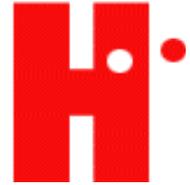


HAEMOPHILIA FOUNDATION AUSTRALIA



PLASMA FRACTIONATION REVIEW

The Review

Haemophilia Foundation Australia (HFA) submits the following comments to the Flood Review on the assumption that accurate data will be provided to the review by NBA and AHCD0 on current and projected usage of plasma derived and recombinant clotting factors in Australia which is not in the public domain, and that the Review has access to relevant regulatory and technical information about the safety profile of treatment products registered for use in Australia. HFA will comment on world wide trends and the specific needs of the Australian bleeding disorders' community. HFA will provide comment on selected aspects of the Terms of Reference.

These comments are made in the context of the FTA side letter and the requirement to review fractionation services for the Australian community and consider the potential impact of increased competition and access to new markets upon the requirements of the bleeding disorders' community. In this submission HFA will comment on the implications of allowing the fractionation of blood collected in Australia by USA based companies.

This submission relates to the needs of people with clotting factor deficiencies who require factor VIII for haemophilia A and von Willebrand disorder and factor IX for haemophilia B and other products for rarer bleeding disorders. However, we note the issues for the Flood Review relate to a wider range of treatments, and that the main driver in terms of demand and supply of blood products is immunoglobulin where demand is increasing exponentially in Australia.

Haemophilia Foundation Australia does not oppose competition nor tendering for blood products. If competition and tendering for contracts to supply products for Australians leads to enhanced capacity for a secure supply of treatment products that meet safety, quality and efficacy standards there may be cost savings. The key issue is that the Australian government must retain its control over how the blood donated freely by Australian donors is used. Australians have a strong preference for blood products produced in Australia, and will not accept those which are manufactured overseas or produced from plasma of overseas donors.

All steps necessary should be taken to maximise Australia's capacity to supply blood products to as many Australians who need them, and imported products made from overseas plasma should only be used for residual needs. The haemophilia community supports policy that will retain Australia's capacity to fractionate Australian plasma in Australia and recommend arrangements which will encourage this outcome.

Background

Treatment for haemophilia in Australia is now primarily with recombinant factors VIII and IX. Until August 2004 government policy meant that Australians with haemophilia would not be treated with recombinant factor VIII (rFVIII) or recombinant factor IX (rFIX) unless they were under 18 and were not infected with HIV or hepatitis C. The impact of the transmission of blood borne viruses in plasma derivatives in the 1980's and early 1990's, and the more recent circumstances of vCJD in UK blood, required countries to find alternative sources for plasma and add more stringent donor deferral policies, and later to escalate plans to increase access to recombinant treatment products as these were considered safer alternatives to plasma derivatives for those who could use them.

In Australia around 80% of the bleeding disorders' community is treated with recombinant clotting factors. Plasma derived factor VIII is used by around 20% of patients with haemophilia A for clinical reasons (including tolerisation) or personal choice and those with Willebrand disorder who require plasma concentrates containing von Willebrand factor.

A commitment to self sufficiency of blood in Australia to date has meant that people with haemophilia and von Willebrand disorder have almost always used replacement concentrates fractionated by CSL from blood collected from voluntary donors by ARCBS. Blood products for very rare disorders are imported as required. Adequate supply has depended upon the availability of donors and the capacity of the fractionator to keep pace with demand.

There have been acute and chronic replacement therapy shortages from time to time which have resulted in restricted treatment or delayed access to tolerisation or surgery. This difficulty was alleviated to a certain extent in 1995 when recombinant products were imported to Australia to address the chronic shortage. The switch to recombinant became possible in August 2004 when governments provided adequate funding to allow all people access regardless of age and blood borne viral status. This switch occurred later in Australia than in many countries with similar health care standards, which were acting to minimise the risk of emerging pathogens such as vCJD that could be transmitted through blood. The risk of vCJD infection through blood was of paramount concern when blood donors in the UK were found to have vCJD. What was at first considered a theoretical risk later became a reality and there have now been three cases in the UK where recipients of transfused fresh blood have become infected with vCJD, probably from the transfusion. Although there has been no known transmission of vCJD through fractionated products, this is nevertheless a risk that needs to be taken into account. This issue also has considerable relevance to the confidence the bleeding disorders' community has in the blood supply and its strong preference for treatment products made in Australia with plasma donated by Australians.

In recent years throughout the developed world, best clinical practice was considered to be with recombinant therapy, and in Australia, expert committees on blood safety recommended the use of alternatives to plasma where these were available and the regulatory authority took steps to enhance the safety of plasma derivatives by tighter donor selection and manufacturing requirements. At the same time, clinical practice had also been changing and this affected demand. Many patients are now treated prophylactically, dosage has increased, children are growing older and require higher treatment doses and people are living longer with ongoing clinical and surgery requirements.

Current guidelines for optimal treatment for haemophilia in Australia and overseas, and regulatory and safety requirements mean the Australian blood supply no longer has to support total demand for haemophilia products, however it may meet residual needs for haemophilia and von Willebrand patients requiring plasma derivatives and as a back up for treatment and contingencies in the event of interruptions to the supply of recombinant products.

Blood safety is more robust than ever, and fractionation appears to have a good capacity to remove prions. Emerging technologies for removing prions, promise further improvements. Genetically engineered recombinant products will be increasingly used in the developed world for haemophilia, however there is also expected to be an increasing demand for other products such as immunoglobulins. As Australia cannot be self sufficient for blood products and blood components, it is essential that all steps necessary be taken to ensure adequate supplies of the safest plasma products. It is well recognised that supply and safety are inextricably linked - without adequate supply arrangements to meet demand, the blood supply is not safe.

Global Challenges and Changes

Australia is a relatively small consumer in a changing global blood economy. Increased use of recombinant factor VIII and IX has reduced revenue from plasma derived products. A reduced demand and price for albumin world wide and fluctuating immunoglobulin supply and price has also occurred. Mergers and acquisitions have resulted in fewer international plasma fractionators.

75% of the world's haemophilia population is inadequately treated. A key objective of the World Federation of Hemophilia (WFH) is to increase worldwide supply of safe affordable factor replacement therapy. Although significant inroads have been made to increase the number of people diagnosed and treated this remains a great challenge for the global haemophilia community and its partners. At a recent meeting WFH President Mark Skinner noted the twin economic challenge for everyone is to "bring patients and products to market". However this will be difficult in the current climate where plasma fractionators are contracting, where increased availability and use of recombinant treatment in the developed world has resulted in increased use per patient and increased cost for governments, but it is not insurmountable.

Demand and Supply in Australia

It is expected that treatment of clinical choice and patient preference and expectations in Australia over the next ten years will be with early treatment with 2nd generation recombinant products (containing human albumin in cell culture and as stabiliser in final bottle), and 3rd generation (containing no human or animal albumin in cell culture or as stabiliser in final bottle) recombinant products.

Development work is in progress for the production of 4th and 5th generation recombinant treatments which have a sustained half life and better delivery systems and these are unlikely to be available until 2009 or later. Work on an oral medication is a long way off success.

It is expected that the focus for government purchasers will be on haemophilia therapy rather than expecting a cure during the next 10 years. The developments of gene therapy offer hope for the haemophilia community. Research on the gene therapy delivery systems and necessary clinical trials are expected to progress significantly, however are unlikely to have met safety requirements or will be cost effective in the relevant time period to have any significant impact on the demand for replacement therapy during the 10 year period.

The 2004 World Federation of Hemophilia Global Survey indicates per capita factor VIII usage of 5.32 International Units (IU) and .72 IU for factor IX (in countries with GNP above US\$10,000 per capita) (1). Usage per capita has increased significantly throughout the developed world in recent years in line with revised clinical guidelines and increased access/availability of recombinant factors. It is reported that in some countries the per capita usage is significantly higher than this, and may be around 6-8 IU for factor VIII. In Australia it was 3.14 IU per capita in 1999-2000 (2) and it may now be between 5-6 IU. HFA considers Australia would have been consistently below the usage of other similar health care economies until very recently, resulting in optimal treatment for many people.

The increased cost of supplying sufficient treatment products to the bleeding disorders' community has lead to cost effectiveness of treatment being of significant interest to stakeholders, and there is considerable discussion in world forums about the optimal dosage relative to quality of life outcomes. Even if an optimal dose is determined that equates to less than current prescribing trends, it is likely that usage will continue to rise in Australia as it has done world wide. In the past a 10% increase per annum has been considered a reliable figure for estimate of future demand, however it is unclear whether the plasma derivative/recombinant ratio is stable enough yet in Australia to allow reliable forecasting. HFA recommends that governments should more adequately resource the Australian Bleeding Disorders Registry to ensure accurate and reliable data about clinical practice and requirements.

There are a number of other issues which may also contribute to increased demand for plasma and/or recombinant therapy, such as children treated with prophylaxis continuing this into adulthood (although most children will be using recombinant therapy), people living longer with haemophilia and co-morbidities, including the need for orthopaedic surgery, obesity in children and adults (dose is weight related).

A major consideration for regulatory authorities, clinicians and patients is the risk of inhibitor development in patients using recombinant products and whether product type is of consequence. Planning should take into account that the relationship of inhibitor risk to product type is as yet, inconclusive and for this reason access to both recombinant and plasma derivatives should be maintained. There may be an increased requirement for plasma inventory because of inhibitor development. Supplies of plasma derived product for tolerisation are also necessary and there may be antigenicity issues for people who have been tolerised on plasma and/or those who have an immune response upon switching to recombinant. There is generally a clinical preference for tolerisation with plasma. Clinicians and government officials managing supply and demand will assist the Committee on this issue, however HFA is unaware of new trends since the increased availability of recombinant in Australia. It must be the right of the patient to make these treatment decisions based on sound clinical judgement, and treatment product supplies need to be available for all contingencies. If product type is an issue, then a steady and uninterrupted supply of the treatment products previously used by a patient would be necessary and reserves of plasma derived clotting factors will be essential. Plasma derived haemophilia treatment products manufactured in Australia currently rate among the safest in the world and are a viable option to recombinant in cases where there is no other alternative.

It is suggested that von Willebrand disorder may affect up to 1% of the population and that it may be under diagnosed in many populations. In most cases people with vWD will not be severely affected and will not require treatment with clotting factor. Most people with vWD currently requiring treatment with clotting factor should already be included in the data on Biostate usage in Australia. However, if vWD is under diagnosed, or if diagnostic technologies become more specific, there may well be a higher rate of diagnosis and some of these patients may require concentrates containing von Willebrand factor containing factor VIII resulting in an increase in demand over the next 10 years. Secondary prophylaxis may become increasingly recommended by clinicians which may also lead to an increased demand for plasma derived factor VIII for people with von Willebrand disorder.

External factors may influence demand and supply trends and may affect the sector in terms of availability or logistics. Governments are increasingly required to consider risk management strategies and have sound plans in place in the event of political or economic uncertainty or bioterrorism. It is therefore prudent to consider that external factors may occur which limit or cease the importation of recombinant product into Australia. In such circumstances it will be critical for Australia to have the capacity to independently produce blood products for people requiring replacement therapy and other with other requirements for blood. For this reason HFA strongly supports policy that protects ongoing fractionation capacity in Australia.

HFA has been acutely anxious about the limited supply of Biostate in Australia since it was introduced in 2003. There has effectively been no reserve of plasma derived factor VIII other than the NBA capacity to purchase additional recombinant factor VIII if it was available and could be sourced from its supplier. The availability of imported recombinant products ameliorated this gap in risk management, and provided comfort to haemophilia patients, especially when governments agreed to fund recombinant to appropriate levels, as undoubtedly did decisions to import additional immunoglobulin in short supply in Australia. It has been a long held, and prudent policy objective in Australia to maintain a national reserve, and every effort should be taken to maintain this risk minimisation strategy. The risk to this capability will be threatened if fractionation occurs off shore, and adequate reserves are not maintained in Australia.

If Australia moves to a system of tendering for offshore plasma fractionation, stakeholders would need to accept the previously valued goal of Australian self sufficiency made possible by Australian service providers would no longer be a policy priority. It is unlikely that a new fractionator would consider developing capacity to fractionate in Australia, and this would take many years. It is unlikely that it would be viable for the only Australian based fractionator, CSL, to produce smaller amounts of fractionated products for Australians from Australian plasma in a competitive environment.

HFA believes Australia should maintain its ability to fractionate plasma products and supply product to patients who need product in a timely manner. Whilst it is acknowledged that contingency supplies need to be available if demand cannot be met by CSL, however plasma fractionation services need to be maintained and viable in Australia. Governments need to support this with appropriate policy and resources and should ensure adequate support to the Therapeutic Goods Administration for the regulation of safe and efficacious blood products.

Suppliers should be required to meet production targets and logistics requirements (including adequate and effective rotation plans) to assure supply in contracts. Security of supply is a safety issue, and a risk management approach is necessary.

There also needs to be strong accountability to ensure that a fractionator performs effective and safe fractionation and that the donated blood is not wasted or undervalued – blood is a national resource which has been voluntarily donated in a spirit of goodwill. Individuals donate blood for a number of reasons. Donation rates may be affected if Australians do not want their blood to be fractionated offshore because they do not understand the process or do not support the contract arrangements, or if there is a perception of mismanagement (or waste) of the blood supply.

It is important to realise the difference between plasma products and recombinant products in the context of service provision and that the community has different expectations about blood products made from the blood of donors, compared to recombinant products which are essentially synthetic in nature. Any future arrangements should specify how unused material such as cryopaste would be used. The use of such material for humanitarian purposes or sale requires significant discussion. HFA has raised this issue on several occasions with the Department of Health and Ageing and National Blood Authority.

The World Federation of Hemophilia encourages plasma collectors and fractionators to find ways to exploit plasma or plasma fractions that are currently unused to increase access to the 75% of the world's haemophilia population which is currently untreated. A project of interest is the collaboration between Hema–Quebec, Canadian Blood Services, Canadian Hemophilia Society, and World Federation of Hemophilia which is considering how surplus plasma proteins can be used outside Canada (3).

Whilst the humanitarian benefits are obvious, stakeholder responses may vary. There are fears that blood donors would be disinclined to donate if their blood is fractionated offshore, or that they would be reluctant to donate if unused fractions were to be sold or donated and that blood products were to be used by people other than Australian recipients. However with careful, consultation, transparency and management, innovative options for the sale or donation of these unused proteins may lead to benefits for the global community and an Australian contribution that may be affordable and feasible to all stakeholders. It may be that this issue is the one where leverage can be gained with tenderers. Whilst, HFA acknowledges the significant manufacturing, quality, logistics, regulatory, legal and ethical barriers to this, it is strongly recommended that the Review Committee considers options (4). Pricing benefits for some products may be gained as a trade-off for the capacity to sell or use unwanted proteins in ways currently not possible in the Australian context.

HFA agrees that competitive tendering for fractionation services is a sound concept from an economic and business perspective, however extreme care must be taken to maintain the confidence of donors and blood product recipients. Today, regulation is robust and the level of comfort and confidence with ARCBS and CSL is high. This could be threatened if the community does not have confidence in the successful tenderer or that there is a perception or real impact on quality and safety standards.

There is a strong view in the haemophilia community that the decision of governments to opt for a sole supplier of recombinant factor VIII when the defined blood products tender was let in 2003 left the community vulnerable in spite of assurances about contingency planning in the contract. Many people with haemophilia felt insecure about sole reliance on one imported factor VIII product when others were available. However, HFA considers the issues are somewhat different for the supply of plasma derivatives. There is unlikely to be any benefit in either terms of cost, safety or quality to contract with more than one fractionator for Australia's supply needs, and given that plasma can be fractionated to meet a significant proportion of Australia's fractionation needs by CSL, there would need to be very strong alternative benefits to make a decision to fractionate offshore. In addition to the past history, there is considerable benefit of having an Australian based fractionator of haemophilia products as a back up plan in case of circumstances which interrupt the supply of recombinant products. Where Australia cannot meet demand for other fractionated products, these must be sourced from overseas in line with current Therapeutic Goods Administration safety requirements to ensure a constant sufficiency. If a tender process resulted in operations becoming unviable for CSL due to reduced demand for its products or ongoing business uncertainly then the Australian community would be badly exposed.

Regulation

HFA will not support any reduction or relaxation of regulatory standards that result in reduced quality or safety of fractionation processes or the products produced if there was tendering for plasma fractionation services. The potential for increased and changeable suppliers over time if competitive tendering is adopted, will inevitably require TGA to have increased resources to meet its obligations. Regulatory harmonisation processes currently in progress may assist, however there are local issues which should be taken into account. The Australian blood supply was severely affected by HIV and hepatitis C, but has been kept relatively safe from potential devastation by vCJD by its isolation, quarantine policies and management of risk minimisation for the blood and food supply. The community has been reassured that a relatively safe blood supply has been maintained through regulatory requirements for donor screening and deferral policies which have responded to a changing international environment, and increasing standards for good manufacturing practice. Stakeholders have adhered to agreements to take precautionary steps to minimise risk to blood product recipients and donors. Such achievements may not be possible in an open market. It would be a completely new situation for patients to adjust to overseas fractionation of plasma for haemophilia products and significant reassurance would be required to assure them that Australian plasma is segregated and manufactured according to Australian regulatory mandate.

If plasma fractionation services are to be opened up to international markets, more resources for safety, quality, auditing and regulation of plasma products will be required to manage plasma, particularly if it is to leave Australia for contract fractionation, and for safe and reliable processes for its return. Australians need to have the same level of confidence in the product as they do now. Any change to the current arrangements would need to allow established standards for safety, quality and efficacy and there must be adequate systems for inspection, recalls and look backs, and enforcement. There may also be increased costs in relation to insurances and indemnities created by overseas players in the market, and the risks that come from plasma storage, logistics, licensure and product failure. There are already regulatory difficulties with plasma derived products made from plasma sourced from countries at risk of Transmissible Spongiform Encephalopathies and all possible steps should be taken to avoid a tiered approach to safety. Where possible product should be manufactured from Australian plasma, and

imported plasma should only be used to supplement supply for clotting factor replacement therapies and immunoglobulin.

Increasing Competition

In general terms, competition is adopted to achieve a lower price or cost savings or other benefits. Australia has only one fractionator and this monopoly has led to higher prices for plasma products than might be achieved in an open market. The CSL facility is geared to a certain level of production, and it is unlikely that it could ramp up to meet demand for all products needed for Australian use to reach self sufficiency of all product needs even if sufficient blood donors were available. Nor is it likely to be viable for CSL if it contracts to produce only a part of the Australian requirements for products where the facility is geared for higher amounts. It is undesirable to lose the potential for local fractionation. It is inevitable that some products will need to be imported to Australia, and this includes replacement therapy for rarer bleeding disorders which cannot be viably produced by more than one manufacturer world wide, or where companies produce on compassionate grounds, and for immunoglobulin where demand is not met. With demand increasing exponentially for immunoglobulin, requiring increased importation to supplement the supply available in Australia, competition in this area may be beneficial and a secondary offshore manufacturer may benefit the Australian community. It is also noted that there may be benefits stemming from the pre and post privatisation relationships established between CSL, government and other stakeholders that might not be achievable with other fractionators without such a history and relationship with the Australian community.

HFA is concerned that increased competition for fractionated products may result in a loss of its only fractionator. Current trends suggest it is unlikely that a second fractionator in the Australian market would commission a new Australian facility. Australia should therefore value its fractionation capacity and develop this capability to most suitably meet its needs.

Security of supply exists if a reliable supply of treatment products is available to meet the needs of people who use these products. The products should be available in sufficient quantities to maintain optimal health and quality of life. Supply safety (security) requires demand and supply management that takes into account all the steps necessary from blood collection to delivery of product to patient, and should include strategies that manage risks and ensures continuous monitoring to prevent crises. This plan would also include the establishment of reserves and rotation arrangements to prevent waste and alternative suppliers as a back up.

Safety, quality and efficacy must be a priority and if this can be achieved in a competitive environment it would be acceptable, however compromise may result in unwanted health care costs or liability for failure to provide treatment and this may become significantly more expensive in the long term. Surety of supply over a period of time is essential to achieve safety and this may not be possible where contracts change in an open market situation.

Further steps after production and delivery are also important. Effective and transparent record keeping, product tracking and robust recall procedures and enforcement must be built into the blood system to minimise and manage safety breaches and kept under review.

Australian collection facilities must be confident the starting material is free of any known viruses. If a safety breach occurs, Australian collection facilities need to be capable of identifying that the incident did not originate in the starting material. It has dire consequences when trying to identify the source of any infection or contamination in the final product, and will be more complicated in an environment of competition with more stakeholders. The bleeding disorders community remains concerned about the risks of viruses and agents that might come through the blood supply and for this reason HFA has advocated strongly for sufficient funding to provide recombinant clotting factor instead of plasma

derivatives to minimise these risks. The tragic past history of blood borne infections through the blood supply in Australia remains foremost in the minds of people with haemophilia and von Willebrand disorder. Most of those who can use recombinant therapy have switched to recombinant or are in the process of doing so, and those who continue to require concentrates manufactured from pooled plasma require confidence that all systems in place to manage the blood products they use are safe and efficacious.

References:

- (1) World Federation of Hemophilia Global Survey, Montreal 2004
- (2) Working Party on the Supply and Use of Factor VIII and Factor IX in Australia, April 2003
- (3) Sher, G in presentation at 4th WFH Global Forum on the Safety and Supply of Treatment for Bleeding Disorders, September 2005
- (4) Bernouf, T in presentation on Unused Plasma and Plasma Fractions at the 4th WFH Global Forum on the Safety and Supply of Treatment for Bleeding Disorders, September 2005