Submission to the Department of Health and Ageing Review of Australia's Plasma Fractionation Arrangements

by the Australian Haemophilia Centre Directors' Organisation (AHCDO)

AHCDO is the peak medical body for haemophilia and related bleeding disorders in Australia and its membership consists of the medical directors of haemophilia treatment centres. AHCDO was incorporated in Victoria in 2000 however its membership had previously met for many years as the Medical Advisory Panel of Haemophilia Foundation Australia. AHCDO maintains the Australian Bleeding Disorder Registry (ABDR), a database established in part to track prevalence, treatment and outcomes of people with bleeding disorders.

Plasma derived fractionation products are used for the treatment of bleeding disorders and it is in this context that AHCDO now makes this submission.

1. Projected demand for plasma products

In 2002, prior to the introduction of readily accessible recombinant products for all patients, AHCDO predicted that demand for all Factor VIII and Factor IX coagulation products would each grow by about 10% per year for the then foreseeable future[1].

The demand for plasma derived products for the treatment of bleeding disorders has reduced significantly however since the introduction of increased funding for, and consequently improved access to, recombinant treatment products in late 2004. Nevertheless, there remain some bleeding disorders for which no recombinant treatment product is available and patients with these disorders may continue to receive plasma derived treatment products. There are also a number of patients who, either through personal preference or for specific clinical indications, have elected to continue using plasma derived treatment products.

Patients requiring treatment for von Willebrands Disorder

The majority of patients who must continue to receive plasma derived products for the management of their bleeding disorder have von Willebrands Disorder (vWD), as there is no alternative recombinant treatment available. People with severe type 3 vWD always require von Willebrands factor (vWF) containing plasma derived products for the treatment of haemorrhages or prophylaxis and approximately 20% of those with vWD (severe type 1 and type 2) will require VWF containing concentrates to treat haemorrhages and for prophylaxis to cover surgery.

Data from the Australian Bleeding Disorder Registry (ABDR) shows that in 2005 there were 56 patients with severe vWD, 124 with moderate vWD and 696 with mild vWD in Australia[2] and that 2,004,500IU of plasma derived product were used in the treatment of 71 patients. In the past, prior to the increased funding of recombinant

[1] 'Projected Demands for Coagulation Factors' AHCDO November 2002

[2] ABDR does not include all NSW data

products, vWD patients were responsible for only a small proportion (<5% in 2003) of the total volume of plasma derived products used within the bleeding disorder community, however it is anticipated that this group of patients will use the majority of plasma derived products henceforth. Indeed, in 2005 almost 32% of all plasma derived FVIII was used by vWD patients and this figure rises to over 48% when reviewing usage by patients who were treated exclusively with plasma derived FVIII.

Unfortunately, estimating the amount of plasma derived product that will be used by this patient group is not as straight forward as predicting the volume used by haemophilia A patients, who often require prophylactic treatment. vWD patients tend to only require treatment after experiencing trauma or a surgical event. Nevertheless, an examination of usage trends is possible. The proportion of vWD patients treated and the average amount of plasma derived product used per treated patient between 2002 and 2005 is shown in Table 1. Using data from the ABDR, AHCDO predicts that there will be a similar pattern in product use for this patient group over the next 10 years, unless a recombinant product becomes available during this period.

Table 1 Usage and treatment for vWD patients

Year	Proportion of vWD pts treated* (%)	Average issue (IU/treated person)
2002	8	25,177
2003	5	30,404
2004	7	23,735
2005	7	28,232

***** Proportion of vWD patients treated who are recorded on the ABDR

The ability to accurately predict how much plasma derived product will be used in the treatment of people with vWD is further complicated in that not all treatment is conducted through the Haemophilia Treatment Centre network, and consequently is not recorded on the ABDR. It is estimated that a small but significant proportion of vWD patients receive their treatment from private practitioners and/or institutions with no way to monitor usage.

There may also be an increase in the usage of plasma derived product associated with increased secondary prophylaxis for vWD.

Patients requiring treatment for rarer bleeding disorders

It is pertinent that there are a number of other rarer bleeding disorders which rely on imported plasma based products as the only or preferred method of management. Factor V deficiency is currently treated with fresh frozen plasma as there is no safe virally inactivated plasma derived or recombinant Factor V concentrate. Although this is a rare disorder the short half life often leads to the need for intensive treatment.

Patients receiving treatment for haemophilia

The number of patients with Haemophilia A recorded on the ABDR who received treatment with plasma derived products during 2005 is 86. However, when product use is examined on a monthly basis it transpires that most of these patients had switched to the recombinant treatment product by years end (n=51). Of the 34

patients who used the plasma derived product exclusively 13 had severe Haemophilia A (total issues 1,546,250IU), 6 had moderate Haemophilia A (total issues 358,250IU) and 15 had mild Haemophilia A (total issues 239,150IU). The volume of plasma derived Factor VIII used by these patients (2,143,650IU) represents about 4% of the total volume of Factor VIII recorded by the ABDR in 2005. Only 4 patients are recorded as receiving prophylactic treatment.

The average age of the patients continuing to use plasma derived treatment product exclusively is 41 years (standard deviation=15 years) and more than 80% are over 30 years of age (n=28). As the haemophilia population ages the amount of orthopedic surgery, and consequently the amount of treatment product required, increases. Consequently it is predicted that if these patients continue to receive only plasma derived product the amount of product used by this cohort may increase- however this may be off set by the reduced usage associated with younger cohorts, where recombinant product is the preferred treatment.

Similarly, the number of patients with Haemophilia B recorded on the ABDR who received treatment with plasma derived products during 2005 is 20. Of the 14 patients who used the plasma derived product exclusively 7 had severe Haemophilia B, 4 had moderate Haemophilia B and 3 had mild Haemophilia B.

The average age of the patients continuing to use plasma derived treatment product exclusively is 40 years (standard deviation =10 years) and again an increase in usage in this small cohort can be expected associated with increasing orthopedic surgery.

In 2003, 58% of the total FIX product used for the treatment of Haemophilia B was plasma derived however this had fallen to 22% by 2005.

In some instances, the reason given by some patients to their clinicians for not using recombinant product is a fear of developing an inhibitor. The development of an inhibitor compromises the patient quality of life and increases the cost of treatment There is very little research available world wide to indicate if inhibitor formation is more or less likely when using a recombinant product and the issue remains contentious. Nevertheless, there are anecdotal reports, particularly for Haemophilia B, that some patients associate the use of recombinant product with the development of an inhibitor and these patients will continue to use plasma derived products. It is anticipated that the number of patients choosing to remain on plasma derived treatment products for this reason will remain very small.

The only treatment to eliminate an inhibitor is immune tolerization. This may be undertaken with either plasma derived or recombinant product. Again, there is a paucity of data to suggest which treatment product is most efficacious and although the recent, as yet unpublished, national guidelines for the use of recombinant and plasma derived Factor VIII and FIX recommend the use of recombinant product due to its higher safety profile, there may be clinical circumstances, such as mild haemophilia A or when tolerisation has failed using recombinant product, where tolerisation with plasma derived product is preferred. In addition, some patients might prefer the use of plasma derived product for tolerisation, particularly if they perceive that the recombinant product was the cause of the inhibitor.

AHCDO believes that over the next 10 years the number of Haemophilia A and B patients choosing to undergo treatment with plasma derived products will gradually decrease. Nevertheless, there will remain a small group of patients for whom plasma derived product is clinically indicated.

Patients receiving treatment for other indications

The plasma derived prothrombin complex concentrate Prothrombinex, which is used to treat Factor II and Factor X deficiencies, is increasingly being used to treat warfarin overdose. There has been a trend away from treating warfarin overdose with fresh frozen plasma as Prothrombinex is a safer product, with both heat and viral inactivation steps included in the manufacturing process of the latest product. Indeed, the consensus guidelines developed by the Australasian Society of Thrombosis and Haemostasis[3] recommend the use of Prothrombinex for major bleeding during warfarin therapy.

2. Requirements to ensure safety, quality and efficacy of fractionation products

In the past significant numbers of the bleeding disorder community have contracted blood borne viruses as a result of contaminated plasma fractionation treatment products. Risks of contamination are reduced with the use of recombinant treatment products and even more so with third generation recombinant products which contain no animal or human products in the cell culture and purification processes. Nevertheless, although recombinant treatment products are the treatment of choice for many bleeding disorder patients, as previously discussed there remain some patients who continue to be treated with plasma derived products. It is imperative that these fractionation products are manufactured to the highest standards, including viral inactivation procedures, to ensure safety against all known viral and non viral (eg prions) contamination risks, that potential new contaminants are monitored and that processes undergo continual assessment to identify areas for improvement. Further, where areas for improvement are identified and new safety measures are developed, it is essential that appropriate steps are taken to implement the improvement without delay.

[3] Gallus AS, Baker RI, Chong BH, Ockelford PA, and Street AM, Consensus guidelines for warfarin therapy, *MJA* 2000; 172: 600-605