

**AUSTRALIAN HEALTH MINISTERS' ADVISORY
COUNCIL**

BLOOD AND BLOOD PRODUCTS COMMITTEE

**REPORT OF THE WORKING PARTY ON THE SUPPLY
AND USE OF FACTOR VIII AND FACTOR IX IN
AUSTRALIA**

April 2003

Table of contents

<u>Membership of the Working Party</u>	iii
<u>Abbreviations and acronyms</u>	iv
<u>Executive summary</u>	1
<u>Section One: Introduction</u>	8
<u>Background to the policy context</u>	8
<u>The need for a review</u>	11
<u>Structure of this report</u>	13
<u>Section Two: Supply and demand for factors VIII and IX in Australia</u>	15
<u>Supply of factor VIII</u>	15
<u>Demand for factor VIII</u>	17
<u>Conclusion on supply and demand for factor VIII</u>	22
<u>Supply of factor IX</u>	23
<u>Demand for factor IX</u>	25
<u>Section Three: Review of the policy on supply levels of recombinant factors VIII and IX</u>	27
<u>Recombinant factor VIII</u>	27
<u>Recombinant factor IX</u>	27
<u>Relative effectiveness and safety of recombinant and plasma-derived products</u>	28
<u>Section Four: Review of criteria for accessing recombinant products</u>	31
<u>Continuing use of recombinant products</u>	32
<u>Section Five: Future supply of plasma-derived coagulation products</u>	34
<u>New CSL high-purity factor VIII</u>	34
<u>Potential surplus products</u>	34
<u>Section Six: Cost of increasing the availability of recombinant products</u>	36
<u>Section Seven: Funding arrangements for coagulation products</u>	38
<u>Section Eight: Future plasma collection requirements</u>	41
<u>Section Nine: Progress in implementing the findings and recommendations of the 1995 Working Party on Factor VIII Supply</u>	42
<u>Specific recommendations and responses</u>	42
<u>Issues highlighted by the 1995 report</u>	44
<u>Appendix A: List of submissions received by the Working Party in the consultation process</u>	45
<u>Appendix B: Findings and recommendations of the 1995 report of the Working Party on Factor VIII Supply</u>	46

<u>Appendix C: Australian Health Ministers' Advisory Council Consensus Statement on Increasing Factor VIII Supply</u>	51
<u>Appendix D: Clinical guidelines on factor VIII prophylaxis</u>	52
<u>Appendix E: Revised clinical guidelines on treatment using factors VIII and IX, including prophylaxis</u>	54
<u>Appendix F: Subsequent developments relevant to this report</u>	56

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Abbreviations and acronyms

AHF	anti-haemophilic factor
AHMAC	Australian Health Ministers' Advisory Council
ARCBS	Australian Red Cross Blood Service
B&BPC	Blood and Blood Products Committee
BRISC	Blood Review Implementation Steering Committee
CASCH	Clinical Advisory Sub Committee — Haemophilia
CSL	CSL Limited
FVIII	Factor VIII
FIX	Factor IX
IU	international unit
IVIG	intravenous immunoglobulin
NBDR	National Bleeding Disorder Registry
NBTC	National Blood Transfusion Committee
NHMRC	National Health and Medical Research Council
pdFVIII	plasma-derived factor VIII
pdFIX	plasma-derived factor IX
PBAC	Pharmaceutical Benefits Advisory Committee
PUP	previously untreated patient
rFVIII	recombinant factor VIII
rFIX	recombinant factor IX
SECTSE	Special Expert Committee on Transmissible Spongiform Encephalopathies
vCJD	variant Creutzfeldt–Jakob Disease

Executive summary

This report outlines the findings of a Working Party established in 1998 by the Blood and Blood Products Committee (B&BPC) of the Australian Health Ministers' Advisory Council (AHMAC), to review the use of factor VIII and factor IX in Australia. The final meeting of the Working Party was in November 2000, and the major conclusions and recommendations contained in this report are those of the Working Party at that time. Although this report was actually finalised in 2003, it reflects the position of the Working Party and the supply and demand situation as at December 2000. Major developments since the Working Party's last meeting are summarised in Appendix F. However, it should be noted that the recommendations of the Working Party, as outlined in this report, remain valid and largely unchanged, except for Recommendations 1A and 1B.

The need for a review (Section 1)

Recombinant factor VIII was introduced in the mid-1990s to make up a shortfall in the supply of plasma-derived factor VIII produced in Australia. Use of the recombinant product has steadily increased since its introduction, with Commonwealth and State and Territory Governments sharing the costs.

Many people with haemophilia A have a preference for being treated with recombinant factor VIII on the grounds they would have little or no exposure to existing or future blood-borne pathogens. However, the supply of recombinant factor VIII is limited in Australia. Thus, access to the product is restricted to patients who comply with clinical criteria established by an expert clinical group.

Additional funding for plasma collection has led to an increase in the supply of plasma-derived factor VIII. This situation has raised two key policy questions:

- Should patients who received recombinant products regularly be obliged to revert to a plasma-derived product just because supply of that product has increased to a point where this is possible?
- Should access to recombinant products be increased in light of overseas trends, safety concerns and patient preference?

The Working Party was therefore asked to review the use of recombinant factor VIII in Australia. Once a recombinant factor IX product became available in Australia in 2000, it raised similar issues concerning product choice (although supply is not an issue for factor IX, as there has never been a shortage of the plasma-derived product in Australia). Therefore, the Terms of Reference for the Working Party (given below) were expanded to include consideration of appropriate access and funding criteria for recombinant factor IX.

Similarly, the Terms of Reference for the Working Party were also expanded to include consideration of the recommendations made by the AHMAC B&BPC's *Review of the Use of Intravenous Immunoglobulin (IVIg) June 2000*, upon its release.

Key findings

Supply and demand for factors VIII and IX (Section 2)

The supply of both plasma-derived and recombinant factor VIII, which has steadily increased since 1995, is not evenly distributed among the States and Territories.

Demand for plasma-derived and recombinant coagulation products is difficult to assess because of a lack of detailed demographic and clinical information. The National Bleeding Disorder Registry (NBDR) will eventually provide such information, although New South Wales does not contribute data to the registry — a significant drawback given that this State has about 40% of the haemophilia population.

Australia probably requires more factor VIII to meet current treatment needs and will require a steady increase to keep pace with population growth and increasing longevity in the haemophilia community. The Working Party agreed an annual supply target for factor VIII of 3.3 international units (IU) per head of population, unless and until more comprehensive data become available. This new target would increase the annual supply of factor VIII by about 5 million IU.

There has been no chronic shortage of factor IX in Australia and the Working Party agreed an annual supply target of 0.6 IU per head of population.

Policy on supply levels of recombinant factors VIII and IX (Section 3)

The Working Party considered policy on recombinant factors VIII and IX. It concluded that, as part of the general response to the threat of variant Creutzfeldt-Jakob Disease (vCJD) to the blood supply, the recombinant products should be used whenever clinically indicated, and should contain no blood component.

There was no clear evidence on whether there is any significant difference between plasma-derived and recombinant coagulation products in terms of clinical or cost effectiveness.

A national tolerisation¹ program is needed to ensure that best practice treatment protocols are used and there is equity of access for patients from all jurisdictions.

Criteria for accessing recombinant products (Section 4)

The Working Party sought advice from the Clinical Advisory Sub Committee — Haemophilia (CASCH) on the policy for accessing recombinant factor VIII, contained in the consensus statement from AHMAC on increasing the factor VIII supply and clinical guidelines on factor VIII prophylaxis (given at Appendix C and Appendix D respectively). The CASCH recommended changes to the guidelines (Appendix E) —

¹ Tolerisation refers to the induction of immune tolerance ('desensitisation'). This process is used to remove the inhibitors to factor VIII present in some people with haemophilia. It involves giving a regular dose of clotting factor for a period of usually 3-12 months, and is successful in about 80% of cases.

in particular, the inclusion of recombinant factor IX and an expanded order of priority for accessing recombinant product.

In response to concerns about continuing use of recombinant products, CASCH recommended that the guidelines be amended to indicate that prophylaxis could be undertaken for patients over the age of 18 years. Also, the Working Party concluded that it was clinically and ethically inappropriate for patients who had never used plasma-derived products, or had begun use of recombinant products under current access guidelines, to be required to revert to using plasma-derived products.

Future supply of plasma-derived coagulation products (Section 5)

If the Working Party's recommendations are accepted, demand for plasma-derived coagulation products will decrease significantly, although about 10–15% of current supply will be needed to treat von Willebrand's Disease, for tolerisation and for patients who choose plasma-derived products.

It is essential that CSL retain the capacity to manufacture factors VIII and IX, in case of an international shortage of recombinant product. The quantities of these products held in the National Reserve should increase to six months' supply. The Working Party also concluded that a national policy on disposal of surplus plasma-derived coagulation products is urgently needed. These issues should be part of any negotiations with CSL for a new Plasma Fractionation Agreement after June 2004.

Cost of increasing the availability of recombinant products (Section 6)

The direct cost of increasing the quantity and proportions of product available in 1999-2000 to those recommended by the Working Party would be about \$32.93 million, increasing Government outlays by about 72%.

Funding arrangements for coagulation products (Section 7)

Current funding arrangements are inimicable to achieving 85% recombinant use in the short term. Funding arrangements for plasma-derived and recombinant products need to be reformed to ensure that additional costs and savings are optimally balanced, funding for new products is facilitated and there is national uniformity in the use of blood products, in line with best practice.

Future plasma collection requirements (Section 8)

If the Working Party's recommendations concerning supply are adopted and the demand for plasma-derived coagulation factors declines significantly, the supply requirement for IVIG will continue to be the major determinant of the quantity of plasma required in Australia.

Progress in implementing the recommendations of the Working Party on Factor VIII Supply (Section 9)

A report by the AHMAC Working Party on Factor VIII Supply, released in February 1995, included 31 conclusions and recommendations. Ten of the recommendations required specific follow-up action. The table below summarises the progress on implementation of these recommendations, as at December 2000.

Recommendation	Progress/implementation as at December 2000
Achieve 2 IU per capita of plasma-derived factor VIII plasma products by end 1996–97	Achieved in 1997–98.
Determine the link, if any, between prophylaxis and tolerisation	Considered by an expert group in 1996. No conclusive evidence.
Determine clinical and cost effectiveness of tolerisation	Considered by an expert group in 1996. Clinical and cost-effective treatment protocols recommended and accepted in 1997.
Introduce a higher purity product with a second viral inactivation step (Biostate®) as a matter of urgency	Significant delays with introduction.
Achieve 2 IU of factor VIII in each jurisdiction by the end of 1996–97	Only achieved by two jurisdictions in 1996–97. All jurisdictions have now achieved supplies in excess of this target.
Decide on recombinant factor VIII funding arrangements	50:50 funding agreed by Health Ministers in 1995.
Clinical protocols and guidelines for factor VIII usage.	Developed by expert group in 1995 and subsequently endorsed by AHMAC.
Establish an AHMAC committee for blood policy issues.	B&BPC established in 1995.
Establish a national register of people with haemophilia.	National Bleeding Disorder Registry (with the exception of New South Wales) established and operational.
Develop a nationally consistent approach to genetic counselling and screening for haemophilia.	No evidence that a national approach has been developed or proposed.

Summary of Recommendations

In summary, the Recommendations indicate that:

- as part of the general response to the threat of variant Creutzfeldt-Jakob Disease (vCJD) to the blood supply, recombinant factors VIII and IX should be used whenever clinically indicated
- a target of at least 85% recombinant usage is indicated on clinical grounds
- in normal circumstances, once patients are treated with recombinant products, this should continue
- equitable and consistent implementation of the proposed new arrangements will require the introduction of new funding arrangements.

If the recommendations of this report are accepted, the demand for plasma-derived coagulation products will decline significantly over time. For the foreseeable future, intravenous immunoglobulin (IVIG) requirements will dictate plasma collection targets. There will, however, be a continuing need for some plasma-derived factors VIII and IX to meet residual clinical needs, and to provide emergency supplies in the event that there is a shortage of recombinant product.

List of recommendations

Recommendation 1 — supply of factors VIII and IX

The Working Party recommends that:

- A. a national supply target of 3.3 IU per head of population be agreed for factor VIII

(Taking into account the developments outlined in Appendix F, the Working Party now proposes a new Recommendation 1A as follows:

- A. “a national supply target of 3.75 IU per head of population be agreed for factor VIII”)

- B. a national supply target of 0.6 IU per head of population be agreed for factor IX

(Taking into account the developments outlined in Appendix F, the Working Party now proposes a new Recommendation 1B as follows:

- B. “a national supply target of 0.7 IU per head of population be agreed for factor IX”)

- C. the factor IX target be adjusted to reflect the 25% increase in dosage required for the recombinant product

- D. these targets be reviewed regularly in line with changing treatment standards and more comprehensive demographic data from the NBDR

- E. the Commonwealth work with clinicians to improve the quality and usefulness of data in the NBDR
- F. New South Wales be encouraged to provide regular haemophilia patient data in a form that is compatible with the NBDR.

Recommendation 2 — policy on factors VIII and IX

The Working Party recommends that:

- A. the current restrictions on access to recombinant factors VIII and IX be removed as rapidly as possible, and that these products be used whenever clinically indicated, in order to improve patient safety
- B. best-practice clinical guidelines that promote clinical and cost-effective use of recombinant and plasma-derived coagulation products are promulgated
- C. jurisdictional agreement to a timetable for achieving a target of 85% recombinant use is obtained in the shortest time possible, and the target reached by 2004 at the very latest
- D. a national tolerisation program be implemented as soon as possible to ensure that patients have equity of access to treatment
- E. access to the tolerisation program and priority for treatment be determined by an expert clinical group established for that purpose
- F. treatment protocols for tolerisation be approved by the expert clinical group to ensure clinical and cost effectiveness, and equity of access to available product.

Recommendation 3 — access to recombinant products

The Working Party recommends that:

- A. once patients are treated with recombinant products, this practice should continue
- B. where the availability of product or financial constraints require prioritisation for the use of recombinant products, the following order of priority be used:
 - i) previously untreated patients
 - ii) children who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
 - iii) adults (> 18 years) who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
 - iv) virally infected children
 - v) adults infected with hepatitis C
 - vi) adults infected with other viruses.

Recommendation 4 — future supply of plasma-derived products

The Working Party recommends that:

- A. the Commonwealth take into account the residual and contingency needs for plasma-derived coagulation products in any negotiations with CSL for a new Plasma Fractionation Agreement after June 2004
- B. the Commonwealth pursue the possibility of establishing international markets for surplus plasma products as one means of ensuring that Australia maintains a capacity to manufacture sufficient plasma-derived coagulation products for residual use and for contingencies
- C. the National Reserve of plasma-derived factors VIII and IX be increased to six months' cover, in parallel with any increase in the use of recombinant products (and this reserve be periodically rotated with freshly manufactured stock).

Recommendation 5 — funding arrangements for coagulation products

The Working Party recommends that:

- A. the costs of recombinant and plasma-derived coagulation products, as well as any savings from substitution between these products, be shared equitably between the Commonwealth and the States and Territories
- B. future funding and supply planning arrangements for plasma-derived and recombinant products be on a national basis, in line with jointly agreed national criteria.

Recommendation 6 — future plasma collection requirements

The Working Party recommends that plasma collection requirements in Australia should be established by reference to the clinically justifiable need for IVIG.

Section One: Introduction

1.1 This report outlines the findings of a Working Party established in 1998 by the Blood and Blood Products Committee (B&BPC) of the Australian Health Ministers' Advisory Council (AHMAC) to review the use of factor VIII and factor IX in Australia. The final meeting of the Working Party was in November 2000, and the major conclusions and recommendations contained in this report are those of the Working Party at that time.

1.2 Factors VIII and IX are used in the treatment of haemophilia A and B, respectively. These proteins were originally derived from human plasma, but in recent years, recombinant forms (produced by cloning the relevant gene), have become available. Recombinant factors VIII and IX differ from their plasma-derived counterparts in that they contain little or no human protein either during the manufacturing process or in their final form, and their supply is (in theory) unlimited.

Background to the policy context

1.3 Policies have been developed over the last decade to improve both supply and access to best practice treatment for people with haemophilia.

1.4 Supply was initially the main driver of policy on factor VIII. In the early 1990s, Australia's supply of factor VIII was the equivalent of about 1.6 international units (IU) per head of population. This was below both the minimum recommended by the World Health Organization (2 IU) and the World Haemophilia Foundation (3.5 IU). The quantity available in Australia at that time was sufficient to provide emergency and 'on demand' treatment, but insufficient to meet emerging treatment standards for prophylaxis and tolerisation. The haemophilia community advocated an increase in domestic production and the importation of recombinant products to make up the difference.

1.5 In June 1994, AHMAC considered the issue of the supply of factor VIII and agreed that:

- the adequate provision of factor VIII was an issue for joint consideration by Commonwealth and State and Territory Governments
- any strategy to increase supply needed a national approach to ensure efficient and equitable allocation
- costs should be jointly shared
- AHMAC would prepare a report on the cost implications of introducing recombinant product.

1.6 The AHMAC Working Party on Factor VIII Supply was established later that year. In February 1995, it recommended a series of measures to increase factor VIII supply (Appendix B). In response to the Working Party's recommendations, Health Ministers agreed in June 1995 to increase factor VIII supply in Australia by:

- providing additional funding to the Red Cross Society so that it could collect more plasma to boost the production of plasma-derived factor VIII by CSL
- supplementing this increase by importing recombinant factor VIII on a 50:50 cost-shared basis between the Commonwealth and State and Territory Governments.

1.7 Ministers also agreed to the establishment of a standing committee of AHMAC to provide advice on the supply, safety and funding of blood products. The B&BPC was duly established. Among its first acts were the preparation of a consensus statement on increasing factor VIII supply (Appendix C) and the commissioning of a group of clinical experts to prepare guidelines on factor VIII prophylaxis (Appendix D). These initiatives were subsequently approved by AHMAC.

1.8 Both the consensus statement and the clinical guidelines noted a clinical preference to use recombinant factor VIII but a limited supply of the product. Both stipulated that access to the recombinant product would be based on the following order of clinical priority:

- previously untreated patients
- patients with no serological evidence of hepatitis B, hepatitis C and human immunodeficiency virus (HIV)
- children, with younger children receiving priority over older children.

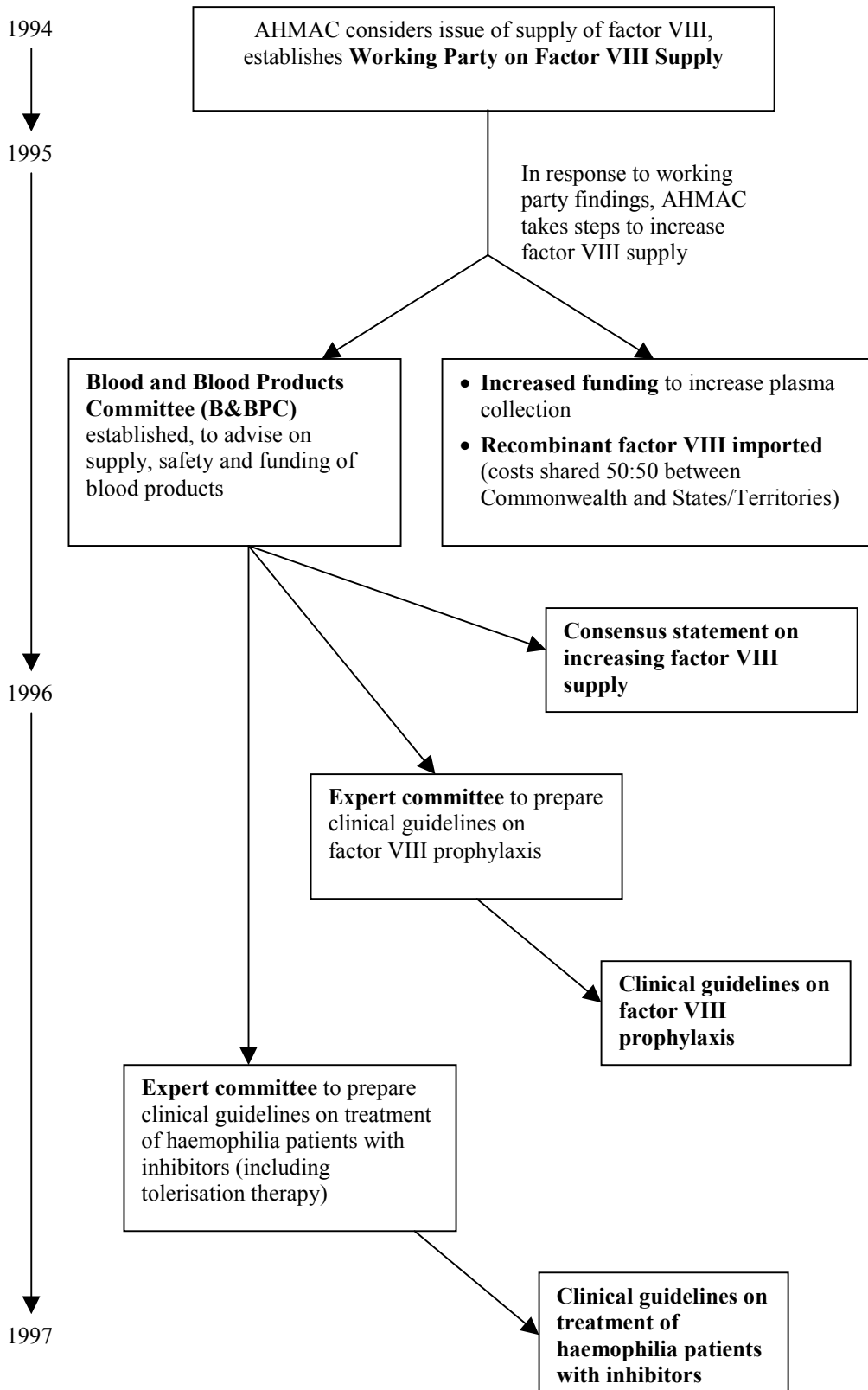
1.9 Thus, the focus of policy now expanded beyond supply, to take into account the need for products with the highest standards of safety and quality, that would allow all patients to receive treatment that was in line with best practice.

1.10 In 1996, B&BPC commissioned an expert group to develop clinical protocols for treating haemophilia patients with inhibitors to factor VIII, including tolerisation therapy.² The expert group reported in January 1997. On the basis of cost benefit analysis, it recommended that patients with persistent inhibitor titres above a specified level (0.5 Bethesda Units) should be tolerised. The expert report specified an order of priority starting with children under 14. It noted that tolerisation was only possible if sufficient factor VIII was available and specifically suggested this could come from plasma-derived factor VIII or from the supplementary supply of recombinant factor VIII.

² Tolerisation refers to the induction of immune tolerance ('desensitisation'). This process is used to remove the inhibitors to factor VIII present in some people with haemophilia. It involves giving a regular dose of clotting factor over a short period of time, and is successful in about 80% of cases.

1.11 These policy developments are summarised in Figure 1.1, below.

Figure 1.1 Policy milestones concerning factor VIII, 1994–1997



Recombinant factor VIII

1.12 Recombinant factor VIII was initially introduced in Australia in 1995 to fill the gap between the quantity of plasma-derived factor VIII produced in Australia and the quantity needed to meet standards for best practice treatment. Use of the recombinant product has steadily increased since its introduction, with Commonwealth and State and Territory Governments sharing the costs. Because, at that stage, the recombinant product was viewed simply as a supplement to plasma-derived factor VIII, Governments also provided additional funding to increase the volume of plasma collected by the Australian Red Cross Blood Service (ARCBS), to increase the supply of the plasma-derived product.

1.13 Many people with haemophilia A have a preference for being treated with recombinant factor VIII on the grounds they would have little or no exposure to existing or future blood-borne pathogens. However, as a supplement to the plasma-derived product, the supply of recombinant factor VIII is limited. Thus, access to the product is restricted to patients who comply with clinical criteria established by an expert clinical group.

Factor IX

1.14 In contrast to the situation with factor VIII, there has never been a shortage of factor IX in Australia. In 1998, CSL replaced its factor IX product, Prothrombinex-HT, with MonoFIX, a more highly purified product. As explained below, a recombinant factor IX product (BeneFIX) became available in Australia in the latter half of 2000, raising similar issues on product choice to those outlined for factor VIII.

The need for a review

1.15 As the supply of plasma-derived factor VIII has increased (through the additional funding for plasma collection), two key policy questions emerged:

- Should patients who received recombinant products regularly be obliged to revert to a plasma-derived product just because supply of that product has increased to a point where this was possible?
- Should access to recombinant products be increased in light of overseas trends, safety concerns and patient preference?

1.16 This situation raised a range of policy, operational, financial, ethical and legal issues. The current Working Party was therefore established in 1998, to review the use of recombinant factor VIII in Australia. Once a recombinant factor IX product became available in Australia in 2000, it raised similar issues concerning product choice. Although there has never been a shortage of plasma-derived factor IX in Australia, the availability of a recombinant product resulted in people with haemophilia B wanting access to it, on similar terms to their haemophilia A counterparts. Therefore, the Terms of Reference for the Working Party (given below) were expanded to include consideration of appropriate access and funding criteria for recombinant factor IX.

1.17 Similarly, the Terms of Reference for the Working Party were also expanded to include consideration of the recommendations made by the AHMAC B&BPC's *Review of the Use of Intravenous Immunoglobulin (IVIG) June 2000*, upon its release.

Terms of Reference

1.18 The Terms of Reference for the review were as follows:

Review the current *AHMAC Consensus Statement on Increasing Factor VIII Supply* and the *Clinical Guidelines on Factor VIII Prophylaxis* and make recommendations where changes in current policy are warranted. The review is to include:

- the current evidence for the relative safety and effectiveness of recombinant and plasma-derived Factor VIII;
 - the principle of only supplying those who fit the clinical preferential criteria for recombinant Factor VIII beyond the period when there is an adequate supply of plasma-derived Factor VIII; and
 - the overall cost implications of providing all people with haemophilia access to the Factor VIII product of their choice. This should take into consideration the current contract between the Commonwealth and CSL Ltd.
2. In the event that the current guidelines and consensus statement for the use of both recombinant and plasma-derived Factor VIII are no longer seen as appropriate, develop national guidelines for the use of Factor VIII (both plasma-derived and recombinant) including guidelines for prophylaxis and a national tolerisation program.
 3. Examine the extent and use of Factor IX in Australia and, if necessary, recommend access criteria to recombinant Factor IX. Report on the extent that these access criteria should be comparable with those recommended for Factor VIII. If applicable, recommend appropriate funding arrangements.
 4. Determine the amounts of both plasma-derived and recombinant Factor VIII and Factor IX required to meet current and future demand, dependant on any recommendations made and the cost to implement.
 5. In view of the conclusions in 2, 3 and 4 above review and make recommendations on the level of plasma collected for processing at CSL. The review is to take into consideration the recommendations made by the AHMAC Blood and Blood Products Committee's *Review of the Use of Intravenous Immunoglobulins (IVIG) June 2000*.
 6. Review progress on the recommendations made in the *1995 Report of the Working Party on Factor VIII*.

1.19 In reaching its conclusions, the Working Party was required to take into account:

- evidence of any difference in safety between plasma-derived and recombinant products

- funding implications for Governments
- the impact of CSL production and the implications for the policy of national self-sufficiency in blood products
- the impact on plasma collections by ARCBS.

Consultation process

1.20 The Working Party met from 1998 to 2000. As part of its deliberative process, it sought written submissions from interested parties and from the public in general. A total of 20 submissions were received (listed in Appendix A). The submissions provided the Working Party with a broad cross-section of views and concerns. The Working Party would like to take this opportunity to thank the people and organisations that made submissions.

Draft report

1.21 The Working Party provided a draft summary report to B&BPC in November 2000. The summary recommended a substantial and rapid increase in the availability of recombinant factors VIII and IX, primarily as a logical extension of the policy that was then in place regarding vCJD.

1.22 The draft summary recommended a target of at least 85% for recombinant product on clinical grounds. An issue that would impede the implementation of this recommendation is the funding split between Governments for blood products was not conducive to rational decision-making and allocative efficiency.

1.23 A lack of uniformity in the utilisation of blood products in line with best practice could result in inequity and inequality for some patients.

1.24 The B&BPC noted these problems and sought further consideration of the issues.

1.25 The draft summary also suggested that the then recently announced Commonwealth review of the Australian blood banking and plasma products sector (the National Blood Review) could provide guidance on these issues. Consideration of these remaining issues was deferred by the Working Party while the National Blood Review considered these and other related issues in the context of a system-wide approach to the management and funding of the Australian blood sector. Relevant subsequent developments are summarised in Appendix F.

1.26 The draft summary report forms the basis for the findings and recommendations given in this report.

Structure of this report

1.27 The subsequent sections of this report set out the findings of the Working Party on:

- supply and demand for factor VIII and factor IX in Australia

- rationale for increasing the availability of recombinant factors VIII and IX
- criteria for accessing recombinant products
- implications for future domestic production of plasma-derived coagulation products
- the net cost of increasing the availability of recombinant products
- Commonwealth and State and Territory funding arrangements for coagulation products
- the impact of an increased supply of recombinant products on plasma collection
- progress on the recommendations of the 1995 Report of the Working Party on Factor VIII Supply.

Section Two: Supply and demand for factors VIII and IX in Australia

2.1 This section describes the supply and demand for factors VIII and IX in Australia. Both proteins can be derived from human plasma or produced in recombinant form. The recombinant products are produced by cloning the relevant gene in non-human cell lines. Thus, unlike the supply of plasma-derived products, that of recombinant factors VIII and IX is (in theory) unlimited. Also, the recombinant products contain little or no human protein either during the manufacturing process or in their final form. This is seen as a critical safety advantage, although current methods of viral inactivation of plasma-derived factors VIII and IX are considered to result in a product that has a very low risk of transmitting known viruses.

2.2 Plasma-derived factor VIII is made by CSL Limited from plasma collected by the ARCBS. Supply levels therefore depend on the volume of plasma collected and the yield from processing. Recombinant factor VIII is imported from a number of overseas suppliers.

2.3 MonoFIX, a CSL product that contains purified and concentrated factor IX, was introduced by CSL in 1998. The new product replaced Prothrombinex-HT, which contained mainly factor IX but also factor II and factor X. Before the introduction of MonoFIX, Australia imported some supplies of plasma-derived factor IX to treat those people who could not be treated with Prothrombinex-HT. An imported recombinant factor IX (BeneFIX) became available in Australia in the latter half of 2000.

2.4 In contrast to the situation with factor VIII, there has been no chronic shortage of factor IX in Australia. A greater quantity of factor IX could be produced from the plasma collected by the ARCBS, but CSL only manufactures enough to meet prevailing demand.

Supply of factor VIII

2.5 The supply of factor VIII, both plasma-derived and recombinant, has increased in Australia since 1995, as shown in Table 2.1. The combined supply of the recombinant and plasma-derived products has increased steadily, reaching 3.14 IU per head of population in 1999-2000, an increase of about 69%.

Table 2.1 Annual supply of plasma-derived and recombinant factor VIII in Australia, from 1995-96 to 1999-2000

	1995-96	1996-97	1997-98	1998-99	1999-00
pdFVIII					
Total production (IU m)	31.09	30.44	37.63	42.62	47.14
Per capita (IU)	1.70	1.64	2.01	2.25	2.45
rFVIII					
Total supply (IU m)	2.77	5.84	8.32	10.70	13.22
Per capita (IU)	0.15	0.32	0.44	0.57	0.69
Total per capita (IU)	1.85	1.96	2.45	2.82	3.14

IU = international units; m = million; pdFVIII = plasma-derived factor VIII; rFVIII = recombinant factor VIII

^a Figures are for financial years. They show production by CSL for Australian consumption and include stock held in the National Reserve of plasma products.

Source: Commonwealth Department of Health and Aged Care

2.6 The production of plasma-derived factor VIII is directly related to the quantity of plasma collected by the ARCBS. Between 1995 and 1999, the Commonwealth, States and Territories provided special funding to increase the supply of plasma, and thus increase the supply of factor VIII. The quantity of plasma-derived factor VIII available in any year in a jurisdiction is directly related to the quantity of plasma collected by the ARCBS Business Unit in that jurisdiction and to how much (if any) additional plasma-derived product can be obtained from any surpluses held by other jurisdictions.

2.7 In the case of recombinant factor VIII, supply is determined directly by State and Territory Health Authorities. Their decisions are based on one or more of the following factors:

- the quantity they need to supplement their plasma-derived supply in order to meet justifiable clinical need
- the quantity of product required for people already receiving recombinant product
- broader financial and public health policies.

2.8 Therefore, recombinant and plasma-derived product is not distributed evenly among the States and Territories.

Table 2.2 Availability of factor VIII by jurisdiction in 1999-2000

	NSW	VIC	QLD	SA	WA	TAS	NT	ACT	Total
pdFVIII (IU m)	11.60	10.22	8.69	4.11	5.36	1.25	0.44	0.84	42.51
rFVIII (IU m)	4.25	3.28	2.36	1.81	1.49	0.09	0.00	0.00	13.28
Total (IU m)	15.85	13.50	11.05	5.92	6.85	1.34	0.44	0.84	55.79
Total per capita (IU)	2.45	2.82	3.09	3.95	3.63	2.68	2.26	2.71	

IU = international unit; m = million; pdFVIII = plasma-derived factor VIII; rFVIII = recombinant factor VIII

Note: the national per capita volume of plasma-derived product is less than the amount shown in Table 2.1 because of timing differences between production and receipt of products and because of net additions to the National Reserve. Totals do not always correlate due to rounding.

Source: For pdFVIII — Australian Red Cross Blood Service data provided to CSL and subsequently to the Commonwealth Department of Health and Aged Care; for rFVIII — States and Territories advice to the Commonwealth Department of Health and Aged Care

2.9 The relatively high availability of factor VIII in South Australia is explained in part by the high concentration of haemophilia patients in that State: South Australia has 7.8% of the national population but 13.5% of patients with haemophilia (as shown in Table 2.3). The figures for Tasmania and the Northern Territory result from an opposite situation.

Demand for factor VIII

The need for national data

2.10 Assessing demand for factor VIII is difficult because specific demographic and clinical data are lacking. The 1995 Factor VIII Working Party noted this, and recommended that a national register of all people with haemophilia and related bleeding disorders be established for health planning and epidemiology. With Government funding, a group of clinicians established the National Bleeding Disorder Registry (NBDR).

2.11 The NBDR records demographic and clinical information about the patients who are treated in Australia's 13 Haemophilia Treatment Centres, except those in New South Wales. When it becomes fully operational, the registry will help Governments to plan production and make purchasing decisions, and provide an epidemiological tool for assessing need and analysing treatment outcomes.

2.12 Currently, the NBDR does not include data for New South Wales patients, apparently because privacy issues must be resolved before that State's Haemophilia Treatment Centres can provide data directly to the registry. This lack of input is a significant drawback, because patients from New South Wales represent almost 40% of the Australian haemophilia population (Table 2.3 and Table 2.8).

2.13 When the current Working Party was considering supply issues, there were insufficient data from the newly established NBDR to draw firm conclusions about future demand for factor VIII from those jurisdictions participating in the registry. The Working Party considers the NBDR essential to future planning, and encourages health authorities and clinicians to work together so that the registry becomes fully operational as soon as possible. The Working Party also encourages New South Wales authorities to participate as fully as possible in the registry, initially by using the registry's data definitions and data collection protocols.

Indirect measures of demand for factor VIII

2.14 In the absence of detailed epidemiological data, the Working Party considered other indirect measures of demand:

- unmet need at the jurisdictional level
- unmet demand for tolerisation
- unmet demand for prophylaxis
- the extent of any surplus inventory
- unmet demand due to restrictions on access to recombinant factor VIII
- the situation in comparable countries.

Unmet need for factor VIII at the jurisdictional level

2.15 The uneven distribution of product between jurisdictions (Table 2.2) suggests that some might still have unmet need. There is an uneven distribution of people with haemophilia among the jurisdictions. Table 2.3 shows the jurisdictional distribution of people with haemophilia A and severe haemophilia A. Patients with severe haemophilia A are the major users of factor VIII, accounting for a significant proportion of total consumption.

2.16 The data in Table 2.3 suggest that South Australia and the Australian Capital Territory should have significantly higher than average consumption of factor VIII. The supply data in Table 2.2 bears out this suggestion for South Australia, but only partially for the Australian Capital Territory. More generally, comparing Table 2.3 with Table 2.2 suggests that some jurisdictions may still require additional product to satisfy all reasonable clinical demand, notwithstanding differences between jurisdictions in the proportion of patients with severe haemophilia A.

Table 2.3 Occurrence of haemophilia A and severe haemophilia A, by jurisdiction

	Population, as a % of total population in Australia	No of people with haemophilia A	As % of haemophilia A population	No of people with severe haemophilia A	As % of severe haemophilia A population
NSW	33.7	503	38.5	121	27.5
VIC	24.9	317	24.3	117	26.6
QLD	18.6	147	11.3	81	18.4
SA	7.8	177	13.5	52	11.8
WA	9.8	110	8.4	47	10.7
TAS	2.4	22	1.7	8	1.8
NT	1.0	na	na	na	na
ACT	1.6	31	2.4	14	3.2
Total^a	99.8	1307	100.1	440	100

na = not available

^a Totals do not always sum to 100% due to rounding.

Sources: Survey of Haemophilia Services in NSW and ACT (NSW Department of Health, September 2000) and National Bleeding Disorder Registry, November 2000. Note: the two data sources are not strictly compatible, so the data are only broadly indicative.

Unmet demand for factor VIII for tolerisation

2.17 There is anecdotal evidence that some patients who would benefit from therapy for tolerisation to factor VIII inhibitors are not receiving treatment, possibly because of a shortage of factor VIII in a jurisdiction or because of pressure to balance competing demands for limited health care funds.

2.18 In 1997, an expert group commissioned by the B&BPC recommended:

- the immediate introduction, wherever clinically indicated, of tolerisation therapy for children up to 5 years of age who have factor VIII inhibitors
- the staged implementation, given sufficient reserves of factor VIII, of tolerisation therapy, wherever clinically indicated, for children between the ages of 5 and 14 who have factor VIII inhibitors.

2.19 The expert group ascertained that, in July 1996, there were 33 patients with high-titre inhibitors and that seven of these were awaiting tolerisation therapy. Information obtained from the Clinical Advisory Sub Committee — Haemophilia (CASCH) suggests that, in the intervening period, several young patients have been tolerised. The CASCH advised in July 1999 that:

... there are no children in Australia under 5 years of age requiring tolerisation for inhibitors to FVIII or FIX. There are some patients in the 5–14 year age group who may be suitable for tolerisation, however additional information needs to be sought from the ACT and NSW on the suitability of their patients for tolerisation.

2.20 The CASCH identified 13 patients in the 5–14 year age group who might be suitable for tolerisation in relation to factor VIII inhibitors, and three patients in the same age category with inhibitors to factor IX. Some of these patients have received tolerisation therapy.

2.21 As new patients develop inhibitors to factor VIII, there will be a continuing need for tolerisation therapy. The quantity of product required is relatively high and increases with the weight of the patient. However, the number of patients who would benefit from tolerisation will generally be small and, in overall terms, a tolerisation program for patients under 14 years old would account for less than 3% of the current supply. Thus, the demand for tolerisation is not a major component of overall demand and there is no clear evidence of significant unmet need.

Unmet demand for factor VIII for prophylactic treatment

2.22 Prophylaxis is a major determinant of factor VIII supply. The Working Party was concerned that not all patients who would benefit from prophylaxis were currently receiving this treatment, and that the initial cohort of prophylaxis patients would need an increased supply as their ages and weights increased. The CASCH provided the following information.

Currently [1999] within Australia (excluding NSW) the national data base shows there is estimated to be 96 patients between the ages of 11 and 18 eligible for prophylaxis of which only 45 are on prophylaxis. If all these patients continued with prophylaxis over the age of 18 it is estimated an additional 3 million units annually will be required.

2.23 Data from the NBDR for November 2000 suggests that this situation improved in the intervening period (Tables 2.4 and 2.9). 64 patients (excluding New South Wales patients) with severe haemophilia A and B between the ages of 11 and 18 are eligible for prophylaxis, and 56 of these are receiving it (ie 88% compared to the CASCH figure of 47% in 1999).

Table 2.4 Severe haemophilia A by age and use of prophylaxis, November 2000

Severe haemophilia A		
Age category	Prophylaxis	No prophylaxis
0–5	22	15
6–10	37	7
11–18	52	6
Subtotal	111	28
Adult	26	154
Total	137 (43%)	182 (57%)

Note: Does not include data for New South Wales

Source: National Bleeding Disorder Registry, November 2000

2.24 In its 2000 survey, New South Wales identified 129 patients with haemophilia A and B, of whom 45 (35%) were receiving prophylactic treatment; this compares to 42% for the other jurisdictions. The data in Table 2.4 and from New South Wales suggest that there is still some unmet prophylactic need, but this is difficult to quantify without further clinical data. Using the CASCH estimate as a guide and including New South Wales, a further 3–4 million IU of factor VIII are probably required.

2.25 The total quantity of product needed by patients in the initial prophylaxis cohort will increase as the cohort ages, increasing the requirement for factor VIII in the short to medium term. However, this effect will ‘plateau’ over time, as new patients commence treatment (usually at a young age) and patients over 18 undergo modified treatment regimens more consistent with clinical need and lifestyle. It is difficult to estimate how much of the effect of the ageing of the initial cohort has already ‘washed through’ the system, but some allowance for this phenomenon must be made in setting supply targets for the next few years.

2.26 In summary, there is currently unmet demand for factor VIII for prophylactic treatment, and additional increases in demand can be expected in the short to medium term due to the ageing of the initial cohort of prophylaxis patients.

Surplus inventory of factor VIII

2.27 There is a policy of establishing a National Reserve of plasma-derived factor VIII, and, since 1997, product has been accumulated for contingencies. Also, at any one time, the stock held by the ARCBS may exceed the amount issued to patients and clinicians. In addition, there is likely to be product issued to Haemophilia Treatment Centres but not issued.

2.28 Despite an increase in production in recent years, data on stockholdings within the ARCBS indicate no significant national surplus of product. The average monthly closing balance of plasma-derived factor VIII held by the ARCBS nationally in 1999-2000 was the equivalent of just over two months’ usage. The implication is that the Australian health care system requires at least the current level of factor VIII supply to meet demand.

2.29 The target for the National Reserve is three months’ cover, but cover has never exceeded six weeks. Nevertheless, the size of reserves and stockholdings suggests that Australia is not yet oversupplied with plasma-derived factor VIII.

2.30 Recombinant factor VIII is bought as needed, and neither the Commonwealth nor the States and Territories have policies of establishing reserves. However, some jurisdictions have contracts with suppliers that require the suppliers to have available within the jurisdiction, for delivery within 24 hours, a quantity of product (eg equivalent to one week’s usage).

Unmet demand due to restrictions on access to recombinant factor VIII

2.31 Interpretation of the current guidelines for accessing recombinant factor VIII may restrict the quantity of recombinant product available in some jurisdictions. Given patient preference for recombinant product, some patients and clinicians may

be deferring some elective treatment unless or until the recombinant product becomes more widely available. The extent of any such ‘pent-up’ demand is not known.

International comparisons

2.32 In the absence of precise measures of justifiable clinical need in Australia, an international comparison is illustrative but not conclusive, because the demographic and epidemiological data from different countries has not been standardised for confounding variables.

2.33 It is difficult to obtain current data for all relevant countries and there does not appear to be a single authoritative source for such data. Table 2.5 shows the results for selected countries.

Table 2.5 Consumption of factor VIII for selected countries

Country	International Units per capita	Percentage recombinant	Data year	Data source
Australia	3.1	22	2000	a
Canada	4.4	100	2000	b
Germany	3.8	55	1998	d
New Zealand	2.6	36	2000	c
Sweden	6.5	50	1998	d
United Kingdom	3.5	48	1999	e
United States	3.4	75	2000	b

Sources:

a — As indicated elsewhere in this report

b — Personal communication from Haemophilia Foundation Australia

c — Personal communication from Haemophilia Foundation of New Zealand

d — European Haemophilia Consortium, 1999 survey

e — United Kingdom Haemophilia Doctors Organisation Report on the Annual Returns for 1999

2.34 The data suggest that Australia has a good overall supply of factor VIII, but is undersupplied in recombinant factor VIII. However, the results should be interpreted with considerable caution, particularly because the data for the different countries cover different periods. There have been considerable changes internationally over the past three years as a result of policies to reduce the risk of variant Creutzfeldt–Jakob Disease (vCJD) and the increasing availability of recombinant product. A better comparison would be the average usage of factor VIII per treated patient, which would reflect the incidence and prevalence of haemophilia in each country. However, because of the way supply and demand data are reported internationally, such a comparison is not possible.

Conclusion on supply and demand for factor VIII

2.35 Supply levels of factor VIII are around 3.1 IU per head of population. However, there are still some patients who do not receive best practice care because of tight supply in some jurisdictions, largely because of the funding arrangements in the blood sector. The policy issue for the haemophilia community is now less to do

with overall supply than with being able to choose products that offer the highest standards of safety and quality and to receive treatment in line with best practice. The policy issue for Governments has always been to balance the additional cost of new products for haemophilia patients against other needs in the health sector. The absence of clear evidence on cost effectiveness or demonstrable risk reduction has complicated policy development in this area.

2.36 Based on the findings and analysis outlined above, Australia probably requires more factor VIII to meet current treatment needs and will require a steady increase to keep pace with population growth and increasing longevity in the haemophilia community. The possibility that not all eligible patients are receiving adequate prophylactic treatment, and the impact on demand of the ageing of the initial cohort of prophylaxis patients, also suggest that more product will be needed.

2.37 The Working Party found insufficient evidence to reach a firm conclusion about the amount of factor VIII needed, but recommends that an annual supply target of 3.3 IU per head of population should be adopted, unless and until better planning data become available. The new target would increase the annual supply of factor VIII by about 5 million IU.

Supply of factor IX

2.38 In contrast to the situation with factor VIII, there has been no chronic shortage of factor IX in Australia. More factor IX could be produced from the quantity of plasma collected by the ARCBS, but CSL only manufactures enough to meet prevailing demand. Before CSL's introduction of a new, highly purified factor IX product (MonoFIX) in 1998, some patients used imported monoclonal factor IX. Since the introduction of MonoFIX, all plasma-derived factor IX needs have been met from domestic production.

2.39 A recombinant factor IX product (BeneFIX) became available in Australia in the latter half of 2000. Differences between the recombinant and plasma-derived factor IX proteins mean that about 25% more recombinant product is needed to achieve the same clinical result as an equivalent plasma product; that is, 25% more of the recombinant product is required to replace a dose of plasma-derived product.

2.40 Table 2.6 shows the supply of plasma-derived and recombinant factor IX for 1999-2000.

Table 2.6 Annual supply of plasma-derived and recombinant factor IX in Australia, 1999-2000

	1999-00
pdFIX	
Production (IU m)	11.04
Per capita (IU)	0.58
rFIX	
Production (IU m)	0.00
Per capita (IU)	0.00
Total production (IU m)	11.04
Total per capita (IU)	0.58

IU = international units; m = million ; pdFIX = plasma-derived factor IX; rFIX = recombinant factor IX

Note: there are no figures for recombinant factor IX as BeneFIX only became available subsequent to the 1999-2000 financial year.

Source: Commonwealth Department of Health and Aged Care

2.41 Table 2.7 shows the per capita distribution of both plasma-derived and recombinant factor IX among the States and the Territories in 1999-2000.

Table 2.7 Per capita distribution of factor IX by jurisdiction, 1999-2000

	NSW	VIC	QLD	SA	WA	TAS	NT	ACT
pdFIX (IU m)	2.80	3.90	1.20	0.61	0.88	0.66	0.16	0.83
rFIX (IU m)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total (IU m)	2.80	3.90	1.20	0.61	0.88	0.66	0.16	0.83
Per capita (IU)	0.43	0.82	0.32	0.47	0.41	1.41	0.84	2.66

IU = international units; m = million; pdFIX = plasma-derived factor IX; rFIX = recombinant factor IX

Note: there are no figures for recombinant factor IX as BeneFIX only became available subsequent to the 1999-2000 financial year.

Source: Commonwealth Department of Health and Aged Care

2.42 As with factor VIII, the per capita distribution of factor IX is uneven among the different jurisdictions. However, the distribution of people with haemophilia B and severe haemophilia B is more consistent with the general population distribution among the jurisdictions than is the case for haemophilia A, as shown in Table 2.8. The notable exceptions are Tasmania and the Australian Capital Territory, which both have a relatively high proportion of severe haemophilia B patients. The difference in per capita supply between the jurisdictions could also reflect differing treatment protocols.

Table 2.8 Haemophilia B and severe haemophilia B, by jurisdiction

	Population, as a % of total population	No of people with haemophilia B	As % of haemophilia B population	No of people with severe haemophilia B	As % of severe haemophilia B population
NSW	33.7	103	39.2	30	44.8
VIC	24.9	60	22.8	17	25.4
QLD	18.6	45	17.1	7	10.5
SA	7.8	25	9.5	5	7.5
WA	9.8	17	6.5	3	4.5
TAS	2.4	3	1.1	2	3.0
NT	1.0	na	na	na	na
ACT	1.6	10	3.8	3	4.5
Total^a	99.8	263	100	67	100.2

na = not available

^a Totals do not sum to 100% due to rounding

Sources: Survey of Haemophilia Services in NSW and ACT (NSW Department of Health, September 2000) and National Bleeding Disorder Registry, November 2000. Note: the two data sources are not strictly compatible, so the data are only broadly indicative.

Demand for factor IX

2.43 As with factor VIII, the demand for factor IX would best be measured using demographic and clinical data, which the NBDR will eventually provide. However, until such information is available, demand can be estimated from current usage, which should closely approximate demand, given that there is no reason for an undersupply of factor IX.

2.44 Data from the NBDR suggests that some eligible patients are not receiving prophylaxis (Table 2.9) or tolerisation, but the high level of stocks suggests that supply is not a factor preventing patients from receiving these therapies.

Table 2.9 Severe haemophilia B, by age and use of prophylaxis, at November 2000

Age category	Severe haemophilia B	
	Prophylaxis	No prophylaxis
0-5	0	2
6-10	4	0
11-18	4	2
Subtotal	8	4
Adult	4	2
Total	12 (67%)	6 (33%)

Note: Does not include data for New South Wales

Source: National Bleeding Disorder Registry, November 2000

2.45 Demand for recombinant factor IX is probably understated at this stage because States and Territories have to meet half the cost, whereas the Commonwealth meets the full fractionation cost of MonoFIX. Also, demand for plasma-derived factor IX has no impact on required plasma collection volumes. As the use of recombinant factor IX increases, there should be a fall in the use of the plasma-derived alternative.

2.45 On the basis of this information, the Working Party agreed that an annual maximum supply target of 0.6 IU per head of population should be established for factor IX unless and until better planning data become available. This target might need to be adjusted as more recombinant product is used, for the reasons outlined in the previous paragraph.

Recommendation 1 — supply of factors VIII and IX

The Working Party recommends that:

- A. a national supply target of 3.3 IU per head of population be agreed for factor VIII
- B. a national supply target of 0.6 IU per head of population be agreed for factor IX
- C. the factor IX target be adjusted to reflect the 25% increase in dosage required for the recombinant product
- D. these targets be reviewed regularly in line with changing treatment standards and more comprehensive demographic data from the NBDR
- E. the Commonwealth work with clinicians to improve the quality and usefulness of data in the NBDR
- F. New South Wales be encouraged to provide regular haemophilia patient data in a form that is compatible with the NBDR.

Section Three: Review of the policy on supply levels of recombinant factors VIII and IX

Recombinant factor VIII

3.1 The increasing availability of plasma-derived factor VIII between 1996 and 2000 brought a number of issues to a head. In 1995, AHMAC decided that the cost of imports of recombinant factor VIII should be shared equally between the Commonwealth on the one hand and State and Territory Governments on the other. This decision implied that recombinant factor VIII would supplement the supply of plasma-derived factor VIII until production of the latter could be increased sufficiently to meet clinical need. Health Ministers also supported the policy of national self-sufficiency in blood products, which means that Australia should rely as far as possible on domestic production for its supplies.

3.2 However, the supply situation is complicated by demand specifically for recombinant product. Clinicians, patients and their advocates have always espoused a policy of product choice in relation to coagulation products. This policy was based partly on understandable concerns about the potential for patients contracting as yet unknown and undetectable blood-borne pathogens from plasma-derived products. Supporters of this policy acknowledged the recent safety record of plasma-derived products in relation to known pathogens, but considered that recombinant products offered a greater degree of safety.

3.3 Clinicians, patients and advocates were also concerned that patients who had been treated with recombinant factor VIII during the supply shortage might be obliged to use plasma-derived product once the shortage eased. They sought a relaxation of the access guidelines adopted by AHMAC in 1995, so that more recombinant product could be made available. However, this would reduce the need for plasma-derived product, with implications for the domestic fractionation program.

3.4 The task of the Working Party was to review the clinical guidelines for access to recombinant factor VIII in the light of:

- the current evidence for the relative safety and effectiveness of recombinant and plasma-derived factor VIII
- the principle of only supplying recombinant factor VIII to those who fit the clinical preferential criteria for the recombinant product, once an adequate supply of plasma-derived factor VIII was established
- the overall cost implications of providing all people with haemophilia with access to the factor VIII product of their choice, taking into consideration the current contract between the Commonwealth and CSL.

Recombinant factor IX

3.5 The availability of a recombinant factor IX in Australia in 2000 raised similar issues to those outlined above for factor VIII. As an immediate first step, patients with

haemophilia B want the same access criteria as patients with haemophilia A. They also want product of choice in the longer term. The Working Party was asked to recommend criteria for access to recombinant factor IX and to report on the extent to which these access criteria should be compatible with those recommended for factor VIII.

Relative effectiveness and safety of recombinant and plasma-derived products

Safety

3.6 The 1995 Factor VIII Working Party concluded that there was no evidence that one product (plasma-derived or recombinant) was safer than the other. At that time, recombinant factor VIII had not been used long enough for any long-term safety issues to emerge. Also, recombinant products then available used albumin as a stabiliser, and therefore carried some of the risks associated with a plasma-derived product.

3.7 However, development of albumin-free recombinant factor VIII was well advanced by 2000. The new generation of recombinant factor VIII products will thus be entirely divorced from the blood supply, providing them with a comparative advantage over their plasma-derived counterparts in terms of risk to patients from any future blood-borne pathogens.

3.8 Variant Creutzfeldt–Jakob Disease (vCJD) emerged as a threat to the blood supply in the late 1990s, and many countries, including Australia, adopted the precautionary principle in response. Although the risk was theoretical and there was no scientific evidence that the prion associated with vCJD could be transmitted by blood or blood products, Australian Health Ministers decided to defer blood donors who might have been exposed to the pathogen during a period of residency in the United Kingdom. The Working Party concluded that, on similar grounds, this risk reduction strategy should be applied to patients with haemophilia.

3.9 Consistent with overseas policies, a second strategy to reduce the risk of blood-borne pathogens could be the use of substitutes for blood products when available. People with haemophilia, especially those with severe haemophilia, are exposed to virtually the entire national blood supply. The donor screening and testing procedures adopted by the Australian Red Cross Blood Service (ARCBS) and the viral inactivation processes used by CSL have a proven record in virtually eliminating the risk from known high-risk pathogens, such as hepatitis and human immunodeficiency virus (HIV). However, with no test for vCJD, the risk was increased, albeit theoretically.

3.10 On the basis of this type of safety argument, the Working Party agreed to recommend that recombinant products that contained no blood component should be used wherever clinically indicated. The recommendation applies equally to recombinant factor VIII and recombinant factor IX. These conclusions are tantamount to providing product choice for clinicians and patients. Advice from Haemophilia Foundation Australia and clinicians was that initially around 85% of patients would choose to use recombinant products. Over time, the percentage of patients choosing recombinant products would increase.

Clinical effectiveness

3.11 The Working Party found no conclusive evidence from the literature that one product type (plasma-derived or recombinant) is more clinically effective than the other. Clinical experience in Australia shows that recombinant factors VIII and IX are as effective as their plasma-derived alternatives for the prophylactic and general treatment of haemophilia A and B.

3.12 Similarly, the Working Party found no clear evidence on whether recombinant factors VIII and IX are as effective as the plasma-derived products for tolerisation, although both types are effective in most cases. Further work is necessary to determine whether a low-dose treatment regime is as effective as high-dose treatment.

Cost effectiveness

3.13 The available literature suggested that there was still no clear indication of which product was the more cost effective and under what treatment circumstances. As with safety, not enough time had passed to determine the long-term costs and benefits of recombinant factors VIII and IX. Such information is needed for a comprehensive cost–utility or cost-effectiveness analysis.

3.14 Providing product of choice will cost more (see Section 6 for more details) and Governments may need to balance increased outlays for people with haemophilia against other health priorities. However, the Working Party recommends that the current restrictions be lifted as rapidly as possible. Not to do so would be inconsistent with the timetable for implementing broader vCJD risk minimisation measures and would ultimately be counterproductive.

3.15 As explained in Section 2, most jurisdictions have tolerated some patients in the past few years, using product that was not otherwise required for mainstream treatment. However, some patients have not received treatment because insufficient product was available. Thus, a national tolerisation program is required to ensure that best-practice treatment protocols are used and to ensure equity for all patients. Such a program would require the creation of a national funding pool, to which each jurisdiction would contribute equitably.

Recommendation 2 — policy

The Working Party recommends that:

- A. the current restrictions on access to recombinant factors VIII and IX be removed as rapidly as possible, and that these products be used whenever clinically indicated, in order to improve patient safety
- B. best-practice clinical guidelines that promote clinical and cost-effective use of recombinant and plasma-derived coagulation products are promulgated
- C. jurisdictional agreement to a timetable for achieving a target of 85% recombinant use is obtained in the shortest time possible, and the target reached by 2004 at the very latest
- D. a national tolerisation program be implemented as soon as possible to ensure that patients have equity of access to treatment
- E. access to the tolerisation program and priority for treatment be determined by an expert clinical group established for that purpose
- F. treatment protocols for tolerisation be approved by the expert clinical group to ensure clinical and cost effectiveness, and equity of access to available product.

Section Four: Review of criteria for accessing recombinant products

4.1 The policy on accessing recombinant factor VIII is contained in two statements, each of which was endorsed by the Australian Health Ministers' Advisory Council (AHMAC) in 1995:

- AHMAC consensus statement on increasing factor VIII supply (Appendix C)
- Clinical guidelines on factor VIII prophylaxis (Appendix D).

4.2 The order of priority for access to recombinant factor VIII given in these two documents is:

- previously untreated patients
- patients who have been previously treated with plasma-derived factor VIII but who have no serological evidence of ongoing infection with hepatitis B, hepatitis C or human immunodeficiency virus (HIV)
- children, with younger children receiving priority over older children.

4.3 In response to the supply and treatment changes that had occurred since 1995, the Working Party asked the CASCH to review the clinical guidelines that had been endorsed by AHMAC in that year. The amended CASCH guidelines are in Appendix E.

4.4 If the policy of product choice recommended in this report is taken up, the amended CASCH guidelines are relevant for the transitional period between current supply arrangements and revised arrangements to reflect product choice. If the recommendation is not accepted, the guidelines will provide a clinically justifiable basis for distributing recombinant products in the future.

4.5 The Working Party agreed with the order of priority for access to recombinant products recommended by CASCH, but preferred to make the order of patient access more explicit, in order to avoid future confusion or uncertainty. The Working Party therefore recommended the following order of priority (which is consistent with CASCH advice):

- previously untreated patients
- children who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
- adults (> 18 years) who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
- virally infected children
- adults infected with hepatitis C

- adults infected with other viruses.

Continuing use of recombinant products

4.6 Clinicians and advocates for haemophilia patients had two concerns in relation to the continuing use of recombinant products:

- the implication in the clinical guidelines that once patients on prophylaxis reached the age of 18, prophylaxis was no longer necessary or, if it was, that ongoing access to recombinant factor VIII was no longer assured
- that access to recombinant product would be reduced as plasma-derived supplies increased.

4.7 In relation to the first of these concerns, the Working Party sought advice from CASCH, which advised that:

No conclusions regarding prophylaxis for patients over 18 were made. It was noted that some form of prophylaxis may be appropriate, particularly for those patients that have progressed from the paediatric HTC's [Haemophilia Treatment Centres]. Currently each case is assessed individually and an individual treatment regime [is] modified to suit.

4.8 As a result, CASCH recommended to the Working Party that the clinical guidelines be amended to indicate that prophylaxis could be undertaken for patients over the age of 18, provided that supplies of factor VIII and factor IX permit such treatment.

4.9 In relation to the second concern, the Working Party concluded that it was clinically and ethically inappropriate for patients who had never used plasma-derived coagulation products, or who had begun use of recombinant products under the current access guidelines, to be required to change to using plasma-derived products. Nevertheless, there may be occasions where plasma-derived product is optimal or clinically necessary for patient care.

4.10 If the Working Party's recommendations on the expanded use of recombinant factors VIII and IX are accepted, the question of changing to plasma-derived products as supply increases becomes redundant.

Recommendation 3 — access to recombinant products

The Working Party recommends that:

- A. once patients are treated with recombinant products, this practice should continue
- B. where the availability of product or financial constraints require prioritisation for the use of recombinant products, the following order of priority be used:
 - i) previously untreated patients
 - ii) children who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
 - iii) adults (> 18 years) who have been treated with plasma-derived factors VIII or IX and have no evidence of hepatitis B, hepatitis C or HIV infection
 - iv) virally infected children
 - v) adults infected with hepatitis C
 - vi) adults infected with other viruses.

Section Five: Future supply of plasma-derived coagulation products

5.1 If the Working Party's recommendations to allow product of choice are accepted, the demand for plasma-derived factors VIII and IX will decline significantly in the future. However, some Australian patients will still require plasma-derived coagulation products, notably those with von Willebrand's Disease, some patients undergoing tolerisation and those who wish to continue to use plasma-derived products by personal choice. The Working Party estimates that this requirement could be met from about 15% of total supply and could be expected to decline over time to less than 10%.

5.2 The Working Party considered whether increasing reliance on recombinant coagulation products was at odds with the policy of national self-sufficiency in blood and blood products. The policy is expressed in Appendix 19 of the Australian Guidelines for the Registration of Drugs, which says in part:

Intending sponsors of products derived from human blood plasma should note that Australia favours national self-sufficiency in products derived from human blood or plasma, believing that a policy of not being reliant on donors in other countries is not only in the national interest but an international responsibility. Blood products sourced from foreign countries will only be registered if the foreign product has a demonstrably significant clinical advantage over the local product.

5.3 Clearly, this policy is aimed at plasma-derived products rather than recombinant ones.

New CSL high-purity factor VIII

5.4 The 1995 Factor VIII Working Party recommended that CSL begin production of a new, high-purity factor VIII product (with two viral inactivation steps) as a matter of urgency. Despite the prospect of a significant reduction in domestic demand for plasma-derived factor VIII, the current Working Party supports the release of the new product (Biostate®), because it will be a more clinically effective and a safer product than AHF (High Purity).

5.5 The yield of this new product per kilogram of plasma is likely to be lower than of the current product. Rather than increasing plasma collections to make up the shortfall for factor VIII, funds should be used to buy more recombinant factor VIII.

Potential surplus products

5.6 One way to ensure that CSL continues to manufacture plasma-derived factors VIII and IX at reasonable prices (and reduce the need to spread fixed costs over fewer products) would be to develop an export market for excess production. However, exporting products sourced from Australian blood donations opens up several sensitive issues for the ARCBS, blood donors and the community as a whole. The idea also needs to be assessed in terms of the international obligations that underpin the policy of national self-sufficiency, which is based, in part, on the principle that nations have an international responsibility to be self-sufficient in blood

products. Selling or giving products may be seen as undermining this principle. In addition, there may be legal or ethical issues arising from trade in a blood product, particularly one that Australians have declined to use on the grounds of risk minimisation, albeit only as a precaution.

5.7 The development of a national policy on the disposal of surplus plasma-derived coagulation products is urgently required, both to optimise production at CSL and to avoid the negative perception that some part of a precious donation is being wasted. Complementary or alternative strategies, such as humanitarian aid, should also be investigated.

5.8 The current contract between the Commonwealth and CSL expires on 30 June 2004.

Recommendation 4 — future supply of plasma-derived products

The Working Party recommends that:

- A. the Commonwealth take into account the residual and contingency needs for plasma-derived coagulation products in any negotiations with CSL for a new Plasma Fractionation Agreement after June 2004
- B. the Commonwealth pursue the possibility of establishing international markets for surplus plasma products as one means of ensuring that Australia maintains a capacity to manufacture sufficient plasma-derived coagulation products for residual use and for contingencies
- C. the National Reserve of plasma-derived factors VIII and IX be increased to six months' cover, in parallel with any increase in the use of recombinant products (and this reserve be periodically rotated with freshly manufactured stock).

Section Six: Cost of increasing the availability of recombinant products

6.1 To minimise risk, the Working Party recommends using recombinant products wherever clinically indicated. However, this would create a considerable additional cost to the taxpayer. With limited funds available for health services, increased outlays for one intervention are usually at the expense of another.

6.2 Table 6.1 shows the estimated costs of providing the following quantity and mix of coagulation products:

- 3.3 IU of factor VIII per capita — 85% recombinant and 15% plasma-derived
- 0.6 IU of factor IX per capita — 85% recombinant and 15% plasma-derived.

Table 6.1 Cost of meeting the recommended quantity and mix of coagulation products

Product quantity and proportions	Total cost (\$ million) ^a	Increase in cost (\$ million)
Cost of products in 1999-2000	45.95	
Cost of current quantity of products: 85% recombinant ^b and 15% plasma-derived	75.74	29.79
Cost of recommended quantity: ^c 85% recombinant and 15% plasma-derived	78.88	32.93

IU = international units

^a All options costed at 1999-2000 prices; population taken from September 2000 ABS Report 3101.0 – Australian Demographic Statistics

^b Note: there are no figures for recombinant factor IX as BeneFIX only became available subsequent to the 1999-2000 financial year.

^c Recommended quantities are 3.3 IU per capita of factor VIII and 0.6 IU per capita of factor IX.

Source: Derived from data held by the Commonwealth Department of Health and Aged Care

6.3 Table 6.1 shows that that the direct cost of increasing the quantity and proportions of product available in 1999-2000 to those recommended here would be \$32.93 million, increasing Government outlays on these products by 72%.

6.4 Potential savings within the ARCBS result from the reduced requirement for plasma-derived factors VIII and IX. Factor VIII has to be made from plasma that is collected and frozen within 24 hours, whereas other products can be made from plasma recovered from blood cooled over a longer period. The cost to the ARCBS of collecting plasma within the present time constraints will be significantly reduced if requirements for plasma-derived factor VIII are reduced to 15% or less. Although it is not possible to determine the reduction in ARCBS outlays, the savings made would defray the additional cost of providing more recombinant products.

6.5 Another potential source of savings is a reduction in the unit price of recombinant products, which might happen because the quantity required would more

than treble. As an indication of the effect of price change on the financial outcome, a 10% reduction in the price of recombinant products and a 10% increase in the price of plasma-derived factor VIII would reduce the estimated cost of the above recommendations from about \$79 million to about \$74 million.

Section Seven: Funding arrangements for coagulation products

7.1 Under current arrangements, the cost of coagulation products is shared between the Commonwealth and the States and Territories as shown in Table 7.1.

Table 7.1 Intergovernmental cost-sharing arrangements for coagulation products

Product	Commonwealth share (%)	State/Territory share (%)
ARCBS cost of collecting plasma for fractionation:		
– operating	40	60
– capital	50	50
CSL fractionation costs	100	0
Recombinant products	50	50

ARCBS = Australian Red Cross Blood Service

Source: Commonwealth Department of Health and Aged Care

7.2 Actual outlays in 1999-2000 for fractionation of coagulation factors and for imported recombinant products are shown in Table 7.2. The cost of collecting plasma for fractionation is not included, because no reduction in volume will occur as a result of requiring less plasma-derived factors VIII and IX. As indicated in Section 6, some savings may be achievable by reducing the requirement for rapidly frozen plasma for manufacturing factor VIII.

Table 7.2 Jurisdictional outlays for coagulation products, 1999-2000

Product	Commonwealth \$m	State/Territory \$m	Combined outlay \$m
Plasma-derived products (CSL fractionation costs)	30.88	0	30.88
Recombinant products	7.53	7.53	15.06
Total	38.41	7.53	45.94
% of combined outlays	(84%)	(16%)	(100%)

Source: Commonwealth Department of Health and Aged Care.

7.3 A significant increase in the supply of recombinant product with a corresponding decrease in the supply of plasma-derived product would disproportionately favour the Commonwealth by reducing its outlays for fractionation, although the savings would probably be limited to the reduction in variable costs. Table 7.3 shows the jurisdictional outlays for the recommended supply levels.

Table 7.3 Jurisdictional outlays for coagulation products at the recommended supply levels and proportions

Product	Commonwealth	State/Territory	Combined outlay
	\$m	\$m	\$m
Plasma-derived products (CSL fractionation costs)	5.17	0	5.17
Recombinant products	36.85	36.85	73.69
Total	42.02	36.85	78.86
% of combined outlays	53%	47%	100%

Note: Recommended quantities are 3.3 international units (IU) per capita of factor VIII and 0.6 IU per capita of factor IX, with 85% recombinant and 15% plasma derived.

Source: Commonwealth Department of Health and Aged Care.

7.4 Comparison of Tables 7.2 and 7.3 shows that the Commonwealth's share of the total outlay for coagulation products would decline from 84% to 53%, and that its outlay would increase by only \$3.61 million (ie \$42.02 million – \$38.41 million).³ The combined outlay for the States and Territories would increase by approximately \$29.32 million — a significant deterrent to liberalising the recombinant access criteria in the short term. Also, the current inequality of access to coagulation products between jurisdictions could be exacerbated if jurisdictions adopted different targets and timetables for implementing the proposed recommendations.

7.5 Even if the Commonwealth were to share some of its savings with the States and Territories to reduce their costs, this would not necessarily ensure a national approach or an agreed national timetable.

7.6 An alternative might be to fund recombinant factors VIII and IX under the provisions of Section 100 of the *National Health Act 1953*, which currently covers the cost of erythropoietin, another recombinant blood product. Such a scheme would significantly favour the States and Territories and be an expense to the Commonwealth, but was not explored further.

7.7 In conclusion, the current funding arrangements will not support the achievement of 85% recombinant use in the short term. Funding arrangements for plasma-derived and recombinant products need to be reformed to ensure that:

- additional costs and savings are optimally balanced
- funding for new products is facilitated
- there is national uniformity in the use of blood products, in line with best practice.

³ Commonwealth outlays do not include any potential increase in the prices of other CSL products as a result of a reduction in demand for plasma-derived factors VIII and IX.

7.8 Without such a system-wide approach to Commonwealth and States and Territories funding for blood and recombinant products, the current inequities and inequalities will persist.

Recommendation 5 — funding arrangements for coagulation products

The Working Party recommends that:

- A. the costs of recombinant and plasma-derived coagulation products, as well as any savings from substitution between these products, be shared equitably between the Commonwealth and the States and Territories
- B. future funding and supply planning arrangements for plasma-derived and recombinant products be on a national basis, in line with jointly agreed national criteria.

Section Eight: Future plasma collection requirements

8.1 The Working Party was required to make recommendations on requirements for future levels of plasma processing at CSL, taking into consideration its own findings and those of the *Review of the Use and Supply of Intravenous Immunoglobulins (IVIG) in Australia* (2000). The latter report considered current and future requirements in Australia for intravenous immunoglobulin (IVIG). It recommended an increase in IVIG supply that would have to be met by an increase in plasma collections by the ARCBS. Thus, demand for IVIG, not factor VIII, is now the driver of plasma collection in the Australian system.

8.2 One consequence of the need for more IVIG is the potential for CSL to manufacture more factor VIII. An important policy question is the impact on CSL if and when there is a significant and sustained switch to recombinant coagulation products. If the recommendations in this report concerning supply are adopted, and the demand for plasma-derived coagulation factors declines significantly, the supply requirement for IVIG will continue to be the major determinant of the quantity of plasma required in Australia.

8.3 In relation to future plasma collection requirements, three specific issues arise:

- The need for fresh frozen plasma will decline in favour of recovered plasma, which may reduce ARCBS outlays.
 - However, the savings in this area are ultimately limited by the demand for cellular products and the most cost-effective means of collecting and handling blood components.
- If it is agreed that ‘surplus’ factors VIII and IX can be manufactured by CSL and sold on international markets or provided as humanitarian aid, the situation might arise where the demand for plasma for factor VIII exceeds the quantity required to meet domestic needs.
 - As a matter of policy, this quantity should not exceed the quantity required to meet the need for IVIG or any other product that might ultimately determine Australia’s plasma requirements.

8.4 On this basis, the Working Party recommends that annual plasma collection targets be set by reference to the clinically justified need for IVIG.

Recommendation 6 — future plasma collection requirements

The Working Party recommends that plasma collection requirements in Australia should be established by reference to the clinically justifiable need for IVIG.

Section Nine: Progress in implementing the findings and recommendations of the 1995 Working Party on Factor VIII Supply

9.1 The current Working Party was asked to review the progress made in implementing the recommendations of the Working Party on Factor VIII Supply, which reported in February 1995. The 31 findings and recommendations of that Working Party are in Appendix B.

Specific recommendations and responses

9.2 Ten of the 31 findings are recommendations of the 1995 report required follow-up action. They are listed below, together with progress as at December 2000.

Recommendation A3 and response

Recommendation A3 — A target for plasma production, to produce 2.0 IU per capita of plasma-derived Factor VIII, should be achieved by the end of the 1996–97 financial year.

9.3 The States and Territories and the Commonwealth provided special funding to increase plasma collection, with the specific aim of increasing the supply of factor VIII. The target was not achieved until 1997–98 (see Section 2, Table 2.1).

Recommendation A4 and response

Recommendation A4 — The issue of whether prophylactic treatment increases the need for tolerisation therapy should be evaluated by an expert independent panel of clinicians and epidemiologists so that the impact of prophylaxis and tolerisation on the use of Factor VIII may be more accurately determined.

9.4 In 1996, the B&BPC commissioned an expert group to consider, among other things, the issues raised in this recommendation. At the time, the evidence was inconclusive and it remains so.

Recommendation A5 and response

Recommendation A5 — The potential high cost of tolerising therapy for people with haemophilia who have inhibitors should be examined as a matter of urgency and that the cost/benefits of alternative therapies (eg recombinant Factor VIIa, Factor IX, FEIBA) should be explored and documented.

9.5 In 1996, the B&BPC commissioned an expert group to consider, among other things, the issues raised in this recommendation. The expert group assessed the clinical and cost benefit of tolerisation therapy and recommended a tolerisation regime that focused on patients aged between 5 and 14, where the cost effectiveness was clearly evident. A national tolerisation program has not been implemented at the time of writing this report.

Recommendation B4 and response

Recommendation B4 — The Working Party recommends that CSL commence production of the new high purity product (with a second viral inactivation step) as a matter of urgency.

9.6 Licensing and production issues have delayed the release of this product (Biostate®).

Recommendation C4 and response

Recommendation C4 — All States should review current production capacity and efficiency of BTSs [Blood Transfusion Services] in order to achieve at least 2.0 IU per capita per annum production of plasma-derived Factor VIII by the end of the 1996–97 financial year.

9.7 Only two States reached the production target by the end of 1996–97. All jurisdictions have now increased plasma collections to the point where the supply of plasma-derived factor VIII exceeds 2 IU per capita. The increasing use of recombinant factor VIII has reduced the need to meet targets for the plasma-derived product.

Recommendation D4 and response

Recommendation D4 — The funding mechanism for recombinant Factor VIII should be decided by Health Ministers with the main options for consideration being:

- Referral to PBAC [Pharmaceutical Benefits Advisory Committee] for consideration of funding Factor VIII under Section 100 arrangements for highly specialised drugs, with appropriate protocols to ensure its use does not compromise the use of Australian plasma-derived Factor VIII.
- A Commonwealth/State/Territory cost shared arrangement.

9.8 In 1995 AHMAC agreed to a 50:50 cost-sharing arrangement.

Recommendation E2 and response

Clear and nationally agreed clinical protocols for the uses of Factor VIII in the treatment of haemophilia should be developed by the NHMRC [National Health and Medical Research Council] as a matter of urgency. Priority should be given to the development of protocols for prophylaxis and tolerisation.

9.9 The clinical protocols were developed not by the NHMRC but by an expert clinical group established by the B&BPC in 1995. The guidelines were subsequently approved by AHMAC.

Recommendation E6 and response

The Working Party strongly recommends that an AHMAC committee on blood and blood products be established to consider policy issues as they emerge.

9.10 As a result of this recommendation, AHMAC established the B&BPC in 1995.

Recommendation F1 and response

A national register of all people with haemophilia should be established as a desirable objective for the purposes of health planning and epidemiology.

9.11 The B&BPC brokered agreement between the jurisdictions and the Medical Advisory Panel of Haemophilia Foundation Australia (HFA) for the funding and development of a national register. The NBDR is now operational and collects data from all jurisdictions except New South Wales.

Recommendation F2 and response

A nationally consistent approach to prenatal counselling and screening programs to enable people to make informed choices is a desirable objective.

9.12 Genetic counselling is available, but there is no evidence that it is structured and provided in a nationally consistent manner.

Issues highlighted by the 1995 report

9.13 The 1995 report of the Working Party on Factor VIII Supply highlighted the following particular features of the Australian situation at that time:

- the uneven distribution of people with haemophilia between States and Territories creates disproportionate demand for factor VIII in some States and Territories
- there are varying levels of plasma production efficiency between States and Territories, and a lack of controls and incentives in the funding system to increase output
- there is no established mechanism to redistribute factor VIII between States and Territories
- there is a disincentive inherent in the current system for States and Territories to increase plasma collection beyond their needs, despite the potential for their excess capacity to be used by other jurisdictions
- the differences between haemophilia treatment practice in each State and Territory reflect varying availability of factor VIII and, in turn, reflect (at least partly) differing levels of efficiency and effectiveness of blood transfusion services.

9.14 Despite some progress on these issues, it is evident from the findings of this report that these problems still persist.

**Appendix A:
List of submissions received by the Working Party in the
consultation process**

Number	Name
1	Confidential
2	Haemophilia Foundation Australia
3	Confidential
4	Confidential
5	Confidential
6	Confidential
7	Confidential
8	Confidential
9	Confidential
10	Confidential
11	Confidential
12	Confidential
13	Confidential
14	Confidential
15	Wyeth Australia Pty Ltd
16	Bayer Australia Ltd
17	Rhone-Poulenc Rorer Australia Pty Ltd
18	Medical Advisory Panel for Haemophilia, Haemophilia Foundation Australia
19	Australian Red Cross Blood Service
20	CSL Limited

Appendix B: Findings and recommendations of the 1995 report of the Working Party on Factor VIII Supply

A Increased supply level of factor VIII

- A1 Any increase in the supply level of factor VIII should be achieved through a combination of increased Australian plasma-derived product and the purchase of recombinant product.
- A2 Based on current international best practice, the management of persons with severe haemophilia A includes prophylaxis for those under 18 years, where such treatment is clinically indicated. It is recommended that Australia provide sufficient factor VIII, through a combination of plasma-derived and recombinant products, to support this practice.
- A3 Due to time constraints and incomplete data, the Working Party was unable to accurately quantify the projected demand for, and hence recommend the supply levels of factor VIII, taking into account the use of factor VIII for prophylaxis in severe haemophilia A. It is recommended that States and Territories, using data provided by clinicians and Haemophilia Foundation Australia, as a matter of urgency, undertake a detailed study of the existing and potential demand for factor VIII, in view of the move towards prophylactic treatment.
- In the interim, a national target range of between 2.5 to 3.0 IU of factor VIII per capita per year should be established to support prophylactic treatment.
 - The required level is likely to vary from State to State depending on the demography of people with haemophilia. National treatment protocols will need to be established to precisely determine the required level. However, this process should not delay the achievement of optimal on-demand and prophylactic therapy and these should be adopted as a priority.
 - In addition, a target for plasma production, to produce 2 IU per capita of plasma-derived factor VIII, should be achieved by the end of the 1996–97 financial year.
- A4 The issue of whether prophylactic treatment increases the need for tolerisation therapy should be evaluated by an expert independent panel of clinicians and epidemiologists so that the impact of prophylaxis and tolerisation on the use of Factor VIII may be more accurately determined.
- A5 The potential high cost of tolerising therapy for people with haemophilia who have inhibitors should be examined as a matter of urgency and the cost/benefits of alternative therapies (eg factor VIIa, factor IX, FEIBA) should be explored and documented.

B Product quality

- B1 No factor VIII product whether plasma-derived or recombinant can be assumed to be free of any risk including viral risk and therefore any decision as to which product should be imported to supplement local supply should be determined by cost, availability and Therapeutic Goods Administration (TGA) licensing criteria.
- B2 The view that current plasma-sourced factor VIII carries a higher risk of viral contamination than synthetic factor VIII cannot be established, especially since human-sourced albumin is used to stabilise the recombinant product. The Working Party notes that there is a strong clinical and patient preference for recombinant factor VIII in the treatment of previously untreated patients (PUPs) and hepatitis C negative people with haemophilia, however this is a matter which requires ongoing investigation.
- B3 The Working Party is satisfied that, on the available information, the decision by CSL, in consultation with haemophilia clinicians, to move to a high purity product rather than a very high purity one is justified on the basis of achieving a reasonable balance between quality, yield and specific activity.
- B4 The Working Party recommends that CSL commence production of the new high purity product as a matter of urgency.
- B5 The Working Party considers that the current evidence does not confirm immunological compromise through the use of factor VIII products with less than a 'very high' purity level. However, this situation needs to be monitored by clinical bodies and health authorities.

C Improving plasma supply

- C1 The Working Party considers that the principle of national self-sufficiency in plasma products is highly desirable but acknowledges that this cannot always be achieved in practice.
- C2 The Working Party notes that it is the collection of plasma which is the cost and production driver for all the blood transfusion services (BTSs) in Australia.
- C3 Whilst factor VIII is the current principal cost and production driver for plasma products, an almost equal amount of plasma is required to meet the demand for other products such as Intragam and albumin. Consequently, the following facts need to be underlined:
- If local production of plasma-derived factor VIII was ceased, cost savings would be negligible because a similar volume of plasma would still need to be collected and processed to produce adequate levels of other plasma products.
 - Anti-haemophilia factor, which includes factor VIII, is one of the first products to be separated during fractionation of plasma and is therefore produced in the manufacture of other plasma products.

- Given the above, factor VIII is a good indicator for an adequate level of plasma supply in Australia.
- C4 All States and Territories should review current production capacity and efficiency of BTSs in order to achieve at least 2 IU per capita per annum production of plasma-derived factor VIII by the end of the 1996–97 financial year.
- The timing and cost of achieving this target will vary for each State and any review will need to consider:
 - the efficiency of current plasma production processes;
 - the integration and TGA licensing of non-metropolitan collection centres; and
 - the need to increase plasma production capacity.
- C5 The achievement of at least 2 IU of plasma-derived factor VIII per capita should be included as a requirement in service agreements between health authorities and BTSs.
- C6 It is possible to increase plasma supply above the 2 IU level and this should be considered on the basis of cost/benefit as an alternative to any purchase of factor VIII products. This should apply to the redistribution of product between States and Territories as well as to the purchase of imported factor VIII products.
- C7 Arrangements to facilitate interstate redistribution of blood products should be established including agreement on unit price. However, interstate transfers should occur only if the exporting State has a surplus after its own needs, based on nationally agreed levels of treatment, have been met.
- C8 Any price signals associated with reimbursement for blood products redistributed between States and Territories should exclusively reflect marginal collection and handling costs without any component of a price for plasma per se.
- C9 It should be noted that interstate redistribution of blood products may require amendments to reflect State and Territory legislation that covers human tissue and trade practices issues.

D Costs and funding

- D1 The estimated additional national cost of recombinant factor VIII, at current indicative price, required to achieve a maximum level of 3 IU per capita is approximately \$13 m to \$21 m per annum, assuming a level between 2 IU and 2.4 IU is achieved with Australian plasma-derived factor VIII.
- D2 Whatever funding mechanism is put in place to purchase factor VIII, it must not compromise the overall cost/benefit to the nation of enhancing plasma supply as opposed to purchasing additional factor VIII.

- D3 Furthermore, the demonstrable need to produce at least the current levels of plasma products other than factor VIII must be part of any cost/benefit considerations.
- D4 The funding mechanism for recombinant factor VIII should be decided by Health Ministers with options for consideration being:
- Referral to PBAC [Pharmaceutical Benefits Advisory Committee] for consideration of funding factor VIII under Section 100 arrangements for highly specialised drugs, with appropriate protocols to ensure its use does not compromise the use of Australian plasma-derived factor VIII.
 - A Commonwealth/State/Territory cost shared arrangement.

E Factor VIII distribution and monitoring

- E1 All blood and blood substitute products should be distributed in the most cost efficient manner with attention to a capacity for forward planning and bulk purchasing as required.
- E2 Clear and nationally agreed clinical protocols for the use of factor VIII in the treatment of haemophilia should be developed by the NHMRC as a matter of urgency. Priority should be given to the development of protocols for prophylaxis and tolerisation.
- E3 Accountability for the use of all factor VIII, plasma and non plasma-derived, should rest at the hospital level. Recording requirements should as a minimum include patient identification, product source, treatment use and the quantity used.
- E4 Responsibility for monitoring overall factor VIII use should rest at the State level with existing BTS User Committees, which should in turn report on a regular basis to the respective State and Territory Health Authority.
- E5 The Working Party has concluded that there is a need for a continuing Commonwealth and State and Territory forum, which includes a regular information exchange, to deal with blood and blood products and the relationship between respective parties (ie State and Commonwealth Governments, the NBTC [National Blood Transfusion Committee], BTSs, the Red Cross Society and clinicians). Such a forum does not currently exist and has led to respective parties taking decisions in isolation.
- E6 The Working Party strongly recommends that an AHMAC standing committee on blood and blood products be established to consider policy issues as they emerge.

F Further issues

- F1 A national register of all people with haemophilia should be established as a desirable objective for the purposes of health planning and epidemiology.
- F2 A nationally consistent approach to prenatal counselling and screening programs to enable people to make informed choices is a desirable objective.
- As part of an overall counselling and screening service, prenatal diagnostic techniques should be made available as a routine part of the health care system for those for whom specific risk of haemophilia has been demonstrated.

Appendix C: Australian Health Ministers' Advisory Council Consensus Statement on Increasing Factor VIII Supply

In line with the decision by Australian Health Ministers in June, additional resources will be provided to increase factor VIII supply to sufficient levels to extend prophylactic use, wherever clinically indicated, to people with severe haemophilia A up to 18 years of age.

The commencement date for the new treatment level may differ in each State and Territory depending on the time required to achieve an adequate supply of factor VIII, but will be no later than 1 July 1996.

Consistent with the principle of maximising Australian plasma production, supply will be predominantly from the local plasma-derived source and will be supplemented, wherever necessary, with imported recombinant factor VIII.

Continuing efforts will be made to increase Australian plasma production. It is noted that Health Ministers agreed that a level of 2.0 IU per capita per year would be achieved by 1 July 1997 by all States and Territories.

The level of additional factor VIII required will be determined by each State and Territory through an estimate of demand based on the following clinical guidelines on factor VIII prophylaxis.

The primary purpose of additional funding for prophylactic treatment is to minimise morbidity and maximise quality of life. However, it is expected that people with haemophilia will exercise reasonable precautions in limiting their voluntary exposure to high risk of injury. Prophylactic treatment should therefore be accompanied by patient education about such risks.

It is apparent that there is a clinical preference to use recombinant factor VIII with previously untreated patients (PUPs) and patients with no serological evidence of ongoing infection with hepatitis B, hepatitis C or HIV. At clinical discretion, preferential access to the recombinant factor VIII for these patients can be allowed from the quantity of recombinant factor VIII required to supplement overall supply.

However, there should be no expectation that preferential use of recombinant factor VIII for such patients will extend to situations of major spontaneous episodes of bleeding or other calls for therapy which require large quantities of factor VIII (eg tolerising therapy, planned surgery).

Appendix D: Clinical guidelines on factor VIII prophylaxis

[Prepared by an Expert Working Group of the AHMAC Committee on Blood and Blood Products, 21 November 1995]

1. The goal of prophylaxis is to improve quality of life for patients with severe haemophilia A by maintaining sufficient factor VIII levels to prevent spontaneous joint bleeding and the morbidity associated with complications of joint bleeds.
2. Factor VIII prophylaxis is recommended for all children with severe haemophilia A up to the age of 18 years. If the supplies of factor VIII permit, consideration should be given to extending prophylaxis treatment to severe haemophilia A patients older than 18 years.
3. For the purposes of these guidelines, children have severe haemophilia when they have major spontaneous bleeds into joints and their factor VIII levels are less than 5%.
4. The recommended dosage range for factor VIII prophylaxis is 25–40 IU per kilo, three times a week or more frequently as required. The amount of factor VIII used for prophylaxis will vary from patient to patient but for each patient will be the minimum amount of factor VIII required to prevent spontaneous joint bleeding.
5. The age at which prophylaxis therapy is introduced will vary from one to two years to around five years depending on the number and severity of bleeds and whether the patient and his family are willing to comply with the prophylactic treatment regimen.
6. Within the proposed limits on supply, the recommended priority groups for receiving the recombinant factor VIII for prophylaxis are, in order :
 - a) Previously untreated patients (PUPs);
 - b) Patients who have been previously treated with plasma-factor VIII but who have no serological evidence of ongoing infection with hepatitis B, hepatitis C or HIV; and
 - c) Children — younger children receive priority over older children.
7. At this time, there is inadequate evidence to support a recommendation that HIV positive patients be a priority group for receiving recombinant factor VIII.
8. Factor VIII usage and selected clinical and laboratory outcome indicators should be routinely monitored and evaluated for all patients on prophylaxis.
9. All patients receiving prophylaxis should have their treatment coordinated and monitored by a designated Haemophilia Treatment Centre.

10. It is expected that people with haemophilia will exercise reasonable precautions in limiting their voluntary exposure to high risk of injury. Prophylactic treatment should therefore be accompanied by patient education about such risks.

Appendix E: Revised clinical guidelines on treatment using factors VIII and IX, including prophylaxis

[These are the clinical guidelines revised by the Clinical Advisory Sub Committee — Haemophilia, September 2000]

1. The goal of prophylaxis is to improve quality of life for patients with severe symptomatic moderate haemophilia A and B by maintaining sufficient factor VIII and factor IX levels to prevent spontaneous joint bleeding and the morbidity associated with complications of joint bleeds.
2. Factor VIII and factor IX prophylaxis is recommended for all children with severe haemophilia A and B up to the age of 18 years. If the supplies of factors VIII and IX permit, consideration should be given to extending prophylaxis treatment to severe haemophilia A and B patients older than 18 years.
3. For the purposes of these guidelines, children have severe haemophilia when they have major spontaneous bleeds into joints and their factor VIII or IX levels are less than 5%.
4. The recommended dosage range for factor VIII prophylaxis is 25–40 IU per kilo, three times a week or more frequently as required. The recommended dosage for factor IX prophylaxis is 40–60 IU per kilo, twice a week or more frequently as required. The amount of factors VIII and IX used for prophylaxis will vary from patient to patient but for each patient will be the minimum amount of factor VIII or IX required to prevent spontaneous joint bleeding. Please note that the guidelines for factor IX dosage are based on plasma concentrates. The dosage for prophylaxis with recombinant factor IX is not yet known.
5. The age at which prophylaxis therapy is introduced will vary from one to two years to around five years depending on the number and severity of bleeds and whether the patient and his family are willing to comply with the prophylactic treatment regimen.
6. The recommended priority groups for receiving recombinant factor VIII and factor IX for treatment/prophylaxis, are in the following order of priority:
 - a) Previously untreated patients (PUPs).
 - b) Patients who have been previously treated with plasma-derived factor VIII and factor IX but who have no evidence of hepatitis B, hepatitis C or HIV infection.

7. The recommended priority groups for receiving recombinant factors VIII and IX for treatment/prophylaxis (as supplies become available) in addition to the above groups are, in order of priority:
 - a) virally infected children (up to 18 years); and
 - b) virally infected adults.

Appendix F: Subsequent developments relevant to this report (March 2003)

The last meeting of the Factor VIII and Factor IX Working Party was held in November 2000. Since that meeting, there have been a number of developments relevant to the supply, procurement and use of factors VIII and IX in Australia. These developments (the most important of which are described below) are consistent with, and support, the recommendations made in this report.

The only recommendations to be changed are related to the recommended supply targets for factors VIII and IX (Recommendations 1A and 1B), which the Working Party is proposing be amended to take into account the sector developments outlined below. The proposed new recommendations read:

- 1A a national supply target of 3.75 IU per head of population be agreed for factor VIII
- 1B a national supply target of 0.7 IU per head of population be agreed for factor IX.

National Blood Authority

The *Review of the Australian Blood Banking and Plasma Products Sector* (March 2001) concluded that a National Blood Authority (NBA) should be established as a statutory body under Commonwealth legislation, to provide national management and oversight of the Australian blood supply. In response to this conclusion, such an authority will begin operating on 1 July 2003.

The NBA's functions will include:

- national supply planning and management
- contingency planning
- overall management of national supply contracts on behalf of jurisdictions.

This new arrangement will ensure that the supply of blood, blood-related products and blood-related services in Australia is adequate, safe, affordable and well managed.

Under a national tendering process, the NBA will be the sole purchaser of blood and blood products on behalf of jurisdictions, and will thus be in a position to negotiate the best possible uniform price for products. Jurisdictions will order products through the NBA from an approved national price list, and will transfer their contract management functions and supply planning to the NBA. New arrangements for funding and special agreements for high-cost products will be established, providing incentives to increase efficiency and improve risk management across the sector.

Special Expert Committee on Transmissible Spongiform Encephalopathies

In July 2002, the National Health and Medical Research Council established the Expert Committee on Transmissible Spongiform Encephalopathies (SECTSE). The committee has made the following recommendation in relation to plasma-derived products:

Although the theoretical risks from plasma derived AHF (anti-haemophilic factor) are very small, they cannot be said to be totally negligible. It is prudent to recommend that, as soon as feasible, AHF be made available in recombinant form, or a product of a purification process that is proven to reduce prion content by at least 7 logs.

AHF (High Purity), the plasma-derived factor VIII produced by CSL Limited, had a relatively low level of purification, with only a single viral inactivation step. In line with SECTSE's recommendation, this product has been cancelled from the Australian Register of Therapeutic Goods and replaced by Biostate®, as indicated below.

Biostate®

Biostate® was introduced on 31 March 2003 and replaces CSL Limited's former plasma derived factor VIII product, AHF (High Purity) for the treatment of haemophilia A in Australia. Biostate® is a higher purity product than AHF (High Purity). Both products are, plasma-derived concentrates of factor VIII, but whereas AHF (High Purity) production involves a single viral inactivation step, Biostate® undergoes two viral inactivation steps and is therefore a safer product. However, the additional viral inactivation process reduces the yield of Biostate® from a given quantity of plasma, when compared to yields of AHF (High Purity).

Governments have agreed to fund the ARCBS to collect additional plasma in 2003-04, and ongoing, to achieve IVIG sufficiency (as the main plasma collection driver), noting that this will provide additional Biostate® as a consequence. Governments have also agreed to purchase additional recombinant factor VIII if production levels of Biostate® are insufficient to meet current demand.

von Willebrands Disease

Neither AHF (High Purity) nor Biostate® is registered under the *Therapeutic Goods Act 1989* for the treatment of von Willebrands Disease. However, advice from the TGA indicates that both products demonstrate pharmaceutical equivalence in the features relating to the biological functions of von Willebrand Factor. On this basis, people with von Willebrands Disease can be treated with Biostate®. CSL has begun the clinical trials needed for Biostate®, including pharmacokinetic studies, to be registered for the treatment of von Willebrands Disease, but it will take several years for these trials to be completed.

Recombinant factor VIII products do not contain von Willebrands Factor and therefore cannot be used to treat von Willebrands Disease.

Australian policy related to blood-borne infections

Since 21 December 2000, Australia has indefinitely excluded from donating blood any donors or potential donors who spent a cumulative period of six months in the United Kingdom between 1980 and 1996. The introduction of this policy reduced the theoretical risk that bovine spongiform encephalopathy (BSE) and variant Creutzfeldt–Jakob Disease (vCJD) might be transmitted by blood transfusion.

In March 2001, the then Commonwealth Minister for Health wrote to his State and Territory counterparts suggesting that the recombinant factor IX product BeneFIX be made available to people with haemophilia B as a logical risk minimisation strategy, consistent with the decision to defer blood donors who have been exposed to BSE in the United Kingdom. The Minister proposed access guidelines that mirrored those for recombinant factor VIII and 50:50 cost sharing arrangements. Most States began supplying BeneFIX from early 2001–02.

In February 2003, a national vCJD workshop was held in Australia to provide stakeholders with current national and international information relating to the risks of transmission of vCJD associated with blood transfusion. The outcomes and recommendations of the workshop are still being formulated and, although they could have an impact on plasma collections by the ARCBS, they are not known at the time of writing this report.

Australian Haemophilia Centre Directors' Organisation and the National Bleeding Disorder Registry

The Australian Haemophilia Centre Directors' Organisation (AHCDO) is the national medical body for haemophilia in Australia. Funded by the Commonwealth, the organisation provides expert clinical advice to Governments on the treatment of people with bleeding disorders and will be instrumental in the development of clinical use guidelines for haemostasis factors.

The establishment of the National Bleeding Disorder Registry (NBDR) was initiated by the then Medical Advisory Panel of Haemophilia Foundation Australia (now AHCDO) to address the lack of consistent and up-to-date information about people with haemophilia in Australia and their use of blood products. The NBDR collects data from haemophilia treatment centres on the number of people with haemophilia, the severity of their Disease, demographic characteristics, treatment regimens and products. This type of information is vital for management of supply and demand of haemostasis products, and for the development of clinical guidelines. Discussions are ongoing with NSW Health to incorporate data from New South Wales in the NBDR.

Cost of recombinant products

Since December 2000, the costs of recombinant factors VIII and IX have increased. The overall costs of meeting the recommendations of this Report in full (taking into account the proposed new recommended targets outlined in Recommendation 1A and Recommendation 1B), as at March 2003, are summarised in Table F.1 below.

Table F.1 Cost of meeting the recommended quantity and mix of coagulation products as at 31 March 2003

Product quantity and proportions	Total cost (\$ million)^a
Cost of December 2000 recommended quantity of products ^b : 85% recombinant and 15% plasma-derived	83.30
Cost of March 2003 recommended quantity of products ^c : 85% recombinant and 15% plasma-derived	91.95

IU = international units

^a All options costed at 2002-03 prices and are only estimates; population taken from September 2002 ABS Report 3101.0 – Australian Demographic Statistics

^b Recommended quantities as at December 2000 are 3.3 IU per capita of factor VIII and 0.6 IU per capita of factor IX.

^c Proposed new recommended quantities as at March 2003 are 3.75 IU per capita of factor VIII and 0.7 IU per capita of factor IX.

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