processes are not risk free …

Various measures have been introduced to eliminate infection agents. Some practices are more effective than others. While most of these measures have proven effective in eliminating enveloped viruses (HIV, HBV and HCV) they have proved less effective for non-enveloped viruses (mainly HAV and parvovirus B19).[27]

This is of particular relevance as new viruses continue to be identified. For example, in early April this year, two new viruses were identified. An 'oceanic' virus, which is a non-enveloped vesivirus, has been identified in post transfusion and post dialysis patients developing hepatitis and in patients with clinical hepatitis. Additionally vesivirus antibodies were detected in normal donors and donors with abnormal liver function tests.[28] A second virus has been identified in Taiwan in hepatitis patients with Non A - E hepatitis including one patient with fulminant hepatitis and also in some healthy individuals. While it is too early to assign significance to either virus, new viruses are cause for substantial concern.[29]

Each step in the process of manufacturing plasma products can affect the safety of the end product, for example:

- The risk profile of the donors' pool (for example, factors such as whether donors are paid or not, the number of first time donors, donor deferrals and the prevalence of infectious disease in the general population impacts the risk of infectious units entering the plasma pool);
- The testing of plasma inputs for infectious markers and the type and sensitivity of the test utilised;
- The size of the plasma pool, which is a factor because larger pools mean a product recipient is exposed to more donors;
- The number and type of viral and pathogenic removal steps (some viral inactivation techniques are more effective against particular infectious agents than others and most have residual risks for particular pathogens[30]);

[26] Simon HU, and Spath PJ, 'IVIg – mechanisms of action', Allergy 2003: 58, pp 543-552, p543

[27] Farrugia A, 'variant Creutzfeldt-Jakob disease and haemophilia – Further guidance on assessing the risks of plasma-derived products for treating haemophilia', WHF TSE Task Force Risk Assessment October 2004, pp1-11, p9.

[28] Smith AW, Iverson PL, Skilling DE et al, 'Vesivirus Viremia and Seroprevalence in Humans', Journal of Medical Virology 2006,78, pp693-701.

[29] Yeh C-T, TSao M-L, Lin Y-C et al, 'Identification of a Novel Single-Stranded DNA Fragment Associated with Human Hepatitis', Journal of Infectious Disease 2006:193, pp1089-1097.

[30] Farrugia A, 'variant Creutzfeldt-Jakob disease and haemophilia – Further guidance on assessing the risks of plasma-derived products for treating haemophilia', WHF TSE Task Force Risk Assessment October 2004, pp1-11, p8.

- The extent, if any, of prion removal; and
- Compliance with current good manufacturing practices (pathogenic removal techniques are only useful if the steps in the manufacturing processes are carried out properly).

The ARCBS believes it is vital that fractionation services for Australian plasma products are at least as clinically efficacious and as safe as products currently manufactured by CSL Limited.

The NBA's policy of using these products as the inventory for Australia's National Reserve of plasma products presents many challenges as follows:

- To ensure appropriate product traceability each new product code needs to be included in the ARCBS's blood management system, as well as every hospital blood management system.
- The National Reserve inventory needs to be rotated into the general clinical supply before the products' 'use by' dates expire. Clinicians have complained that patients are being forced to swap from Intragam P to the alternatives and back again. Ameratunga *et al* have reported adverse effects as a result of changing IVIg products, and that caution should be exercised when changing IVIg products as they are not biologically equivalent.[31]
- There is a need to ensure health professionals are adequately informed about each new product, particularly differences relating to adverse reaction profiles and administration requirements to ensure that the products can be safely administered.

The ARCBS believes that ARCBS should be funded to collect additional plasma to allow the National Reserve to be primarily comprised of products fractionated under the Plasma Fractionation Agreement. This would be a one-off investment and would avoid the challenges detailed above.

… Australia's regulatory environment is world best practice …

Australia's regulator for blood and blood products, the TGA, is internationally recognised as one of the three leading regulatory agencies of its type in the world.

Its regulatory framework for blood collection, distribution and plasma fractionation draws on best practice requirements from the EU and North America, and the adoption of EU standards. In addition, as a result of CSL Limited providing plasma fractionation services for countries in the Asia Pacific Region (Singapore, Hong Kong, Malaysia and New Zealand), and concerns about the potential for cross-contamination of Australian plasma through the use of shared plant facilities, the TGA has required CSL Limited to segregate the processing of Australian plasma through the use of exclusive fractionation columns.

Furthermore, the regulation of all aspects of plasma collection and fractionation by a single regulator has created an integrated regulatory environment that, together with Australia's island status, has enabled rapid and effective responses to new and emerging threats to the blood supply.

[31] Ameratunga R, Sinclair J, Kolbe J, 'Increased risk of adverse events when changing intravenous immunoglobulin preparations', Clinical and experimental immunology, 2004 Apr;136(1):111-3.

… segregation of Australian plasma provides an additional world leading level of protection …

It is common throughout the world for fractionation schemes to include chromatographic processes in addition to precipitation techniques (Cohn fractionation) as the chromatographic processes generally deliver higher yields and higher quality products. However, the chromatographic resins are not amenable to harsh chemical agents for cleaning columns as is steel equipment. With the advent of vCJD and prion resistance to inactivation/elimination through non-damaging column cleansing techniques, there is a significantly heightened concern about the dangers of cross-contamination between batches of plasma for fractionation.

Given it is now common for major commercial fractionators to process plasma through their plant from several different country collection sources, segregation of Australian plasma for processing through exclusive fractionation columns minimises the potential for cross contamination.

The TGA requirement for segregation also meets the concerns raised by the Australian Government's Auditor-General who noted that any risk of cross-contamination would be ameliorated and the national health interest enhanced if the TGA were to extend its regulatory arrangements for processing of blood products prepared from imported plasma at CSL Limited's Broadmeadow fractionation facilities.[32]

The ARCBS strongly supports the segregation of Australian plasma collections during plasma fractionation processing. It is important to note that following the introduction of this TGA requirement, the US FDA, through its Transmissible Spongiform Encephalopathies Advisory Committee, engaged the Plasma Protein Therapeutics Association (PPTA), the global association of the major producers of plasma therapeutics, to examine the possibility of requiring similar segregation requirements for US plasma collections. The approach was opposed by the industry at that time. Given that the hearings of the FDA's Transmissible Spongiform Encephalopathies Advisory Committee were held in 2001 against the backdrop belief that transmission of vCJD through blood or blood products was only a theoretical risk, the applicability of mandatory segregation is even more relevant today, considering this theoretical risk has been proven a reality.[33]

… the TGA is a vigilant regulator armed with powerful domestic sanctions …

CSL Limited's fractionation services are subject to licensing approval by the TGA. The TGA has at its disposal some of the most powerful sanctions able to be used against non-complying manufacturers available to any regulator in Australia and in line with those available to the Australian Competition and Consumer Commission (ACCC). Besides having the capability to suspend or cancel a license to manufacture, and/or cancel the product registration, criminal proceedings can be brought against company executives involving substantial gaol terms for any breech which knowingly puts public health and safety at risk.

[32] Australian National Audit Office, 'The Sale of CSL', Audit Report No. 14, 1995-96.

[33] Food and Drug Administration Transmissible Spongiform Encephalopathies Advisory Committee Minutes of 9th Meeting held 28 June 2001

As a result of the recommendations of the Joint Committee of Public Accounts and Audit concluding plasma fractionation is an area which requires an active regulator and a high level of vigilance[34], the TGA has undertaken the most intensive of audit surveillance programs, including a high proportion of unannounced audits, of CSL Limited's compliance with the code of good manufacturing practice.

This Good Manufacturing Practice (GMP) audit program gives the ARCBS, governments and the patient community, the highest levels of assurance of the quality of CSL Limited plasma fractionation services and products.

… but these domestic penalties and criminal sanctions cannot be replicated in overseas fractionation contracts …

While Australia will be able to include financial penalties and other contractual sanctions in any toll fractionation services agreement with an overseas plasma fractionator, its 24 hours a day, 365 days a year capacity for vigilance and oversight cannot be replicated overseas with the force of domestic criminal sanctions as they can be applied under statutory regulations for services provided in Australia.

There are well known instances of sub-standard practices and non-compliance with good manufacturing practices, as well as cover-ups of processing failures and activities which place the health and safety of individuals at risk. Catastrophic events have also occurred, such as the HIV infected blood from South Africa, processed by European fractionators after being relabelled as being from Canada, and then sold on to China and India, exposing thousands of people to significant risk of contracting HIV and HCV as a result.

There cannot be the same level of certainty and confidence that off shore manufacturing process failures, equipment breakdowns, potential cross contamination and accidental or deliberate mixing of Australian collections with oversees collections would be reported, given the size of the commercial loss which may be involved, particularly in view of the large batch sizes utilised in fractionation services.

Historically, Australia, like other comparable countries, has experienced contamination of the blood supply from agents such as HIV and HCV, and other countries have experienced specific catastrophic transmission of infectious agents through plasma products.

Powerful sanctions and disincentives in the hands of a strong, vigilant regulator, acting in the national interest, and using its domestic statutory provisions, provide substantial incentives for manufacturers to be open, transparent and compliant and ensure the safest possible plasma fractionation services possible.

Given the significant diminution in certainty and confidence that could arise about the safety of off shore fractionation services, particularly with the large scale fractionation services being developed in Asia and the sub-continent, the ARCBS recommends the Review Committee should find that any plasma fractionation services to process Australian plasma be undertaken in Australia.

[34] Joint Committee of Public Accounts and Audit, Audit Report No. 24, 1999-2000, Commonwealth Management and Regulation of Plasma Fractionation.

… plasma fractionation products supplied to the Australian market must be benchmarked for prion clearance …

Since the description of vCJD, the Human form of BSE in 1996, concerns have been expressed about the capacity for transmission of vCJD by transfusion. Actions were taken by many countries to limit such theoretical transmission by restrictions on donors travelling to, or transfused in, countries where there had been a substantial epidemic of BSE.

The pathogenic prion form PrP^{Sc} from vCJD has been found in tonsils, spleen, thymus, nodes and lymphoid tissue in the gut (such as in the appendix) even before the onset of clinical disease. Prion disease has been detected in blood or its components in experimental animal models, with at least 40% of the infectivity plasma associated. Infectivity is also present in cryroprecipitate and Cohn fractions 1-3.[35] Transfusion transmission of prions has been shown in animal systems, for example, sheep and hamsters.

Fears of transfusion transmission in humans were heightened when the Transfusion Medicine Epidemiology Review in the UK in 2004 identified a patient with vCJD, who had developed symptoms 6.5 years after receiving a blood transfusion from a donor 3.5 years before the donor developed symptoms of vCJD.[36]

Further confirmation arose from a second case of blood transfusion from a donor who subsequently developed vCJD, when the recipient who died of a non-related condition was found to have vCJD prions in lymphoid tissue A third case reported in 2006 developed vCJD eight years after transfusion of blood products from a donor who developed vCJD 20 months after the implicated donation

While there have been no cases attributed to fractionated products to date, in the UK recipients of coagulation factors and intravenous immunoglobulin designated to be high risk have been informed and are being monitored.

In examining a probable link between transfusion and vCJD infection, a review of blood transfusion policies in the UK and a risk assessment on the implications for plasma therapy recipients was commissioned by the UK Department of Health. The commissioned research concluded that the infectivity concentrations in blood were likely to be highest in the buffy coat fraction, followed by those in plasma and the whole blood. (See Table 8 below.) Moreover, the report stated that levels of the infectious agent present in a full unit of blood would probably be sufficient to cause infection in recipients. The UK Health Protection Agency also evaluated the risk of different plasma products in an attempt to determine which were most likely to carry the greatest degree of vCJD infectivity. Recipients of factor VIII, factor IX and antithrombin were estimated to have the highest risks: administration of even a single one-vial dose of these products was determined to be sufficient to cause transmission of the disease. Intravenous immunoglobulin (IVIg) and large doses of albumin were concluded to be of medium risk, and anti-D and intramuscular IVIg were determined to be of low-risk of infectivity.[37]

[35] Ironside J, Head M, 'Variant Creutzfeldt-Jakob disease: risk of transmission by blood and blood products', Haemophilia (2004), 10, (Suppl. 4), pp64-69, p67

[36] Ironside J, Head M, 'Variant Creutzfeldt-Jakob disease: risk of transmission by blood and blood products', Haemophilia (2004), 10, (Suppl. 4), pp64-69, p67

[37] Ironside J, 'Variant Creutzfeldt-Jakob disease: risk of transmission by blood and blood therapies', Haemophilia (20064), 12, (Suppl. 1), pp8-15, p12.

Table 8: Selected infectivity of blood components[38]

	Volume (mL unit $^{-1}$)	Infectivity (ID_{50}/unit)	Infectivity concentration (ID_{50}/unit
Whole blood	450	900	2.0
Plasma	225	480	2.1
Filtered plasma	225	480	2.1
Red cells	212	219	1.0
Buffy coat	14	201	14.9

As recipients of plasma therapies appear to possess the highest risk of contracting vCJD,[39] it is crucial every fractionator attempting to obtain marketing approval in Australia for a plasma product undertake and submit the results of actual animal studies benchmarking prion clearance rates for their particular fractionation service.

The TGA required CSL Limited in 2001 to undertake animal experiments to demonstrate the potential for clearance of prions through its fractionation processes for all plasma products manufactured at its Broadmeadows facility in Melbourne. The risk of including an infectious agent in a plasma pool depends on the prevalence of the agent, the number of donations included in the pool and the prion clearance rates of the various manufacturing steps. Estimation of the risk of prionemia in the donor population and subsequent restrictions on donations from donors estimated to be at higher risk represent an important plank in the risk minimisation process It is strongly recommended that for each fractionation system each step in the process needs to be compared as well as the overall additive steps in prion reduction.

Chronically transfused individuals, such as people with haemophilia, are ultimately exposed even with small donor pool sizes and low prevalence of agents because of their extremely high frequency of transfusion of plasma products.[40] The NHMRC Special Expert Committee on Transmissible Spongiform Encephalitis (SECTSE) therefore recommended to the TGA that it set a 7 logarithmic_{10} reduction in prion clearance for plasma fractionated products for people with haemophilia A because of their exposure to large pooled donations as well as their high frequency of usage of these products.[41]

The TGA should make it mandatory for actual prion clearance benchmarking results from their fractionated products be submitted for evaluation of any plasma product seeking marketing approval for supply in Australia. The European Medicines Agency has recently also recommended manufacturers of plasma based products assess the prion clearance rates of their manufacturing processes.[42]

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[38] Ironside J, 'Variant Creutzfeldt-Jakob disease: risk of transmission by blood and blood therapies', Haemophilia (20064), 12, (Suppl. 1), pp8-15, p12.

[39] Gregori L, McCombie N, Plamer D, et al, "Effectiveness of leucoreduction for removal of infectivity of transmissible spongiform encephalopathies from blood:, The Lancet, Vol364, August 7, 2004, pp529-531, p529.

[40] Farrugia A, 'variant Creutzfeldt-Jakob disease and haemophilia – Further guidance on assessing the risks of plasma-derived products for treating haemophilia', WHF TSE Task Force Risk Assessment October 2004, pp1-11, p4.

[41] Australian Health Ministers Advisory Committee's Jurisdictional Blood and Blood products Committee, 'Report of the working party on the supply and use of Factor VIII and Factor IX in Australia', 2003, p62

[42] European Medicines Agency, "CHMP Position Statement on Creutzfeldt-Jakob Disease and Plasma-Derived and Urine-Derived Medicinal Products', London, 23 June 2004, EMEA-CPMP-BWP2879-02-rev 1, pp1-17, p9.

… and emerging risks are minimised by our integrated, self-contained, domestically regulated environment.

Australia's integrated domestic blood system minimises exposures to emerging risks because plasma is collected from Australian donors for fractionation in Australia. This is further enhanced by the high level of openness and transparency amongst clinicians, Australian health institutions, researchers, the ARCBS, the domestic fractionator and the TGA. This generates cooperation and commitment to free exchange of information, and engenders a high degree of confidence amongst critical players in the blood system, which provides a fundamental strength to the Australian blood system that ultimately benefits Australian users and potential users of blood products.

The ARCBS believes that Australian governments should only ever allow importation of plasma products where shortages occur, or for niche products which are not available domestically. The deliberate strategy of importing an increasing proportion of blood products by purchasing off-the-shelf finished product, utilising plasma sourced from paid donor collections, provides a less safe blood system.

Recommendations

11. The ARCBS strongly supports the current best practice regulatory model overseen by the TGA for protection of the Australian plasma fractionation services provided by CSL Limited and recommends there be no diminution in these requirements for any alternative fractionation provider.

12. The ARCBS strongly supports the segregation of Australian plasma collections to avoid potential cross contamination during plasma fractionation processing.

13. The ARCBS believes the National Reserve should be primarily comprised of products fractionated under the Plasma Fractionation Agreement with CSL Limited to ensure continuity of treatment regimes as well as for national self-sufficiency objectives.

14. The ARCBS recommends, to the extent practicable, IVIg products transfused to Australian patients should be manufactured from Australian plasma collections.

15. The ARCBS is of the view that powerful domestic penalties and criminal sanctions enabling stringent regulatory oversight cannot be replicated in any overseas toll fractionation contract. Therefore, the ARCBS recommends the Review Committee should find that any plasma fractionation services to process Australian plasma should be undertaken in Australia to ensure maximum confidence in Australia's blood supply.

16. The ARCBS strongly recommends the Review Committee find that any plasma fractionated blood products supplied to the Australian public be benchmarked for prion clearance using acceptable animal model studies as part of the TGA's marketing approval and manufacturing licence requirements.

17. The ARCBS believes the Review Committee should conclude Australia's integrated blood system provides the best protection against unknown emerging risks, ensuring the safest blood system practicable for Australia.

12 Terms of Reference 3 and 4 – Increasing competition

Australia's Health Ministers have re-affirmed the self-sufficiency policy for Australia and ruled out 'off-the-shelf' purchase of imports …

As noted in the discussion under term of reference 1 (Section 10), Australia has moved away from self-sufficiency for plasma products with 21% of IVIg demand forecast to be satisfied through the importation of off-the-shelf alternative products in 2006-07.

However, in April 2006, Australian Health Ministers re-affirmed Australia's commitment to the self-sufficiency policy and advised Australia will only seek to import plasma products to meet product shortages or product shortfall "in a very narrow range of circumstances where there is an inability to meet clinical need through the domestic supply, and where supply chain risks must be addressed."[43]

The ARCBS believes it can meet Australian plasma collection targets to satisfy domestic demand provided appropriate long term planning and approval processes are in place and adequate resourcing of the plan is approved. This would include sufficient National Reserves to ensure supply chain risks are adequately addressed. Current plasma productivity in Australia shows that in those jurisdictions which have prioritised self sufficiency, it has already been achieved.

… leaving three options for provision of fractionation services of Australian plasma collections …

There are three options for providing plasma fractionation services to meet Australia's domestic demand for plasma products.

- Option 1 - the renegotiation of the current Plasma Fractionation Agreement with CSL Limited into the future;
- Option 2 - open tender/procurement for fractionation services to be undertaken in Australia by a plasma fractionation provider(s) under domestic regulatory arrangements; or
- Option 3 - open tender/procurement processes for fractionation services to be undertaken either off shore or through a combination of off shore and Australian facilities by a fractionation service provider(s) which meets TGA's manufacturing approval requirements.

… but off shore toll fractionation services raise significant regulatory, security of supply, logistical issues of supply and national security concerns …

Given that the ARCBS is the owner of the blood collected from Australian donors, and any plasma products subsequently manufactured from these blood collections, fractionation services provided by a toll fractionator located off shore raise substantial concerns with respect to regulatory, security of supply, logistical (such as extended transport, supply lead times and storage times) and potential national security issues. They also have significant cost implications and some of the major cost impacts are highlighted in our analyses of these issues.

[43] Australian Health Ministers Council, Meeting of 7 April 2006

(i) Regulatory issues

Term of reference 2 sets out in detail why domestic management of manufacturing by a vigilant, best practice regulator, providing 24 hours a day, 365 days a year oversight, armed with powerful domestic sanctions, including criminal penalties, is unable to be replicated in overseas supplier contracts.

As noted earlier, these powerful sanctions and disincentives in the hands of an Australian regulator, acting in the national interest, using domestic statutory provisions to oversee plasma fractionation services undertaken in Australia, ensures the safest possible manufacturing of plasma products from Australian plasma collections.

Australia has, like the USA, Canada and EU countries, been risk averse in its blood safety initiatives, spending in excess of $18m per year to implement Nucleic Acid Testing (NAT) to substantially reduce the chance of an infectious unit of blood being non-detected in the window period for HIV or HCV. Studies in the USA and EU have revealed this expenditure produces one extra Quality Adjusted Life Year (QALY) gained at a cost of $US2m.[44]

It is generally accepted that less than $40,000 per QALY is an appropriate target to assess the potential viability of health interventions. However, the introduction of NAT demonstrates that national governments are prepared to spend in the order of $AUD2.6m per QALY to secure a safer blood supply. In light of this, therefore, it is incomprehensible why the governments of Australia would wish to risk one of the safest blood supplies in the world, and substantially erode the confidence of the Australian community in the safety of blood supply, for what might be at best incremental cost savings in the name of 'free trade' and 'competition'.

As noted, the TGA has imposed stringent regulatory requirements on the collection and processing of plasma by the ARCBS and the further manufacture of that plasma by CSL Limited. In addition to being licensed to undertake these activities, ARCBS and CSL Limited must demonstrate compliance with the *Code of GMP (cGMP)* and standards based on the Council of Europe guidelines and the British Pharmacopoeia and associated monographs. These requirements would continue to apply to the ARCBS and any alternative fractionator.

CSL Limited has developed detailed specifications, in consultation with the ARCBS, for the supply of plasma which set out requirements for packing, labelling, delivery times, documentation and declarations for release quality. A new off shore fractionator will impose new specifications on ARCBS and it is likely that minimum limits will be set for the size of plasma consignments to minimise the need (and therefore the costs) for the fractionator to store plasma until there is sufficient for a batch to be manufactured. While there are economies of scale associated with transporting larger volumes of plasma in a single consignment, there are also increased risks and a transport failure could potentially result in the loss of a large volume of plasma with a high potential for stock-out of the subsequent plasma derivative blood products.

There will be additional regulatory impacts for an off shore fractionator. If the TGA does not, or cannot, enforce the segregation of Australian plasma, it is likely the fractionator will be required to provide regular data on the incidence of infectious agents and testing methodologies, and the efficacy of cleaning regimes to provide assurances of safety to the TGA. The TGA would also need to undertake targeted, unannounced audits to provide assurance on compliance.

[44] Allain J, 'Transfusion risks of yesterday and today' Transfusion Clinique et Biologique, Vol. 10(1), February 2003, pp1-5, p5.

Export of Australian plasma to an off shore fractionator would increase the scrutiny of the TGA in areas such as plasma transport, contract management and supplier assessment, review and management. This scrutiny would impact both ARCBS and the fractionator and increases the costs of regulation and compliance.

The TGA is fully cost recovered and would likely undertake at least some GMP audits of the external fractionator. These costs would be passed on to the ARCBS, as the owner/sponsor of plasma products manufactured from plasma fractionation services, and are estimated to be in excess of $200,000 pa (based on three auditors conducting a four day audit twice a year and including travel time).

(ii) ARCBS manufacturer performance audits

The ARCBS and CSL Limited do not currently audit each other as both organisations are licensed and audited by the TGA, although the ARCBS/CSL Limited GMP agreement stipulates that audits may be conducted with prior approval.

In the event that fractionation was transferred off shore, initial and ongoing audits carried out by the ARCBS on the offshore fractionator would be a critical component of supplier performance review and management. It is also likely that ARCBS would be subjected to audits by the overseas fractionator's national regulatory authority and may be required to meet that regulator's requirements (for example, if the fractionator is located in the USA, the national regulatory authority is the USFDA). This situation would have the potential to apply restrictions that are not currently relevant or appropriate for Australia, for example related to certain tropical diseases, from which ARCBS has a TGA exemption for Northern Australia.

The ARCBS estimates this additional cost to Australia's blood system could be in the order of $20,000pa (based on two auditors for 2.5 days, two audits per year inclusive of travel costs)

(iii) Logistics

The logistics and cost of transport of frozen plasma overseas would have a significant impact on ARCBS operations.

Currently the ARCBS despatches frozen plasma from eight dispersed locations around Australia direct to CSL Limited in Melbourne. If plasma is to be shipped off shore, then the ARCBS would need to obtain and manage suitable warehousing space which met all regulatory requirements for the security and storage of frozen plasma at or below -20^{o}C. The warehouse would have to have the capacity to accommodate at least the volume/weight of plasma required for a batch as specified by the overseas fractionator and have additional capacity to allow for any delays in shipping in order to avoid wastage or storage at local ARCBS sites.

ARCBS would be responsible for managing the transport from the warehouse to the final shipping point and again on the arrival back in Australia of the finished products. This would require investment in additional capacity to manage the inventory of finished stock on return. Due to economies of scale of transport, the volumes involved in this are likely to be substantial for each shipment.

It is assumed that transport would be by ship rather than air on cost grounds. However it should be noted that as transport by ship takes weeks rather than days, ARCBS would need to collect additional plasma and maintain higher levels of inventory as a buffer to cover not only the extended processing time and resultant additional "work in progress" plasma, but also the risks inherent in extended transportation. This additional collection is likely to be substantial compared with the current arrangement with Australia's domestic fractionator.

There are significant practical implications arising from the requirement to maintain full cold–chain supply at or below -20˚C for extended distances and the regulatory oversight required. These include the selection and validation of packaging and shipment over the required distance/timeframe to maintain temperatures at or below -20^{o}C as well as meeting International Air and Transport Association (IATA) regulations (for example, limits on dry ice and packaging requirements) and managing any potential limitations on volume of plasma imposed by air or sea carriers.

The risks associated with the distances and length of time of transport would significantly increase the potential for product loss or reduced yield. These risks include the failure to meet transport times due to delayed shipments, inclement weather and mechanical problems. Delays in transport have the potential to cause temperature fluctuations within the shipment. While extreme fluctuations will result in the loss of the plasma, fluctuations within acceptable limits will result inevitably in reduction in yield.

To manage this more complex logistical environment, the ARCBS would need to enhance its IT capability and systems support which would have significant cost and operational implications.

Current plasma logistics and potential for change

The current infrastructure and logistics of plasma transport to CSL Limited is based on historic jurisdictional arrangements which are currently under review. There are 18 processing sites around Australia from which ARCBS despatches frozen plasma to CSL Limited. For transport efficiency reasons, these are consolidated such that CSL Limited receives deliveries from eight points within the ARCBS network in either refrigerated vehicles (where there is enough volume of plasma transported to utilise such vehicles) or in ambient temperature vehicles where volumes are managed in validated temperature controlled shippers. Current shipment frequencies are based on balancing the optimal utilisation of refrigerated vehicles or shippers with the limited frozen plasma storage capacity within current ARCBS sites. A summary of current shipment quantities and frequencies by ARCBS despatch location to CSL Limited is included in Table 9.

Table 9: Current ARCBS shipment details

ARCBS consolidated despatch point	Shipment frequency to CSL	Shipment type	Shipment quantity in multiples of
Adelaide	daily	Shipper	130kg
Alice Springs	fortnightly	Shipper	7.5kg
Brisbane (last point of despatch for QLD)	fortnightly	ARCBS refrigerated truck	3000kg
Canberra (last point of despatch for NSW and ACT)	weekly	ARCBS refrigerated truck	1700kg
Darwin	weekly	Shipper	7.5kg
Hobart	weekly	Shipper	9kg
Melbourne	daily	Shipper	150kg
Perth	twice per week	Shipper	150kg

The current cost incurred in transporting fresh frozen plasma to CSL Bioplasma is approximately $560,000 pa. This includes both the expense incurred from the use of third party transport providers plus the operational cost of the ARCBS owned refrigerated vehicles, based on the proportion of time that they are used for delivering fresh frozen plasma to CSL Bioplasma.

The annual cost includes pickup from all points of fresh frozen plasma processing within the ARCBS network and the return of the empty shipping containers to the ARCBS sites. The current arrangements for shipping fresh frozen plasma to CSL Limited are presently being reviewed for optimisation opportunities as part of a national logistics review for all blood and blood products recently commissioned by the ARCBS.

Cost implications of off shore shipping of plasma

Four shipment scenarios have been assessed to determine the potential shipment quantities and frequencies that could occur when transporting fresh frozen plasma to an overseas fractionator. These scenarios range from the least cost but greatest product supply risk (use of 40ft high cubic refrigerated sea freight containers), to the greatest cost but least inventory/supply risk (use of daily airfreight). For each of the shipment scenarios assessed, the annual quantity of deliveries is modelled on 2005-06 supply levels, to determine the proportion of the annual supply that each shipment would represent. Clearly, with more frequent despatch of smaller quantities, the lower the risk of complete product loss or delay to return for supply.

A summary of this assessment has been included in Table 10.

Table 9: Annual shipment quantities for overseas fractionation of Australian plasma

Shipment scenarios	Outbound fresh frozen plasma		Inbound plasma fractionated products	
	2005-06 annual quantity of shipments	% of annual supply per shipment	2005-06 annual quantity of shipments	% of annual supply per shipment
Regular weekly despatch of 20ft refrigerated container, whether full or not, by sea freight	52	1.9%	52	1.9%
Despatch of dedicated 20ft refrigerated container, once full, by sea freight	44	2.3%	24	4.2%
Despatch of dedicated 40ft high cube cubic refrigerated container, once full, by sea freight	19	5.3%	10	10%
Daily despatch by air freight	365	0.3%	212	0.5%

New Storage facilities

It is important to observe that no current ARCBS facility is capable of storing the accumulated frozen plasma for loading a 20ft or 40ft refrigerated container, nor are any of the current ARCBS facilities fitted with the necessary container loading dock and refrigerated air lock to ensure the frozen plasma remains within temperature specification whilst loading the containers. Possible solutions in the event of the introduction of an overseas fractionator for Australia's plasma fractionation could include contracting a third party with appropriate facilities to store the plasma for accumulation and loading the containers and/or including the appropriate facilities in the specification of the planned future ARCBS facilities in Sydney or Melbourne. In either case, the facilities would need to be licensed by the TGA as compliant with the code of GMP. The cost of a GMP compliant warehouse has been estimated at a minimum of $300,000 to fit out an existing warehouse shell with annual running costs of around $100,000 pa.

Balancing cost of freight and supply risk

It is recommended that if fractionation of Australia's fresh frozen plasma were to occur overseas that the appropriate balance of cost and supply risk minimisation would be to sea freight the fresh frozen plasma to an overseas fractionator within fully utilised 20ft refrigerated containers. The use of the smaller 20ft containers limits the exposure of loss of product in any one shipment to no more than 2.3% of a years supply, based on 2005-06 supply levels.

For the return of the fractionated products back to Australia, it is recommended that the appropriate balance of cost and supply risk minimisation would be to sea freight the largest volume product, Albumex, in 20ft containers as each batch is produced. Albumex represents 60% of the packaged cubic volume of all the fractionated products (based on current packaging and 2005-06 supply) and is the only fractionated product that allows storage at ambient temperature rather than 2 to 8 deg C. Transporting each batch of Albumex as it is produced, assuming that manufacturing batch sizes are no larger than 5 tonnes, ensures that no shipment of this product represents more than 2.5% of a year's supply of this product or has a fractionation value exceeding $200,000.[45]

For the remaining fractionated products, where the average fractionation value of a packaged cubic metre of product averages over $500,000,[46] it is important to limit the quantity of each shipment to ensure that no one shipment's value, or proportion of that product's annual supply, is too great. Therefore, to limit shipment quantities and to reduce the risk and time exposure to a container going out of temperature specification, the ARCBS recommends that each product, as it is produced, be air freighted to Australia.

The estimated incremental freight cost based on the ARCBS recommended transport method for the combined plasma transport to an overseas fractionator and the return of the fractionated products, is estimated to be in the range of $1.5m to $2m pa based on current 2005-06 volumes and the locations modelled. Three destinations and four shipment scenarios and an optimal combination of these scenarios have been analysed for indicative cost and lead time implications. A summary of the cost and total transit lead times associated with each of the scenarios modelled and the assumptions made is included in Table 10 below.

[45] Based on estimated third party rates for storage and handling and the ARCBS 2005-06 supply plan

[46] Based on an assumption that average FFP pallet=1.2m^3 of product and that fractionated products pallet=1m^3 of product

Table 10: Frozen plasma shipment to overseas fractionator – transport implications

		Incremental freight cost pa. $k fractionator location			**Incremental days inventory** fractionator location		
Shipment scenario's	Shipment scenario supply risk rating	Los Angeles USA	Chicago USA	Stockholm Sweden	Los Angeles USA	Chicago USA	Stockholm Sweden
Outbound - Fresh frozen plasma transport to overseas fractionator							
seafreight - weekly in dedicated 20' refrigerated container	Medium	427	568	472	32	43	53
seafreight - maximising utilisation of 20' refrigerated container	Medium	361	481	399	39	50	60
seafreight - maximising utilisation of 40' high cube refrigerated container	High	215	263	244	46	57	67
airfreight	Low	4,383	5,489	7,655	3	3	4
Inbound - Plasma fractionated products transport to Australia from overseas fractionator							
seafreight - weekly in dedicated 20' refrigerated container	High	552	793	533	27	34	50
seafreight - maximising utilisation of 20' refrigerated container	High	255	366	246	34	41	57
seafreight - maximising utilisation of 40' high cube refrigerated container	High	142	188	145	62	69	85
airfreight	Low	1,826	2,327	2,432	3	3	4
Use sea freight in 20' containers for each batch of Albumex and airfrieght all other products	Low	1,179	1,568	1,410	12	14	18
Combined Outbound and Inbound							
seafreight - weekly in dedicated 20' refrigerated container	High	979	1,362	1,005	59	77	103
seafreight - maximising utilisation of 20' refrigerated container	High	616	847	645	73	91	117
seafreight - maximising utilisation of 40' high cube refrigerated container	High	357	451	389	108	126	152
airfreight	Low	6,209	7,816	10,087	6	6	8
seafreight maximising utilisation of 20' refrigerated containers for outbound plasma and for inbound fractionated products use seafreight in 20' refrigerated containers for each batch of Albumex and airfrieght for all other products.	Medium	1,540	2,049	1,809	51	64	78

Increased inventory to cover lead times in return of products

In addition to the annual cost implications associated with the storage and transport of fresh frozen plasma overseas and the return freight of the finished derivative products, there would need to be a one off inventory adjustment to accommodate the delay in availability of finished plasma and plasma fractionated product in transit. The total inventory of plasma and plasma fractionated products would need to be increased (in the order of 80 to 120 days cover), based on the overseas fractionator destinations modelled. The total increase in inventory cover comprises increases in transport time, batch size and safety stock to accommodate variation in supply associated with fractionating plasma overseas. A breakdown of the estimated required inventory increase is included in Table 11.

Table 11: Inventory increase in days cover due to lead times

	Incremental days inventory		
	Plasma outbound	Finished Products inbound	Total
In transit inventory - includes accumulation time to fill containers, container pickup and customs clearance, overseas transit time and destination unloading, customs clearance and delivery.	39 to 60	12 to 18	51 to 78
Safety stock – cover shipping times covers variation in shipping times and schedules and variation in fractionator manufacturing schedules. An allowance of 50% of in transit inventory has been assumed.	20 to 30	6 to 9	26 to 39
Batch size – larger likely If minimum batch size doubled on current - increase in the total inventory would be around 3 days cover to allow for accumulation of the additional plasma to facilitate the larger batch size.	3		3
Cumulative days inventory increase	62 to 93	18 to 27	80 to 120

Key assumptions made in the development of this evaluation were:

- Cost and lead times are based on freight rates, transit times and indicative seasonal variation provided by current ARCBS airfreight and sea freight providers based on the ARCBS 2005-2006 supply plan volumes. The cost of dry ice has been included where required.
- The overseas fractionator takes responsibility for the plasma once their transport agent receives the shipment in Australia, and maintains responsibility for the fractionated products until they are delivered back to ARCBS. Therefore the overseas fractionator is responsible the incremental transport insurance.
- All sea freight utilises refrigerated containers, with fresh frozen plasma consolidation in Melbourne
- All products are fractionated at one overseas site
- The overseas fractionator has the same product production frequency and minimum product production run as the current situation with CSL
- The overseas fractionated product mix and packaging characteristics are the same as current CSL plasma fractionated products
- Incremental day's inventory includes the time required to build stock to fill the shipping container and the transit and clearance times. No increase in safety stock has been assumed in this evaluation.
- Inbound fractionated products are transported in dedicated containers
- Envirotainers® (temperature regulated airfreight containers) are used for all inbound airfreight of Plasma fractionated products
- Fully utilised container shipment quantities are based on achieving 70% utilisation of the suppliers stated internal container capacity.
- The scenario supply risk evaluation was based on the proportion of supply that each container represents, whether the container requires refrigeration below ambient temperature and the transit time.

The one off cost to purchase the additional inventory required to implement overseas fractionation, including additional fresh frozen plasma and fractionated products production, is estimated to be of the magnitude of $16m to $27m[47].

If an overseas fractionator utilised multiple sites to fractionate products then any transport cost between production facilities should be included in the fractionators' product costing.

In addition to the new freezer storage space required to accumulate the fresh frozen plasma before loading sea containers, the fractionated product ambient and cool room storage capacity for the ARCBS sites would also need to be increased. The ARCBS fractionated product storage capacity would also require expansion to allow for the storage of the national inventory reserve that CSL currently holds and the increase in safety stock required to manage risk associated with implementing the longer transit times of an overseas fractionator. The national inventory reserve for fractionated products is based on the current CSL fractionation arrangements including production lead times and batch quantities, not all products currently have a National Reserve allocation, but where they do, products average three months worth of supply. It is also required that a minimum of two batches of each fractionated product be available in Australia at any one time in case of product recall. Therefore, increases in batch size by overseas fractionators will potentially have a multiplier effect on the required inventory holding capability in Australia.

Based on current supply and national plasma derivative reserve volumes, the incremental ARCBS product storage requirement would be in the order of 85m^2 to 92m^2 of additional storage area , with a split of approximately 60% ambient and 40% cool room. No current ARCBS site can accommodate this additional storage requirement, therefore possible solutions in the event of the introduction of an overseas fractionator for Australia's plasma fractionation could include the contracting of a third party with appropriate cool room facilities to store the increased inventory of plasma fractionated products and/or including the appropriate facilities in the specification of the planned future ARCBS facilities in Sydney or Melbourne. It is estimated that outsourcing the incremental fresh frozen plasma storage and handling and the incremental fractionated product storage and handling would cost in the vicinity of $60,000 to $80,000 pa.

(iv) Management of product recalls

Management of product recalls involving an external toll fractionator will be considerably more difficult than under present arrangements with CSL Limited.

First, the dialogue to establish the need and *raison d'être* for a recall will be most likely across differing time zones, and therefore be problematic, particularly if clinicians and external medico/scientific experts have to be involved.

Second, the open, transparent confident information sharing relationship with CSL Limited is unlikely to be replicated and problem reporting and investigations will be drawn out. Besides the possible safety issues that are pre-eminent in this scenario (as a result of delays in decision making), the recall process will be logistically more difficult, with product returns having to be sent back overseas, adding a further layer of cost. On the assumption that recall activity will be of a similar order to current domestic experience, and that ARCBS as owner of the plasma and plasma fractionated products will bear the sole responsibility for managing the recall, the ARCBS estimates the additional costs associated with recall activity to be in the order of $400,000 pa.

[47] Data provided in a letter to ARCBS from the NBA on 20 December 2005 for insurance purposes

(v) *National supply and security concerns*

… and Australia's national interest and security is not well served by off shore fractionation services …

In deciding the best approach in Australia's national interest, there are several key issues to be considered.

- There are considerable potential risks to Australia's supply if it continues to move significantly away from its current policy of self-sufficiency to a situation of dependence upon supply of plasma products fractionated overseas. What would Australia's position be if a serious new blood-borne disease were to become endemic in the overseas country, potentially threatening the safety of plasma products?
- EU countries have exposures to BSE, and the USA has already reported one case of BSE, while Australia remains BSE-free to date. In recent years, the USA has also been the source of a substantial outbreak of West Nile Virus.
- Equally, Australia itself could become the locus of a new blood-borne infection. Clearly, to manage such a risk Australian governments would need contingency options.

Building the capacity for national self-sufficiency in plasma collection and fractionation arrangements requires a systematic and steady incremental approach – with adequate lead times and resources. If Australia's current capacity were wound back too far, or CSL Limited moved its operations off shore as a result of underutilisation of its Broadmeadows facilities, it could take a long time and huge financial investment, to rebuild such vital national infrastructure. Canada is currently facing such a challenge with only 150 tonnes of native plasma available for fractionation from its blood program; and the ARCBS understands Canada is now seeking to be self-sufficient and no longer reliant on plasma from the USA.

There are advantages to maintaining the current domestic fractionation arrangements through the CSL Limited facility at Broadmeadows (Victoria). These include:

a) local proximity (which has significant logistical benefits given the large volumes of material which must be input and processed);
b) the safety benefits of the powerful domestic regulatory oversight and the complete segregation of fractionation services for Australian requirements; and
c) for economic reasons, such as exposures to variations in currency exchange rates and loss of employment opportunities for Australian scientists, researchers and technical experts.

Australia plays an important leadership role in the Asia Pacific region, and continues to provide a source of technical expertise and support to developing nations in the region. Having a highly developed capacity both in the collection and fractionation of plasma products provides opportunities for sharing this expertise with our less developed neighbours on both a humanitarian basis and a commercial basis, and maintains Australian jobs, skills and technical 'know how'.

… ARCBS believes the only suitable option for increasing competition is to tender for fractionation services capacity in Australia.

The ARCBS believes it is vital to preserve self-sufficient plasma fractionation capacity in Australia. Any perceived diminution in the pursuit of DoHA's guiding principle of maintaining the safest possible blood supply will have a significant negative impact on the confidence in the blood supply of both donors and recipients, and the Australian community more broadly.

The market research undertaken by the ARCBS demonstrates that the community expects that governments will do everything in their power to make blood collection and plasma products as safe as possible. Studies have confirmed that patients will move to riskier private collections if they perceive there to be an increased risk in the public system.

Therefore, the ARCBS believes that the safest, most secure, highest quality, reliable, open and transparent blood system to meet Australia's plasma fractionation needs results from having domestic fractionation services on Australian soil, overseen by a best practice regulator underpinned by powerful domestic laws. If increased competition is an objective, then the ARCBS believes that tenders can be invited for domestic plasma fractionation services to be undertaken within Australia. This does not contravene WTO guidelines which enable countries to have country specific national requirements for the protection of public health and safety.

Under such a competitive model, current TGA regulations allow tendering companies to utilise their plants for toll fractionation providing Australian plasma for fractionation is segregated in the manufacturing process through the use of exclusive processing equipment for Australian plasma only.

Recommendations

18. The ARCBS believes the Review Committee should note that the use of external fractionation services will cause significant regulatory, security of supply and national security concerns.

19. The ARCBS believes the Review Committee should note that the use of external fractionation services will add in the order of $3m annual expenditure to the cost of Australia's blood system and there will be initial one off costs of $16m to $29m.

20. The ARCBS urges the Review Committee to pursue integration of Australian fractionation services by maintaining self-sufficient fractionation capacity in Australia.

21. The ARCBS believes the only viable option for increasing competition for fractionation services is to have a tender process for fractionation services to take place on Australian soil.

13 ARCBS Conclusions and Recommendations

Australians would prefer their blood to be kept in Australia.

Research undertaken by Worthington Di Marzio showed that 96% of people prefer that blood and blood products collected by the Australian Red Cross Blood Service stayed in Australia for use in the Australian health system.

This shows that the community overwhelmingly supports the position of the ARCBS for self-sufficiency in the blood supply.

The research also showed that 95% of existing donors, and 91% of non-donors, support another cornerstone of blood donation in Australia – voluntary, unpaid donors.

In terms of the blood supply system, being 'safe' is an absolute minimum. The ARCBS framework is, safe, safer, safest to ensure Australia has the safest and most secure blood supply possible.

This is why we have a concern with any moves to take plasma fractionation off shore.

If a requirement of the AUSFTA is to introduce competition to plasma fractionation, then the ARCBS believes this fractionation should take place on Australian soil, as currently happens, under Australian regulations and law.

Australia has one of the best regulators in the world in the TGA but the TGA does not have the capacity to apply their considerable statutory powers outside of Australia.

Overseas fractionation services do not provide the same of level of certainty.

Australians have the right to ask if competition for the sake of the Australia-US FTA is more important than the guarantee of one of the safest and most secure blood supply systems in the world.

Recommendations

1. ***The ARCBS recommends that the Review Committee endorses self-sufficiency as an ongoing goal for Australia for both fresh blood and blood products, and reaffirms its importance in ensuring the safest blood supply in Australia.***
2. ***The ARCBS also recommends the Review Committee should use self-sufficiency as an overall guiding principle in determining its position on future arrangements for plasma fractionation services in Australia.***
3. ***The ARCBS believes the Review Committee should address the need to maintain adequate domestic fractionation capacity to meet Australia's future needs for plasma products.***
4. ***The ARCBS believes the Review Committee's conclusions and recommendations should, therefore, reiterate the importance of a fundamental cornerstone of the Australian blood service being based on non-remunerated voluntary donors.***
5. ***The ARCBS also believes the Review Committee should recommend that Australian governments legislate to enshrine the right of employees to donate blood during their working day without loss of earnings.***

6. ***The ARCBS strongly urges the Review Committee to ensure future plasma fractionation services for Australian plasma do not impact on levels of public confidence in the Australian blood system.***

7. ***The ARCBS believes the Review Committee should place significant importance on the promotion of openness and transparency already achieved by Australia's integrated blood system.***

8. ***The ARCBS recommends the Review Committee should note that until 2002-03 Australia was self-sufficient in very large scale plasma requirements for IVIg and blood clotting factors, and that the ARCBS believes that given adequate funding, Australia can meet self-sufficiency targets in the future.***

9. ***The ARCBS recommends the Review Committee should examine the approach adopted by the NBA to progressively increase Australia's dependence on imports to 15% in 2005-06 and to almost one quarter of Australia's requirements in 2006-07 in the light of Australia's long held commitment to national self-sufficiency.***

10. ***The ARCBS believes that the Review Committee should recommend that improved medium and long term planning processes be introduced to model the demand for plasma products.***

11. ***The ARCBS strongly supports the current best practice regulatory model overseen by the TGA for protection of the Australian plasma fractionation services provided by CSL Limited and recommends there be no diminution in these requirements for any alternative fractionation provider.***

12. ***The ARCBS strongly supports the segregation of Australian plasma collections to avoid potential cross contamination during plasma fractionation processing.***

13. ***The ARCBS believes the National Reserve should be primarily comprised of products fractionated under the Plasma Fractionation Agreement with CSL Limited to ensure continuity of treatment regimes as well as for national self-sufficiency objectives.***

14. ***The ARCBS recommends, to the extent practicable, IVIg products transfused to Australian patients should be manufactured from Australian plasma collections.***

15. ***The ARCBS is of the view that powerful domestic penalties and criminal sanctions enabling stringent regulatory oversight cannot be replicated in any overseas toll fractionation contract. Therefore, the ARCBS recommends the Review Committee should find that any plasma fractionation services to process Australian plasma should be undertaken in Australia to ensure maximum confidence in Australia's blood supply.***

16. ***The ARCBS strongly recommends the Review Committee find that any plasma fractionated blood products supplied to the Australian public be benchmarked for prion clearance using acceptable animal model studies as part of the TGA's marketing approval and manufacturing licence requirements.***

17. ***The ARCBS believes the Review Committee should conclude Australia's integrated blood system provides the best protection against unknown emerging risks, ensuring the safest blood system practicable for Australia.***

18. ***The ARCBS believes the Review Committee should note that the use of external fractionation services will cause significant regulatory, security of supply and national security concerns.***

19. The ARCBS believes the Review Committee should note that the use of external fractionation services will add in the order of $3m annual expenditure to the cost of Australia's blood system and there will be initial one off costs of $16m to $29m.

20. The ARCBS urges the Review Committee to pursue integration of Australian fractionation services by maintaining self-sufficient fractionation capacity in Australia.

21. The ARCBS believes the only viable option for increasing competition for fractionation services is to have a tender process for fractionation services to take place on Australian soil.